Preparation and Characterisation of Floating Tablets to Target the Stomach

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Abstract of Research

Gastroretentive drug delivery systems might enhance bioavailability of some drugs formulated in sustained release dosage forms by providing a longer residence time in the stomach. The aim of this study was to develop and evaluate a swellable floatable gastroretentive drug delivery system utilizing an effervescent mechanism. Tablets were based on a binary (1:1) mixture of hydroxyethyl cellulose and sodium alginate gel forming polymers, with sodium bicarbonate, calcium carbonate or sodium carbonate gas generating agent. The variables affecting drug release and floating properties were investigated, such as tablet crushing strength, wet granulation (to compare the effects of powders versus those of granules), type and ratio of the gas forming agent. The possible interactions between model drug and excipients were analysed using differential scanning calorimetry and Fourier transform infrared spectroscopy. The drug release characteristics, floating capacity and swelling behaviours of drug-loaded matrix tablets were evaluated in 0.1 M HCl (pH 1.2) at 37°C ± 0.5°C. Release data were analysed by fitting the power law model of Korsmeyer–Peppas, which describes the drug release from polymeric systems. The stability of all tablets (stored at 40±2°C and 80±5% RH for 3 months) prepared from a granular origin was evaluated for their apparent density, drug release rate, and floating capacity. It was found that most tablets prepared through wet granulation showed acceptable physical properties. The effect of the granulation process on the drug release rate from all formulations at different crushing strength levels revealed that the granulation process reduced drug release rate. Generally, increasing the tablets' crushing strength level of all formulations, either prepared from powder or granules, decreased their drug release rate. In addition, increasing the gassing agent concentration from 10% to 20% (w/w) increased the drug release rates of formulations prepared originally from a powder mixture at all levels of crushing strength, especially in the case of sodium bicarbonate or calcium carbonate. For tablets prepared from granules, increasing calcium or sodium carbonate gassing agent increased the drug release rate. On the contrary, a decrease in drug release rate was noted when sodium bicarbonate level was increased. Generally, increasing the concentration of gassing agent decreased the floating lag time for tablets based on sodium bicarbonate or calcium carbonate and increased it for those with sodium carbonate. However, increasing tablet crushing strength increased the lag time of all tablets. Most tablets floated on the surface of the dissolution medium and showed an adequate floating lag time (< 30 min) and floated for more than 8 hours. Tablets containing the model drug pentoxifylline showed better stability results in comparison to those of cefalexin monohydrate in either closed or open containers. Pentoxifylline tablets manufactured with 20% (w/w) calcium carbonate were promising with respect to their floating lag time, floating duration, swelling ability, sustained drug release rate, and stability results. An *in vivo* investigation of these promising tablets against a reference solution of pentoxifylline was performed by oral administration of 5.75 ± 0.15 mg to rats. Compared with the reference solution, the maximum plasma concentration (C_{max}) of the tablets decreased, while the time to reach this concentration (T_{max}) and the $t_{1/2}$ were prolonged. This study shows that a binary mixture of hydroxyethyl cellulose and sodium alginate, together with different gassing agents at variable levels, offers an exciting opportunity to develop sustained release preparations.

Research Activity

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Other publications:

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Aljaberi, A., Ardakani, A., Khdair, A., Abdel-Rahim, S.A., Meqdadi, E., Ayyash, M., Alobaidi, G.M., and Al-Zoubi, N. (2013). Functionality evaluation of prosolv easytab® in comparison to physical mixtures of its individual components. . *Drug Del. Sci. Tech*., 23 (5): 499-504.

Al-zoubi, N., Alkhatib, H.S., Alobaidi, G., Abdel-Rahim, S., Obidat, W., and Malamataris, S. (2015). Optimization of pH-independent chronotherapeutic release of verapamil HCl from three-layer matrix tablets. *Int. J. Pharm.* 494(1):296-303.

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List of abbreviations

%	Percentage
°C	Celsius
Å	Angstrom
$AUC_{0-\infty}$	Area under the curve from zero to infinity
AUC_{0-t}	Area under the curve from zero to specific time
BP	British pharmacopoeia
cAMP	cyclic adenosine monophosphate
CI	Carr's index
cm	Centimetre
C_{max}	Maximum plasma concentration
Cp_t	Plasma drug concentration observed at specific time
D	Apparent density
DMU	Dissolution medium uptake
DSC	Differential scanning calorimetry
e.g.	For example
Eq.	Equation
F	Percentage of weight loss
F_{rel}	Relative bioavailability
FTIR	Fourier-transform infrared
g	Gram
GIT	gastrointestinal tract
h	Tablet height
h	Hours
HEC	Hydroxyethyl cellulose
HCl	Hydrochloric acid
IR	Infrared
K_0	The release rate constant of zero order kinetic model
K_1	The release rate constant of first order kinetic model
K_e	Elimination rate constant
k_H	The release rate constant of Higuchi kinetic model
k_{HC}	The release rate constant of Hixson-Crowell model
k_p	The release rate constant of Korsmeyer–Peppas kinetic model
M	Molar
m	Tablet diameter
MCC	Microcrystalline cellulose
mg	Milligram
min	Minute
ML	Mass loss percentage
ml	Milliliter
mm	Millimeter
N	Newton
n	Release exponent
N.A	Not applicable
ng	Nanogram
nm	Nanometre

Oz	Ounce
pH	Numeric scale used to specify acidity or alkalinity of an aqueous solutions
Psi	Pounds per square inch
Q	Amount of drug released at time t
Q_0	Initial amount of drug
Q_t/Q_∞	The fractional drug released at time t
R^2	correlation coefficients
Rpm	Rotation per minute
SD	Standard deviation
T	Time
$t_{1/2}$	Half life
T_{max}	Time to reach maximum plasma concentration
USP	United states pharmacopoeia
W	Tablet weight
w/w	Weight per weight
w_1	weight before friability test
w_2	weight after friability test
W_d	Dry weight of tablet
W_i	Initial weight of tablet
W_w	Wet weight of tablet
ε	Tablet porosity
Mm	Micrometre
Π	The circular constant
ρ_{tablet}	Apparent density of tablets
ρ_{true}	True density of powder or granules

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Chapter One: Introduction

1.1 Overview

Drug administration through oral route has been reported to be the most popular route of drug administration due to safety considerations, patient compliance, and flexibility of oral dosage forms design than most other dosage forms (Chen et al., 2010a, Gupta and Robinson, 1992). Tablets and capsules are the most common marketed oral dosage forms; still, tablets are more widely marketed because of patient swallowing convenience, ease of handling, and lower manufacturing cost (Ilić et al., 2013). Oral controlled release formulations that are able to deliver the drug locally or systemically at predetermined rates for a specified period of time have become an integral part of research centers and pharmaceutical industry due to their many benefits over conventional dosage forms. Such systems can reduce the frequency of dosing which suites patients with chronic illnesses and improve their compliance. Also, they can reduce side effects due to better control of therapeutic drug concentrations. However, the development costs required for some controlled release formulations may be expensive, and they should not be crushed or chewed as loss of drug release control as well as toxicity may be achieved (Nokhodchi et al., 2012). Despite the oral route advantages, it has its own challenges on the controlled drug delivery systems. Food and gastric physiological conditions such as transit time, motility, ions, pH and enzymes can influence bioavailability of drug loaded in oral controlled release systems (Singh et al. 1968; Drewe et al., 1992; Abrahamsson et al. 2004). One of the major obstacles is when drugs show variability in absorption throughout the gastrointestinal tract (GIT). This can decrease bioavailability as drugs are not being fully absorbed once passed the limited area of absorption. Some drugs show region specific absorption (absorption window), most commonly from the upper part of the small intestine (Harder et al., 1990; Rouge et al., 1996).

Most drug molecules are absorbed as un-ionized forms by passive diffusion but solubility and stability of the drug molecule are of critical value for successful biological membrane crossing. Yet, drug molecules experience a wide pH range as they pass through the gastrointestinal tract (GIT) which can influence their extent of ionization, solubility, and stability. This can lead to variable absorption or an absorption window.

Polar drug molecules (e.g. cimetidine) generally have good absorption from the proximal small intestine, but have poor absorption from the large intestine or colon part of the gastrointestinal tract (Adkin et al. 1995; Corrigan, 1997). Furthermore, some drugs are substrates of certain enzymes present in a particular part of the gastrointestinal tract which can lead to regional variability in these drugs absorption (Chungi et al., 1979). Intestinal metabolic enzymes, cytochrome P450 (CYP3A), are largely present in the intestinal epithelium with levels rising slightly from the duodenum to the jejunum and then declining in the ileum and colon. Drugs that are substrates of CYP3A enzyme display regional variability in their absorption due to the non-uniform enzyme distribution along the gastrointestinal tract. Similarly, drugs which depend on certain systems of facilitated transport process like carriers and pump systems show higher regional specificity because of the dominance of these systems in only certain parts of the gastrointestinal tract (Ritschel and Kearns, 1999). For example, angiotensin enzyme inhibitors and β-lactam antibiotics (e.g. cephalexin) depend on peptide transporters located in the small intestine (Zhang et al., 2010).

Carriers, such as P-glycoprotien, are involved in the secretion of organic molecules from the blood back into the intestinal lumen which may affect drug absorption (Benet and Cummins, 2001). P-glycoprotien which is located on the mucosal surface of intestinal epithelial cells is responsible for low and variable bioavailability of various compounds such as propranolol and felodipine (Siegmund et al., 2003). Thus drugs with site-specific absorption window are difficult to be designed as oral controlled drug delivery systems because time available for drug absorption will be limited and after crossing the absorption window, the drug will have negligible or no absorption. Accordingly, it has been a challenge to develop desirable oral sustained release dosage forms maintained at the targeted area inside gastrointestinal tract (GIT). Gastroretentive drug delivery systems provide dosage forms with longer residence time in the stomach and sustained release behaviour which can improve bioavailability as well as acting locally on the stomach (Kagan et al., 2006; Murphy et al., 2009).

Many drugs are considered good candidates to be benefit from gastroretentive delivery systems. Such drugs include those that a) have narrow absorption window such as acyclovir (Bhosale et al., 2012; Ruiz-Caro et al., 2012), atenolol (Rouge et al., 1998; Lal and Datta, 2015), furosemide (Klausner et al., 2003a; Meka et al., 2009), levodopa (Klausner et al., 2003b; Ngwuluka et al., 2013), metformin (Ali et al., 2007; Ige and Gattani, 2012), metoprolol (Malode et al., 2015; Biswas and Sahoo, 2016), and riboflavin (Hamdani et al., 2006; Gröning et al., 2007); b) show low solubility within the alkaline environment of the intestine such as ofloxacin (Chavanpatil et al., 2006; Qi et al., 2015) verapamil (Dürig and Fassihi, 2000; Sawicki, 2002), and diazepam (Sungthongjeen et al., 2008); c) unstable in the colonic environment such as captopril (Gröning et al., 2007; Jiménez-Martínez et al., 2008); and d) indicate local activity in eradication of the stomach *Helicobacter pylori* such as amoxicillin (Rajinikanth et al., 2007; Badhan et al., 2009) and metronidazole (Ishak et al., 2007; Loh and Elkordy, 2015). Nevertheless, drugs that have adverse effects on the gastric mucosal lining, are unstable in the acidic conditions of the stomach, or are absorbed equally throughout the entire GIT are not suitable for use as in gastroretentive delivery systems.

1.2 Gastric anatomy and physiology

1.2.1 Stomach

The stomach is positioned in the left upper part of the abdominal cavity immediately under the diaphragm. The stomach size following a meal can swell up to 1500 ml; but after emptying food a collapsed state can be obtained with resting volume of 25–50 ml (Waugh and Grant, 2001). Anatomically, as shown in (Figure 1-1), the stomach is divided into four regions: fundus, body, antrum, and pylorus. The proximal part of the stomach (fundus) functions as a reservoir. It adjusts to the increased volume during eating by relaxation of the fundal muscle fiber which results in greater curvature. The proximal stomach controls the gastric emptying of liquids by applying basal pressure in the stomach due to slow and sustained contractions. Also, a steady pressure is also applied by fundus which gradually presses gastric solid contents towards the distal part of the stomach.

The distal part (antrum) has a thicker muscular wall to facilitate mechanical grinding and homogenisation of food, after which pumping the contents toward the pylorus to accomplish gastric emptying. The pylorus is a sphincter located between the antrum and the duodenum that functions as a mechanical stricture to the transit of large particles into the small intestine (Wilson and Washington, 1989). The body of the stomach is lined with several types of cells that secrete up to 2-3 liters of gastric juice daily. For example, goblet cells secrete mucus, parietal (oxytntic) cells secrete acid and intrinsic factor, and peptic (chief) cells secrete the precursor of pepsin (pepsinogen) (Dressman et al., 1990). The stomach provides barrier to delivery, therefore, very little absorption occurs from this site (Wilson and Washington, 1989). More significant absorption occurs outside the stomach where the duodenum has epithelial surface with transporters for peptides (Ogihara et al., 1999) and metals (Cousins and McMahon, 2000; Barley et al., 2001).

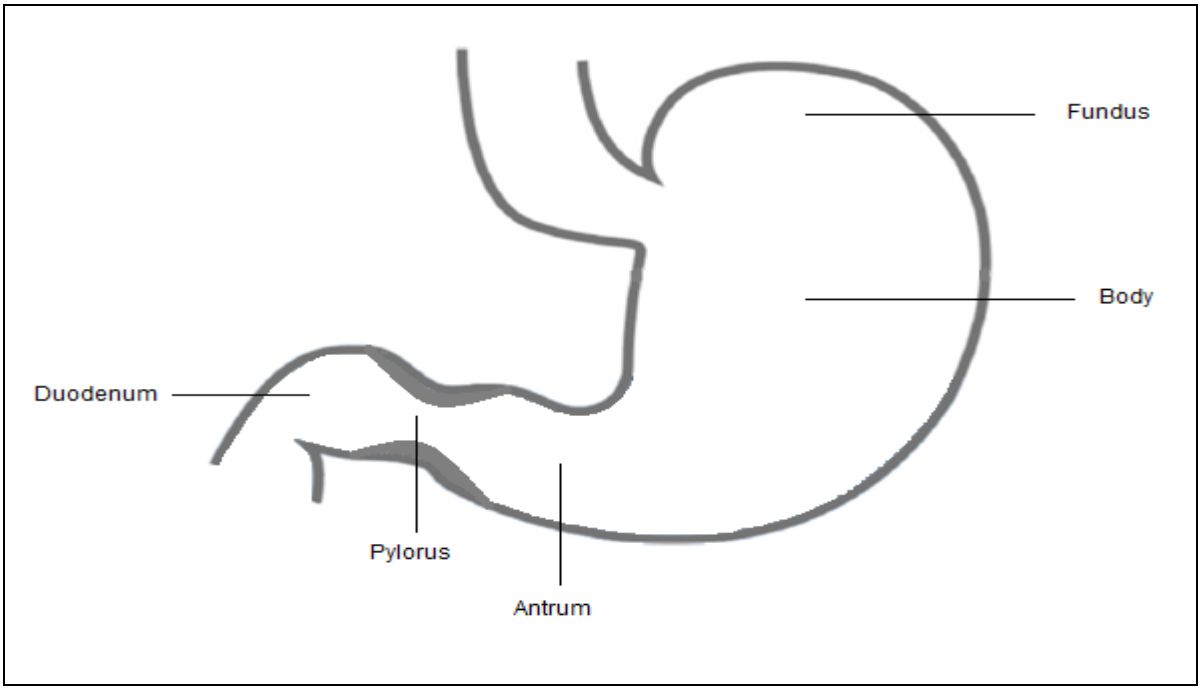

Figure 1-1: The stomach parts (Wilson and Washington, 1989).

1.2.2 Gastric pH

The gastric pH is variable between subjects as well as in the same subject where numerous factors such as food, disease, presence of gases, fatty acids, and other fermentation products can modify the pH value (Dressman et al., 1990; Talukder and Fassihi, 2004). According to food type the gastric pH can be increased from 1.8 (at resting time) to 3-5, but milk can raise it to over 6, however the pH returns to basal level within approximately 2 h after food ingestion is completed (Wilson and Washington, 1989). Age, pathological conditions and drugs may influence the gastric pH value. Holt et al. (1989) reported that 20% of elderly people show either diminished (hypochlorohydria) or no gastric acid secretion (achlorohydria) which elevates the basal pH value above 5.0. Furthermore, elevated gastric pH due to significant reduction in the gastric acid secretion was reported in some pathological conditions such as pernicious anemia and AIDS (Benn and Cooke, 1971; Varis et al., 1979). Drugs like proton pump inhibitors significantly reduce gastric acid secretion and elevate the gastric pH over 6.0 (Laine et al., 2008). Outside the stomach, pH values tends to increase gradually due to the bicarbonate secreted by the pancreas and the duodenal mucosa where the proximal duodenum pH may rise as high as 4 pH units from the stomach (Benn and Cooke, 1971). It is important to take in consideration the gastric pH in selecting a drug substance and excipients for designing oral drug delivery systems. Nevertheless, the gastric emptying time corresponding to the fast and fed states has an enormous influence on the proposed efficacy of such dosage forms.

1.2.3 Gastric motility and emptying rate

Gastric emptying occurs during both fasting and fed states, yet, there are marked differences between the patterns of motility of both states. During the fasting state inter digestive series of electrical events occur, which cycle both through the stomach and the intestine every 2 to 3 h (Vantrappen et al., 1979; Pawar et al., 2011a). This is called inter digestive myloelectric cycle or migrating myloelectric cycle, which can be divided into the following four phases.

Phase-I or basal phase, lasts from 40 to 60 min with rare contractions. Phase-II or pre burst phase, lasts for 40 to 60 min with intermittent action potential and contractions. Phase-III or burst phase, is a short phase of intense (lasts for 4 to 6 min), and characterized by large regular contractions with a frequency of 4–5 per min (Rubinstein et al., 1988) and maximal pyloric opening (Ehrlein, 1988). It is known as “house keeper wave”, and due to that all the undigested material is swept out of the stomach down to the small intestine. Phase-IV lasts for 0 to 5 min and occurs between phases-III and I of two consecutive cycles.

In the fed state, the gastric emptying rate is slowed since the onset of migrating myloelectric cycle is delayed (Wilson and Washington, 1989). The motor activity in the fed state is induced 5–10 min after ingestion of a food and continues as long as food remains in the stomach. It can last 2–6 h regarding amount of food ingested (Hasler, 1995). Feldman et al. (1984) reported that the time required for the stomach to be half emptied from liquid, digestible solid and indigestible solid phases (10 oz of soft drink, scrambled egg and radio-opaque markers) was 30 ± 7 min, 154 ± 11 min and 3.5 ± 0.5 h respectively. Emptying of liquids from the stomach is based on slow contractions produced in the proximal stomach. However, larger particles require longer time to be milled into a suitable size to pass through the pylorus. After emptying digestible materials into the small intestine, residues of large undigested solids, which cannot pass through the pylorus, will be retro-pulsed from the pylorus and distal antrum to the proximal antrum and stomach body (Kelly et al., 1973; Ehrlein, 1980; Shalaby et al., 1992a) and will be kept in the stomach till they swept out by house keeper waves of the fasted pattern motility (Wilson and Washington, 1989).

1.2.4 Factors influencing gastric emptying rate

Several factors can influence the gastric emptying rate. For example meals with balanced content of fat, carbohydrate, and protein, the emptying process will depend on its nutritive density (Hunt and Stubbs, 1975). Nonetheless, meals with high acidity, osmolarity, calorific value are emptied later than the others (Hunt and Knox, 1972). Also, a prolongation in gastric emptying time after a succession of meals in comparison to that after a single meal has been reported (Iannuccelli et al., 1998a).

Fluids temperature and volume can also influence the gastric emptying time. Fluids at body temperature are emptied more rapidly in comparison with higher or lower temperature ones. Also, large volume fluids can leave the stomach more rapidly than smaller volumes (Wilson and Washington, 1989). Stress increases the gastric emptying rate, while depression slows it down. In general, women and elderly have a slower gastric emptying rate than men and young people respectively (Kaus and Fell, 1984; Reddy et al., 1999). Although, Ollerenshaw et al. (1987) reported that exercise and body posture may influence the gastric emptying, Mojaverian et al. (1988) had observed no significant effect of standing or flat on back positions on gastric residence time. Concomitant intake of some kinds of drugs acting as anticholinergic agents like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide, cisapride can alter the gastric emptying rate (Kaus et al., 1984). Furthermore, Triantafyllou et al. (2007) reported a decrease in the gastric emptying rate of patients with type I and type II diabetes, however, a delay in the gastric emptying which may be frequently accompanied by constipation was reported in patients with Parkinson's disease (Krygowska-Wajs et al., 2009).

1.2.5 Gastric emptying time of dosage forms

Presence of food in the stomach can produce a significant effect on dosage forms emptying rate. Nonetheless it can increase, decrease, or delay drug absorption rate (Heading et al., 1973). For liquid dosage forms, it was reported that small volumes (10 to 20 ml) of such dosage forms were emptied from fasted volunteers' stomach within 1 h (Jenkins et al., 1983), however more than 2 h was required to empty them from stomach under fed condition (May et al., 1984). Large tablets and capsules are treated by the stomach as an indigestible materials either they are intact or in large fragments (Wilson and Washington, 1989). It was demonstrated that when non-disintegrating tablets taken before meals they were emptied from the stomach within highly variable time ranging from 5 min to 3 h depending on the inter digestive myloelectric cycle (Kaus et al., 1984); but when taken after meals, the emptying became around 2 to 3 h if the meal was light and up to 12 h if the subject was fed in regular intervals (Wilson et al., 1989).

In addition to the stomach state (fed or fast), size of the dosage form is another parameter that can influence the gastric emptying of non-disintegrating tablets. In the fasted state, the gastric emptying of large single unit dosage forms is changeable. It depends on the time of arrival in the stomach in relation to activity of inter digestive myloelectric cycle. Units larger than 1.9 cm, the pylorus mean diameter (Salessiotis, 1972), are retro pulsed in the antrum and several phases of myoelectric activity take place when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of these solids (Park et al., 1984). Under the fed state, the gastric waves are delayed and the gastric residence time can be significantly increased (Mojaverian et al., 1985). Studies revealed that the gastric residence time of tablets in the fed state can also be influenced by their size. Although, tablets larger than the pylorus, were retained in the stomach for as long as the digestive phase was maintained and emptied during the housekeeping waves (Davis et al., 1984), tablets with diameter less than 7 mm left the stomach during the digestive phase (Kinget et al., 1998). The dosage form density can also alter the gastric emptying rate. Dosage forms with densities less than that of the gastric fluids can float and can be kept away from the pylorus for a prolonged period of time as they can be protected from the peristaltic waves of the stomach.

A study of effect of size of floating and non-floating capsules on the gastric residence time revealed that the floating units were more likely to be kept in the stomach compared with the non-floating units. Regarding body posture, the upright position enhanced the gastric retention of the low density capsules that floated on top of the gastric contents, however, the supine position increased the gastric retention time of the non-floating capsules (Timmermans and Möes, 1994). Multi-particulate systems or pellets contained in a hard gelatine capsule can also be used orally to control the drug release. It was demonstrated that the gastric emptying of pellets from fasted subjects was dependent on how quickly they can disperse in the small volume of the gastric fluid available in the stomach and they tended to empty as a series of boluses (Christensen et al., 1985; Hunter et al., 1982). In fed conditions, Meyer et al. (1985) reported that spheres emptying rate was dependent on their size and density. The smaller the spheres the faster they emptied from the stomach.

Also, spheres with higher or lower density than that of the gastric fluid, tended to sink to the base of the stomach or to float on the gastric content respectively. Such spheres emptied more slowly in comparison with spheres of similar density to food. Generally, multiple-unit dosage forms such as, beads, pellets, and granules have a more predictable and reproducible gastrointestinal transit in comparison with single-unit modified-release formulations (Varum et al., 2010). It is believed that gastric emptying is the major factor controlling the absorption of all materials ingested by oral route. As discussed earlier, many variables can influence the gastric pH, motility, and emptying rate including physiological state of the patient and design of the pharmaceutical dosage form which may affect drug bioavailability. Consequently, it is important to design a dosage form that can overcome physiological adversities like short residence times and unpredictable gastric emptying rates.

1.3 Gastroretentive delivery systems

Over the last three decades, numerous gastroretentive dosage forms have been designed and developed by pharmaceutical industry. Increasing gastric residence time can be achieved either by expandable systems, mucoadhesive systems, high-density systems, superporous hydrogels, magnetic systems, or floating systems.

1.3.1 Expandable systems

Such systems can show an increase in their volume and/or shape by swelling or unfolding to achieve longer gastric residence time. Swellable systems (Figure 1-2) are based on hydrophilic polymers such as hydroxypropylmethyl cellulose, polyethylene oxide and carbopol which increase in size after hydration with the gastric fluids. The swelling is usually results from osmotic absorption of water. Unfoldable systems (Figure 1-3) are based on biodegradable polymers that are folded and encapsulated in a carrier. In the stomach the system unfolds to its initial geometrical shape due to carrier degradation and become too large to pass through the pylorus (Gardner et al., 1986).

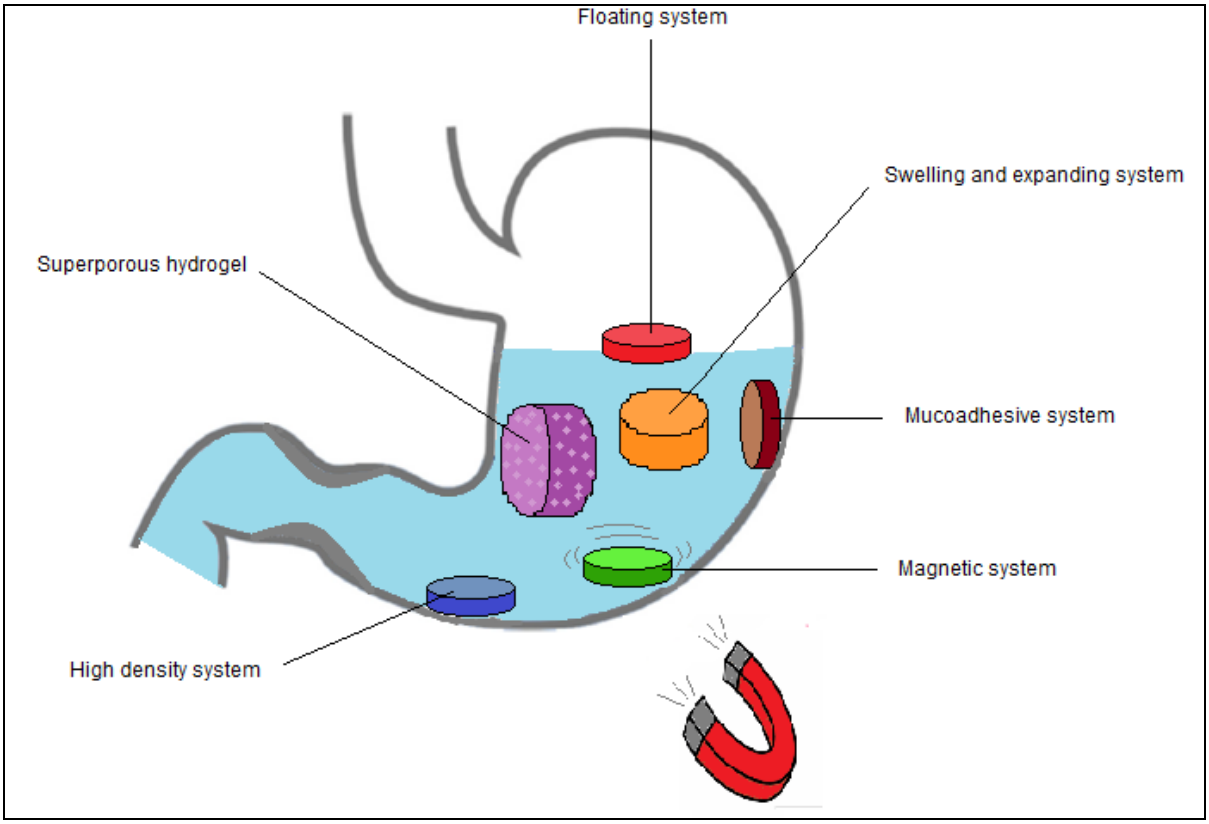

Figure 1-2: Schematic presentation of gastroretentive delivery systems (Alzaher et al., 2016)

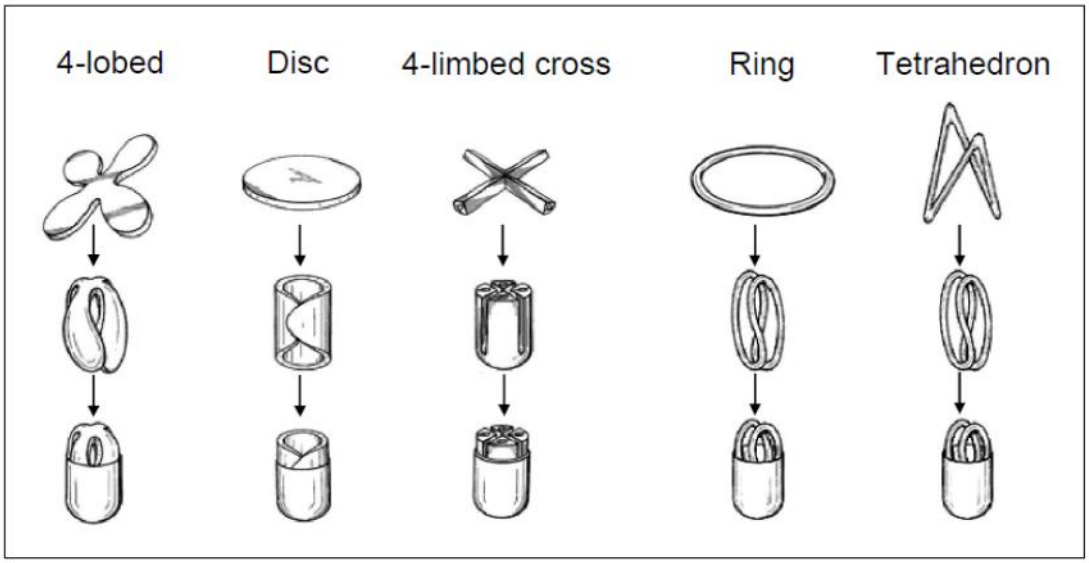

Figure 1-3: Schematic presentations of gastroretentive unfoldable systems (Gardner, 1986)

Generally, expandable systems should have convenient size to be easily swallowed by patients, and the resulted systems size inside the stomach should not be smaller than that of the pylorus. Nevertheless, during fasting, the expandable systems can sweep from the stomach by inter digestive myloelectric cycle unless they are extremely large in size. Accordingly, in order to prevent gastric obstruction either singly or by accumulation, biodegradable polymers should facilitate their easy elimination from the stomach at the end of the drug delivery process (Klausner et al., 2003c). Expandable systems were investigated by researchers. Regarding swellable systems, Mamajek and Moyer, (1980) evaluated a device composed of a drug reservoir surrounded by a swellable polymer and coated by an elastic outer polymeric permeable membrane to control drug release. Also, Urquhart and Theeuwes, (1984) designed and evaluated tiny pills coated by wax to control drug release and dispersed in a matrix of polymeric hydrogel. The system could swell up to 50-folds of its original size in body fluids. Shalaby et al. (1992b) evaluated enzyme-digestible hydrogels based on polyvinylpyrrolidone crosslinked with albumin. The system was successful to show gastric residence time in dogs more than 24 h under fasted conditions. Gröning et al. (2007) developed a drug-loaded collagen freeze-dried sponge which was pressed and coated with a thin layer of magnesium stearate to avoid contact with saliva. In the stomach, the tablet expanded to almost its original size. El-Zahaby et al. (2014) developed swellable tablets (plug-type) loaded with levofloxacin for *Helicobacter pylori* eradication. Tablets were based on *in situ* gel forming polymers, such as gellan gum, sodium alginate, pectin and xanthan gum cross linked calcium or aluminum chloride. Results showed that the drug release was dependent on nature of the matrix and type of the cross linker used to form the plug-type tablets.

For unfoldable systems, different geometric forms were investigated. Caldwell et al. (1988a,b) developed and evaluated tetrahedron, ring and planar membrane of bio-erodible polymer enclosed within a capsule. Tetrahedron devices had longer gastric residence time than the other tested shapes of similar size. Sonobe et al. (1991) patented a ‘‘Y’’ shape system, with three erodible arms serving as a drug reservoir and whose rate of degradation controlled the gastric retention time.

A spring unfoldable system was evaluated by Curatolo and Lo, (1995) with arms fixed by a gelatin band which could dissolve in the stomach, releasing the mechanically preferred extended form. Klausner et al. (2003b) developed a dosage form based on unfolding polymeric membranes loaded with levodopa. The gastroretentive dosage form was able to maintain the drug concentrations within the therapeutic level (> 500 ng/ml) over 9 h. Verma et al. (2014) developed and evaluated cinnarizine polymeric films of ethylcellulose and hydroxypropylmethyl cellulose containing different amounts of stearic acid that were folded into hard gelatin capsules. Authors revealed that in the first hour of the *in vitro* dissolution test, the drug had immediate release followed by a gradual release over 12 h. Mechanical property of the expanding systems is considered a vital parameter for their gastric retention. Although size of the expanding systems is important, systems lack high rigidity will not be retained in the stomach (Klausner et al., 2003b). Moreover, the mechanical shape memory of the unfolding systems, is relatively short-lived (Klausner et al., 2003d), they are difficult to industrialize and may not be cost-effective (Hwang et al., 1998).

1.3.2 Superporous hydrogels

Superporous hydrogels (Figure 1-2) are based on cross-linked hydrophilic polymers with average pore size > 100 µm in comparison with 10 nm to 10 µm pore size of conventional swellable systems. Consequently, they can rapidly absorb significant volume of aqueous fluids by capillary action to swell and create an open channel structure that can avoid premature gastric emptying by house keeper waves and increase the gastric residence time (Chavda et al., 2012). Superporous hydrogels can be classified according to their swelling and mechanical properties into three different generations. The first generation (conventional superporous hydrogels) has rapid and high swelling ratio but has mechanical fragility. Equilibrium swelling with this generation can be achieved in < 1 min with an increase in system volume by more than 1000 times in some cases (Chen et al., 1999; Chen and Park, 2000a).

The second generation (superporous hydrogel composites) has quick and moderate swelling ratio (a few hundred times of the original volume) with superior mechanical properties (to withstand pressure by the gastric contraction) by adding a composite material such as croscarmellose sodium (Chen and Park, 2000b). Such systems showed gastric retention in fasted dogs for 2-3 h after which they broke into pieces and emptied into the intestine, however, they kept in the stomach for > 24 h when dogs were in the fed state (Chen et al., 2000). The promising third generation for gastroretention (hybrid superporous hydrogels) has a very high mechanical or elastic property. The hybrid superporous hydrogels are prepared by adding a hybrid agent such as polysaccharides including sodium alginate, pectin, chitosan or synthetic water-soluble hydrophilic polymers such as polyvinyl alcohol that can be cross-linked after formation of superporous hydrogel (Omidian et al., 2005). For example the synthesis of acrylamide-based superporous hydrogel in the presence of sodium alginate which could be cross-linked by calcium ions. This formulation was able to stretch up to 2–3 times its original length showing resilience and a rubbery property in its fully water-swollen state (Omidian et al., 2006). Recently, El-Said et al. (2016) evaluated an extended release superporous hydrogel hybrid system using gellan gum, guar gum, polyvinyl alcohol and gelatin in dogs. Results revealed an increase in baclofen bioavailability and the effectiveness of the designed system. Generally, there is a lack of information in the literature about superporous systems.

1.3.3 Mucoadhesive systems

Mucoadhesive systems (Figure 1-2) are based on natural or synthetic mucoadhesive polymers such as poly(acrylic acid), chitosan, cholestyramide, tragacanth, sodium alginate, carrageenan, carbopol, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, sephadex, sucralfate, polyethylene glycol, dextran, poly(alkyl cyanoacrylate), and poly-lactic acid that have ability to adhere to epithelial surface of the stomach to increase gastric residence time. Four different theories exist to explain the adhesion mechanism (Tao et al., 2009). First of all is the electronic theory, involving attractive electrostatic forces between the glycoprotein mucin network and the mucoadhesive polymers (Derjaguin et al., 1977).

Secondly is the adsorption theory, where secondary forces such as Van der Waals forces and hydrogen bonding are responsible for mucoadhesion (Kinloch, 1980). Thirdly is the wetting theory, as mucoadhesive polymers are able to spread and develop close contact with the mucus layers (Kaelbe, 1977). And finally, the diffusion theory, which based on a physical entanglement of mucin strands and the flexible polymer chain, or an interpenetration of mucin strands into the porous structure of the polymer substrate (Voyutskii, 1963). However, the exact mechanism of mucoadhesion is not yet completely understood. Smart and Kellaway (1989) reported extended gastric retention time of dosage forms coated with carbomer polymer in mice. Akiyama and Nagahara (1999) evaluated mucoadhesive microspheres based on a mixture of amoxicillin and carbopol 934P which was dispersed within a matrix of polyglycerol esters of fatty acids. After oral administration, microspheres were able to adhere to the stomach mucosa in Mongolian gerbils and to show higher anti *Helicobacter pylori* activity in comparison with an amoxicillin suspension. Jackson et al. (2000) reported extended gastric residence times with ability to coat the gastric mucosa uniformly of the positively charged ion-exchange resin colestyramine.

Hejazi and Amiji (2002) prepared chitosan microspheres loaded with tetracycline by ionic precipitation with sodium sulfate. The drug release from the microspheres showed dependency on the dissolution medium pH, where ~ 70 and 90% of the drug was released after 3 and 8 h at pH 3.5 and 5.0 respectively. Also, they investigated the gastric residence time of chitosan-based microspheres loaded with tetracycline gerbils (Hejazi and Amiji, 2003). The gastric residence time of the microspheres was independent of the gastric pH within the range of 1.0 – 4.5, but, the drug concentration in the stomach was similar to that of an aqueous solution. Later, increased gastric residence time in fasted gerbil stomach was reported for chitosan-based microspheres prepared by ionic precipitation followed by chemical crosslinking with glyoxal and loaded with tetracycline in comparison with non-crosslinked microspheres and tetracycline solutions (Hejazi and Amiji, 2004). After 2 h, 17% of the crosslinked microspheres remained in the fasted stomach, whereas only 10% of the non-crosslinked systems were retained. Sakkinen et al. (2003) reported that granules containing microcrystalline chitosan and furosemide exhibited slow release characteristic with higher AUC than that of the conventional dosage form due to their mucoadhesive properties.

Preda and Leucuta (2003) presented significant retardation of gastric emptying of a mucoadhesive system based on polyacrylic acid in gelatin microspheres in rats. Higo et al. (2004) presented promising mucoadhesive properties of tetracycline– sucralfate complex prepared under acidic conditions. Higher percentage of the complex was retained on the gastric mucosa in rats compared with the physical mixtures of tetracycline and sucralfate after 3 h. Schmitz et al. (2005) developed minitablets based on low molecular-weight heparin and thiolated polycarbophil was used as the mucoadhesive carrier material. Hydroxyethyl cellulose was used as a non-mucoadhesive control. In contrast to thiolated polycarbophil-based delivery systems, the control formulations were not observed in the gastric lumen of rats at 4 h after administration. Liu et al. (2005) developed a promising mucoadhesive microspheres loaded with amoxicillin for the treatment of Helicobacter pylori infection. Ethylcellulose was used as matrix to control the drug release and carbopol 934P as mucoadhesive polymer. Results showed that the system could retain in gastrointestinal tract for an extended period of time. Later Tao et al. (2009) evaluated acyclovir mucoadhesive microspheres based on similar composition in rats. Results showed prolonged residence time of microspheres in the gastrointestinal tract with relatively steady plasma drug concentrations within 8 h after oral administration.

Zate et al. (2010) developed a mucoadhesive tablet loaded with venlafaxine hydrochloride using carbopol 971 P as the mucoadhesive agent and Eudragit® RS-PO and ethylcellulose as controlled release polymers. Results revealed that increasing the carbopol 971 P concentration increased the residence time up to 12 h and more ethylcellulose retarded the drug release. Jha et al. (2011) demonstrated an increase in the absorption, bioavailability and sustained release of raloxifene hydrochloride from mucoadhesive microspheres based on cyclodextrin(s) and different proportions of carbopol and hydroxypropylmethyl cellulose. Pund et al. (2011) developed a biphasic mucoadhesive tablet to deliver loading and maintenance dose rifampicin. The tablet was retained in the stomach for more than 320 min. Mini-tablets of rosuvastatin calcium with mucoadhesive properties using pre-activated thiolated pectin derivative as a mucoadhesive agent were formulated (Hauptstein et al., 2013).

Results demonstrated improved mucoadhesion with sustained release of rosuvastatin calcium over 36 h for the designed system in comparison with mini-tablets prepared with the pre-activated thiomer, the thiolated intermediate and unmodified pectin. Pandey et al. (2013) prepared a bilayer mucoadhesive rate controlling film of lercanidipine HCl using a combination of Eudragit® RSPO and RLPO, and a mucoadhesion film, combining various hydrophilic polymers. *In vivo* studies in rabbits showed that drug release was controlled for over 12 h, with enhanced bioavailability. Jelvehgari et al. (2014) designed multiple unit bilayer discs loaded with metformin using carbopol 934P as a mucoadhesive polymer and ethylcelullose as a drug retarding polymer. It was found that this system was successful to show good drug release properties. Sodium alginate, xanthan and karaya gum were used as mucoadhesive polymers to develop a mucoadhesive tablet of lafutidine (Patil and Talele, 2015). Results suggested an adequate drug release rate was provided with 10 h adhesion in the rabbit stomach.

An advantage of mucoadhesive systems in the stomach is the short pathways due to the close contact with the gastric mucosa for drugs targeting the stomach, such as antibiotics against *Helicobacter pylori*. Although the concept of mucoadhesion gains increasing interest, only a few successful approaches to develop gastroretentive mucoadhesive systems have been reported. They are challenged by the stomach turnover, the mucus layer renewal, and the high stomach hydration that decreases the mucoadhesion of polymers (Kockisch et al., 2003). Also, targeting the gastric mucus with mucoadhesive polymers is difficult because they can stick to various surfaces they come in contact with (Khosla and Davis, 1987). Regarding safety aspects, oesophageal binding might present a challenge for such devices (Wang et al., 2000).

1.3.4 High density systems

These systems (Figure 1-2) can sink to the bottom of the stomach (below the pylorus) as they have a density higher than that of the gastric fluid (> 1.004 g/cm^3) and tend to withstand the peristaltic movements of the stomach wall (Clarke et al., 1993; Bardonnet et al., 2006).

High density excipients such as iron powder, barium sulfate, titanium dioxide, and zinc oxide could be used to formulate high density systems (Devereux et al., 1990). Bechgaard and Ladefoged (1978) evaluated influence of density or diameter of pellets on the gastric transit time. An extension of 5.8-25 h of the gastric residence time depending more on the pellets density rather than on the pellets diameter was reported. Riner et al., (1982) and Cardinal (1985) presented promising results of high density systems in ruminants. Also, Devreux et al. (1990) reported that pellets with density of at least 1.5 g/cm^3 have significantly higher gastric residence time either in fasted or fed conditions. Later, it was demonstrated that an increase in the gastric residence time of pellets could be achieved with density values range 2.4-2.8 g/cm^3 (Clarke et al., 1995).

Simoni et al. (1995) reported a better bioavailability of sinking enteric-coated tablets loaded with ursodeoxycholic acid in comparison to floating enteric-coated tablet and hard gelatine capsules in 12 healthy volunteers. Still, Davis et al. (1986) showed that *in vivo* data did not confirm the effectiveness of the high density systems in exdending the gastric residence time, as the stomach state at time of administration was the main determining factor. Gupta and Robinson (1995) reported that these devices did not extend significantly the gastric residence time. Furthermore, Rouge et al. (1998) evaluated effect of immediate release system, a high density system and a low density system gastric residence times. Results indicated that the high density system did not show any significant extension of the gastric residence time as results were 0.5, 1, and 2 h respectively. Till present, there is a lack in information about successful approach describing a gastroretentive device based only on high density.

1.3.5 Magnetic systems

These systems (Figure 1-2) are designed to increase the gastric residence time because of attractions between the pharmaceutical dosage which contains magnetically active elements and a magnet which is placed under the abdomen, near the stomach (Lopes et al., 2016). Primarily, magnetic granules were designed as a drug delivery system to oesophageal mucosa in oral administration (Ito et al., 1990).

Fujimori et al. (1994) evaluated a magnetic tablet containing 50% w/w ultra-ferrite with hydroxypropyl cellulose and cinnarizine in beagle dogs by the application of a magnetic field. The tablet was successful to remain in the stomach for 8 h with sustained drug release. Later, Fujimori et al. (1995) reported a delay for 3 h in the gastric emptying time of a bilayer magnetic tablet loaded with acetaminophen. Gröning and Berntgen (1996) incorporated a small magnet within a drug loaded capsule and guided it with an extracorporeal magnet attached to the abdomen. The gastric residence time of the device was effectively delayed. Later, Gröning et al. (1998) investigated acyclovir serum concentration after oral administration of magnetic depot tablets and the influence of extracorporeal magnet to control gastroretentive transit. The drug plasma concentrations showed an increase in acyclovir absorption with a gastric residence time of 12 h was obtained. Practically, the magnetic field can retain the dosage form and control its gastric residence time; however, the external magnet device could decrease the patient compliance (Hwang et al., 1998).

1.3.6 Floating systems

The floating drug delivery systems were early described in the literature as early as 1968 (Davis, 1968). These systems (Figure 1-2) are designed to have a bulk density lower than the gastric fluid (< 1.004 g/cm^3) so they can remain buoyant for prolonged period of time without affecting the gastric emptying rate (Whitehead et al., 1998). One of the drawbacks of floating drug delivery systems is that they require an adequate level of fluids in the stomach for the system to float effectively, but, administration of a glass full of water (200–250 ml) can overcome such disadvantage (Pawar et al., 2011b). Floating drug delivery systems can be classified into non-effervescent systems or effervescent systems.

1.3.6.1Non-effervescent floating systems

Non-effervescent floating drug delivery systems are based mainly on gel forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as sodium alginate, polycarbonate, polyacrylate, polymethacrylate, and polystyrene. After oral administration, these systems will swell in the gastric fluid and maintain a relative stability of shape and a bulk density less than that of the gastric fluid. Accordingly, this will assist the floating process of these dosage forms, and slow drug release will be achieved by diffusion through the formed gel barrier (Sheth and Tossounian, 1984).

Hydrodynamically Balanced System (HBS^{TM}) is a single unit dosage form that was primarily developed by Sheth and Tossounian (1984) as non-effervescent floating systems. They are composed of one or more hydrophilic polymers (such as hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, agar, carrageenan or alginic acid) in which the drug is embedded and the mixture is usually enclosed in a gelatin capsule (Figure 1-4). After administration, the capsule dissolves upon contact with the gastric fluid and the polymer (or polymeric mixture) swells to facilitate floating and to control the drug release by diffusion and erosion of the gel barrier (Sheth and Tossounian, 1984). The HBS maintains surface hydration and buoyancy due to continuous erosion of the surface which allows water penetration to the inner layers of the system (Reddy and Murthy, 2002). Low density HBS (Madopar®) was developed by incorporation of fatty excipients to reduce water penetration and erosion of the system (Erni and Held, 1987; Jansen and Meerwaldtt, 1990). Later, a bilayer formulation was developed from swellable polymers and only one of them was loaded with misoprostol so that buoyancy and drug release could be optimized independently (Oth et al., 1992). Results demonstrated a mean gastric residence time > 3 h and > 10 h following a single meal and a succession of meals respectively.

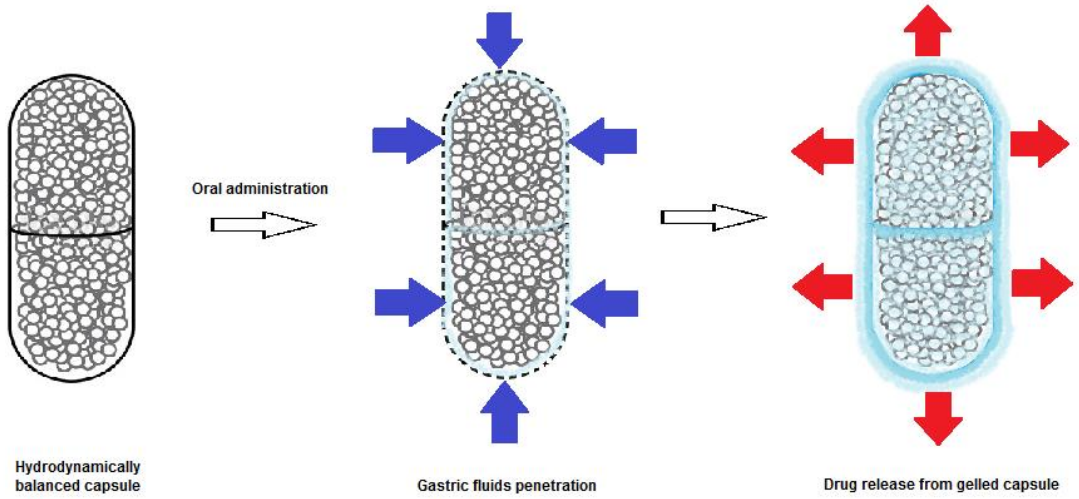

Figure 1-4: Schematic presentation of Hydrodynamic Balanced System (Ushimaru et al., 1987)

Krogel and Bodmeier (1999) designed a multifunctional drug delivery system based on a matrix of hydroxypropylmethyl cellulose loaded with drug and placed on both sides of an impermeable polymeric cylinder of polypropylene. The system was successful to achieve buoyancy due to the air entrapped in the core of the cylinder. Streubel et al. (2003) developed and evaluated floating controlled drug delivery systems based on low-density polypropylene foam powder, matrix-forming polymer, drug and filler. Results showed that foam powder-containing tablets could float at least 8 h. Losi et al. (2006) designed a modular technology called Dome Matrix® which characterized by the presence of an empty chamber between the modules that assists the capacity of floatation. Later, Strusi et al. (2008) evaluated the device in healthy volunteers and presented capability of reaching up to 5 h of gastric residence time in humans. Hascicek et al. (2011) assumed flexibility of Dome Matrix® system as the shape of the module and its position in the assembled system could influence the floating and the drug release processes. Sauzet et al. (2009) designed and evaluated a low density floating tablets using a hydrophobic dusty powder excipient with stearic acid to control the drug release. The prepared tablets had a coherent porous structure with good ability to retard the drug release, in which the floating capacity was mainly due to the high porosity of the system.

Non-effervescent floating multiunit dosage forms were also developed to increase gastric residence time. Watanabe et al. (1976) patented a bilayer floating coated shell, containing a hollow polystyrene sphere. Talukder and Fassihi (2001) developed a multiple unit system using Ca^{2+} and low methoxylated pectin, or Ca^{2+}, low methoxylated pectin and sodium alginate. Drying was done either by air convection oven at 40 ˚C for 6 h or by freeze drying. Results showed that the freeze dried beads had hollow spaces inside them and were able to float > 12 h, while the air-dried beads sank. Also, the drug release was 100% and 50% in 10 h from the calcium–pectinate–alginate and the calcium–pectinate beads respectively. Calcium alginate beads loaded with riboflavin were successful to be considered as a potential gastroretentive dosage form (Stops et al., 2008). Singh et al. (2010) developed floating porous beads based on simultaneous ionotropic gelation of alginate and sterculia gum using calcium chloride as a cross-linker.

Another possible approach for multiple unit systems is the use of an air compartment that can provide immediate floating process. Iannuccelli et al. 1998a,b designed floating units composed of a calcium alginate core separated by an air compartment from a membrane of calcium alginate: polyvinyl alcohol. Li et al. (2014) designed novel gastro-floating multi-layer pellets consisted of a porous matrix core with entrapped air, a drug loaded layer (dipyridamole and hydroxypropylmethyl cellulose), a sub-coating layer (hydroxypropylmethyl cellulose), and a drug release retarding layer (Eudragit® NE 30D).

1.3.6.2Effervescent floating systems

Effervescent floating drug delivery systems are classified into raft-forming systems, volatile liquid containing systems and gas generating systems. The first type is a solution composed of an *in situ* gel forming polymer such as sodium alginate along with a gas forming agent such as carbonates or bicarbonates. It tends to form a viscous cohesive gel once swelled with entrapped carbon dioxide bubbles upon contact with gastric fluids. Raft-forming systems have a very low bulk density due to the entrapped carbon dioxide bubbles that enables them to float on the surface of the gastric contents for several hours (Prajapati et al., 2013).

Due to the ability of such systems to produce a layer over the gastric fluids, they are used to deliver antacid drugs such as aluminum hydroxide or calcium carbonate to to reduce gastric acidity and treat gastroesophageal reflux as with Liquid Gaviscon® and Almagate Flot-Coat® (Washington, 1990; Foldager et al., 1991; Fabregas et al., 1994; Havelund et al., 1997). Hampson et al. (2010) evaluated *in vitro* and *in vivo* performance of Gaviscon double action liquid, in which calcium carbonate is the main antacid ingredient, in comparison with alginate/antacid suspensions. Results showed that the new double action formulation was as good as, or better than the other formulations. Foster et al. (2013) developed an *in situ* gel forming system based on a mixture of 1% sodium alginate and 0.625% karaya gum in the presence of a calcium chelator which demonstrated a good *in vitro* / *in vivo* correlation. Recently, Abou Youssef et al. (2015) designed a floating raft system loaded with metronidazole using ion-sensitive *in situ* gel forming polymers. Results demonstrated prolonged gastric residence time and good release rate of metronidazole.

The second type of the effervescent floating drug delivery systems is the volatile liquid containing systems. They contain a chamber of volatile liquid such as ether or cyclopentane that converts into gas at body temperature causing inflation of the chamber in the stomach. The drug release control is achieved by an outer hydrophilic polymeric layer such as alginate and different types of hydroxypropylmethyl cellulose in which the drug is loaded (Sriamornsak et al., 2007b; Baki et al., 2011). Kawashima et al. (1992) used an emulsion–solvent diffusion technique to prepare hollow microspheres of tranilast or ibuprofen. An emulsion (o/w) was prepared by adding a solution of drug and Eudragit® S in an ethanol/dichloromethane to an aqueous solution of polyvinyl alcohol. Evaporation of dichloromethane formed an internal cavity in the microspheres which floated for > 12 h on acidic dissolution media containing surfactant. Later, Thanoo et al. (1993) presented promising floating on simulated gastric and intestinal fluids of hollow polycarbonate microspheres loaded with aspirin, griseofulvin and *p*-nitro aniline, using a solvent evaporation method. Stithit et al. (1998) developed theophylline microspheres using a novel emulsion–solvent evaporation process. Dispersions of theophylline and polymeric mixture of cellulose acetate butyrate and Eudragit® RL 100 were pressurized under carbon dioxide.

Upon release of the pressure, bubbles of carbon dioxide generated microspheres with round cavities enclosed in the dispersed drug polymer droplets with > 24 h floating in pH 1.2 and 7.5 buffers. Streubel et al. (2002) designed verapamil HCl foam-based floating microparticles based on polypropylene foam powder, Eudragit® RS or polymethyl methacrylate polymers using the solvent evaporation method. Results showed *in vitro* floating for at least 8 h depending on the polymer type and initial drug loading of the system. The drug release rate was dependent on the type and amount of polymer used in the microspheres. Also, Sato et al. (2003) and Dube et al. (2014) prepared floating microballoons (or hollow microspheres) containing riboflavin and baclofen respectively. Under fed conditions, riboflavin excretion was sustained with the microballoons in comparison with other dosage forms (Sato et al., 2003). Moreover, Dube et al. (2014) showed that not less than 10 h gastric retention was obtained with baclofen floating microspheres. Oh et al. (2013) applied a new approach to improve bioavailability of metformin using camphor as a sublimation material and polyethylene oxide as a drug retarding agent in formulated floating gastroretentive tablets. Camphor sublimation at body temperature resulted in pores formation in the matrix that allows floating process.

Regarding the third type of the effervescent floating drug delivery systems, gas generating systems, they are prepared with effervescent components such as sodium bicarbonate or calcium carbonate and swellable polymers such as methylcellulose, hydroxypropylmethyl cellulose or polysaccharides, such as chitosan. Due to the reaction of the carbonate gassing agent, present in these formulations, with the stomach gastric acid or with the co-formulated citric acid or tartaric acid in the presence of aqueous fluid, carbon dioxide gas is liberated. The gas bubbles are entrapped in the gel layer formed by hydrocolloids which causes an upward motion of the dosage form and maintains its buoyancy (Baumgartner et al., 2000). Involvement of carbonate gassing agents can provide an alkaline microenvironment for the polymer to initiate gel formation (Deshpande et al., 1997). Moreover, the liberation of carbon dioxide can accelerate hydration of the polymer which is essential for formation of mucoadhesive hydrogel that can assist remaining of the dosage form inside the stomach (Asrani, 1994).

The gassing component can be mixed with the polymeric part in case of single layer tablets (Hashim and Li Wan Po, 1987; Strübing et al., 2008; Yin et al., 2013), as well as capsules (Stockwell et al., 1986; Li et al., 2003; Moursy et al. 2003; Ali et al., 2007). In bilayer tablets, one layer can be formulated for the drug release control and the other layer can contain a mixture of the gassing component and the polymeric material to promote floating (Ingani et al., 1987; Ozdemir et al. 2000; Wei et al., 2001). A special design of multiple unit effervescent floating pills was developed by Ichikawa et al. (1991). The system was based on pills for retarding *p*-amino benzoic acid release surrounded by double layers (Figure 1-5). The inner layer was for the gassing agent component containing both sodium bicarbonate and tartaric acid which were also separated by sub-layer to avoid direct contact between them. The outer layer was containing mainly polyvinyl acetate and purified shellac as swellable membrane layer to prevent escape of liberated gas bubbles and to control the drug release.

Effervescent floating drug delivery systems were successfully prepared as multi-particulate or single unit dosage forms. Atyabi et al. (1996) developed floating beads using ion exchange resin loaded with sodium bicarbonate which were surrounded by a semipermeable membrane to avoid loss of liberated carbon dioxide gas. *In vivo* studies in twelve healthy volunteers of coated and uncoated beads showed that the gastric residence time was 24 h and 1-3 h respectively.

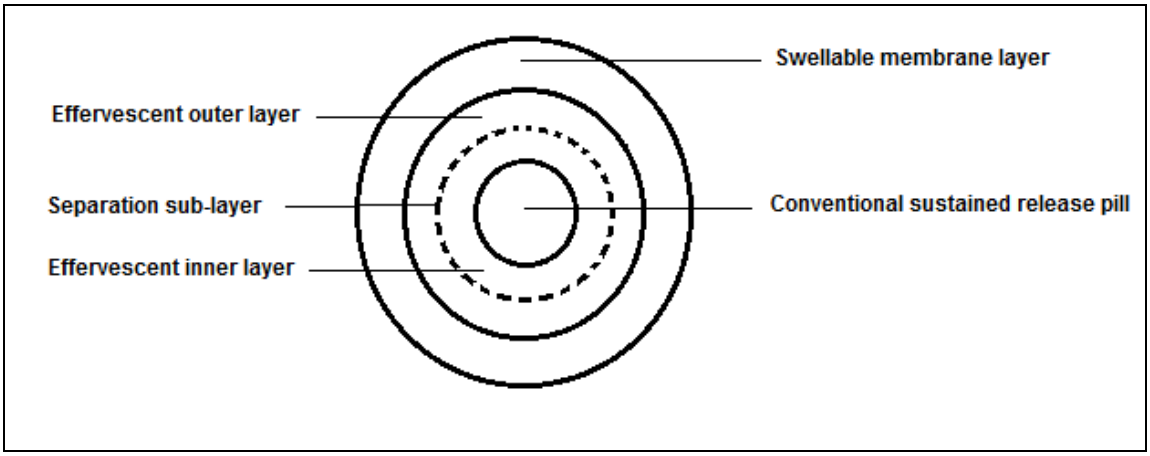

Figure 1-5: Design of multiple unit oral effervescent floating system (Ichikawa et al., 1991)

Choi et al. (2002) evaluated effects of calcium carbonate and sodium bicarbonate as carbon dioxide gas forming agents on floating alginate beads. Authors revealed that the size, floating ability, pore structure, morphology, release rate, and mechanical strength of the floating beads were affected by type and amount of the gassing agent. Although calcium carbonate was less effective as a gas forming agent in comparison with sodium bicarbonate, it produced smaller but stronger floating beads with enhanced drug release control. Later, Amrutkar et al. (2012) developed zolpidem tartarate layered pellets coated with sodium bicarbonate effervescent layer and polymeric membrane of Eudragit® NE 30D. Results revealed that the floating ability and *in vitro* drug release of the pellets were dependent on amount of sodium bicarbonate and coating level of the polymeric membrane. The system showed complete floating within 5 min and maintained its floating for > 10 h.

Multi-particulate effervescent floating formulations were found to be better than single unit dosage forms as they reduce the toxicity risk due to the lower probability of dose-dumping as well as they reduce dependency on the gastric emptying. Multi-particulate formulations were found to be more reliable for gastric emptying patterns than single unit formulations, which suffer from “all or none concept”. Units of multi-particulate systems can be distributed freely throughout the stomach and their transport is less affected by the gastric transit time compared to single unit formulations. Also, they can minimize the risk of local irritation due to avoidance of local high drug concentration (De Brabander et al., 2000; Dey et al., 2008). However, polymers with rapid swelling rate can overcome premature passage of single unit dosage forms through the stomach pylorus especially when the gastric fluid level is low (Chen et al., 2013). Penners et al., (1997) patented an effervescent expandable tablet based on rapidly swelling polymeric mixture of polyvinyl lactams and polyacrylates with gas forming agent. Results demonstrated that the density of the system was reduced and consequently the system tended to float on the gastric contents. The use of hydrophilic matrices has become extremely popular in controlling the release of drugs from oral solid dosage forms as they can achieve a desirable drug profile and are cost effective (Alderman, 1984).

Upon contact with the aqueous medium the hydrophilic polymer swells to form a gel layer on the surface of the system from which the drug releases by dissolution, diffusion and/or erosion mechanism (Nokhodchi et al., 2012). Cellulose derivatives can accommodate tablet formulations due to their ease of compression, ability to load high percentage of drugs and processing variables show negligible influence on their drug release rates (Ebube and Jones, 2004). Hydrophilic polymers, such as cellulose ethers, are probably the most widely investigated polymers in literature as matrices for effervescent floating drug delivery systems. Yang et al. (1999) used tetracycline, metronidazole and bismuth salt (as a triple drug treatment strategy of *Helicobacter pylori* associated peptic ulcers) to design a floating triple layer tablets. Hydroxypropylmethyl cellulose and poly(ethylene oxide) were the drug release retarding polymers. Tetracycline and metronidazole were formulated for controlled delivery and incorporated into the middle layer of the triple-layer tablet. One of the outer layers which was used for gas generation contained a mixture of sodium bicarbonate: calcium carbonate (1:2 ratio) and polymeric mixture of hydroxypropylmethyl cellulose and poly(ethylene oxide. The other outer layer was included bismuth salt as an immediate release layer. The *in vitro* drug release results showed continuous tablets floating with sustained release of tetracycline and metronidazole over 6–8 h.

Ozdemir et al, (2000) developed floating bilayer tablets loaded with furosemide dispersed in 1:1 ratio with β cyclodextrin and evaluated them by *in vitro* and *in vivo* studies. The first layer composed of hydroxypropylmethyl cellulose (4000 and 100), and carboxymethyl cellulose polymers to retard the drug release. The second layer contained a mixture of sodium bicarbonate and citric acid as the gas generating agents. Results showed that tablets compressed at 15 MPa floated at 20 min whereas at higher force (32 MPa) the floating lag time (the time taken for tablets to appear and remain on the dissolution medium surface) was prolonged to 45 min. The *in vivo* studies in six healthy male volunteers demonstrated a gastric retention for 6 h with higher drug bioavailability in comparison with conventional tablets. Baumgartner et al. (2000) developed a matrix-floating tablet containing pentoxifylline, hydroxypropylmethyl cellulose K4 M, Avicel® PH 101, and a mixture of citric acid and sodium bicarbonate as gas generating agents. The floating lag time was 30 seconds and *in vivo* studies in fasted beagle dogs revealed prolonged gastric residence time (240 ± 60 min).

Later, a continuous floating monitoring device and statistical experimental design were used to evaluate effect of formulation variables on the floating properties of gastroretentive drug delivery system based on calcium carbonate as a gassing agent (Li et al., 2002). Results showed that the higher viscosity grade of hydroxypropylmethyl cellulose improved insignificantly (P<0.05) the floating capacity, and different polymers with same viscosity, did not show any significant effect (P<0.05) on the floating process. Also, results demonstrated that magnesium stearate as a hydrophobic agent could significantly improve the floating capacity of the delivery system. Patel et al. (2007) prepared floating tablets using hydroxypropylmethyl cellulose, ethylcellulose, and sodium bicarbonate. All tablets floated > 12 h and the drug release rate of the optimized batch best fitted to the zero order kinetic release model. Gupta and Aggarwal (2007) developed gastroretentive floating delivery system loaded with 5-fluorouracil using hydroxypropylmethyl cellulose, carbopol 934P, sodium bicarbonate, citric acid. *In vitro* studies showed sustained drug release for 24 h and floating for 16 h. In another work, Jaimini et al. (2007) investigated a gastroretentive drug delivery system of famotidine by employing two grades of hydroxypropylmethyl cellulose (Methocel® K100 and Methocel® K15M) and sodium bicarbonate. The effect of citric acid on floating and drug release properties was also investigated. It was reported that a mixture of 130 mg of sodium bicarbonate and 10 mg of citric acid was found to achieve optimum *in vitro* buoyancy; however, decreasing the citric acid level increased the floating lag time as well as the floating duration. Methocel K100 based tablets were found to float for longer durations in comparison with those containing Methocel® K15M.

One year later, the *in vitro* controlled release floating matrices of captopril formulated with variable proportions of hydroxypropylmethyl cellulose (Metolose SH 4000 SR) and sodium bicarbonate, and pressed at different compaction pressures were studied (Jiménez-Martínez et al., 2008). Results indicated that matrices without gassing agent floated > 8 h if compacted at 55 MPa, however, those compacted at 165 MPa could not float till sodium bicarbonate was included in the formulation. The matrices swelling rate increased in the presence of sodium bicarbonate in the formulation which reduced the drug release rate with time. Authors concluded that gas bubbles of carbon dioxide obstructed the drug diffusion path and decreased the matrix coherence.

On the contrary, Sungthongjeen et al. (2008) reported that increasing level of sodium bicarbonate did not show effect on lag time results; however, it increased the drug release rate. They designed floating multi-layer coated tablets based on theophylline core coated with a protective layer of hydroxypropylmethyl cellulose, a gassing agent layer of sodium bicarbonate and a gas-entrapment membrane of Eudragit® RL 30D. Tablet core was prepared either by direct compression or by compression after the wet granulation process. Shorter time to float (lag time) and faster drug release was reported with direct-compressed cores than those using wet-granulated cores. Increasing coating level of gas entrapment membrane increased lag time results but it had minimum effect on drug release rate. Varshosaz et al. (2006) prepared effervescent ciprofloxacin floating tablets based on sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, polyacrylic acid, polymetacrylic acid as drug retarding polymers, and citric acid and sodium bicarbonate as gassing components. Results revealed that increasing the gassing agent base from 5% to 10% (w/w) decreased the floating lag time; however changing the polymer type did not significantly (P<0.05) change the floating lag time. Moreover, carboxymethyl cellulose had higher mucoadhesion property than that of polyacrylic acid. The most desirable formulation contained 10% (w/w) effervescent base, 80% (w/w) carboxymethyl cellulose/ 20% (w/w) hydroxypropylmethyl cellulose, or 80% (w/w) polyacrylic acid/ 20% (w/w) polymetacrylic acid.

In another study, Bomma et al. (2009) developed floating matrix tablets of norfloxacin by the wet granulation technique, using hydroxpropylmethyl cellulose (K4M, K100M) and xanthan gum as matrix forming agents and sodium bicarbonate as gas generating agent. The tablets showed acceptable floating capacity (35 seconds) with extended drug release rate (20-25% in 1 h, 25-45% in 2 h, 55-75% in 4 h, 65-85% in 6 h and 85% after 8 h). Later, Tadros (2010) developed ciprofloxacin gastroretentive controlled release drug delivery system with swelling, floating, and adhesive properties using hydroxypropylmethyl cellulose (HPMC K15M) and/or sodium alginate as polymeric release retarding excipient(s) and sodium bicarbonate or calcium carbonate as a gas generating agent.

Tablets formulated with 21.42% (w/w) HPMC K15M, 7.14% (w/w) sodium alginate and 20% (w/w) sodium bicarbonate or 20% (w/w) calcium carbonate were promising according to floating behaviours, extended adhesion periods and sustained drug release rate. However, stability studies conducted at 40˚C / 75% RH for 3 months showed better physical stability of tablets based on 20% (w/w) calcium carbonate. *In vivo* evaluation of these successful tablets in six healthy volunteers fed with a meal of low calorie after overnight fasting presented a mean gastric residence time of 5.50 ± 0.77 h.

Other water-soluble cellulose derivatives rather than hydroxypropylmethyl cellulose were also investigated. For example, hydroxypropyl cellulose has been formulated in 1:2 ratios with amoxicillin trihydrate to prepare effervescent floating tablets based on sodium bicarbonate and sodium bicarbonate as gassing agents (Hilton and Deasy, 1992). Tablets kept floating for 6 h with good *in vitro* drug release control. However, *in vivo* comparative study with conventional capsules in fasted volunteers indicated lower relative bioavailability and lack of improved efficacy according to other pharmacokinetic parameters. Later, Tokumura and Machida (2006), designed floating tablets based on hydroxypropyl cellulose-H (HPC-H) as it has neither acidic nor basic functional group in its chemical structure and the hydrogel formation is pH independent. Tablets contained 50 mg of amoxicillin, 210 mg of HPC-H, 22.8 mg of sodium bicarbonate, and 17.2 mg of citric acid and coated with HPC-H. These tablets were buoyant for 24 h and showed a sustained-release pattern in water and buffer solutions of pH 1.2 and 6.8. In another study, optimized floating tablets of ofloxacin were prepared via compression coating technique using a mixture of hydroxypropyl cellulose and sodium alginate combined with sodium bicarbonate. Tablets were found to float within 30 seconds and remain buoyant for > 12 h in simulated gastric fluid (SGF) without pepsin. *In vivo* study in rabbits indicated higher relative bioavailability of the ofloxacin after administration of floating tablets in comparison with marketed ofloxacin tablets (Qi et al., 2015).

Moreover, effervescent floating tablets have been formulated by using another water-soluble cellulose derivative. Mixtures of hydroxyethyl cellulose with sodium carboxymethyl cellulose (Chen et al., 2010b) and with chitosan (Chen et al., 2013) were studied. Chen et al. (2010a) aimed to develop an optimal gastroretentive drug delivery system for administering losartan through development of swellable and floatable tablets combining the rapidly swellable hydroxyethyl cellulose with a fine particle size grade (250HHX), sodium carboxymethyl cellulose, and sodium bicarbonate. The best formulation was the one based on 91.67% (w/w) hydroxyethyl cellulose, 3.33% (w/w) sodium bicarbonate and 8.33% (w/w) losartan as per *in vivo* characterization. Selected promising floating tablets showed that the relative bioavailability was approximately 164% in comparison to the immediate-release marketed product (Cozaar®). Later, Chen et al. (2013) developed losartan floating swellable tablets based on 250HHX hydroxyethyl cellulose, chitosan as swellable floatable polymers and sodium bicarbonate as a gassing agent. They evaluated floating lag time and duration and swelling characteristics of prepared tablets. Authors demonstrated that formulations with 3:7 ratio of hydroxyethyl cellulose: chitosan had the best swelling effect, however they had weak structure which is not applicable as a gastroretentive drug delivery system, nevertheless, adjusting the ratio into 5:5 hydroxyethyl cellulose: chitosan showed preferred properties of swelling. Adding sodium bicarbonate assisted the floating ability of all formulations. An optimized losartan formulation composed of 1:1 ratio of both polymers with 20 mg of sodium bicarbonate resulted in the tablets floating for > 16 h and an adjustable *in vitro* drug release rate.

Other polymers were involved in the development researches of effervescent gastroretentive tablets. For example, Talwar et al, (2001) patented a once daily ciprofloxacin floating tablet composed of 69.9% drug, 0.34% sodium alginate, 1.03% xanthan gum, 12.1% cross-linked polyvinylpyrrolidine, and 13.7% sodium bicarbonate. The tablet tended to float and be retained in the stomach or upper part of the small intestine with sustained release of the drug. Also, Moursy et al. (2003) designed floating capsules of nicardipine hydrochloride based on hydrocolloids of high viscosity grades and sodium bicarbonate. *In vitro* studies showed an increase in floating time with increase in proportion of hydrocolloid and presence of sodium bicarbonate.

In vivo studies in rabbit's revealed that drug duration after the administration of the designed floating capsules significantly exceeded that of the commercially available capsules. In another study, Nakagawa et al. (2006) prepared a double compressed tablet of 5-Fluorouracil as a core material with outer layer composed of povidone, Eudragit® RL, and sodium bicarbonate. Results showed sustained drug release by occurrence of a plasma-induced cross-link reaction on the outer layer of the tablet. Bani-Jaber et al. (2011) evaluated metronidazole matrix tablets made of Eudragit® E PO (EE) and/or Eudragit® L-100-55 (EL) at different weight ratios and sodium bicarbonate. The best floating and sustained drug release properties in 0.1 M HCl dissolution medium was achieved by effervescent floating tablets with 50EE/50EL (w/w); however the related non-floating tablets showed significantly faster drug release rate without any floating capacity.

Loh and Elkordy (2015) studied metronidazole floating tablets using hydroxypropylmethyl cellulose K15M, xanthan gum, co-povidone, Eudragit® RL PO, Pluronic® F-127 and/or polypropylene foam powder as drug release controlling agents and sodium bicarbonate with or without citric acid as effervescent agents at different compositions. Results indicated that tablets based on 12.5% (w/w) hydroxypropylmethyl cellulose, 25% (w/w) xanthan gum, 12.5% (w/w) co-povidone and 31.7% (w/w) sodium bicarbonate showed short floating lag time, good floating duration and sustained the drug release for 8 h with a zero order drug release kinetic. Authors concluded that the combinations of hydroxypropylmethyl cellulose K15M and xanthan gum showed synergistic effect in sustaining the drug release. Recently, gastroretentive floating tablets of pregabalin model drug were designed and evaluated using different concentrations of the gums (xanthan gum and guar gum), carbopol 974P NF, hydroxypropylmethyl cellulose K100, and sodium bicarbonate (Kanwar et al., 2016). The *in vitro* drug release studies indicated that matrices containing guar and xanthan gum had higher drug release rate than those containing carbopol 974P NF. Abduljabbar (2016) and Yusif et al. (2016) developed gastroretentive floating-mucoadhesive tablets using mucoadhesive polymers and sodium bicarbonate as a gas forming agent.

1.3.7 Commercially available products

Gastroretentive drug delivery systems like expandable, superporous hydrogel, mucoadhesive, high density, magnetic, and floating have been widely investigated by drug delivery researchers within the last three decades. Many of them have been reported to show promising *in vitro* / *in vivo* results. Yet, only a few of them have been evidenced with clinical trials and proved to be marketed commercially as presented in Table 1-1.

AcuForm™ is one of the well-known polymeric swelling monolithic systems developed by Depomed, USA. Possibility of high drug dose loading and the use of a classical manufacturing process are considered the main advantages of this technology (Prinderre et al., 2011). AcuForm™ platform is a gastric-retentive oral delivery technology for a variety of compounds based on polymer technology. Following ingestion, it has been shown to promote gastric retention and control drug delivery. Chen et al. (2011) reported that in fed state, AcuForm™ gabapentin tablet swells up to three to four times in the gastric fluid, with a diameter larger than that of the pylorus. This enabled gastric retention for about 8-9 h with controlled and prolonged release of gabapentin to the upper intestinal tract. Such results support a once- or twice-daily product with potentially less adverse events.

Another example is Valrelease (15 mg diazepam) which is a slow release floating capsule based on hydrodynamically balanced system (HBS) technology. Conventional 5 mg diazepam tablets are given three times daily, however, Valrelease capsules are given once daily to provide an equivalent plasma diazepam concentration. By controlling the rate of release, C_{max} is decreased relative to that observed when 15 mg is administered as a single dose in tablets. The gradual dissolving of Valrelease capsules over an 8-12 h in comparison with conventional diazepam tablets which dissolve within 15 min generate a smooth onset of action with a prolonged drug release rate (Notari, 1986).

Also, Madopar HBS is a slow-release floating capsule of L-dopa and benserazide based on hydrodynamically balanced system (HBS) technology. Malcolm et al. (1987) presented pharmacokinetic studies in parkinsonian patients and healthy volunteers to evaluate the effect of food and antacid on the absorption of Madopar HBS.

In comparison with conventional Madopar, the drug (L-dopa) is released and absorbed over a period of 4-5 h. The absorption rate is reduced, providing lower peak concentrations of L-dopa but maintaining substantial plasma concentrations for 6-8 h after dosing. The bioavailability of L-dopa is reduced in comparison with conventional Madopar because of incomplete absorption of the drug. No effect of presence or absence of food in the stomach on the drug absorption from Madopar HBS is reported; still concomitant administration of antacids reduces the drug bioavailability. Another example is liquid Gaviscon® which is a raft-forming system with ability to produce a layer over the gastric fluids (raft) to deliver antacid drugs to reduce gastric acidity and treat gastroesophageal reflux (Washington, 1990). *In vitro* and *in vivo* performance of Gaviscon double action liquid in comparison with alginate/antacid suspensions showed that the double action formulation was as good as, or better than the other formulations (Hampson et al., 2010).

Table 1-1: List of some gastroretentive drug delivery systems commercially available.

Product	Drug	Company	Technology
Cytotec	Misoprostol	Pharmacia/Pfizer, USA	Bilayer floating capsules
Baclofen GRS	Baclofen	Sun Pharma, India	Coated multi-layer floating and swelling system
Conviron	Ferrous sulfate	Ranbaxy, India	Colloidal gel forming floating system
Prazopress XL	Prazosin HCl	Sun Pharma, Japan	Effervescent and swelling-based floating system
Liquid Gaviscon	Alginic acid and sodium bicarbonate	Reckitt Benckiser Healthcare, UK	Effervescent floating liquid alginate preparation
Riomet OD	Metformin HCl	Ranbaxy, India	Effervescent floating system
Zanocin OD	Ofloxacin	Ranbaxy, India	Effervescent floating system
Cipro XR	Ciprofloxacin HCl and betaine	Bayer, USA	Erodible matrix-based system
Accordion Pill™ (In phase II trials)	Levodopa and carbidopa	Intec Pharma	Expandable film filled in capsule
Valrelease	Diazepam	Hoffmann-LaRoche, Switzerland	Floating capsule
Eudratec GRS	-	Evonik Industries, Germany	Floating capsule[a]
Soctec™	-	Vectura Group, UK	Floating capsule[b]
Madopar HBS	Levodopa and benserazide	Hoffmann-LaRoche, Switzerland	Floating CR capsule

Adapted from: Sheth, and Tossounian, 1984; Washington et al., 1986; Erni and Held, 1987; Fabregas et al., 1994; Pawar et al., 2011b; Ishak, 2015.

[a] (http://healthcare.evonik.com/product/health-care/en/custom-solutions/oral-drug-delivery/eudratec-grs/pages/default.aspx) Accessed on 10/07/2017

[b] (http://www.vectura.com/oral/oral-drug-delivery-technologies/) Accessed on 10/07/2017

Table 1-1 (continued): List of some gastroretentive drug delivery systems commercially available.

Product	Drug	Company	Technology
Almagate Flotcoat	Aluminum and magnesium antacid	Laboratorios Almirall, Spain	Floating lipophilic particles
Topalkan	Aluminum and magnesium antacid	Pierre Fabre Medicament, France	Floating liquid alginate
Cifran OD	Ciprofloxacin HCl	Ranbaxy, India	Floating tablets
Inon Ace	Simethicone	Sato Pharma, Japan	Foam-based floating system
Coreg CR	Carvedilol	GlaxoSmithKline	Gastro-retention with osmotic system
Cefaclor LP	Cefaclor	Galenix, France	Minextab Floating®
Metformin Hcl LP	Metformin HCl	Galenix, France	Minextab Floating®
Tramadol LP	Tramadol	Galenix, France	Minextab Floating®
Glumetza	Metformin HCl	Depomed, USA	Polymer-based swelling technology: AcuForm™
Gralise	Gabapentin	Depomed, USA	Polymer-based swelling technology: AcuForm™
Janumet XR	Metformine HCl and sitagliptin	Merck, USA	Polymer-based swelling technology: AcuForm™
Nucynta ER	Tapentadol	Janssen, Belgium	Polymer-based swelling technology: AcuForm™
ProQuin XR	Ciprofloxacin HCl	Depomed, USA	Polymer-based swelling technology: AcuForm™
Kadian	Morphine sulfate	Sumitomo Pharma, Japan	Stick type capsule type filled with pellets

Adapted from: Sheth, and Tossounian, 1984; Washington et al., 1986; Erni and Held, 1987; Fabregas et al., 1994; Pawar et al., 2011b; Ishak, 2015.

[a] (http://healthcare.evonik.com/product/health-care/en/custom-solutions/oral-drug-delivery/eudratec-grs/pages/default.aspx) Accessed on 10/07/2017

[b] (http://www.vectura.com/oral/oral-drug-delivery-technologies/) Accessed on 10/07/2017

1.4 Formulation development

Despite the proven advantages, through literature, of the gastroretentive systems for patients, as a few of them have been evidenced with clinical trials and proved to be marketed commercially, it is difficult to identify a single system as the best one for all drug candidates. A case by case evaluation for each drug or drug combination has to be assessed based on dose and the manufacturability of the system. Of all the gastroretentive delivery systems described in the literature, floating systems can show promising potential to achieve this goal. Particularly, combinations of different gastroretentive concepts, such as mucoadhesion and low-density floating, can be expected, for example by using suitable polymers, to be promising to have a significant effect on improving the therapeutic effect of the drug involved (Streubel et al., 2006). Besides, there is a lack of enough information in the literature about floating and drug release rate from pentoxifylline or cefalexin monohydrate gastroretentive drug delivery systems based on binary mixtures of hydroxyethyl cellulose and sodium alginate as drug retarding polymers, and sodium bicarbonate, calcium carbonate, or sodium carbonate as gassing components. This made them suitable for the study regarding research originality.

1.4.1 Type of polymers

Water-soluble cellulose derivatives can be considered one of the best options to design floating tablets with sustained release behaviour (Gerogiannis et al., 1993) and are probably the most widely investigated polymers. However, the increasing demand of pharmaceutical industry for suitable polymers, to achieve a suitable drug release rate, has facilitated screening of a large variety of both synthetic and natural polymers for their ability to sustain the drug release process. The cost of synthesizing a new polymeric substance and testing their safety are highly priced (Ebube and Jones, 2004). An extreme concentration on the use of pharmaceutically approved polymeric blends as matrix excipients to control the drug release has been widely investigated. This can provide several choices for pharmaceutical industry formulators to achieve the best dosage form design.

Accordingly, the aim of this work was to design floating gastroretentive drug delivery matrix tablets based on pharmaceutically approved binary polymeric mixture. Thus, both hydroxyethyl cellulose and sodium alginate were selected to design a floating drug delivery system. One of the most important challenges in developing gastroretentive single unit dosage forms is to avoid rapid gastric emptying and increase the gastric residence time. Polymers with rapid swelling rate upon contact with the gastric fluid have rapid reduction in their density, thus can overcome premature passage of single unit dosage forms through the stomach pylorus especially when the gastric fluid level is low. Cellulose ether hydration rate varies according to the nature of the functional group present as well as its degree of substitution (Roy and Rohera, 2002). Hydroxyethyl cellulose (Figure 1-6) is a hydrophilic cellulosic polymer with non-ionic nature which makes it a pH independent polymer (Angadi et al., 2010). Hydroxyethyl cellulose (Natrosol 250-HHX) has M.W of $1.3x10^6$ which generates viscosity of 3400-5000 cP at 25˚C at 1% concentration. Additionally, it is well known in the literature as a matrix-forming polymer (Chatlapalli and Rohera, 1998; Baumgartner et al., 2002; Larsson et al., 2008; Chen et al., 2010b; Chen et al., 2013). It has the advantage of more swelling rate than both hydroxypropyl cellulose and hydroxypropylmethyl cellulose in purified water (Baumgartner et al., 2006). It also has shown better swelling and floating ability than sodium carboxymethyl cellulose (Chen et al., 2010b). These properties made it suitable over the other cellulose ether derivatives for this study.

Nonetheless, Roy and Rohera (2002) reported that the relatively higher hydrophilicity of hydroxyethyl cellulose was the cause for the drug release rate from their matrices to be higher than that of hydroxypropyl cellulose matrices. Accordingly, sodium alginate with medium viscosity grade (at 25˚C at 1% concentration generates 15-25 cP) was selected in this study to be mixed with hydroxyethyl cellulose to slow down the drug release rate and to retain carbon dioxide gas liberated after acid-base interaction in order to control both floating lag time and floating duration capacities. This viscosity grade was chosen to avoid any drawbacks on the high swelling rate advantage of hydroxyethyl cellulose.

Additionally, sodium alginate is extensively used in the literature, as *in situ* gel forming polymer, in different gastroretentive drug delivery systems such as floating tablets (Talwar et al, 2001; Tadros, 2010; Qi et al., 2015), mucoadhesive tablets (Patil and Talele, 2015); superporous hydrogel (Omidian et al., 2006), and expandable tablets (El-Zahaby et al., 2014).

Sodium alginate (Figure 1-7), is a non-cellulosic water soluble polysaccharide derived from brown seaweeds. It consists primarily of sodium salt of alginic acid, which is a linear copolymer of 1,4-linked β-D-mannuronic acid (M-block) and α-L-guluronic acid (G-block) units (Peppas et al., 2006). Sodium alginate can be easily cross-linked with other multivalent cations such as calcium to form a stable complex assuming the “egg box” model (Gacesa, 1988) (Figure 1-8). Alginate gel can be created during the formulation process (Miyazaki et al., 2000), or in gastric fluids, if suitable conditions of alkaline microenvironment and/or calcium ions are available. Accordingly, addition of sodium alginate to hydroxyethyl cellulose was expected to enhance drug release retardation properties of designed tablets especially in the presence of calcium carbonate. This gas forming agent is also a multivalent cations source, hence it was suggested to have a role in sodium alginate cross-linking to form a stable complex assuming the “egg box” model. Moreover, involvement of carbonate gassing agents can provide a microenvironment for the polymer with an alkaline pH to initiate gel formation (Deshpande et al., 1997). Consequently, the liberated gas bubbles can be entrapped in the formed gel layer to assist an upward motion of designed tablets to achieve short lag time and to maintain their buoyancy over the gastric fluid. A binary mixture of hydroxyethyl cellulose and sodium alginate in (1:1) ratio, which used in the current study, was required to take full advantage of both polymers in the formulation. Still, in the future, more ratios of hydroxyethyl cellulose and sodium alginate mixture, such as 0:1, 0.25:0.75, 0.75:0.25, and 1:0 respectively, could be investigated.

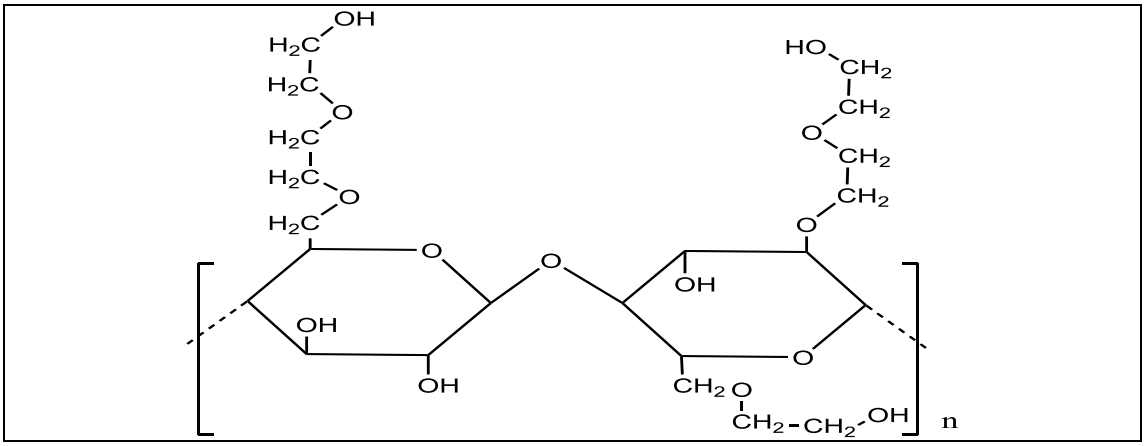

Figure 1-6: Chemical structure of hydroxyethyl cellulose (Zulkifli et al., 2014)

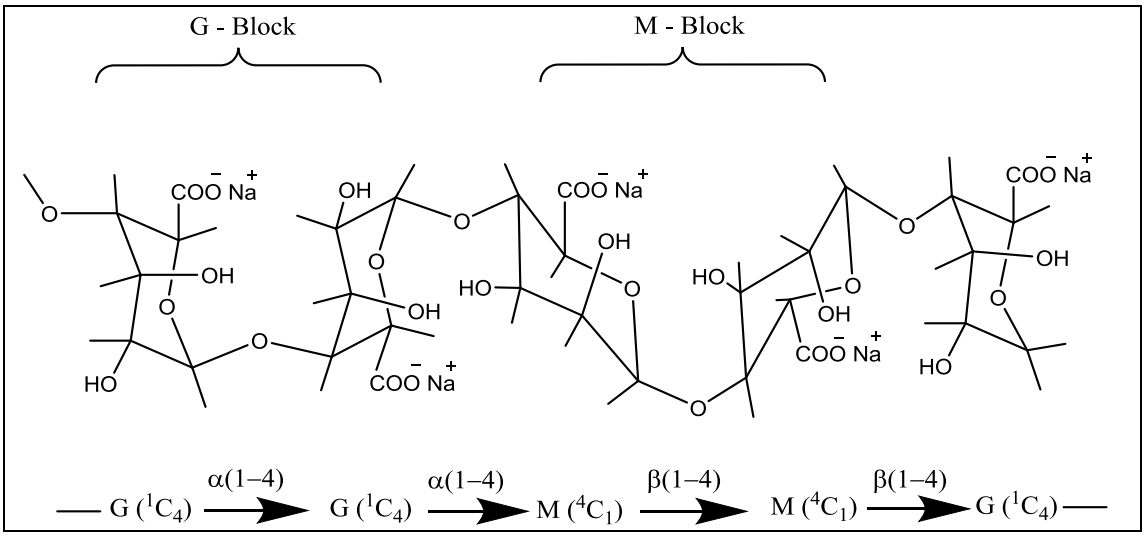

Figure 1-7: Chemical structure of sodium alginate (Steele et al., 2014).

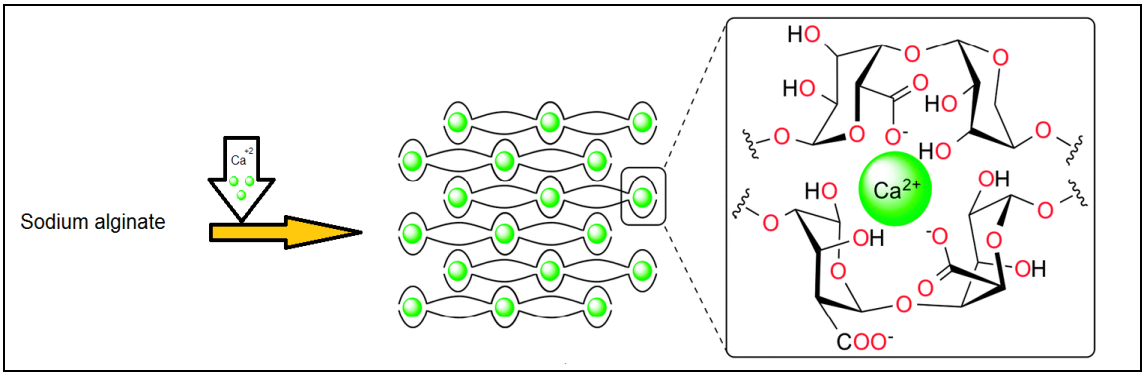

Figure 1-8: Schematic presentation of the 'egg box' model for calcium alginate gel (Kühbeck et al., 2015)

1.4.2 Method of preparation of floating tablets

Sungthongjeen et al. (2008) designed floating multi-layer coated tablets with cores prepared either by direct compression or by compression after the wet granulation process. Results revealed shorter floating lag time and faster drug release rate with direct-compressed cores than those using wet-granulated cores. Ozdemir et al, (2000) showed that bilayer floating tablets compressed at 15 MPa floated at 20 min whereas at 32 MPa the floating lag time was prolonged to 45 min. Also, Jiménez-Martínez et al. (2008) indicated that matrices without gassing agent floated > 8 h if compacted at 55 MPa, however, those compacted at 165 MPa could not float till sodium bicarbonate was included in the formulation. Consequently, it was necessary in this research to study the effect of the wet granulation process on powder mixture properties and to evaluate the differences between application of three crushing strength levels (A: 49–54 N; B: 54-59 N; and C: 59-64 N) on floating capacity of the prepared tablets and their drug release rate.

1.4.3 Type of gas-generating agent

Sodium bicarbonate or calcium carbonate is used to react with the stomach gastric acid or with the co-formulated citric acid or tartaric acid in the presence of aqueous fluid, to liberate carbon dioxide gas. Still, sodium bicarbonate is the predominant gassing agent involved in the design and development of effervescent floating drug delivery systems. Sodium carbonate has also the ability to produce carbon dioxide gas due to acid base reaction (Hapgood, 2009), but, available information in the literature about using it within the floating tablets is inadequate. Choi et al. (2002) evaluated floated beads based on sodium bicarbonate or calcium carbonate. Results showed different porosity percentages, bead gel strengths and floating capacities. It was concluded that calcium carbonate was better as a gas forming agent in alginate bead preparations in comparison with sodium bicarbonate. Additionally, Sriamornsak et al. (2007a) evaluated calcium pectinate gel beads containing sodium bicarbonate, calcium carbonate, potassium carbonate or sodium carbonate as gas forming agents.

Beads were successfully produced with sodium bicarbonate or calcium carbonate only. Porous beads in comparison with dense beads were resulted due to incorporation of sodium bicarbonate and calcium carbonate respectively. Therefore, in this study, it is worth testing sodium carbonate and calcium carbonate beside sodium bicarbonate to evaluate the effect of gassing agent type on the designed system.

1.4.4 Concentration of gas-generating agent

It was reported in the literature that increasing the mass content concentration of gas generating agents reduced significantly the floating lag time of gastroretentive systems (Varshosaz et al. 2006; Goole et al. 2007; Goole et al., 2008) and extended their floating duration (Gupta and Aggarwal, 2007; Nama et al. 2008), but above a certain limit, a disruption in the system integrity and complete loss of floatation capability were noted. A hydrodynamically balanced system (HBS) based on sodium bicarbonate at 8% (w/w) along with hydroxypropylmethyl cellulose K4M showed an *in vitro* floating lag time < 3 min, floating duration > 12 h, and an *in vivo* gastric retention time of 220 min (Nama et al. 2008). Nonetheless, 20% (w/w) of sodium bicarbonate along with hydroxypropylmethyl cellulose K15M and sodium alginate was successful to show a mean gastric retention period of 5.5 h (Tadros, 2010). Thus two concentration levels (10 and 20% (w/w)) of sodium bicarbonate, calcium carbonate, or sodium carbonate were selected (in the current research) beside the control tablets (0% (w/w)) to explore the effect of gassing agent concentrations on the designed system.

1.4.5 Model drug

Two model drugs were selected to be loaded in the designed effervescent gastroretentive tablets individually.

1.4.6 Pentoxifylline

Primarily, pentoxifylline (Figure 1-9) was used as a model drug. Its physicochemical characteristics are presented in Table 1-2. Pentoxifylline or oxpentifylline (Frampton and Brogden, 1995) is a methylxanthine derivative (Steinleitner et al., 1990) that inhibits production of inflammatory cytokines from immune cells and treats or prevents fibrosis (Berman and Duncan, 1989; Berman et al., 1992). Pentoxifylline inhibits phosphodiesterase through both protein kinase_A dependent and independent pathways, which increases intracellular levels of cyclic adenosine monophosphate (cAMP). It was reported that pentoxifylline can decrease oxidative stress during inflammation and suppress the superoxide production of macrophage (Bessler et al., 1986; Costantini et al., 2009). In humans, pentoxifylline was reported to be effective with peripheral vascular disease (Ward and Clissold, 1987), mental dementia (Parnetti et al., 1986), and alcoholic hepatitis (Haber et al., 2003). Studies showed that pentoxifylline at a dosage of 600 to 1200 mg/day, marked overall clinical improvements in about 85% in patients with cerebrovascular disorders (Ward and Clissold, 1987).

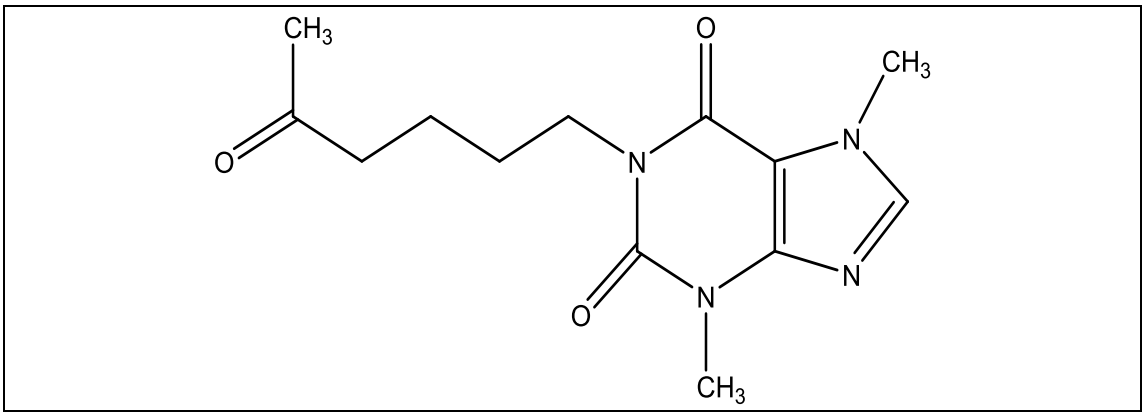

Figure 1-9: Chemical structure of pentoxifylline (BP, 2015)

Table 1-2: Physicochemical characteristics of pentoxifylline.

Parameter	Remarks
Description	White or almost white, crystalline powder.
CAS Number	6493-05-6
Molecular weight	278.3 g/mole
Molecular formula	$C_{13}H_{18}N_4O_3$
Chemical Name	3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione
Solubility	Soluble in water (191 mg/ml at 37°C)[a], freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent). Solubility of pentoxifylline at pH 1.2 was larger than that at pH 6.8[b].

Note: The data is adapted from BP, 2015; [a] Mikac et al., 2010; [b] Otsuka and Matsuda, 1994.

After oral administration, pentoxifylline is rapidly absorbed with peak plasma level reached between 0.29 and 0.41 h and due to the extensive metabolic transformations, pentoxifylline has low and variable bioavailability averaged 20% to 30% (Beermann et al. 1985). It has variable plasma clearance from 1.3 to 1.8 ml/min and less than 1% of the given dose is recovered unchanged from the urine (Hinze et al., 1972; Bryce et al., 1989). Hydroxypentoxifylline [1-(5'-hydroxhexyl)-3, 7-dimethylxanthine] and carboxypentoxifylline [1-(carboxypropy1)-3,7-dimethylxanthine] are the major circulating metabolites of pentoxifylline in human beings. Both pentoxifylline and hydroxypentoxifylline metabolite show the same pharmacologic properties and have an equivalent short elimination half-life ($t_{1/2}$) of 0.8 to 1.8 h (Hinze et al., 1972; Ings et al., 1982; Aviado and Dettelbach, 1984; Beermann et al., 1985). After an oral administration of a sustained-release pentoxifylline formulation to healthy volunteers, an increase 3.4 h in pentoxifylline terminal half-life ($t_{1/2}$), with an absolute bioavailability equal to 20% was reported in comparison with immediate release pentoxifylline capsule (Beermann et al., 1985). The same study showed that pentoxifylline is completely absorbed from the gastrointestinal tract (GIT) when given either in the form of sustained release tablets or immediate release capsules. Pentoxifylline is a suitable candidate for oral sustained release delivery to improve patient compliance and reduce side effects due to better control of the therapeutic drug concentration. Sustained-release 400 mg pentoxifylline tablets (e.g. Trental®) are commercially available in the market to avoid frequent dosing and to maintain therapeutic drug plasma levels. A pentoxifylline floating tablet based on hydroxypropylmethyl cellulose K4M, Avicel® PH 101 as a matrix, and a mixture of citric acid and sodium bicarbonate as a gas forming agents was developed (Baumgartner et al., 2000). The tablets floated within 30 seconds and prolonged gastric residence time was shown in fasted beagle dogs. Pentoxifylline has remarkable properties of high density (Baumgartner et al., 2000) and high water solubility (191 mg/ml at 37°C) (Mikac et al., 2010) which made it an ideal model drug in this study to challenge the ability of the designed gastroretentive tablets to show acceptable floating capacity and acceptable retarding of the drug release process.

1.4.7 Cefalexin monohydrate

Also in this study, cefalexin monohydrate was selected as a second model drug (Figure 1-10). Its physicochemical characteristics are presented in Table 1-3. Cefalexin (BP 2015) or cephalexin (USP, 2012) is a semisynthetic β-lactam first generation cephalosporin antibiotic. It causes bacterial cell lysis as it interferes with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage). Cefalexin is a broad spectrum antibiotic used for treatment of many bacterial infections such as the upper and lower respiratory tract infections except in those infections caused by Haemophilus influenzae (Disney, 1983; Raff, 1983). Also, it is used for treatment of skin, soft tissues, and the genitourinary tract infections. Cefalexin is used in dosages of 1-2 g/day in adults and 20-100 mg/kg/day in children (Disney, 1983). After oral administration, cefalexin is completely and rapidly absorbed in the upper intestine, therefore, it does not disturb the lower bowel flora even with administration of relatively high oral doses, and it has minimal toxicity and adverse side effects (Griffith, 1983). It is a lipophilic weak acid with 5.2 and 7.3 pKa values, and is stable in gastric conditions but degrades in intestinal or alkaline conditions (Marrelli, 1975; Yin et al., 2013).

Measurement of cefalexin uptake in membrane vesicle preparations or in intact enterocytes showed higher uptake in the duodenum than in the jejunum or ileum (Kramer et al., 1993; Tomita et al., 1995). Additionally, absorption of β-lactam antibiotics containing a phenyl-glycine side chain, such as cefalexin, was reported to be a carrier mediated process and saturable at high dose (Tsuji et al., 1979; Tsuji et al., 1981; Nakashima et al., 1984). It has low protein binding to human serum proteins and it has rapid distribution to the tissues other than the spinal fluid (Griffith, 1983). Cefalexin is not significantly metabolized and is not excreted in bile (Barbhaiya, 1996) but it is rapidly cleared from the body by the kidneys, and 70-100% of the dose is recovered in the urine within 6-8 h after each dose (Griffith, 1983).

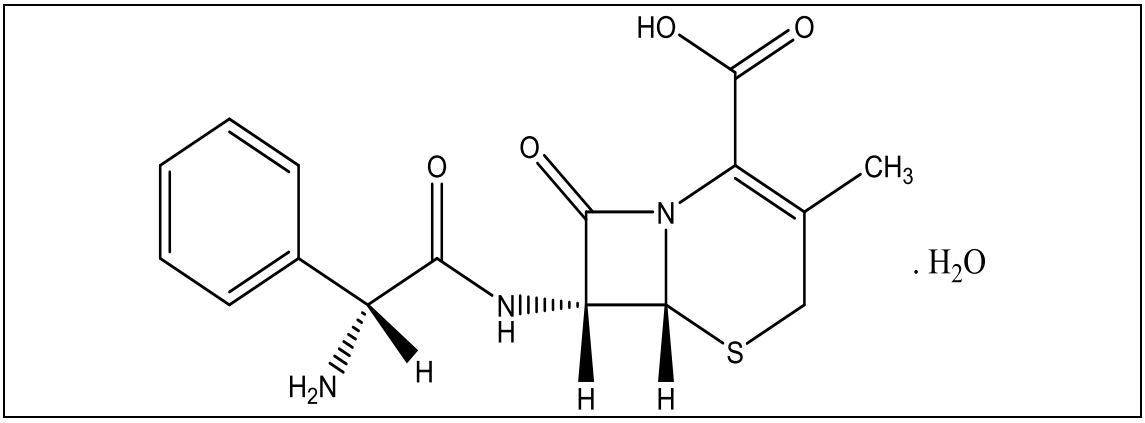

Figure 1-10: Chemical structure of cefalexin monohydrate (BP, 2015)

Table 1-3: Physicochemical characteristics of cefalexin monohydrate.

Parameter	Remarks
Description	White or almost white, crystalline powder.
CAS Number	23325-78-2
Molecular weight	365.4 g/mole
Molecular formula	$C_{16}H_{17}N_3O_4S,H_2O$
Chemical name	(6R,7R)-7-[[(2R)-2-Amino-2-phenylacetyl] amino]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid monohydrate.
Solubility[a]	Solubility in water is 13.5 mg/ml at 25 ˚C. Solubility in water at pH 2.3 is 120 mg/ml at 37 ˚C.

Note: The data is adapted from BP, 2015; [a] Marrelli, 1975.

On an empty stomach, cefalexin shows maximal serum concentration (C_{max}) of 38.8 ± 8.1 mg/L at 65.2 ± 11.1 min (T_{max}) after oral capsule administration of 1000 mg, however during a standard breakfast the C_{max} decreases to 23.1 ± 6.6 mg/L at 112 ± 23.4 min (T_{max}) due to slower oral absorption (Lode et al., 1979). It has a short half-life of approximately 1 h (Davies and Holt, 1972). Therefore, conventional cefalexin products should be administered 3–4 times a day to maintain drug therapeutic range which make it suitable candidate for sustained drug delivery.

Researchers developed cefalexin controlled release double-layer tablets (Martinez-Pacheco et al., 1986), sustained release tablets (Dhopeshwarkar et al., 1994), and controlled release beads (Agnihotri et al., 2006). No significant difference in the clinical responses of sustained release cefalexin granules (L-Keflex) and regular cefalexin capsules (Keflex) in the field of dental infections were reported (Horii et al., 1980). Nonetheless, *in vivo* study results of optimized sustained release tablets along with a fast release capsule showed that the relative bioavailability of cefalexin was reduced by about 30% and very little absorption was seen after 6-8 h (Dhopeshwarkar et al., 1994).

Recently, Yin et al. (2013) prepared cefalexin gastroretentive floating tablets using hydroxypropylmethyl cellulose K100M as a matrix and sodium bicarbonate as a gassing agent. The *in vitro* studies showed floating lag time within 15 seconds and floating duration > 12 h with a satisfactory sustained drug release rate for 12 h. An *in vivo* study was conducted in fed and fasted beagle dogs comparing floating tablets with conventional cefalexin capsules and sustained release tablets. The gastroretentive formulation enhanced cefalexin bioavailability. The relative bioavailability of floating tablets was 99.4% compared with the conventional capsules, whereas sustained release tablets showed only 39.3%.

Therefore, the cefalexin instability at intestinal pH (Marrelli, 1975; Yin et al., 2013) and its narrow absorption window at the upper gastrointestinal tract (GIT) (Griffith, 1983; Kramer et al., 1993; Tomita et al., 1995) made it an ideal model drug in this current study for further investigations regarding gastroretentive delivery systems but not ordinary sustained release delivery systems.

1.5 Posed research questions

1- What is the effect of using binary mixture (1:1) of hydroxyethyl cellulose and sodium alginate on extending the drug release rate of different model drugs and floating capacity of tablets?

2- What is the effect of different formulation parameters (the wet granulation, tablet crushing strength, gassing agent type, and gassing agent concentration) on drug release rate and floating capacity?

1.6 Aims and objectives:

- To prepare floating tablet compositions containing suitable model drug, binary mixture of hydroxyethyl cellulose and sodium alginate gel forming polymers, gassing agent, filler (if required), and lubricant.
- To study the flow properties of different powder mixture formulations and the effect of the wet granulation process on powder mixture properties.
- To investigate the influence of gassing agent type (sodium bicarbonate, calcium carbonate, or sodium carbonate) as well as gassing agent level (10 or 20% w/w) on floating capacity and drug release rate.
- To evaluate the differences between application of three crushing strength levels (A: 49–54 N; B: 54-59 N; and C: 59-64 N) on floating capacity of the prepared tablets and drug release rate from those tablets.
- To analyse the generated data statistically with the aim to evaluate possible significant outcomes of the different formulation parameters on floating and drug release rate.
- To analyse the release kinetics by fitting the generated drug release data to different mathematical models (zero order, first order, Hixson-Crowell, Higuchi, and Korsmeyer–Peppas).
- To investigate the most promising formulations by *in vivo* study to evaluate ability to sustain the drug release.

The thesis has been presented as following:

Chapter one

(Current chapter): Introduction

Chapter two: Material and methods.

Chapter three: Evaluation of the effect of sodium bicarbonate, calcium carbonate, and sodium carbonate as gassing agents on pentoxifylline floating tablets.

Chapter four: Evaluation of the effect of sodium bicarbonate, calcium carbonate, and sodium carbonate as gassing agents on cefalexin monohydrate floating tablets.

Chapter five: Preliminary *In vivo* study in rats.

Chapter six: Conclusions and future work

Chapter seven: References

Chapter Two: Materials and methods

2.1 Materials

Calcium carbonate, cefalexin monohydrate, sodium carbonate, medium viscosity sodium alginate (15-20 cP at 1% at 25˚C), and pentoxifylline were supplied by Sigma-Aldrich (UK), silicified microcrystalline cellulose (Prosolv® 90) was obtained from JRS Pharma (Germany), magnesium stearate was supplied by MEDEX (UK), emitrecitabine, ammonia, formic acid, methanol, and ACE 5 C18 column were obtained by the Jordan Centre for Pharmaceutical Research (Jordan), and hydroxyethyl cellulose (Natrosol™ 250-HHX, 3400-5000 cP at 1% at 25˚C) was generously provided by Ashland (USA).

2.2 Methods

2.2.1 Ultra violet spectroscopy analysis

Spectrophotometric analysis was carried out between 190 and 600 nm to determine maximum absorbance wave length of pentoxifylline (Figure 2-1) and cefalexin monohydrate (Figure 2-2) in 0.1 M HCl solution using ATI Unicam UV2 spectrophotometer, UK. In addition, serial dilutions of 0.5 mg/ml stock solution of pentoxifylline or cefalexin monohydrate were carried out to construct calibration curves as shown in Figure 2-3 and Figure 2-4 respectively. Each dilution point was performed in triplicate and mean values ± standard deviation (SD) are presented.

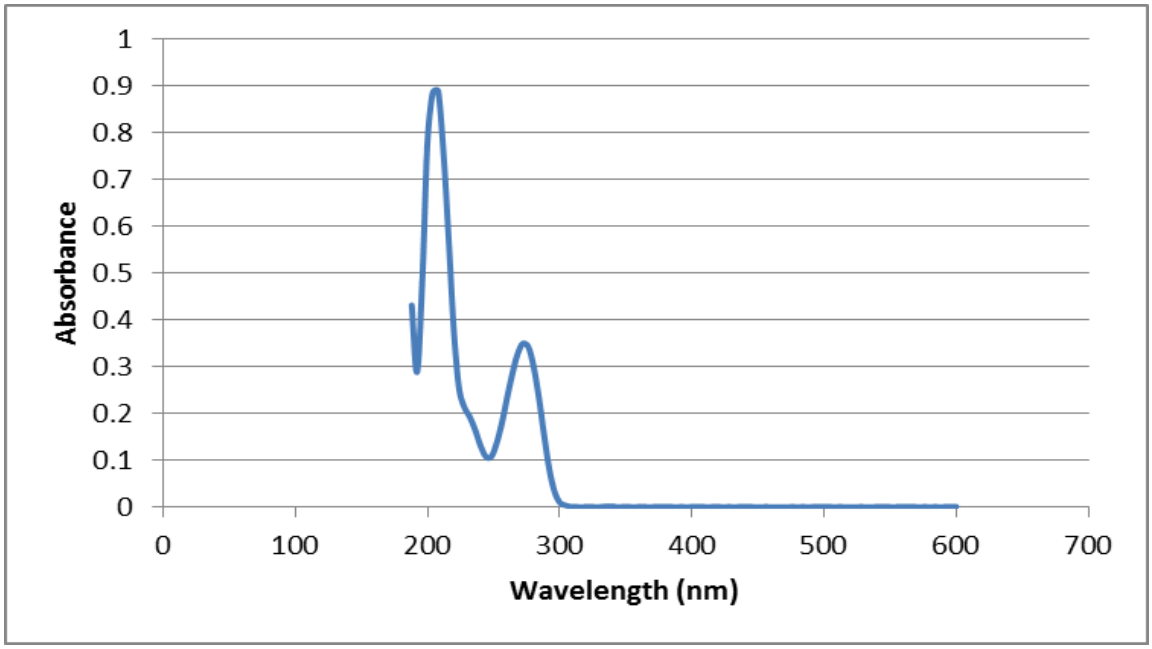

Figure 2-1: UV absorbance spectrum of pentoxifylline in 0.1 M HCl.

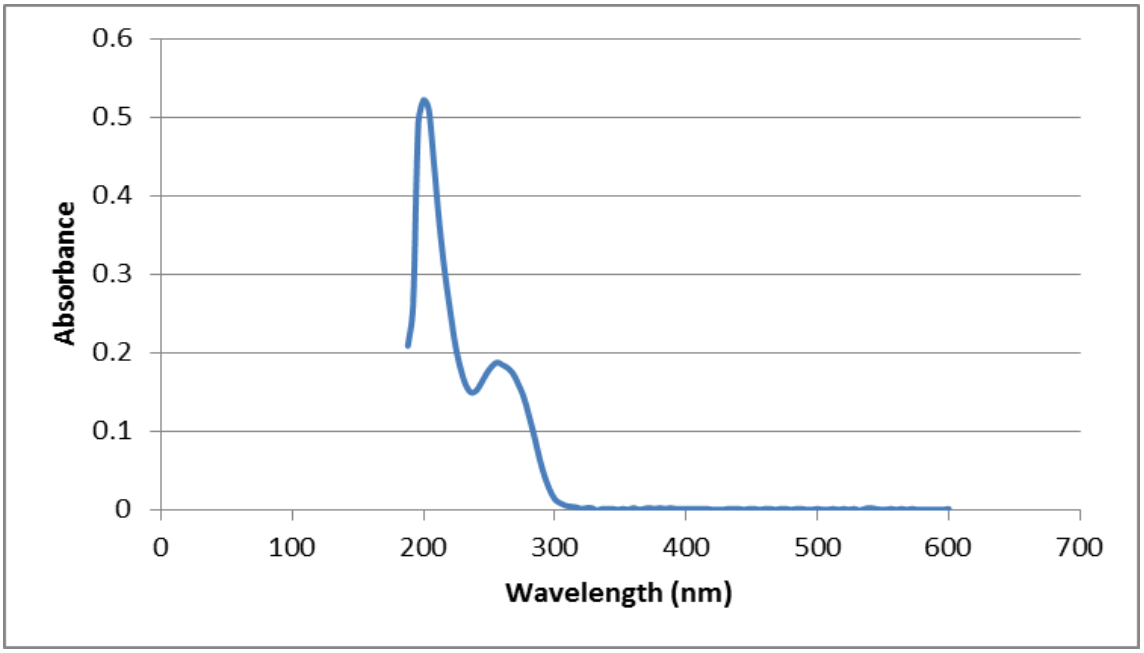

Figure 2-2: UV absorbance spectrum of cefalexin monohydrate in 0.1 M HCl.

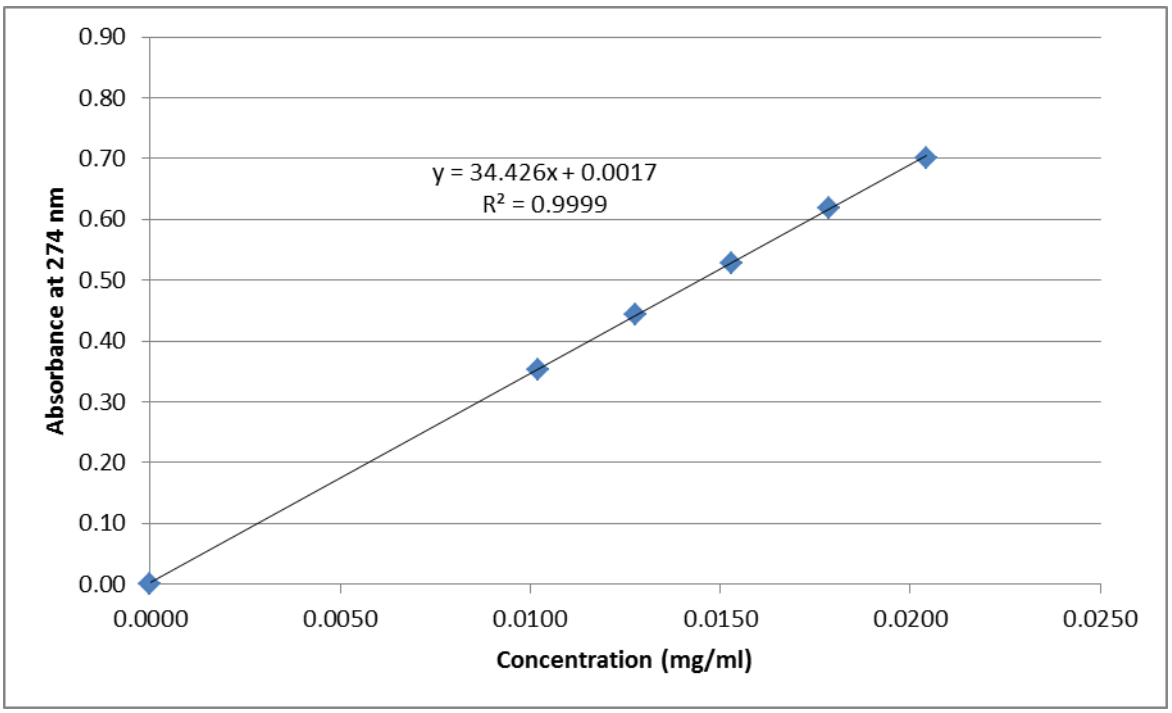

Figure 2-3: Calibration curve of pentoxifylline.
Note: Error bars cannot be seen because they are very small.

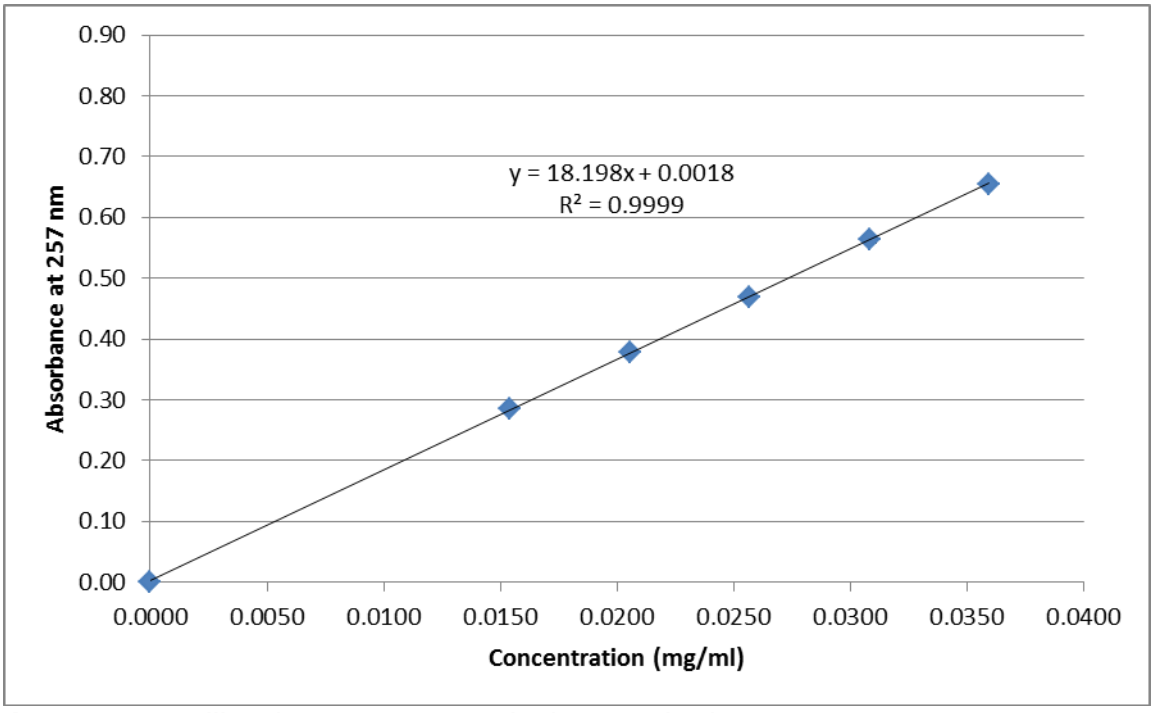

Figure 2-4: Calibration curve of cefalexin monohydrate.
Note: Error bars cannot be seen because they are very small.

2.2.2 Formulation development outline

The formulation development aim, for the gastroretentive floating tablets, was to get formulations based on binary mixture of hydroxyethyl cellulose and sodium alginate (gel forming polymers); sodium bicarbonate, calcium carbonate, or sodium carbonate (gassing agent); filler (if required); and lubricant. The formulations should be suitable for the wet granulation process and for pressing at three crushing strength levels (A: 49–54 N; B: 54-59 N; and C: 59-64 N). The influence of gassing agent concentration was also considered during the formulation development. Several excipients were tried to facilitate manufacturing of the required floating tablets using a single-punch tableting machine (Type 3, Manesty Machines Ltd, UK) equipped with flat-faced punches (9.60 mm), and the compression force was adjusted by decreasing the distance between punches to produce tablets with the required crushing strength levels which was measured using the crushing strength tester. A turbula mixer with a glass bottle, 250 mL, mixing vessel, was used to mix the powders.

Table 2-1 to Table 2-6 show different trials with excipients used with the percentage (%) of each one. In stage I of the formulation development (Table 2-1), the binary mixture (1:1) of hydroxylethyl cellulose and sodium alginate was difficult to be pressed and resulted crushing strengths were below the required levels. Consequently, in stage II (Table 2-2), three different LubriTose™ fillers (MCC, mannitol, and lactose), co-processed with stearate lubricant derivatives, were used at 25% (w/w) to improve powder mixture compressibility. The resulted crushing strengths were not appropriate; they were in range of 29.5-49 N. In the next stage (Table 2-3), the fillers were changed into microcrystalline cellulose (MCC) with different particle size property (Avicel® PH101, PH102, PH105, and Prosolv 90®). The crushing strength was improved to be > 49 N. Therefore, in stage IV of formulation development trials (Table 2-4), wet granulation process was processed using water or polyvinylpyrolidone (PVP) at different concentrations. Powder mixtures were wetted and mixed for 10 min using a Kenwood Chef Kneader before being manually passed through a 1,000 µm sieve. The prepared granules were dried using a drying oven at 60°C overnight (~12 h), and then dried granules passed through 853 µm sieve and granules ≤ 853 µm were used.

Resulted crushing strengths of the prepared granules were not appropriate; they were in range of 10-41 N. In stage V of the formulation development trials (Table 2-5), hydroxyethyl cellulose supplier was changed into Ashland (Natrosol 250-HHX) which is well known in the literature as a matrix former (Chatlapalli and Rohera, 1998; Baumgartner et al., 2002; Larsson et al., 2008; Chen et al., 2010b; Chen et al., 2013). Water as a binder was successful to provide granules with promising crushing strength results. Two levels (20 and 25% (w/w)) of filler (Avicel® PH102 and Prosolv 90®) were tried to enable maximum drug loading ability. At 25% (w/w) filler concentration, both fillers (Avicel® PH102 and Prosolv 90®) were good, however at 20% (w/w), Prosolv 90® revealed better crushing strength results. Finally, in stage VI (Table 2-6), pentoxifylline was successfully loaded to the designed floating tablets. Higher quantity of cefalexin monohydrate were required to be loaded, thus, the filler (Prosolv 90®) was excluded successfully from cefalexin tablets. Water as a binder was effective to provide granules. In order to reduce friction during the automatic pressing (of granulated powders) using a single-punch tableting machine, 0.5% (w/w) magnesium stearate was used. Promising crushing strength results were obtained for the tablets of powder mixture or granules origin.

Table 2-1: Stage I of formulation development trials.

Trial	HEC[a]	Sodium alginate[b]	Gassing agent	Lubricant	Model drug
			Sodium bicarbonate[f]		
1	50%	50%	0%	0%	0%
2	45%	45%	10%	0%	0%
3	40%	40%	20%	0%	0%

[a] Hydroxyethyl cellulose supplied by Sigma-Aldrich (UK), viscosity at 25˚C at 2% is 4500-6500 cP, molecular weight is 7.2×10^4 g/mole.
[b] Supplied by Sigma-Aldrich (UK), viscosity at 25˚C at 1% is 15-25 cP (medium viscosity).

Table 2-2: Stage II of formulation development trials.

Trial	HEC[a]	Sodium alginate[b]	Filler			Gassing agent	Lubricant	Model drug
			LubriTose™ MCC[c]	LubriTose™ mannitol[d]	LubriTose™ lactose[e]	Sodium bicarbonate[f]		
4	37.5%	37.5%	25%	0%	0%	0%	0%	0%
5	33.75%	33.75%	22.5%	0%	0%	10%	0%	0%
6	30%	30%	20%	0%	0%	20%	0%	0%
7	37.5%	37.5%	0%	25%	0%	0%	0%	0%
8	33.75%	33.75%	0%	22.5%	0%	10%	0%	0%
9	30%	30%	0%	20%	0%	20%	0%	0%
10	37.5%	37.5%	0%	0%	25%	0%	0%	0%
11	33.75%	33.75%	0%	0%	25%	10%	0%	0%
12	30%	30%	0%	0%	25%	20%	0%	0%

[a] Hydroxyethyl cellulose supplied by Sigma-Aldrich (UK), viscosity at 25˚C at 2% is 4500-6500 cP, molecular weight is 7.2×10^4 g/mole.

[b] Supplied by Sigma-Aldrich (UK), viscosity at 25˚C at 1% is 15-25 cP (medium viscosity).

[c] Co-processed excipient consisting of NF/EP/JP compliant microcrystalline cellulose (MCC) and glyceryl monostearate NF

[d] Co-processed excipient consisting of USP compliant spray dried mannitol and glyceryl monostearate NF

[e] Co-processed excipient consisting of NF/EP/JP compliant spray dried monohydrate lactose and glyceryl monostearate NF

[f] Supplied by Sigma-Aldrich (UK)

Table 2-3: Stage III of formulation development trials.

Trial	HEC[a]	Sodium alginate[b]	Filler				Gassing agent	Lubricant	Model drug
			Avicel® PH101[c]	Avicel® PH102[d]	Avicel® PH105[e]	Prosolv 90®[f]	Sodium bicarbonate[g]		
13	37.5%	37.5%	25%	0%	0%	0%	0%	0%	0%
14	33.75%	33.75%	22.5%	0%	0%	0%	10%	0%	0%
15	30%	30%	20%	0%	0%	0%	20%	0%	0%
16	37.5%	37.5%	0%	25%	0%	0%	0%	0%	0%
17	33.75%	33.75%	0%	22.5%	0%	0%	10%	0%	0%
18	30%	30%	0%	20%	0%	0%	20%	0%	0%
19	37.5%	37.5%	0%	0%	25%	0%	0%	0%	0%
20	33.75%	33.75%	0%	0%	22.5%	0%	10%	0%	0%
21	30%	30%	0%	0%	20%	0%	20%	0%	0%
22	37.5%	37.5%	0%	0%	0%	25%	0%	0%	0%
23	33.75%	33.75%	0%	0%	0%	22.5%	10%	0%	0%
24	30%	30%	0%	0%	0%	20%	20%	0%	0%

[a] Hydroxyethyl cellulose supplied by Sigma-Aldrich (UK), viscosity at 25˚C at 2% is 4500-6500 cP, molecular weight is 7.2×10^4 g/mole.
[b] Supplied by Sigma-Aldrich (UK), viscosity at 25˚C at 1% is 15-25 cP (medium viscosity).
[c] Supplied by FMC Biopolymer Corp (USA), particle size is 50 µm.
[d] Supplied by FMC Biopolymer Corp (USA), particle size is 100 µm.
[e] Supplied by FMC Biopolymer Corp (USA), particle size is 20 µm.
[f] Supplied by JRS Pharma (Germany), silicified MCC, particle size is 125 µm.
[g] Supplied by Sigma-Aldrich (UK).

Table 2-4: Stage IV of formulation development trials.

Trial	HEC[a]	Sodium alginate[b]	Filler				Gassing agent	Lubricant	Model drug	Liquid binder				
			Avicel® PH101[c]	Avicel® PH102[d]	Avicel® PH105[e]	Prosolv 90®[f]				Water	PVP[g] 2.5%	PVP[g] 5.0%	PVP[g] 7.5%	PVP[g] 10%
25	37.5%	37.5%	25%	0%	0%	0%	0%	0%	0%	Sufficient liquid was added to prepare the wet mass before granulation.				
26	37.5%	37.5%	0%	25%	0%	0%	0%	0%	0%					
27	37.5%	37.5%	0%	0%	25%	0%	0%	0%	0%					
28	37.5%	37.5%	0%	0%	0%	25%	0%	0%	0%					

[a] Hydroxyethyl cellulose supplied by Sigma-Aldrich (UK), viscosity at 25˚C at 2% is 4500-6500 cP, molecular weight is 7.2×10^4 g/mole.
[b] Supplied by Sigma-Aldrich (UK), viscosity at 25˚C at 1% is 15-25 cP (medium viscosity).
[c] Supplied by FMC Biopolymer Corp (USA), particle size is 50 µm.
[d] Supplied by FMC Biopolymer Corp (USA), particle size is 100 µm.
[e] Supplied by FMC Biopolymer Corp (USA), particle size is 20 µm.
[f] Supplied by JRS Pharma (Germany), silicified MCC, particle size is 125 µm.
[g] Polyvinylpyrolidone supplied by Sigma-Aldrich (UK), average molecular weight tried was 10,000 and 40,000 g/mole.

Table 2-5: Stage V of formulation development trials.

Trial	HEC[a]	Sodium alginate[b]	Filler		Gassing agent	Lubricant	Model drug	Liquid binder
			Avicel® PH102[c]	Prosolv 90®[d]	Sodium bicarbonate[e]			Water
29	37.5%	37.5%	25%	0%	0%	0%	0%	Sufficient liquid was added to prepare the wet mass before granulation.
30	33.75%	33.75%	22.5%	0%	10%	0%	0%	
31	30%	30%	20%	0%	20%	0%	0%	
32	37.5%	37.5%	0%	25%	0%	0%	0%	
33	33.75%	33.75%	0%	22.5%	10%	0%	0%	
34	30%	30%	0%	20%	20%	0%	0%	
35	40%	40%	20%	0%	0%	0%	0%	
36	36%	36%	18%	0%	10%	0%	0%	
37	32%	32%	16%	0%	20%	0%	0%	
38	40%	40%	0%	20%	0%	0%	0%	
39	36%	36%	0%	18%	10%	0%	0%	
40	32%	32%	0%	16%	20%	0%	0%	

[a] Hydroxyethyl cellulose (Natrosol 250-HHX) was generously supplied by Ashland (USA), viscosity at 25˚C at 1% is 3400-5000 cP, molecular weight is 1.3×10^6 g/mole.
[b] Supplied by Sigma-Aldrich (UK), viscosity at 25˚C at 1% is 15-25 cP (medium viscosity).
[c] Supplied by FMC Biopolymer Corp (USA), particle size is 100 µm.
[d] Supplied by JRS Pharma (Germany), silicified MCC, particle size is 125 µm.
[e] Supplied by Sigma-Aldrich (UK).

Table 2-6: Stage VI of formulation development trials.

Trial	HEC[a]	Sodium alginate[b]	Filler	Gassing agent	Lubricant	Model drug		Liquid binder
			Prosolv 90®[d]	Sodium bicarbonate[e]	Magnesium stearate[f]	Pentoxifylline[g]	Cefalexin monohydrate[h]	Water
41	27.86%	27.86%	19.9%	0%	0.5%	23.88%	0%	Sufficient liquid was added to prepare the wet mass before granulation.
42	25.10%	25.10%	17.93%	9.87%	0.5%	21.50%	0%	
43	22.28%	22.28%	15.96%	19.87%	0.5%	19.11%	0%	
44	17.66%	17.66%	0%	0%	0.5%	0%	64.18%	
45	15.91%	15.91%	0%	9.85%	0.5%	0%	57.83%	
46	14.13%	14.13%	0%	19.88%	0.5%	0%	51.36%	

[a] Hydroxyethyl cellulose (Natrosol 250-HHX) was generously supplied by Ashland (USA), viscosity at 25˚C at 1% is 3400-5000 cP, molecular weight is 1.3×10^6 g/mole.
[b] Supplied by Sigma-Aldrich (UK), viscosity at 25˚C at 1% is 15-25 cP (medium viscosity).
[c] Supplied by FMC Biopolymer Corp (USA), particle size is 100 µm.
[d] Supplied by JRS Pharma (Germany), silicified MCC, particle size is 125 µm.
[e] Supplied by Sigma-Aldrich (UK).
[f] Supplied by MEDEX (UK).
[g] Supplied by Sigma-Aldrich (UK).
[h] Supplied by Sigma-Aldrich (UK).

To give an outline, Figure 2-5 presents a schematic diagram of this study. The aim was to design and evaluate floating gastroretentive drug delivery matrix tablets with sustained release behaviours for pentoxifylline and cefalexin monohydrate model drugs, using hydroxyethyl cellulose and sodium alginate polymers. Effect of different variables such as formulation variables (wet granulation, type and ratio of sodium bicarbonate, calcium carbonate, or sodium carbonate gas forming agent), and tablet physical properties (tablet crushing strength) on floating capacity and drug release rate was investigated. The kinetics of drug release were investigated *in vitro* in relation to these formulations in 0.1 M HCl dissolution medium and *in vivo* for most promising formulations.

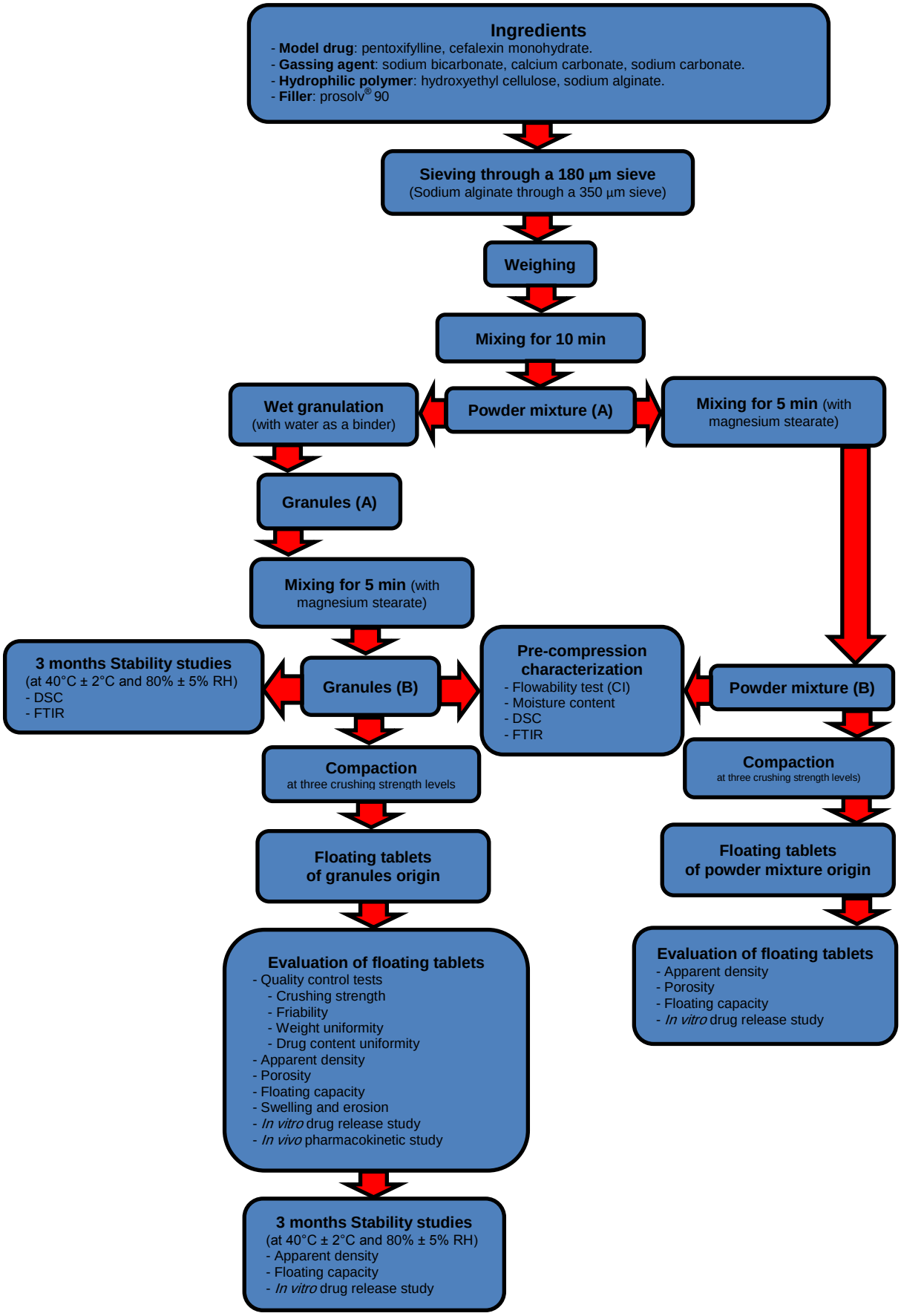

Figure 2-5: Introduction schematic diagram of the practical work.

2.2.3 Preparation of powder mixture and granules containing model drugs

Refer to section 1.4 and section 2.2.2 for the rationale behind selecting the ingredients and their amounts. Powder mixture compositions for the preparation of tablets are shown in Table 2-7 and Table 2-8. Powder blends were prepared using a (1:1) binary mixture of hydroxyethyl cellulose and sodium alginate gel forming agents. Sodium bicarbonate, calcium carbonate or sodium carbonate was added as a gas forming agent at 0%, 10% or 20% (w/w) concentration of the total tablet weight. Pentoxifylline or cefalexin monohydrate was used as a model drug. Primarily, the floating tablet formulations (F1-F7) were tested using only 60 mg of pentoxifylline to invistigate the ability of the designed tablets to show good floating capacity and dug release retardation as pentoxifylline is considered dense and highly water soluble. Later, cefalexin monohydrate was loaded in the formulations (F8-F14) using the same tablets design principle regarding (1:1) binary mixture of the gel forming agents as well as the type and concentration of the gas forming agents.

However, Prosolv® 90 which was used as a filler to enhance the compression process of pentoxifylline formulations was removed from cefalexin monohydrate formulations because they were easier to tablet. Additionally, it was a target to increase cefalexin monohydrate content in the tablets to simulate the effective dose available in the market (500 mg), however because of the tableting machine die volume capacity, only 250 mg drug content was achieved. This increase in the drug content of cefalexin monohydrate was expected to apply further challenge on the properties of the designed floating tablets due to the reduction in the polymeric mixture content. All ingredients were passed through a 180 µm sieve before mixing; sodium alginate was passed through a 350 µm sieve, size suitable for tablet compression. A turbula mixer (Glen Creston Ltd, UK) set at 60 rpm, with a glass bottle, 250 ml, mixing vessel, was used to mix the powders for 10 min.

The wet granulation process was used to modify powder flowability to facilitate automatic compaction of the powder. Powder mixtures were wetted with a sufficient quantity of water and mixed for 10 min using a Kenwood Chef Kneader (Thorn Domestic Appliances Ltd, UK) before being manually passed through a 1,000 μm sieve. The prepared granules were dried using a drying oven (SciQuio Ltd, UK) at 60°C overnight (~12 h) (Larsson et al., 2008), and then dried granules passed through 853 μm sieve and granules ≤ 853 μm were used.

Table 2-7: Composition of prepared pentoxifylline tablets

Ingredients/Formulation	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
Pentoxifylline	60	60	60	60	60	60	60
Hydroxyethyl cellulose	70	70	70	70	70	70	70
Sodium alginate	70	70	70	70	70	70	70
Prosolv® 90	50	50	50	50	50	50	50
Sodium bicarbonate	27.5	62.5					
Calcium carbonate			27.5	62.5			
Sodium carbonate					27.5	62.5	
Magnesium stearate (0.5%)	1.4	1.6	1.4	1.6	1.4	1.6	1.3
Total weight	278.9[a]	314.1[a]	278.9[a]	314.1[a]	278.9[a]	314.1[a]	251.3

[a] Difference in weight was due to raising gassing agent content from 10% to 20% (w/w).

Note: number of moles of the gassing agents used in the formulations is 3.3×10^{-4} (F1), 7.4×10^{-4} (F2), 2.7×10^{-4} (F3), 6.2×10^{-4} (F4), 2.6×10^{-4} (F5), and 5.9×10^{-4} (F6).

Table 2-8: Composition of prepared cefalexin monohydrate tablets

Ingredients/Formulation	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)
Cefalexin monohydrate	250	250	250	250	250	250	250
Hydroxyethyl cellulose	68.8	68.8	68.8	68.8	68.8	68.8	68.8
Sodium alginate	68.8	68.8	68.8	68.8	68.8	68.8	68.8
Sodium bicarbonate	42.6	96.8					
Calcium carbonate			42.6	96.8			
Sodium carbonate					42.6	96.8	
Magnesium stearate (0.5%)	2.2	2.4	2.2	2.4	2.2	2.4	1.9
Total weight	432.4[a]	486.8[a]	432.4[a]	486.8[a]	432.6[a]	486.8[a]	389.5

[a] Difference in weight was due to raising gassing agent content from 10% to 20% (w/w).

Note: number of moles of the gassing agents used in the formulations is 5.1×10^{-4} (F8), 11.5×10^{-4} (F9), 4.3×10^{-4} (F10), 9.7×10^{-4} (F11), 4.0×10^{-4} (F12), and 9.1×10^{-4} (F13).

2.2.4 Preparation of floating tablets

To evaluate the effect of the gassing agent concentration on tablet porosity, floating capacity, swelling, erosion and dissolution behaviours, pentoxifylline or cefalexin monohydrate tablets were automatically pressed (from granulated powders) using a single-punch tableting machine (Type 3, Manesty Machines Ltd, UK) equipped with flat-faced punches (9.60 mm), and the compression speed was 85 rpm. The compression force was adjusted by decreasing the distance between punches to produce tablets with three crushing strength levels (A: 49–54 N; B: 54-59 N; and C: 59-64 N), as measured using the crushing strength tester (Model 2E/205, Schleuniger & Co., Switzerland). Tablets were successfully pressed automatically. However, F5 formulation could not be pressed automatically at the required crushing strength levels (A: 49–54 N; B: 54-59 N; and C: 59-64 N), hence these were pressed manually; the required granules weight was fed directly from the hopper into the die of the single-punch tableting machine and compacted manually.

In order to compare between tablets with same excipient composition before and after granulation, in other words to investigate the possible effects of the wet granulation process on tablet porosity, floating capacity and dissolution behaviour, a group of manually pressed tablets of F1-F14 formulations were prepared. These tablets were pressed from powder blends before granulation where the required powder mixture was weighed, and fed manually into the die of the single-punch tableting machine to produce the desired tablets. Accordingly, granulated powders were compacted automatically but un-granulated powder mixtures were pressed manually. A flow chart for floating tablets preparation is presented in Figure 2-6.

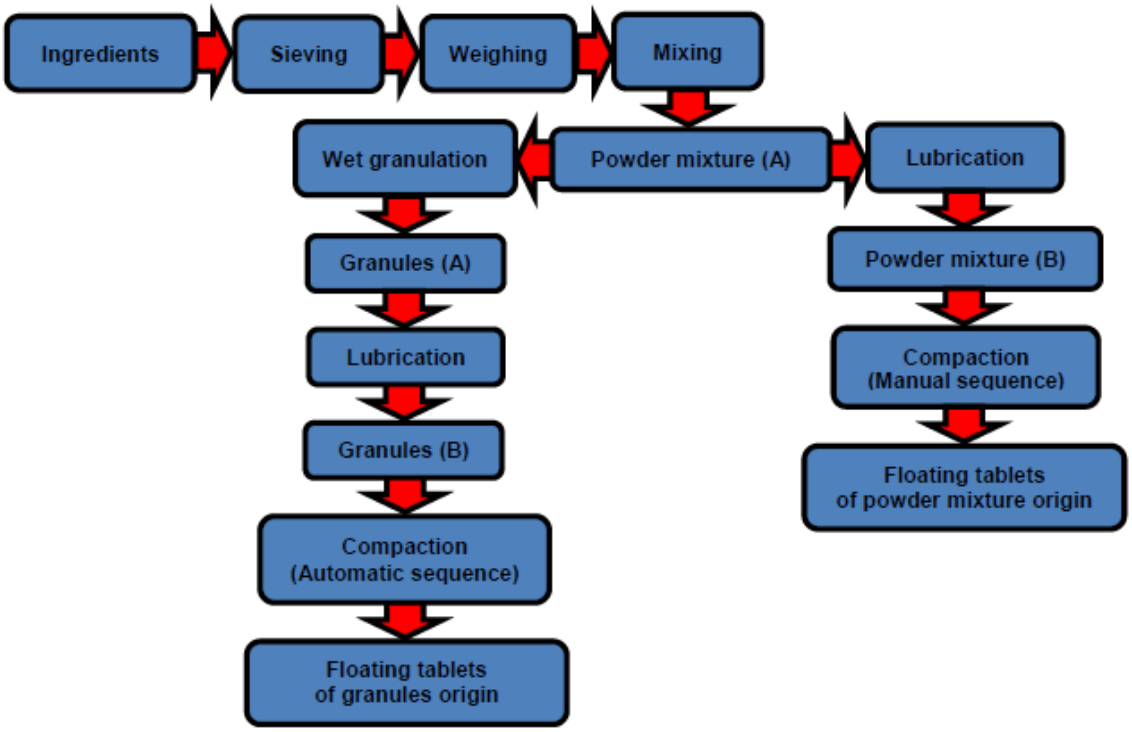

Figure 2-6: Flow chart for prepared floating tablets.

2.2.5 Evaluation of the prepared powders and granules

2.2.5.1Flowability test

Bulk and tapped volumes of 50 g samples of the prepared powder mixture and granules were measured by the tapping apparatus (Copley JV1000, UK). Bulk and tapped densities were calculated as the ratio of the powder weights to the related powder volumes. Carr's compressibility index (CI) was calculated using equation (1) (Carr, 1965):

$$CI = \left(\frac{Tapped\ density - Bulk\ density}{Tapped\ density}\right) \times 100 \qquad \text{Eq. (1)}$$

Measurements were performed in triplicate and the mean values ± SD are presented.

2.2.5.2Moisture content

A Mettler Toledo HG53 Halogen Moisture Analyser (Switzerland) was used to measure the moisture content in a 1 g powder mixture before and after granulation. Measurements were taken in triplicate and mean values ± SD are presented.

2.2.5.3Differential scanning calorimetry (DSC) study

DSC of model drugs, excipients, and all the formulations (prepared from powder mixture and granules) were obtained using a DSC Refrigerated Cooling System (Model Q1000, TA Instruments, UK). Samples of pure materials (2–6 mg) were weighed and transferred into the equipment for analysis in sealed standard aluminum pans, and the calorimetric enthalpy readings were calculated using Q1000, TA software (Suliman et al., 2014). The thermal behaviour of the samples was investigated at a scanning rate of 10˚C / min, from 0 to 260˚C for pentoxifylline and from 0 to 250˚C for cefalexin monohydrate.

2.2.5.4Fourier-transform infrared (FTIR) spectroscopy

Infrared spectra of model drugs and all the formulations (prepared from powder mixture or granules) were obtained using a Perkin Elmer FT-IR system Spectrum BX series (Beaconsfield, Buckinghamshire, UK) in the frequency range of 4000–620 cm^{-1} at 4 cm^{-1} resolution. A few milligrams of each sample were placed in the middle of the sample stage using a micro-spatula, before being compressed by twisting the top of the arm of the sample stage clockwise (Suliman et al., 2014). The data were obtained by Spectrum BX series software version 5.3.1.

2.2.6 Evaluation of floating tablets

Tablets prepared from granules were evaluated for tablet crushing strength, friability, weight uniformity, drug content uniformity, apparent density, porosity, floating capacity, swelling and erosion, dissolution, release data modeling, and stability testing. Tablets prepared from powder mixtures were evaluated only for apparent density, porosity, floating capacity, dissolution, and release data modeling, as these tablets had been compacted manually.

2.2.6.1Tablet crushing strength, friability, weight uniformity, drug content uniformity

To establish tablet crushing strength, ten tablets were randomly selected, their crushing strength examined using a tablet crushing strength tester, and mean values ± SD are presented. For friability, twenty tablets were randomly selected and tested at 100 revolutions using friability test apparatus (Copley FRV 1000, UK). The percentage of weight loss (*F*) was calculated by equation (2) (BP, 2015):

$$F = \frac{w_1 - w_2}{w_1} \times 100\% \qquad \text{Eq. (2)}$$

Where w_1 is the tablet weight before friability test, w_2 is the tablet weight after the test.

For the weight uniformity test, 20 tablets were randomly selected and accurately weighed individually, and the mean weight of all the tablets and percentage deviation from the mean for each tablet are presented. Regarding drug content uniformity, ten tablets were randomly selected, each individual tablet was weighed then crushed, a quantity of the powder was extracted with 100 ml, 0.1 M HCl, and the solution was filtered through a cellulose acetate membrane (0.45 µm). After a suitable dilution in 0.1 M HCl, the absorbance of pentoxifylline and cefalexin monohydrate samples were determined using a UV/Vis spectrophotometer (Model M501, Camspec Ltd, Cambridge, UK) at 274 nm and 257 nm respectively.

Drug content was calculated using the generated calibration data of each model drug (Figure 2-3 and Figure 2-4); the percentages of individual drug content were calculated against the average drug content according to the British Pharmacopoeia (BP) specifications.

2.2.6.2Tablet apparent density and porosity

Tablet height (*h*) and diameter (*m*) were measured using Vernier caliper (Moore and Wright Sheffield England Metric, UK). Tablet weight (*w*) and the circular constant (*π*) were also used to calculate the apparent density (*D*) of the tablets by equation (3) (Ali et al., 2007):

$$D\left(\frac{g}{cm^3}\right) = \frac{w}{\left(\frac{m}{2}\right)^2 \times \pi \times h} \qquad \text{Eq. (3)}$$

The test was performed in six replicate and mean values ± SD are presented.

Tablet porosity (*ε*), was calculated using equation (4) (Sun, 2006):

$$\varepsilon = [1 - (\rho_{tablet}/\rho_{true})] \times 100 \qquad \text{Eq. (4)}$$

Where ρ_{tablet} is the tablet's apparent density and ρ_{true} is the true density of the powder mixture or granule sample measured using a multipycnometer (MVP-D160-E, Quantachrome Instruments, USA). Five replicate measurements of almost 1.8 g and 1.3 g samples of pentoxifylline and cefalexin monohydrate respectively were used. The helium pressure was set to 17 psi, and the difference in helium pressure before and after sample loading was reported to determine the true volume of the samples. Mean values ± SD are presented.

2.2.6.3Tablet floating capacity

Floating capacity was determined under the same conditions and using the same apparatus as for the *in vitro* studies (Section 2.2.6.5). The time taken for tablets to appear and remain on the dissolution medium surface (floating lag time), and the period of time that the tablets constantly floated on the dissolution medium surface (floating duration) were determined visually throughout the drug release studies (Yin et al., 2013). Measurements were taken in triplicate and mean values ± SD are presented.

2.2.6.4Swelling and erosion studies

The initial weights of three randomly chosen tablets were reported. The dissolution medium uptake (DMU) and mass loss (ML) percentage of the tablets were determined using USP Dissolution Apparatus II (Erweka GmbH, Germany) under the same conditions as the drug release study (Section 2.2.6.5). Tablets were carefully withdrawn using a spoon from the medium at same time intervals conditions as the drug release study (at 0.5, 1, 2, 4, 6, 8, 12, and 24 h for pentoxifylline and at 0.5, 1, 2, 4, 6, 8, 10 and 12 h for cefalexin monohydrate). Excess liquid present on the surface of tablets was removed using a filter paper and the tablets were weighed and then dried at 60°C in a drying oven until a constant dry weight was achieved.

Swelling and mass loss percentages were calculated by equations (5) and (6) (Roy and Rohera, 2002):

$$\%DMU = \left(\frac{W_w - W_i}{W_i}\right) \times 100 \qquad \text{Eq. (5)}$$

$$\%ML = \left(\frac{W_i - W_d}{W_i}\right) \times 100 \qquad \text{Eq. (6)}$$

Where W_i is the initial weight of the tablet, W_w is the wet weight of the tablet, and W_d is the dry weight of the tablet and mean values ± SD are presented.

2.2.6.5*In vitro* drug release studies

Drug release studies of the prepared tablets were carried out using USP dissolution apparatus II (Erweka GmbH, Germany) at 37°C ± 0.5°C, and a paddle speed of 50 rpm and 100 rpm for pentoxifylline and cefalexin monohydrate respectively. Pentoxifylline tablets were tested at 50 rpm rotation speed to meet USP dissolution test 6 of pentoxifylline sustained release tablets (USP 2012). For cefalexin, no official monograph is available for sustained release tablets; thus the paddle rotation speed was adapted from the literature (Agnihotri, et al., 2006; Yin et al., 2013). Tablets were placed into 900 ml of 0.1 M HCl (pH 1.2) as a simulated gastric fluid without the presence of gastric enzymes (Tadros, 2010; Oh et al., 2013; Yin et al., 2013; Qi et al., 2015). Samples (10 ml) were withdrawn from the dissolution at 0.5, 1, 2, 4, 6, 8, 12, and 24 h for pentoxifylline and at 0.5, 1, 2, 4, 6, 8, 10 and 12 h for cefalexin monohydrate. Withdrawn samples were replaced with fresh medium, and drug content was determined and the cumulative drug release percentage was calculated. The test was performed in triplicate and mean values ± SD are presented. The pH of the dissolution medium at each sampling time interval was measured by pH-meter (Hanna Instruments HI 8424N Digital, Portable pH Meter, USA). Sink conditions were met for both pentoxifylline and cefalexin monohydrate as the concentration of the active substance in the saturated medium will be greater than the used concentrations.

2.2.6.6Release data modeling and analysis

In order to study the release kinetics, data of *in vitro* drug release studies were fitted to different mathematical models. The zero order model equation (7) which describes systems where the drug release rate is independent on its concentration. However, systems representing a concentration dependent release rate are described by the first order model equation (8). The Hixson-Crowell cube root law equation (9) describes the release kinetics from systems showing a change in surface area and diameter of particles or tablets.

Moreover, Higuchi kinetic model equation (10) represents the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion (Costa and Sousa Lobo, 2001).

$$Q = k_0 t \quad \text{Eq. (7)}$$

$$\log(100 - Q) = logQ_0 - \frac{k_1 t}{2.303} \quad \text{Eq. (8)}$$

$$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = K_H \text{t} \quad \text{Eq. (9)}$$

$$Q = k_H \sqrt{t} \quad \text{Eq. (10)}$$

Where Q is the amount of drug released at time t, Q_o is the initial amount of the drug in tablet, k_o is the zero order release rate constant, k_1 is the first order release rate constant, k_{HC} is the Hixson-Crowell release rate constant, and k_H is the Higuchi release rate constant.

In order to characterise the model drug release mechanism (release data modeling and analysis), the power law model of Korsmeyer–Peppas equation (11) was fitted to the first 60% release data (Korsmeyer et al., 1983).

$$\frac{Q_t}{Q_\infty} = K_p \times t^n \quad \text{Eq. (11)}$$

Where Q_t/Q_∞ represents the fractional drug released at time t, K_p is the Korsmeyer–Peppas release rate constant, and n is the release exponent.

The drug release data were plotted in various kinetic models, including zero-order, first order, Hixson Crowell, Higuchi, and Korsmeyer-Peppas equations.

2.2.7 Stability studies

Regarding the guidance for industry, Q1A(R2), for stability testing of new drug substances and products (ICH, 2003), stress testing of the drug product can help identifying the likely changes that can influence quality, safety, and/or degradation behaviours of the drug substance. The drug product can be maintained under accelerated storage conditions including the effect of elevated temperature and humidity (40°C ± 2°C and 75% ± 5% RH) for 6 months while stored in suitable container closure system that mimics the appropriate marketing package.

In this work, the stability studies were conducted for shorter period of time (3 months) which met those of other gastroretentive dosage form stability studies (Tadros 2010; Acharya et al., 2014), however the stability chambers were maintained at higher relative humidity level (80% ± 5%) instead of ICH requirements (75% ± 5%) to apply further stressful conditions. Furthermore, storage in closed containers is reflective to the storage conditions of the packed pharmaceutical products; however, storage in open containers will raise the stress as the product will be in direct contact with the elevated temperature and humidity. Accordingly, granules and tablets prepared from the granules for all the formulations were packed in open or closed polyethylene (high density type) containers and stored in a stability chamber. Granules were withdrawn after 3 months and analysed by DSC and FTIR spectroscopy as described in sections 2.2.5.3, and 2.2.5.4 respectively. Also, after 3 months, tablets were withdrawn and evaluated for their apparent density, floating capacity, and drug release rate as described in sections 2.2.6.2, 2.2.6.3, and 2.2.6.5 respectively.

2.2.8 Preliminary *in vivo* pharmacokinetic study

Twelve male albino rats weighing 180 ± 20 g were provided by Applied Science Private University, Jordan. The animals were kept in the animal house at an ambient temperature (25 ± 1 °C) for a 12 h dark and 12 h light cycle. The animals were fed a pellet diet and had access to water *ad libitum*.

The experimental protocol was approved by the Research Ethics Committee (University of Sunderland), and all methods were conducted according to the University of Applied Science Private University guidelines. Pentoxifylline tablets (weighing 30 ± 1 mg equivalent to 5.73 mg drug) of F4 formulation were pressed manually (for granulated powders) using a single-punch tableting machine (Type 3, Manesty Machines Ltd, UK) equipped with concave-faced punches (4.00 mm), and the compression force was adjusted to produce tablets with a crushing strength level of 20 ± 1 N, as measured using the crushing strength tester (Model 2E/205, Schleuniger & Co., Switzerland). An aqueous solution of pentoxifylline (2.88 mg/ml) was prepared as a reference.

Rats were randomly divided into two groups and fasted for about 12 h prior to the experiment with a free access to water. The first group (G1) received the oral tablets, and the second group (G2) received the oral reference solution. The preparations (tablet and solution) were loaded directly into the stomach by intra-gastric gavage at a single dose of 5.75 ± 0.15 mg. Blood samples were collected using the tail-bleeding technique into a 0.5 ml mini-collect tubes (K3E K3EDTA) at 0.5, 1, 2, 4, 6, 8, 12 and 24 h, then subjected to centrifugation for 5 min at 13000 rpm (Model M-24, Boeco, Germany) and aliquots of plasma were frozen at − 20 °C before analysis.

Plasma samples (0.2 ml) mixed with 50 µl of an internal standard (20 µg/ml of emitrecitabine) by vortex, before adding 0.55 ml of methanol and mixing, then subjecting the mixture to centrifugation for 10 min at 14000 rpm using a centrifuge (Model 5417C, Eppendorf - Nrtheler - Hinz GmbH, Germany). The resulting supernatant was transferred to a glass insert for analysis, and 2 µl was directly injected into a HPLC-MS/MS system (Model 1200, Agilent Technologies Co., Ltd., Santa Clara, USA) which was equipped with a mass spectrometer (Model API 4000, SCIEX, Toronto, Canada).

Chromatographic separation was based on an ACE 5 C18 column (50 mm x 2.1 mm, 5µm) with a mobile phase composed of [0.2% ammonia (10%), 0.04% formic Acid (10%)] 50% : methanol 50% pumped at a constant flow rate of 0.6 ml/min.

In this pharmacokinetic study, the maximum plasma concentration (C_{max}) and the time required to reach this concentration (T_{max}) were obtained by actual observations of the plasma concentration-time data. The elimination rate constant (k_e) was calculated from the slope of the linear terminal line of the logarithmic plasma concentration-time data, and, the half-life ($t_{1/2}$) was calculated by equation (12) (Jambhekar and Breen, 2009):

$$t_{1/2} = \frac{0.693}{k_e} \qquad \text{Eq. (12)}$$

The area under the curve ($AUC_{0\text{-}t}$) was calculated using the trapezoidal rule from 0 to 24 h, and the area under the curve from zero to infinity ($AUC_{0\text{-}\infty}$) was calculated from ($AUC_{0\text{-}t}$) plus the extrapolated portion C_p/k_e by equation (13) (Kagan et al., 2006):

$$AUC_{0-\infty} = AUC_{0-t} + \frac{Cp_t}{k_e} \qquad \text{Eq. (13)}$$

Where Cp_t is the plasma drug concentration observed at time t. All data are presented as the mean value ± SD.

The relative bioavailability values (F_{rel}) were calculated by equation (14) (Jambhekar and Breen, 2009):

$$F_{rel} = \frac{AUC_{tablet}}{AUC_{solution}} \times \frac{Dose_{solution}}{Dose_{tablet}} \qquad \text{Eq. (14)}$$

2.2.9 Statistical analysis

The statistical software package, SPSS 22 (SPSS Inc., Chicago, USA) was used to perform the statistical analysis by applying the paired-sample *t*-test, and one-way analysis of variance, depending upon the type of data. Post hoc multiple comparisons were applied when necessary, and a *P*-value of <0.05 was considered significant.

Chapter Three: Evaluation of the effect of sodium bicarbonate, calcium carbonate, and sodium carbonate as gassing agents on pentoxifylline floating tablets

In this chapter a swellable, floatable, gastroretentive drug delivery systems utilising an effervescent mechanism was developed and evaluated. Tablets were based on a binary (1:1) gel forming polymer mixture of hydroxyethyl cellulose and sodium alginate, and sodium bicarbonate or calcium carbonate or sodium carbonate as a gas generating agent. Pentoxifylline was used as a model drug since it has a short half-life ($t_{1/2}$) of 0.8–1.8 h (Ings et al., 1982), high density (Baumgartner et al., 2000), and is highly soluble in water (191 mg/ml at 37°C) (Mikac et al., 2010). Consequently, these characteristics made it a suitable candidate for oral sustained release delivery to improve patient compliance and reduce side effects due to better control of therapeutic drug concentration and also made it ideal to challenge the ability of the designed gastroretentive tablets to show acceptable floating capacity and acceptable retarding of the drug release process. The variables that may affect drug release and floating properties were investigated, such as the wet granulation (to compare effects of powder mixtures versus those of granules), type and ratio of the gas forming agent (sodium bicarbonate, calcium carbonate and sodium carbonate). Only 60 mg of pentoxifylline was used in the study to evaluate efficiency of the designed floating tablets; however the drug dose could be scaled up in the future.

3.1 Evaluation of the prepared powders and granules (pre-compression characterisation)

All the prepared powder mixtures and granules of the formulations F1-F7 were evaluated for flowability CI index, moisture content percentage, DSC, and FTIR. The formulations F1-F7 compositions are presented in Table 3-1 (and also Table 2-7).

Table 3-1: Composition of prepared F1-F7 tablets

Ingredients/Formulation	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
Pentoxifylline	60	60	60	60	60	60	60
Hydroxyethyl cellulose	70	70	70	70	70	70	70
Sodium alginate	70	70	70	70	70	70	70
Prosolv® 90	50	50	50	50	50	50	50
Sodium bicarbonate	27.5	62.5					
Calcium carbonate			27.5	62.5			
Sodium carbonate					27.5	62.5	
Magnesium stearate (0.5%)	1.4	1.6	1.4	1.6	1.4	1.6	1.3
Total weight	278.9[a]	314.1[a]	278.9[a]	314.1[a]	278.9[a]	314.1[a]	251.3

[a] Difference in weight was due to raising gassing agent content from 10% to 20% (w/w).

Note: number of moles of the gassing agents used in the formulations is 3.3×10^{-4} (F1), 7.4×10^{-4} (F2), 2.7×10^{-4} (F3), 6.2×10^{-4} (F4), 2.6×10^{-4} (F5), and 5.9×10^{-4} (F6).

3.1.1 Flowability and moisture content for powders and granules

It is important for oral solid dosage forms development (such as tablets) to investigate powder or granules flow properties by making a correlation between rheological test results and manufacturing properties. Many methods are available to test the rheology such as angle of repose, compressibility index (Carr's index) and flow rate through an orifice. Packing studies of powder and granules (bulk density measurements) could be carried out with a tapping apparatus where powder or granules specific volumes before and after tapping is measured and divided by the used masses to calculate bulk and tapped apparent densities to give information about sample rheological properties (Yamashiro et al., 1983). It has been proposed that a small change in apparent density before and after tapping indicates good flow properties (Chan and Heng, 2005). The granulation process is one of the agglomeration techniques where fine solid particles are converted into larger ones by mixing them in the presence of binding liquids using suitable equipment (Wong et al., 2005). It has been reported that the formed granules could improve powder flowability and mechanical strength and could also narrow bulk density and porosity values (Tardos et al., 1997; Iveson et al., 2001). The CI values significantly decreased (P<0.05) following granulation for all the prepared formulations (F1-F7, Table 3-2) which reveals better flow properties of the granules compared to the powder mixture (Gaisford, 2013).

Results for the moisture content and CI value of the formulations F1-F7 before and after granulation are shown in Table 3-2. It is clear that the moisture content percentage significantly decreased (P<0.05) after granulation from 5.37%, 4.76%, 5.83%, 4.91%, 5.70%, 5.51%, and 5.80% to 4.13%, 3.49%, 4.84%, 4.56%, 4.53%, 4.11%, and 3.14% in the formulations F1-F7, respectively. It is important to control the level of moisture content of powder and granules as it can adversely affect on their rheology. Using a drying oven at 60°C overnight (~12 h) until a constant dry weight of the granules was achieved simply by evaporating the free moisture content (unbound water) resulted from the wet granulation process.

The CI values significantly decreased (P<0.05) following granulation for all the prepared formulations (F1-F7,Table 3-2) which reveals better flow properties of the granules compared to the powder mixture (Gaisford, 2013).

Table 3-2: Moisture content and Carr's index with statistical analysis (*p*-value) results of the formulations F1-F7 before and after granulation.

Test	Formulation	Origin of prepared tablets		*P*-value
		Powder mixture	Granules	
Moisture content (%)	F1	5.37 ± 0.06	4.13 ± 0.17	0.005
	F2	4.76 ± 0.08	3.49 ± 0.14	0.003
	F3	5.83 ± 0.06	4.84 ± 0.05	0.001
	F4	4.91 ± 0.02	4.56 ± 0.04	0.010
	F5	5.70 ± 0.14	4.53 ± 0.19	0.003
	F6	5.51 ± 0.12	4.11 ± 0.16	0.004
	F7	5.80 ± 0.09	3.14 ± 0.93	0.043
Carr's Index (CI) (%)	F1	27.74 ± 0.46	16.87 ± 0.33	0.001
	F2	28.53 ± 2.81	17.65 ± 0.64	0.016
	F3	26.57 ± 2.53	16.63 ± 1.69	0.011
	F4	29.81 ± 3.09	16.33 ± 0.43	0.015
	F5	31.06 ± 1.58	15.26 ± 1.85	0.003
	F6	27.02 ± 1.32	16.83 ± 2.05	0.014
	F7	29.67 ± 1.60	15.29 ± 1.67	0.010

Note: The data represents the mean ± SD of three determinations.
For formulation composition, refer to Table 3-1 or Table 2-7.

3.1.2 Differential scanning calorimetry (DSC)

It is important to study the potential interactions between drugs and excipients in the pre-formulation stage during the development of all pharmaceutical dosage forms. Such interactions can alter chemical nature, stability, bioavailability, therapeutic efficacy and safety of drugs. Excipients are important to modify the pharmaceutical formulations; however, they might interact with drugs causing unwanted degradation. DSC is one of the techniques which can screen possible incompatibilities resulting from the appearance, shifts or disappearances of peaks and/or changes in the corresponding thermal enthalpies (Vueba et al., 2005).

Figure 3-1 to Figure 3-7 represent DSC thermograms of pure pentoxifylline, sodium alginate, hydroxyethyl cellulose, Prosolv® 90, sodium bicarbonate, calcium carbonate, and sodium carbonate raw materials respectively. As shown in (Figure 3-1), pure pentoxifylline showed a sharp endothermic peak at 104.80˚C due to drug melting. Sodium alginate had a broad endothermic peak around 114.24˚C and two exothermic peaks at 212.89˚C and 240.02˚C (Figure 3-2). Hydroxyethyl cellulose, Prosolv® 90, sodium bicarbonate, and sodium carbonate presented endothermic peaks at about 94.88˚C (Figure 3-3), 94.50˚C (Figure 3-4), 145.81˚C (Figure 3-5), and 85.75˚C (Figure 3-7) respectively. Calcium carbonate as a gassing agent did not show any thermal activity as presented in (Figure 3-6). The compatibility of pentoxifylline with excipients in the formulations F1-F7 before and after granulation was studied using DSC. An overlapping between hydroxyethyl cellulose, Prosolv® 90, and pentoxifylline endothermic peaks was noted in all the formulations F1-F7. However, the endothermic peak of sodium alginate was shifted from 114.24°C (pure sample) to 124.49-146.86°C and to 120.51-147.26°C in the formulations F1-F7 prepared from the powder mixture and the granules respectively. Sodium bicarbonate endothermic peaks at 157.97°C and 156.27°C were reported for the powder mixture and the granules, respectively: (F1, Figure 3-8) and 158.64°C and 171.70°C (F2, Figure 3-9). The peak of sodium carbonate gassing agent was overlapped with pentoxifylline, hydroxyethyl cellulose and Prosolv® 90 in F5 (Figure 3-12) and F6 (Figure 3-13) formulations prepared either from the powder mixture or the granules.

Although pure pentoxifylline showed a sharp endothermic peak at 104.80°C, a shift to a lower temperature and a decrease in peak intensity were noted for F1 powder mixture and F1 granules with endothermic peaks at 91.84°C and 94.64°C, respectively, and enthalpy values were 25.05 J/g and 23.65 J/g respectively (Figure 3-8). These changes in thermal behaviour of the drug were presented in all other formulations (F2-F7).

Endothermic peaks at 90.27°C and 94.10°C were reported for the powder mixture and granules, respectively: (F2, Figure 3-9), 97.60°C and 95.23°C (F3, Figure 3-10), 95.10°C, and 93.64°C (F4, Figure 3-11), 94.06°C, and 92.80°C (F5, Figure 3-12), 95.34°C, and 97.28°C (F6, Figure 3-13), and 95.85°C, and 96.26°C (F7, Figure 3-14). Moreover, enthalpy for the powder mixture and granules were reported respectively 22.76 J/g and 19.15 J/g for F2, 29.09 J/g and 28.21 J/g for F3, 27.14 J/g and 20.82 J/g for F4, 32.20 J/g and 20.70 J/g for F5, 32.41 J/g and 21.66 J/g for F6, and 34.79 J/g and 30.73 J/g for F7.

These observations reflect the existence of an interaction between the drug and the other components; however, it was not due to any of the gassing agents. As shown in Figure 3-14, the compatibility of pentoxifylline with excipients in the control formulation (F7), with 0% (w/w) gassing agent, before and after granulation represented also a shift to a lower temperature and a decrease in the peak intensity for both F7 powder mixture and F7 granules. Therefore, these changes in the thermograms of the formulations F1-F7 may indicate a certain loss of drug crystallinity, which means some of pentoxifylline crystals converted into the amorphous form during the preparation of both the powder mixture as well as the granules (Vueba et al., 2004). No other thermal event occurred and these interactions do not necessarily indicate incompatibility, but conclusions based on DSC results alone can be often misleading and inconclusive (Mura et al., 1995). Therefore results obtained with DSC should always be confirmed with other tests. Regarding the ICH (Q6A) guidance for specifications: test procedures and acceptance criteria for new drug substances and new drug products, infrared spectroscopy is considered one of the specific tests for drug substance identification (ICH, 1999). Accordingly, FTIR was used in addition to DSC to evaluate potential interactions between the drug and the excipients. Results of FTIR (section 3.1.3) confirmed presence of pentoxifylline characteristic bands for all the formulations F1-F7. Such results approve absence of incompatibility between the drug and the formulation excipients (hydroxyethyl cellulose, sodium alginate, Prosolv® 90, sodium bicarbonate, calcium carbonate, sodium carbonate, and magnesium stearate).

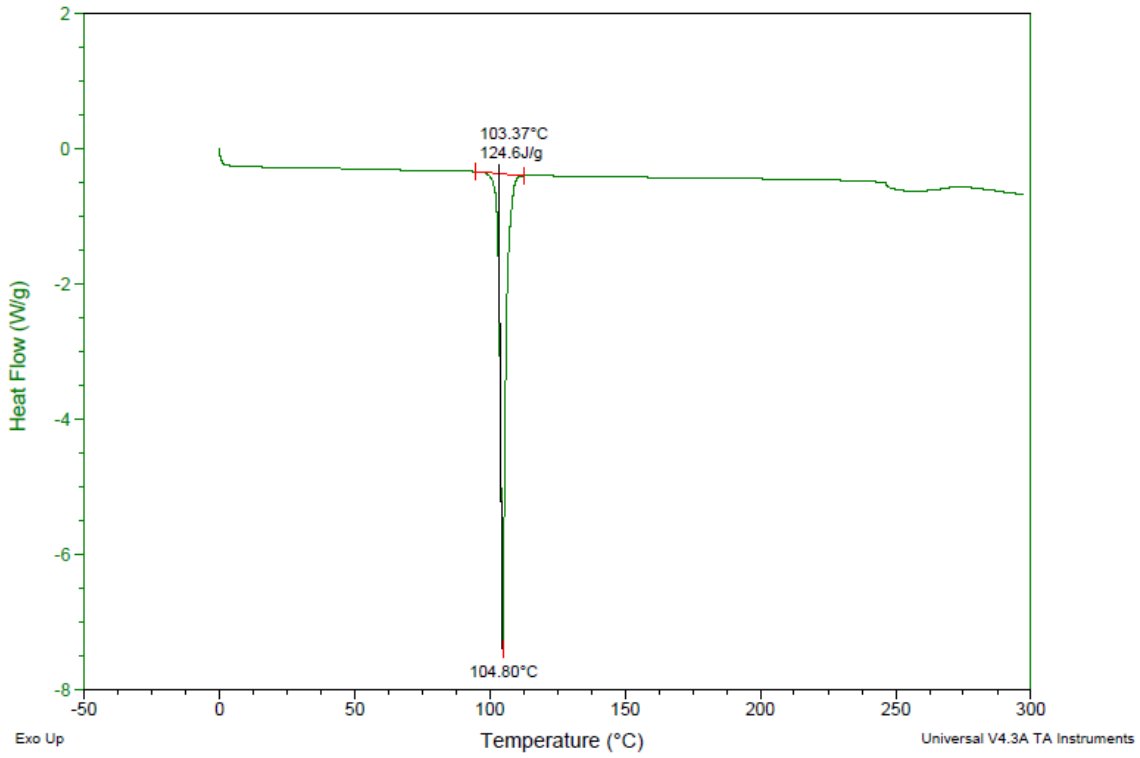

Figure 3-1: DSC thermogram of pure pentoxifylline.

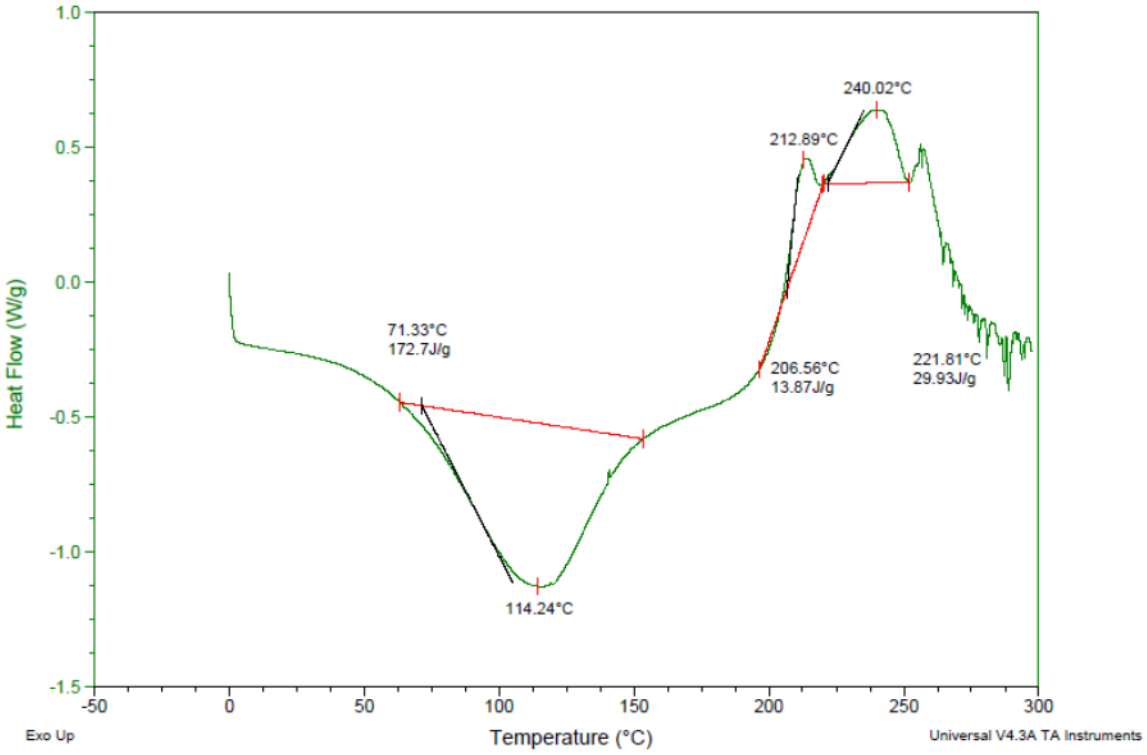

Figure 3-2: DSC thermogram of sodium alginate.

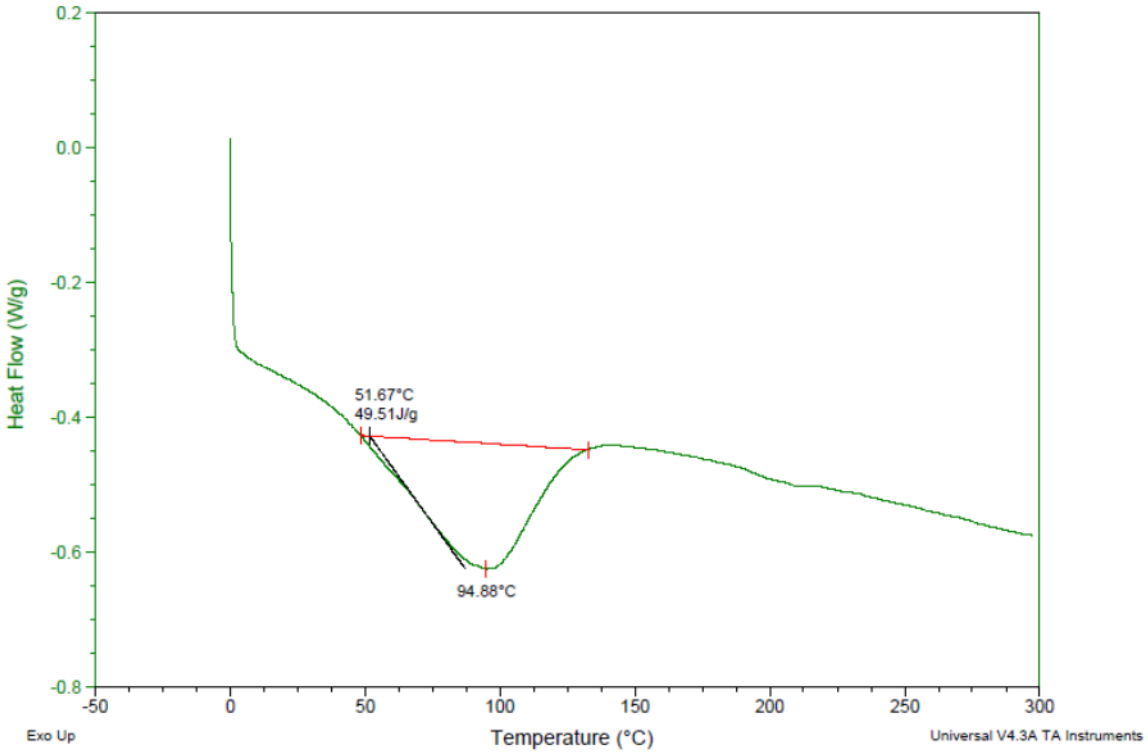

Figure 3-3: DSC thermogram of hydroxyethyl cellulose.

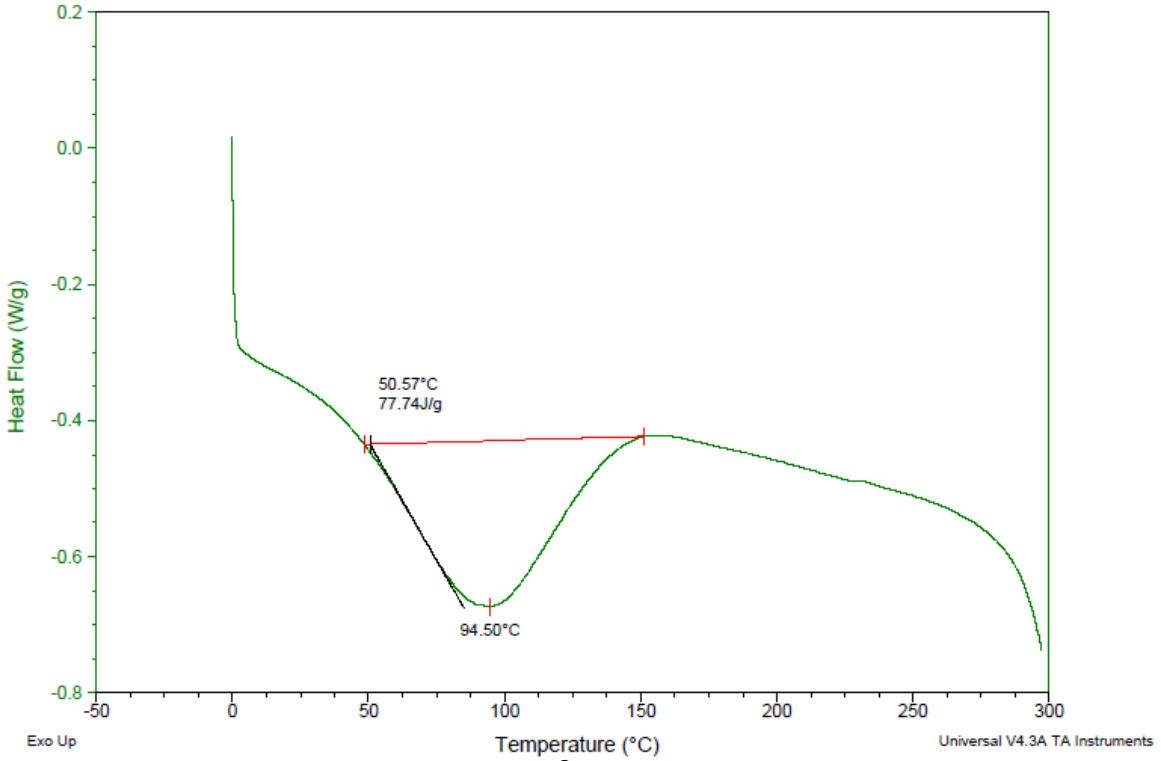

Figure 3-4: DSC thermogram of Prosolv® 90.

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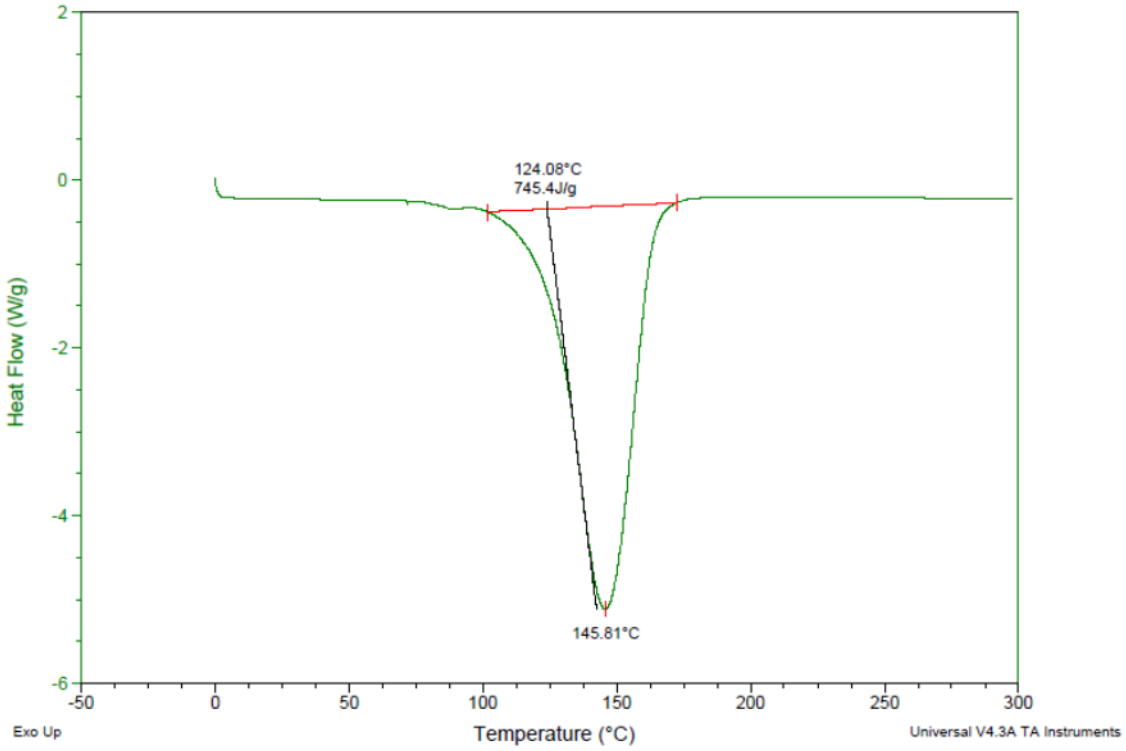


Figure 3-5: DSC thermogram of sodium bicarbonate.

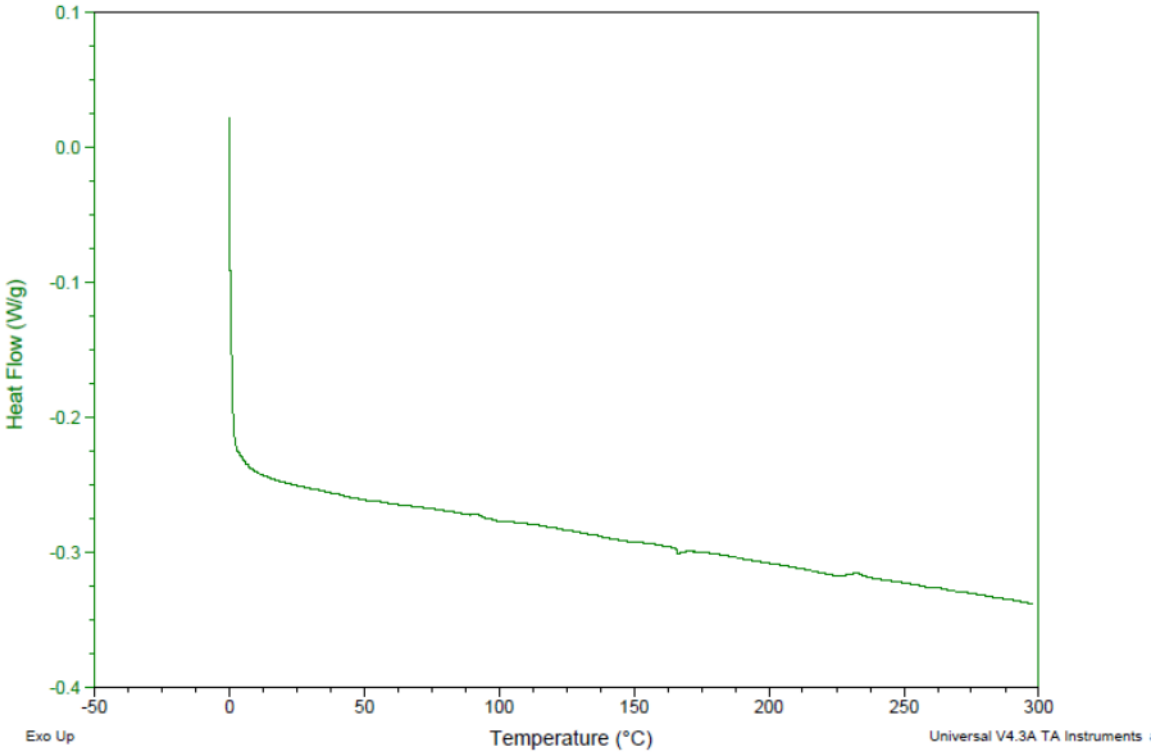


Figure 3-6: DSC thermogram of calcium carbonate.

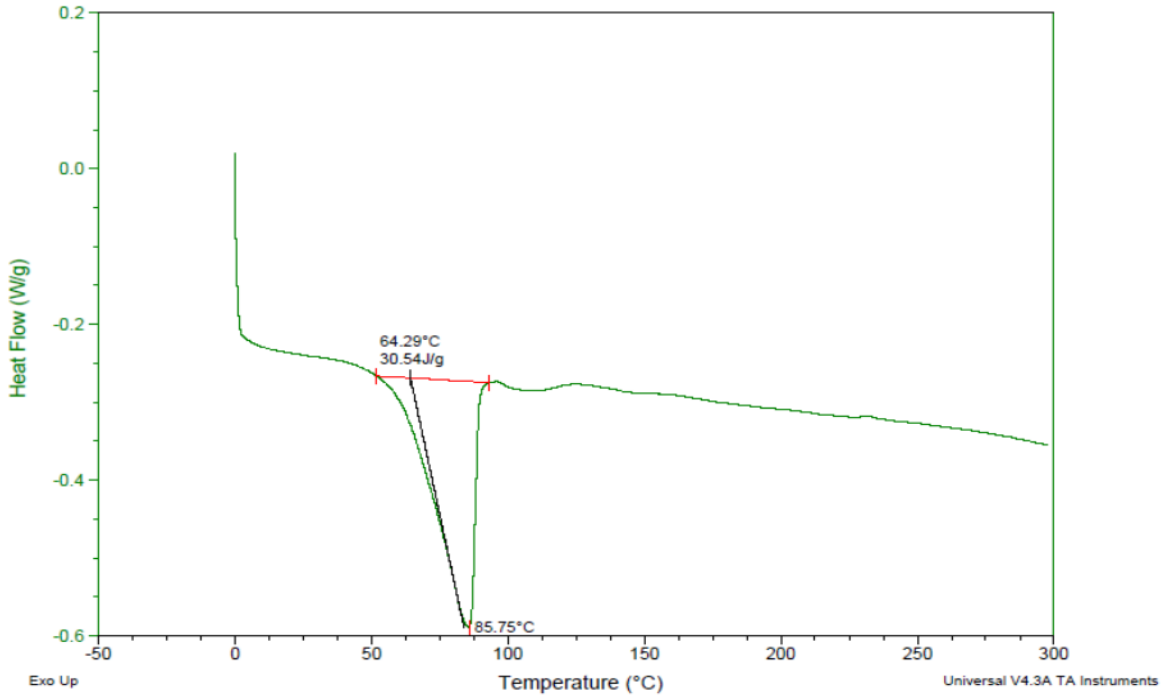


Figure 3-7: DSC thermogram of sodium carbonate

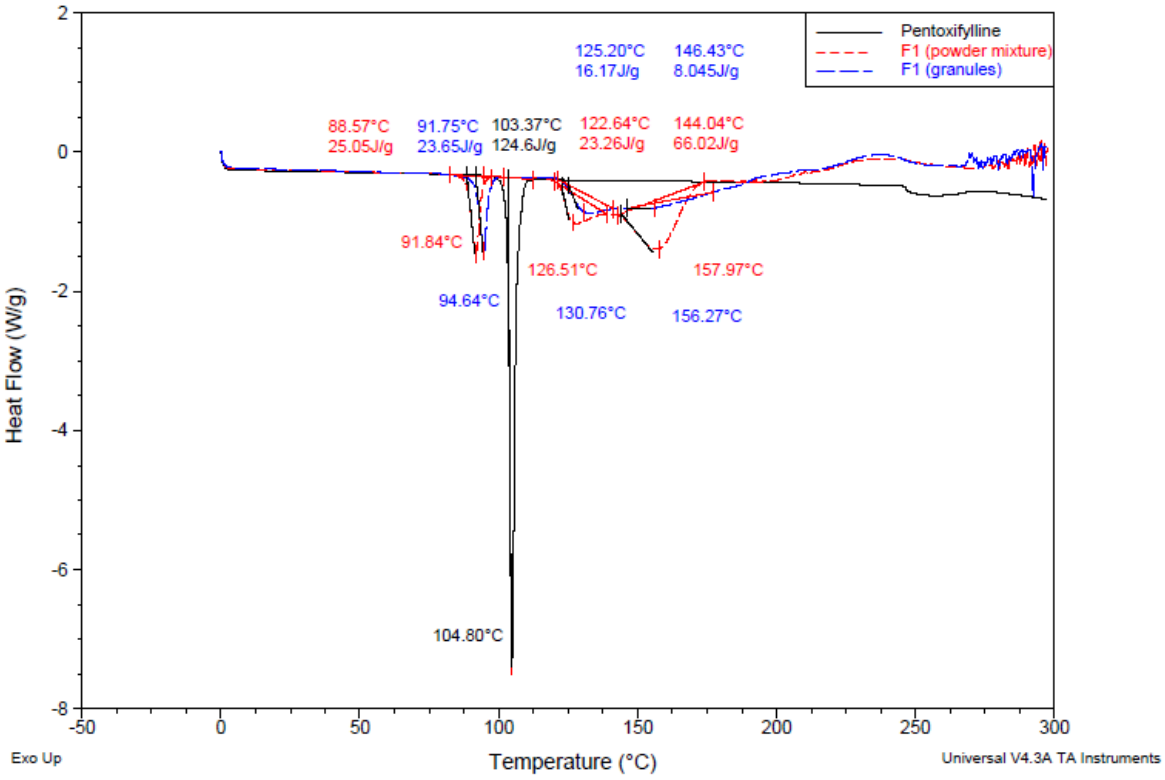


Figure 3-8: DSC thermograms of pure pentoxifylline, F1 powder mixture and F1 granules.
For formulation composition, refer to Table 3-1 or Table 2-7.

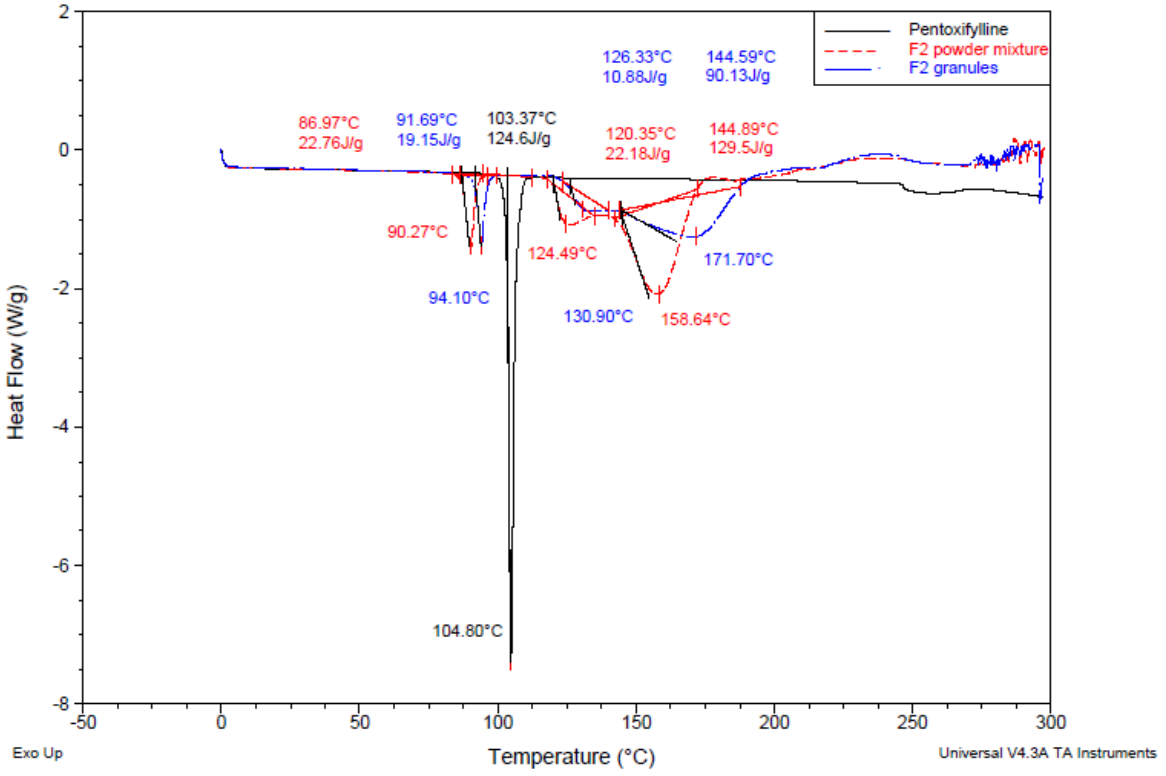


Figure 3-9: DSC thermograms of pure pentoxifylline, F2 powder mixture and F2 granules.

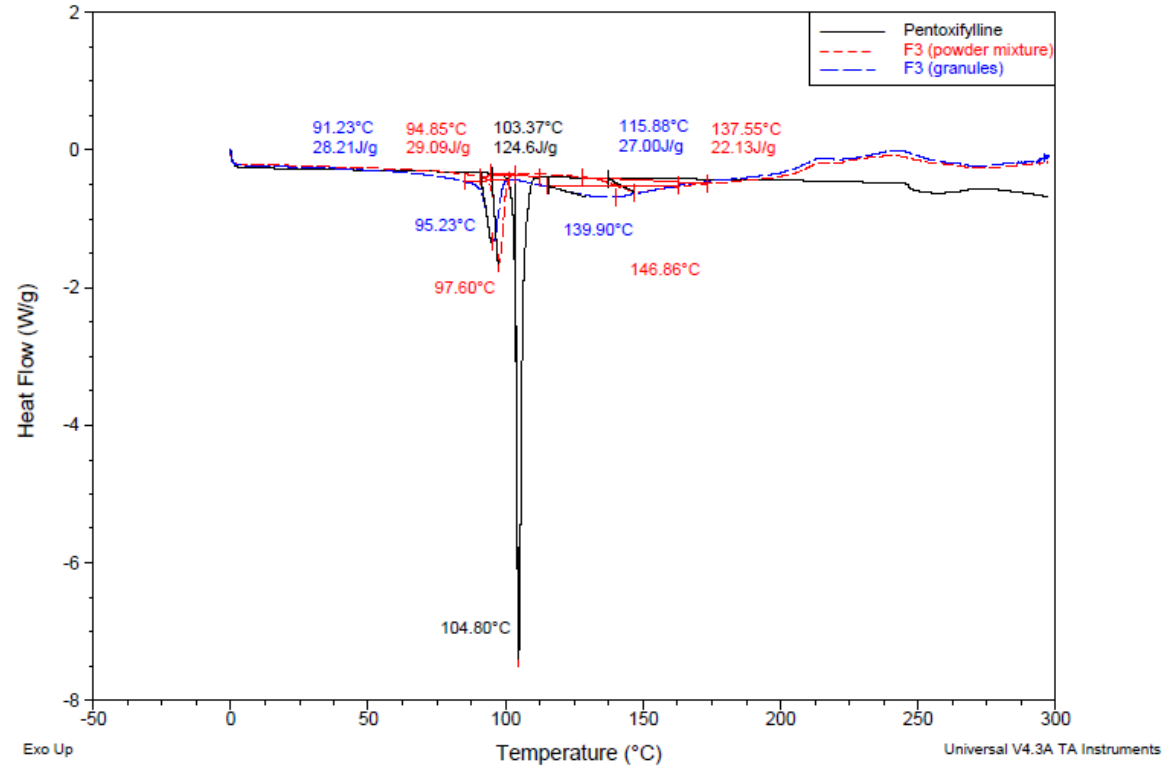


Figure 3-10: DSC thermograms of pure pentoxifylline, F3 powder mixture and F3 granules.
For formulation composition, refer to Table 3-1 or Table 2-7.

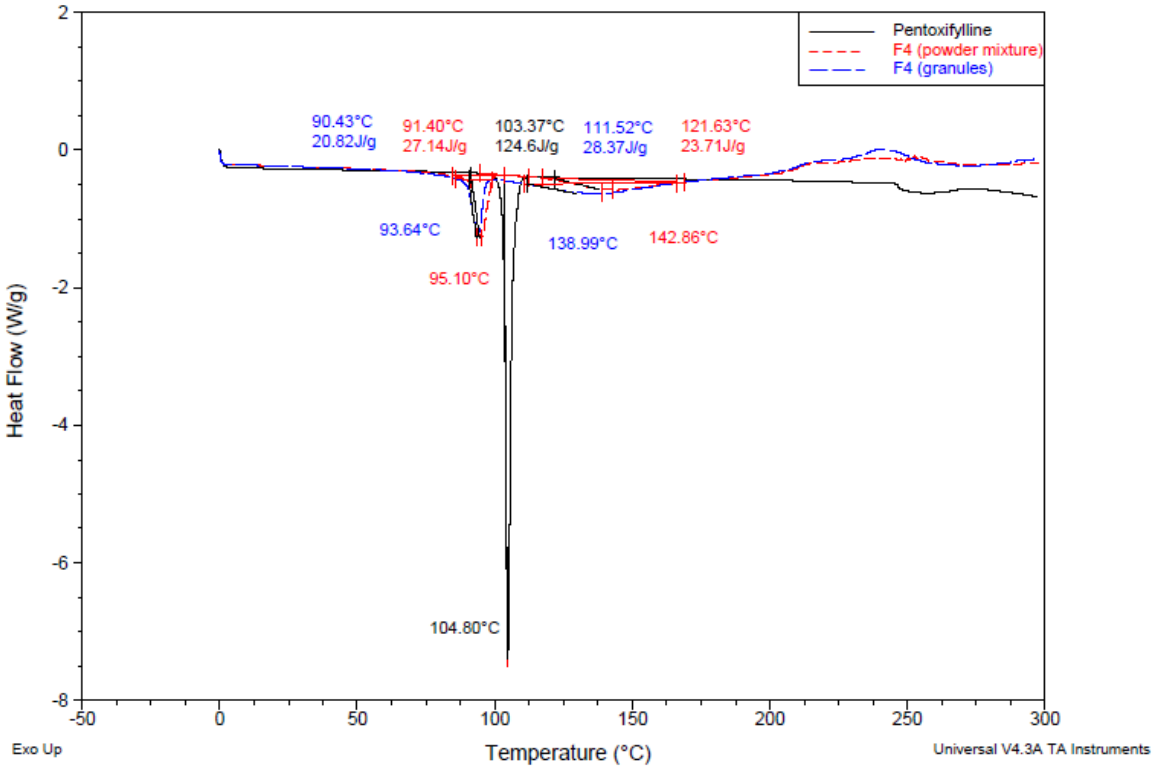


Figure 3-11: DSC thermograms of pure pentoxifylline, F4 powder mixture and F4 granules.

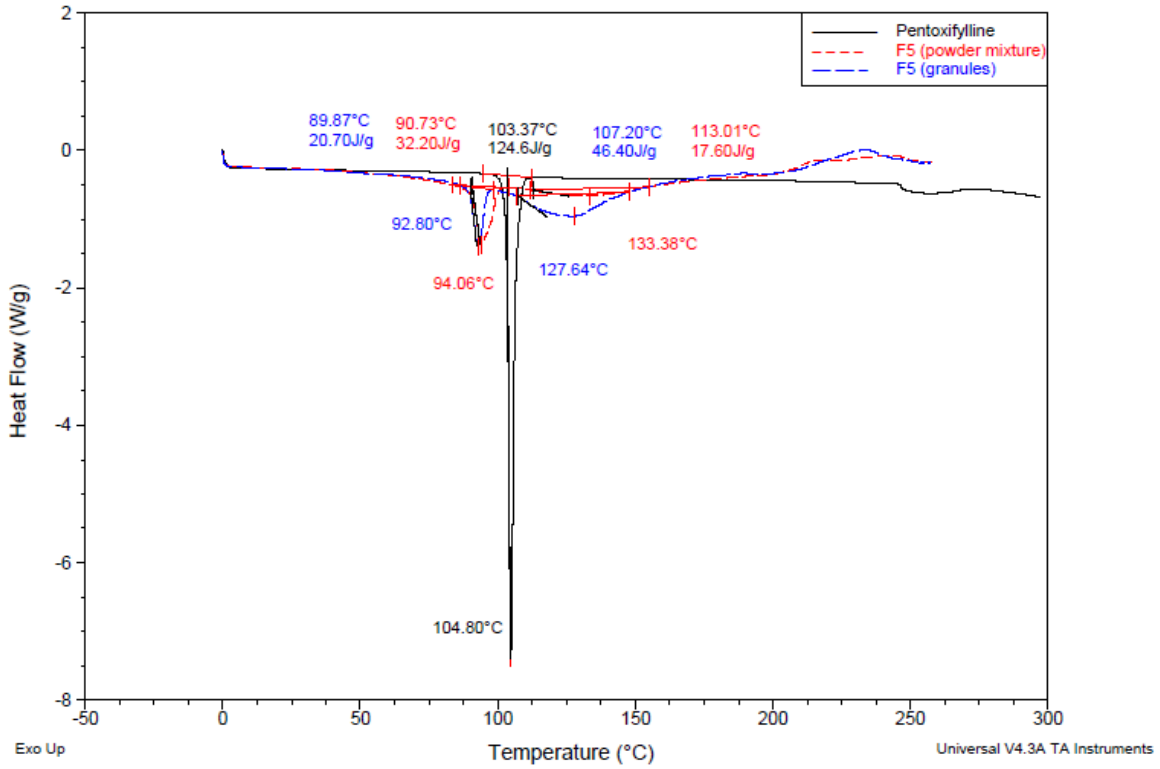


Figure 3-12: DSC thermograms of pure pentoxifylline, F5 powder mixture and F5 granules.
For formulation composition, refer to Table 3-1 or Table 2-7.

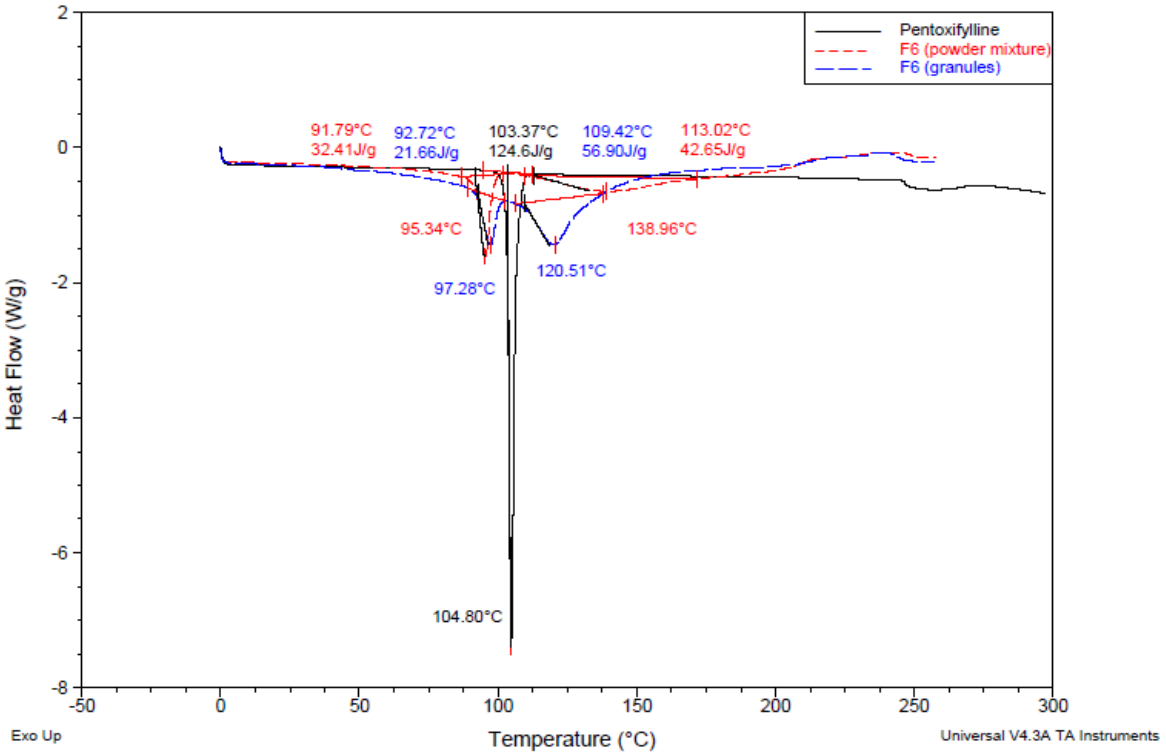


Figure 3-13: DSC thermograms of pure pentoxifylline, F6 powder mixture and F6 granules.

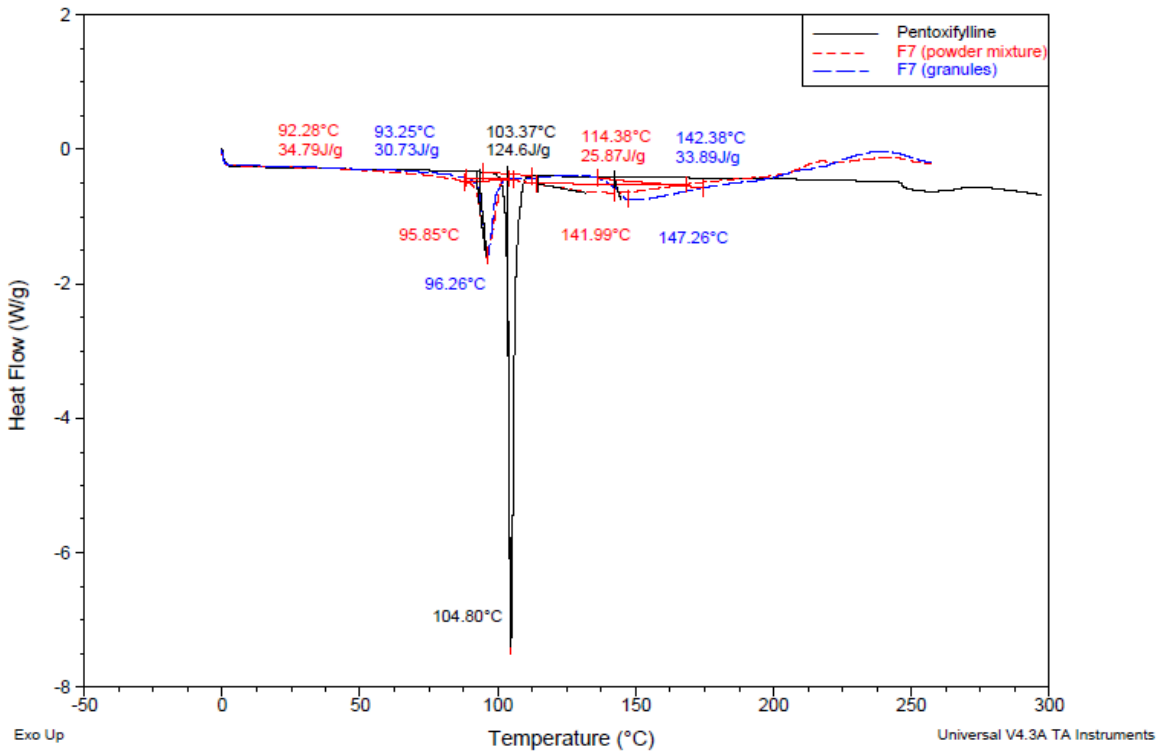


Figure 3-14: DSC thermograms of pure pentoxifylline, F7 powder mixture and F7 granules.
For formulation composition, refer to Table 3-1 or Table 2-7.

The granules of the formulations F1-F7 were stored for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers and evaluated by DSC to investigate possible effects of elevated temperature and humidity on the drug. Figure 3-15 to Figure 3-21 represent DSC thermograms of F1-F7 stability samples respectively. Endothermic peaks at 89.59°C, and 95.81°C were reported for the stability samples in closed and open containers, respectively: (F1, Figure 3-15), 92.44°C, and 95.87°C (F2, Figure 3-16), 87.45°C, and 95.23°C (F3, Figure 3-17), 92.97°C, and 97.03°C (F4, Figure 3-18), 89.03°C and 96.80°C (F5, Figure 3-19), 92.94°C and 96.25°C (F6, Figure 3-20), and 91.89°C and 92.53°C (F7, Figure 3-21). Moreover, enthalpy for the stability samples in closed and open containers were reported respectively 28.41 J/g and 24.09 J/g for F1, 27.20 J/g and 25.16 J/g for F2, 26.52 J/g and 22.88 J/g for F3, 20.99 J/g and 20.91 J/g for F4, 21.67 J/g and 21.98 J/g for F5, 21.43 J/g and 21.15 J/g for F6, and 25.51 J/g and 26.10 J/g for F7.

Results were almost similar to the endothermic peak temperature and the enthalpy of the freshly prepared granules which were respectively: 94.64°C, 23.65 J/g (F1, Figure 3-8) and 94.10°C, 19.15 J/g (F2, Figure 3-9), 95.23°C, 28.21 J/g (F3, Figure 3-10) and 93.64°C, 20.82 J/g (F4, Figure 3-11), 92.80°C, 20.70 J/g (F5, Figure 3-12), 97.28°C, 21.66 J/g (F6, Figure 3-13), and 96.26°C, 30.73 J/g (F7, Figure 3-14). An exception was noted for F3 stability sample in closed container where endothermic temperature decreased from 95.23˚C (fresh granules) to 87.45˚C. However, the FTIR spectra (section 3.1.3) of the stability samples confirmed the presence of pentoxifylline characteristic bands in all the formulations (F1-F7). Generally, this suggests physical stability of pentoxifylline loaded in F1-F7 tablets for 3 months at 40°C ± 2°C and 80% ± 5% RH in either closed or open containers.

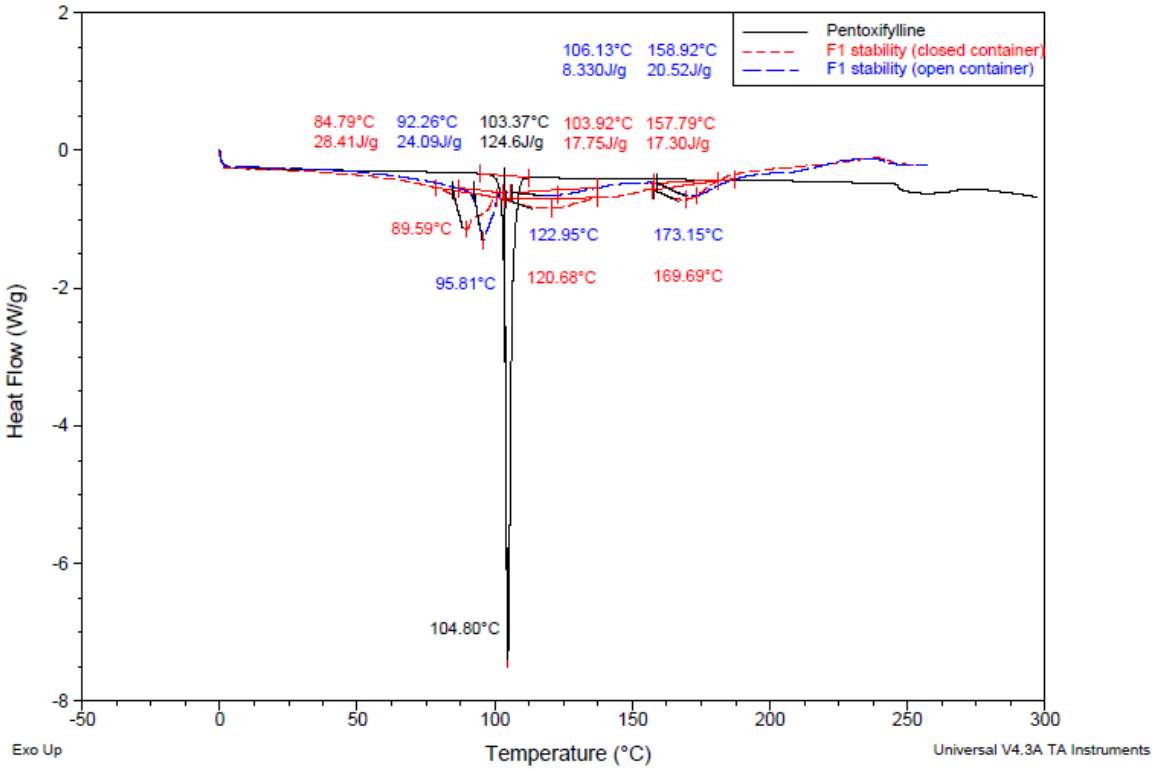


Figure 3-15: DSC thermograms of pure pentoxifylline, F1 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

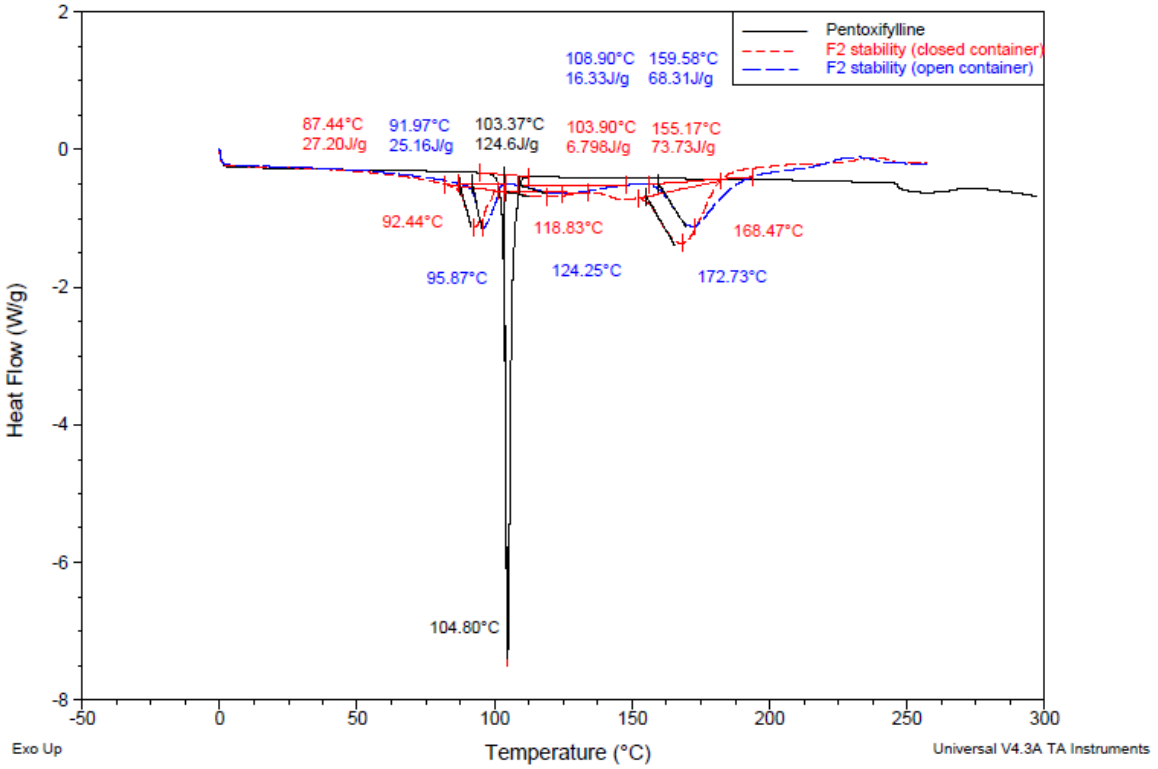


Figure 3-16: DSC thermograms of pure pentoxifylline, F2 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 3-1 or Table 2-7.

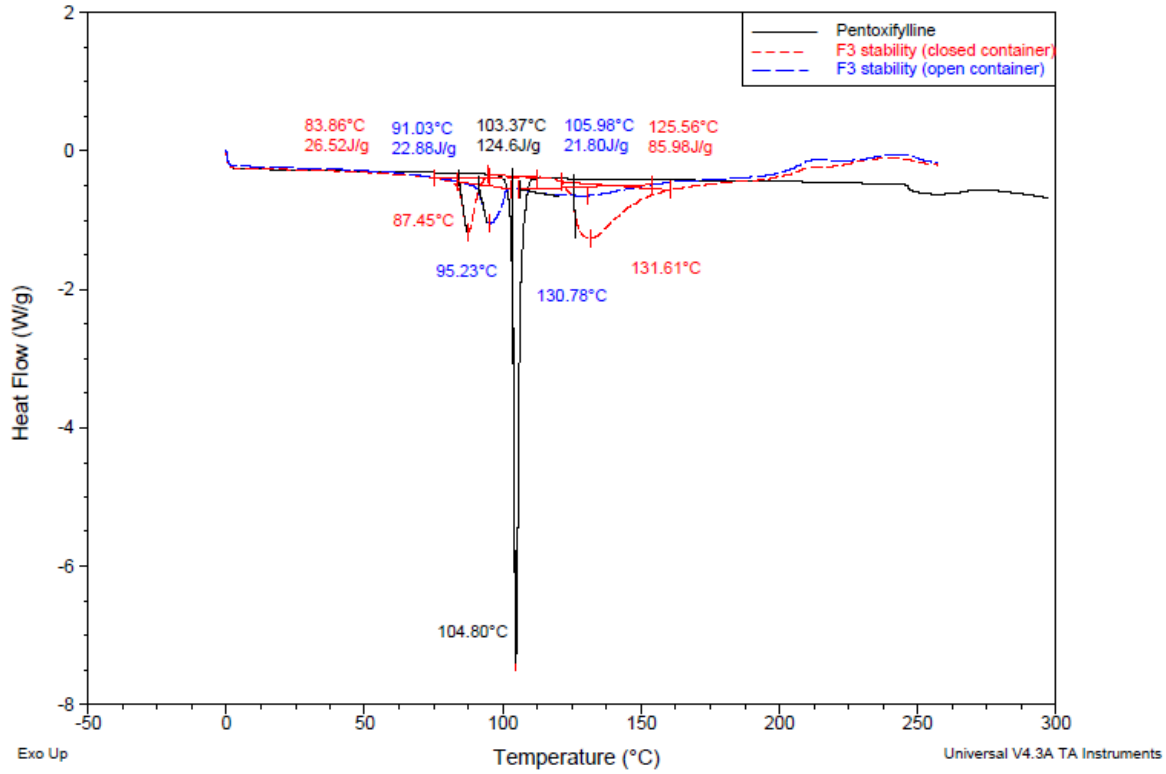


Figure 3-17: DSC thermograms of pure pentoxifylline, F3 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

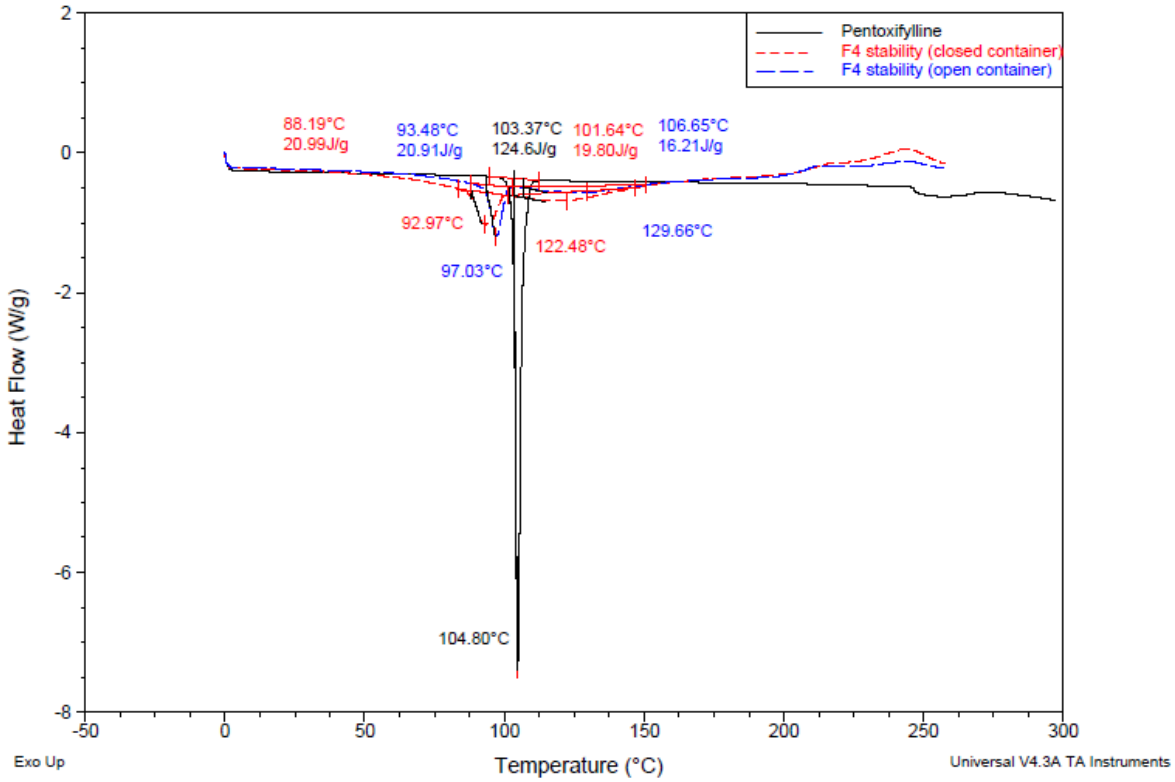


Figure 3-18: DSC thermograms of pure pentoxifylline, F4 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 3-1 or Table 2-7.

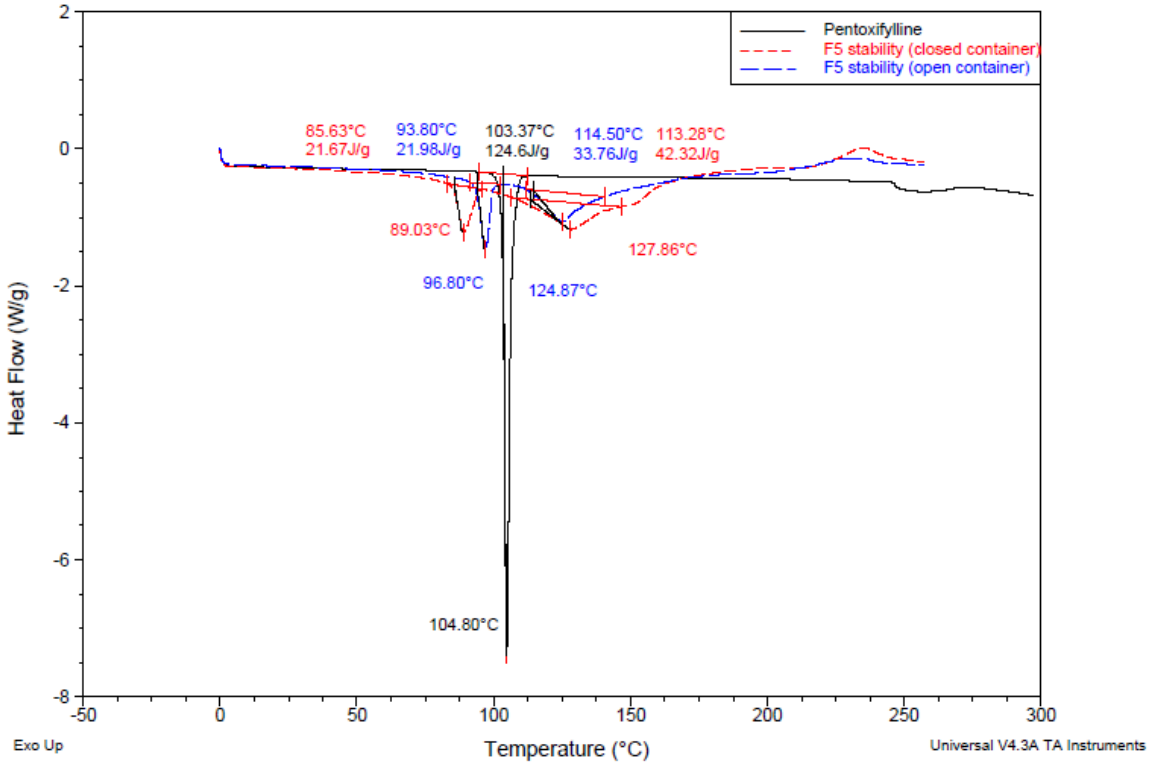


Figure 3-19: DSC thermograms of pure pentoxifylline, F5 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

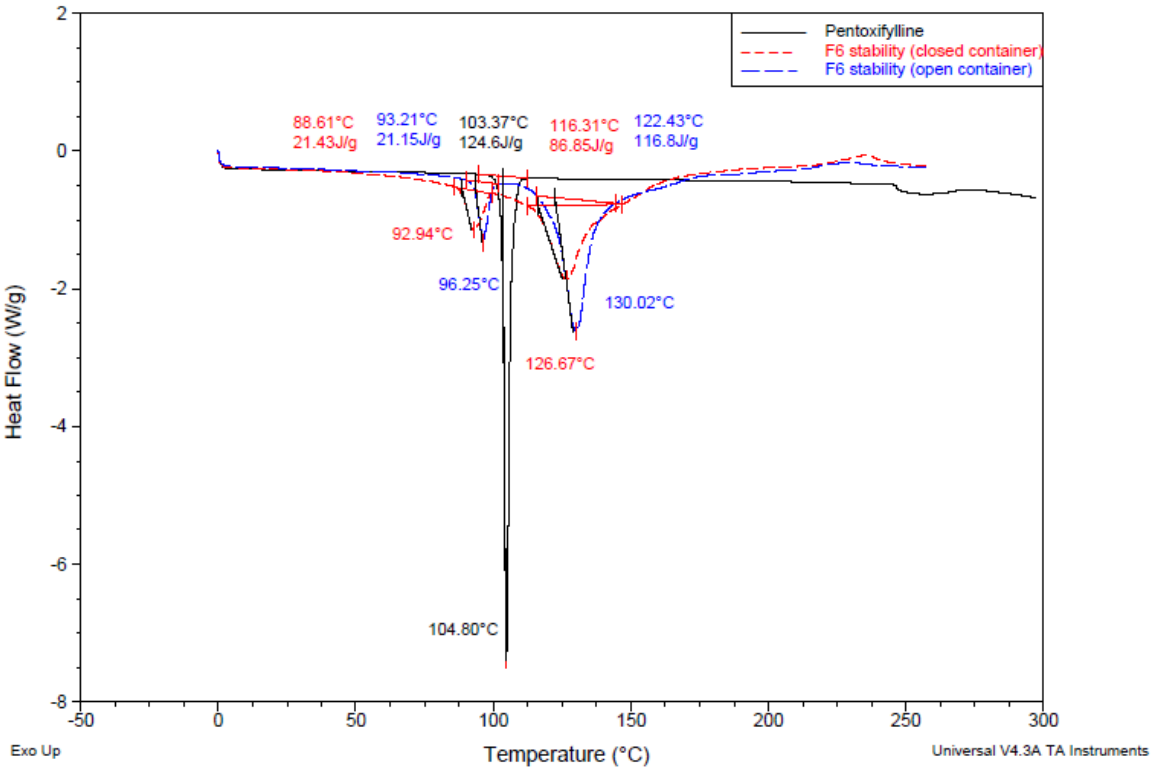


Figure 3-20: DSC thermograms of pure pentoxifylline, F6 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 3-1 or Table 2-7.

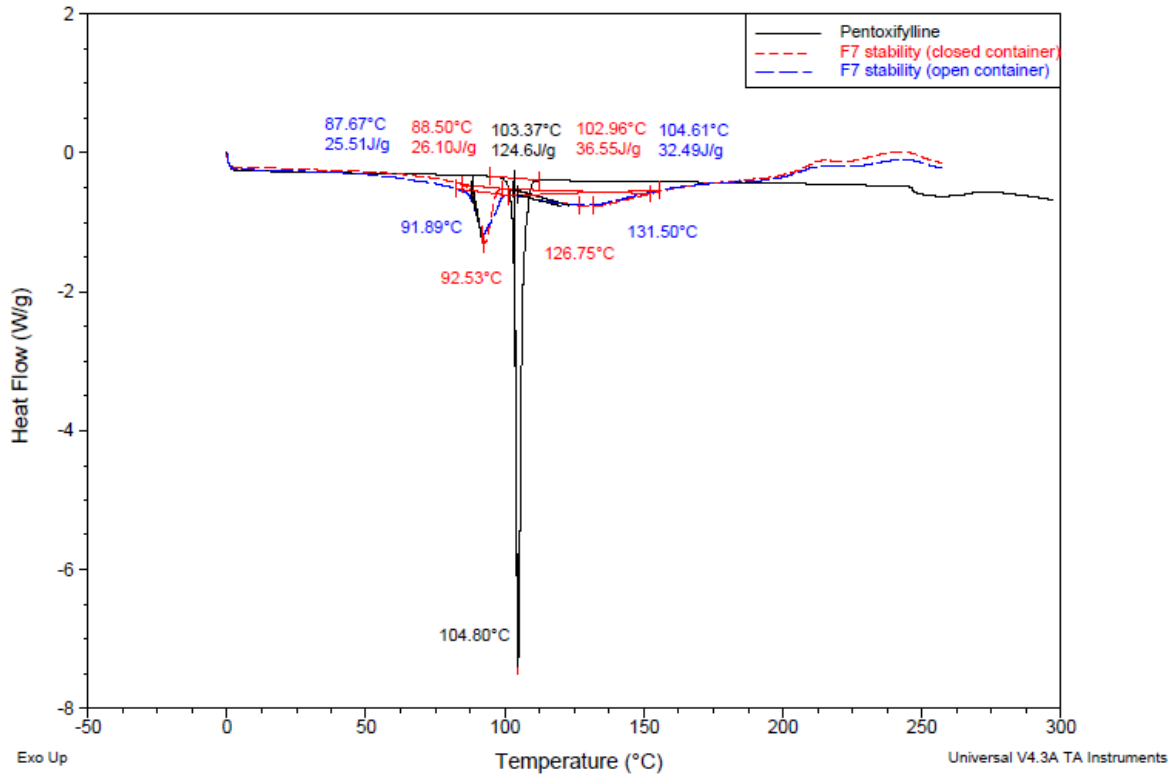


Figure 3-21: DSC thermograms of pure pentoxifylline, F7 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 3-1 or Table 2-7.

3.1.3 Fourier-transform infrared spectroscopy (FTIR)

Fourier-transform infrared spectroscopy was used to study the compatibility of pentoxifylline with excipients (hydroxyethyl cellulose, sodium alginate, Prosolv® 90, sodium bicarbonate, calcium carbonate, sodium carbonate, and magnesium stearate) within the formulations F1-F7 before and after granulation. Figure 3-22 to Figure 3-28 represent the IR spectra of pure pentoxifylline, powder mixture, and granules for all the formulations (F1-F7). Indrayanto et al. (1998) reported that the spectrum of pentoxifylline shows characteristic bands at 2945, 1701, and 1658 cm^{-1} for –CH, –CO, and amide –CO stretching mode, with additional bands present at 1433 cm^{-1} for $–CH_3$ deformation and at 802 cm^{-1} for $–(CH_2)_n–$ skeletal vibration. These characteristic bands were presented (almost at the same wave numbers) at 2943, 1696, and 1655 cm^{-1} for –CH, –CO, and amide –CO stretching mode, with additional bands presented at 1431 cm^{-1} for $–CH_3$ deformation and at 751 cm^{-1} for $–(CH_2)_n–$ skeletal vibration in the spectra of drug-loaded powder mixture and granules of the formulations F1-F7. This confirms the absence of incompatibility between the drug and the formulation excipients.

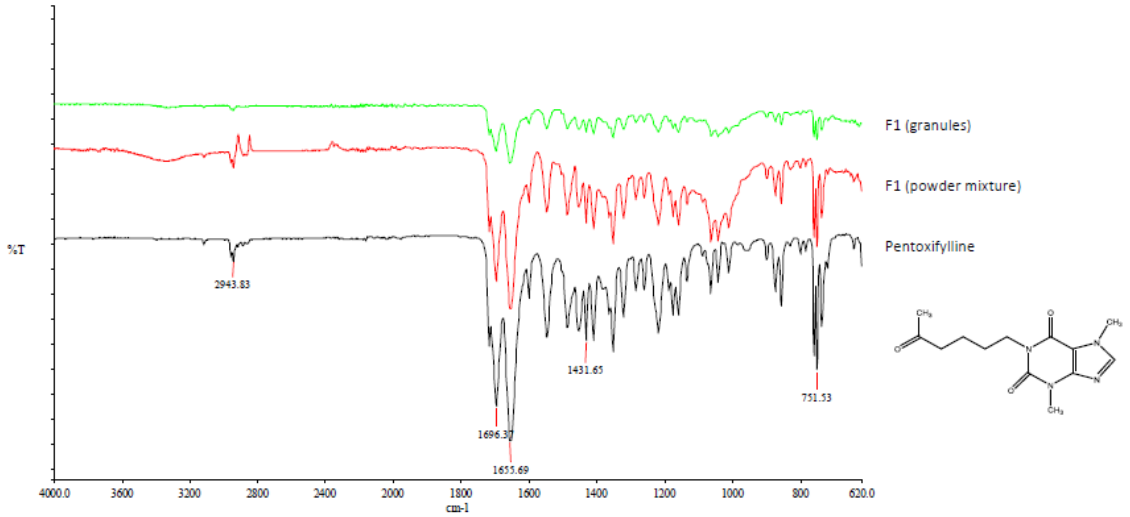


Figure 3-22: FTIR spectra of pure pentoxifylline, F1 powder mixture and F1 granules.
For formulation composition, refer to Table 3-1 or Table 2-7.

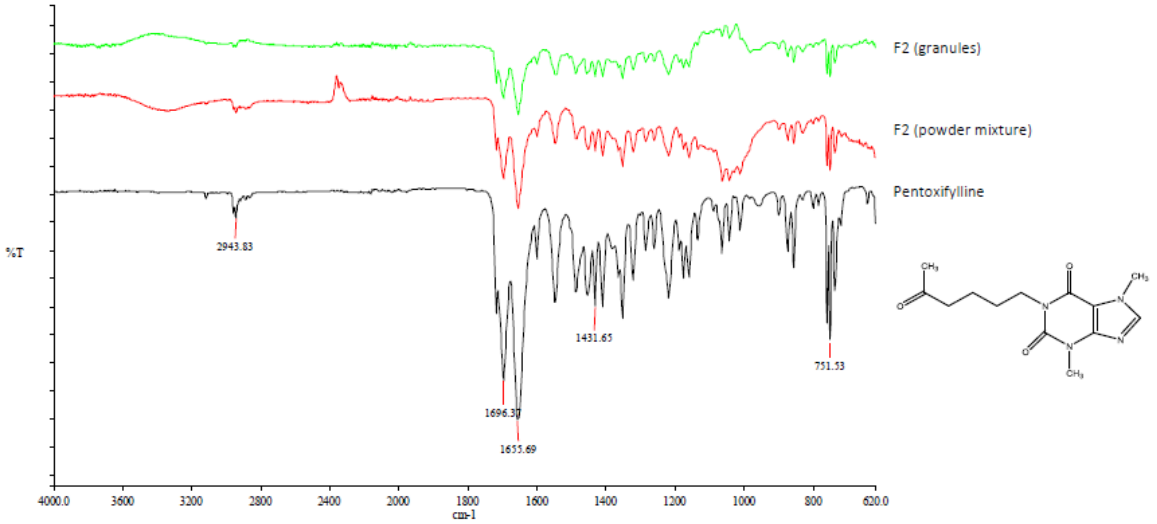


Figure 3-23: FTIR spectra of pure pentoxifylline, F2 powder mixture and F2 granules.

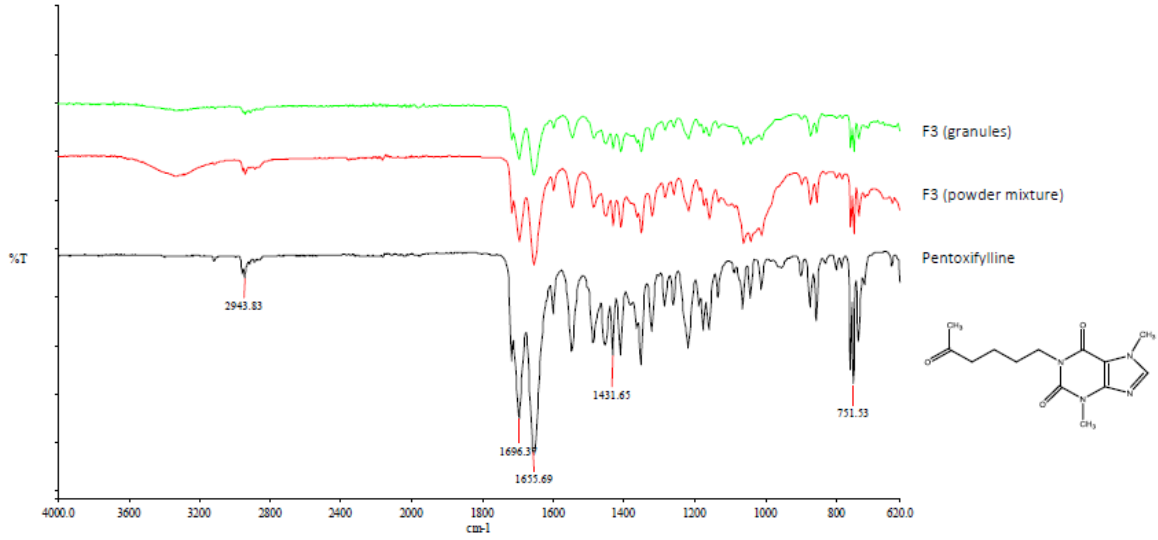


Figure 3-24: FTIR spectra of pure pentoxifylline, F3 powder mixture and F3 granules.
For formulation composition, refer to Table 3-1 or Table 2-7.

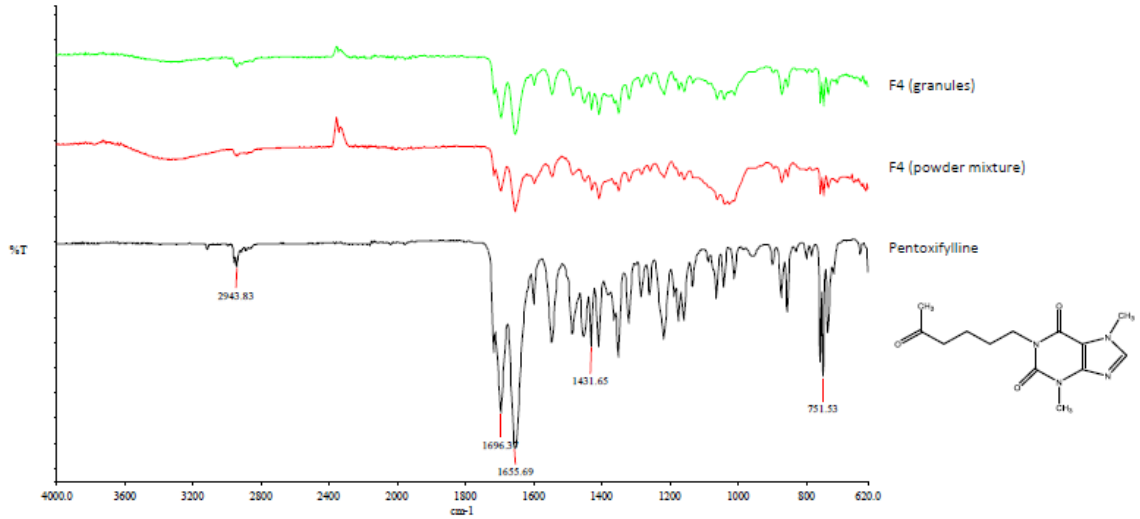


Figure 3-25: FTIR spectra of pure pentoxifylline, F4 powder mixture and F4 granules.

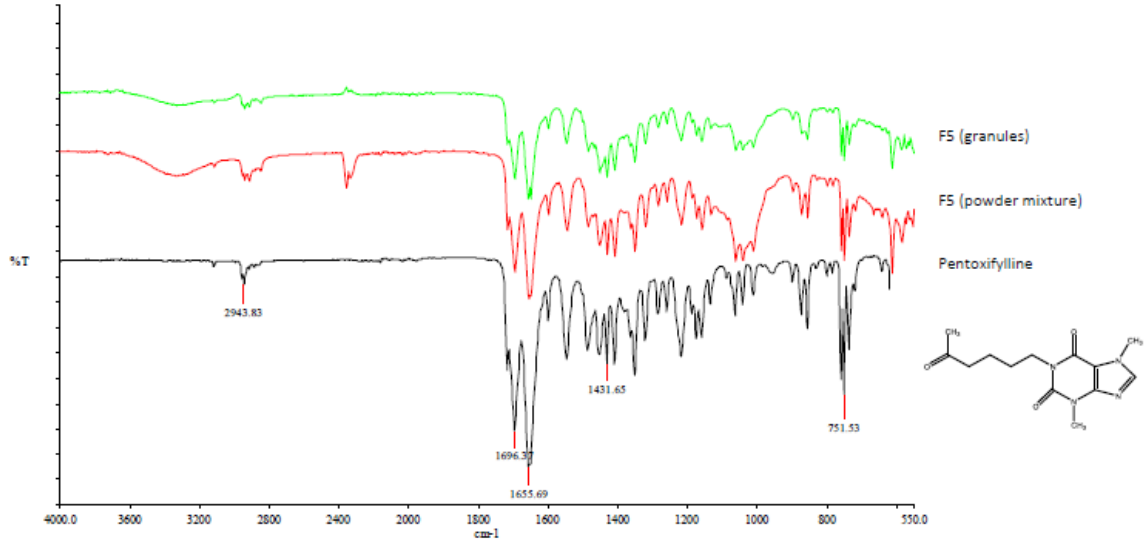


Figure 3-26: FTIR spectra of pure pentoxifylline, F5 powder mixture and F5 granules.
For formulation composition, refer to Table 3-1 or Table 2-7.

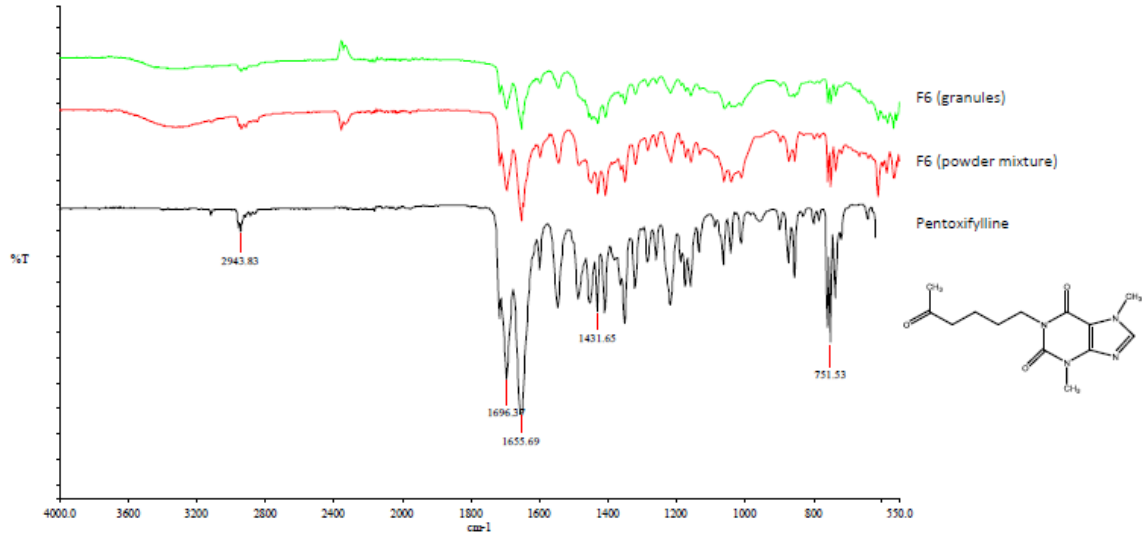


Figure 3-27: FTIR spectra of pure pentoxifylline, F6 powder mixture and F6 granules.

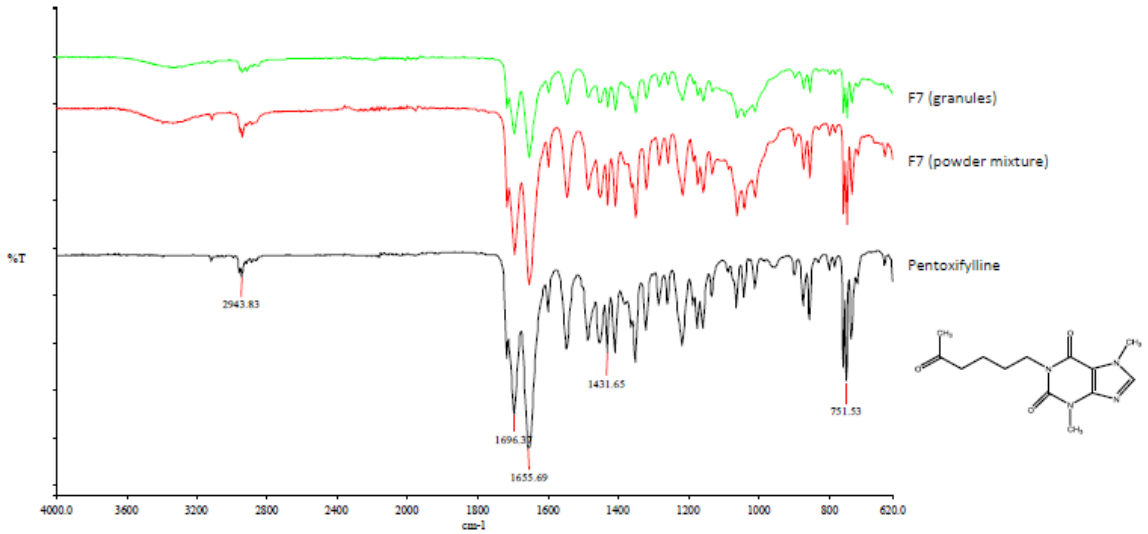


Figure 3-28: FTIR spectra of pure pentoxifylline, F7 powder mixture and F7 granules.
For formulation composition, refer to Table 3-1 or Table 2-7.

Granules of all the formulations (F1-F7) were stored for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers and evaluated by FTIR to investigate possible effects of the stressed conditions on the drug. The IR spectra of (F1-F7) granules after storage are shown in Figure 3-29 to Figure 3-35. The drug characteristic bands of the stability samples (in closed or open containers) of the formulations F1-F7 were presented at 2916–2944 cm^{-1}, 1696–1697 cm^{-1} and 1654–1657 cm^{-1} for –CH, –CO, and amide –CO stretching mode respectively. Additional bands were presented at 1430–1432 cm^{-1} for $–CH_3$ deformation and at 751 cm^{-1} for $–(CH_2)_n–$ skeletal vibration. The IR band at 2359 cm^{-1} was due to carbon dioxide, however, the bands at 3339, 3451, and 3462 cm^{-1} were for water –O–H stretching mode (Stuart, 2004). Generally, a slight variation was noted in comparison with the freshly prepared samples of the formulations F1-F7 (Figure 3-22 to Figure 3-28), still this commonly indicates physical stability of the drug loaded in such formulations for 3 months at 40°C ± 2°C and 80% ± 5% RH in either closed or open containers.

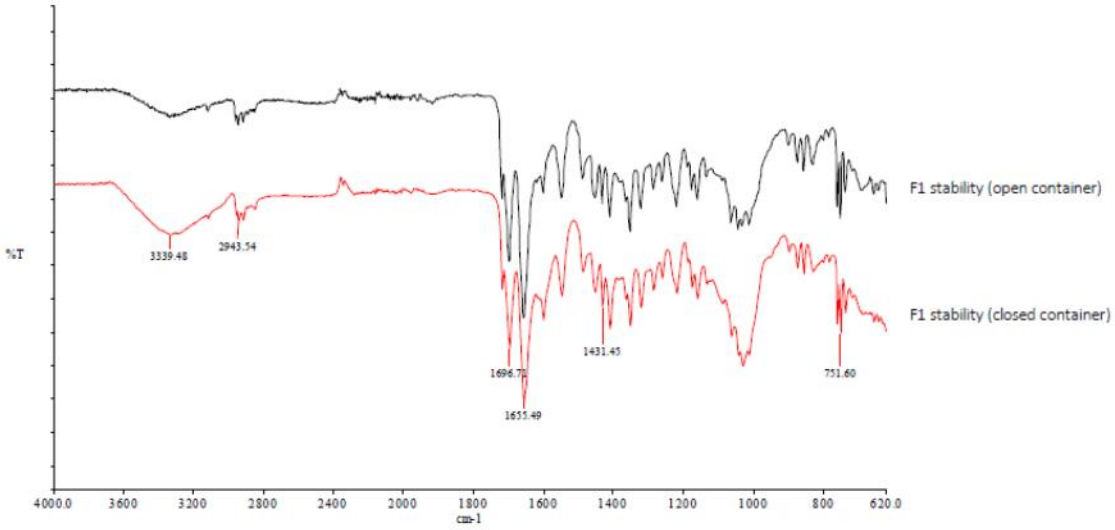


Figure 3-29: FTIR spectra of F1 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 3-1 or Table 2-7.

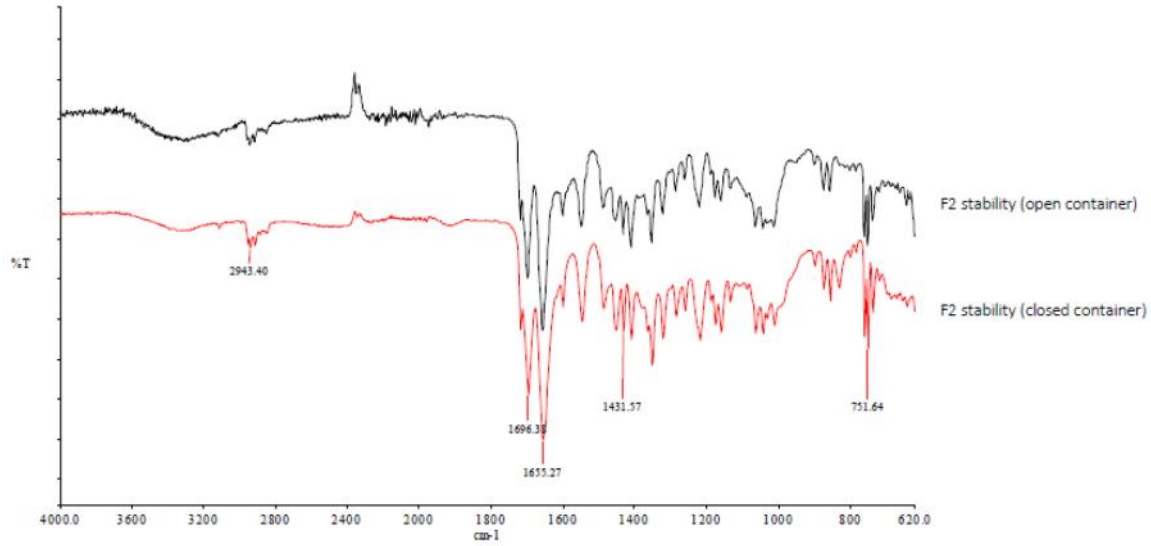


Figure 3-30: FTIR spectra of F2 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

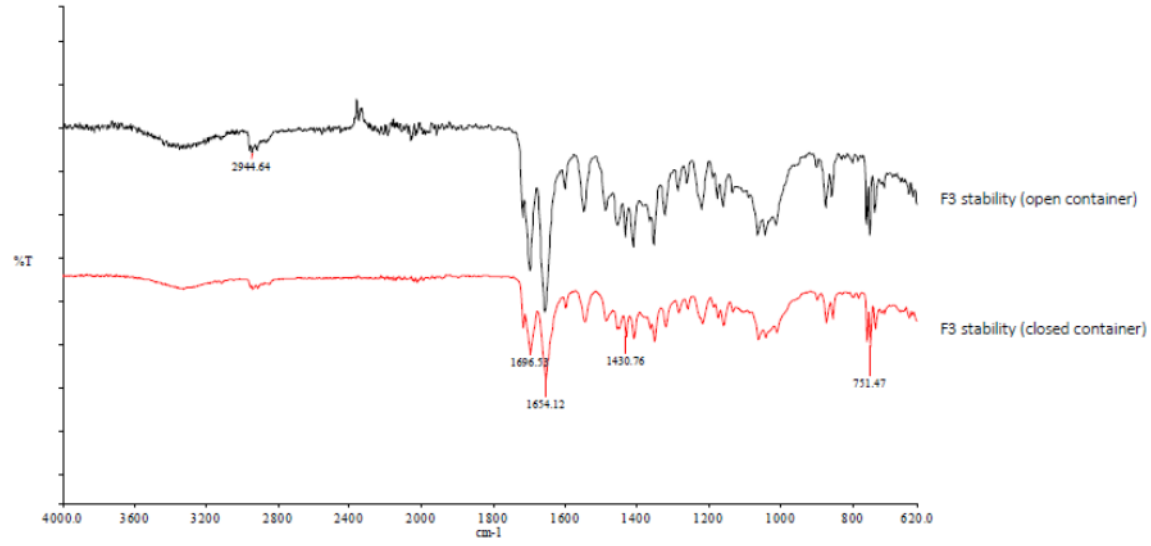


Figure 3-31: FTIR spectra of F3 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 3-1 or Table 2-7.

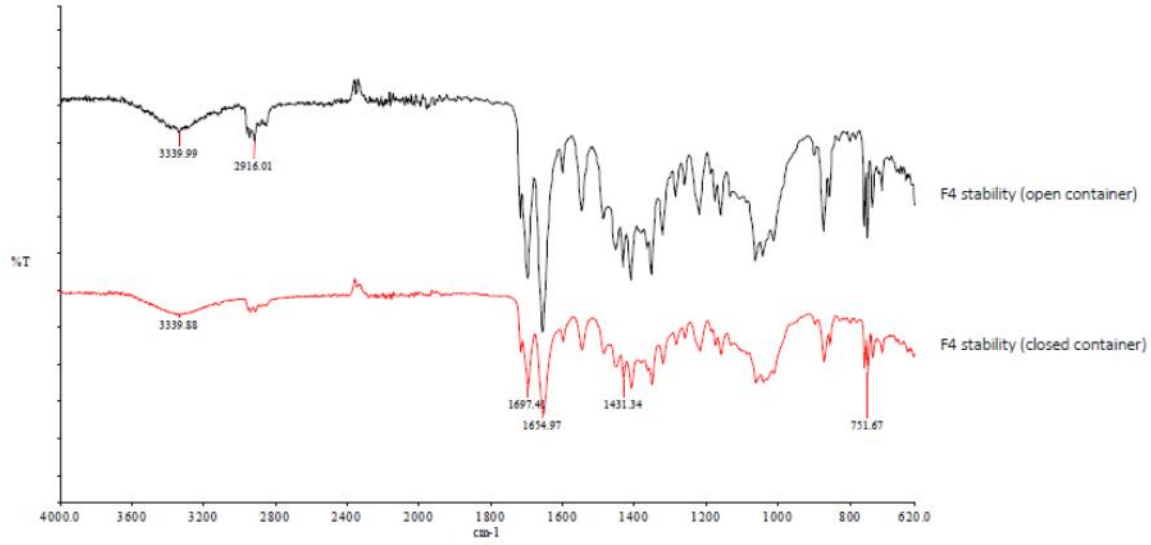


Figure 3-32: FTIR spectra of F4 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

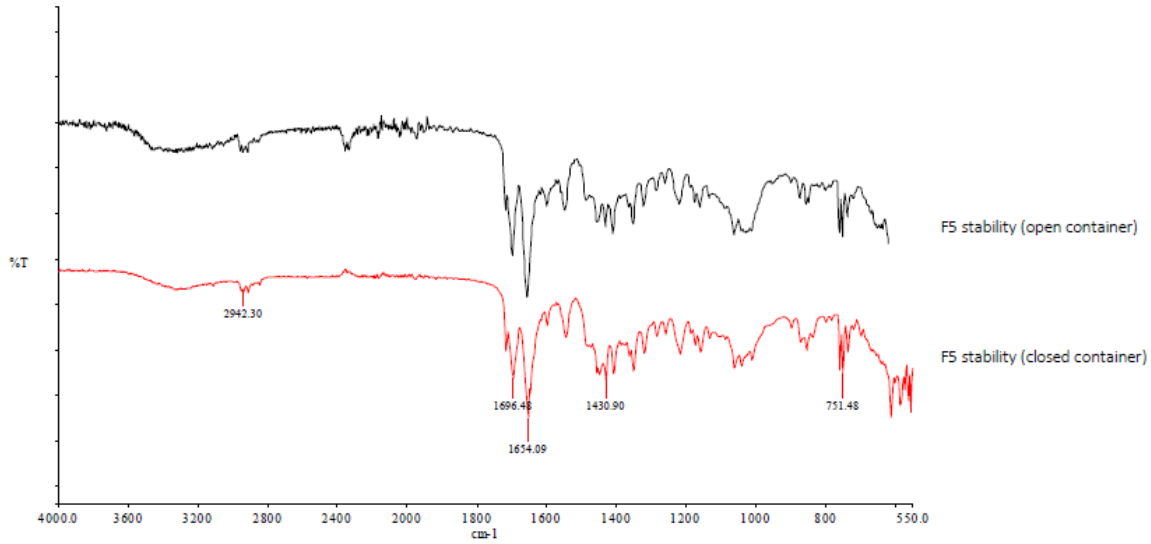


Figure 3-33: FTIR spectra of F5 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 3-1 or Table 2-7.

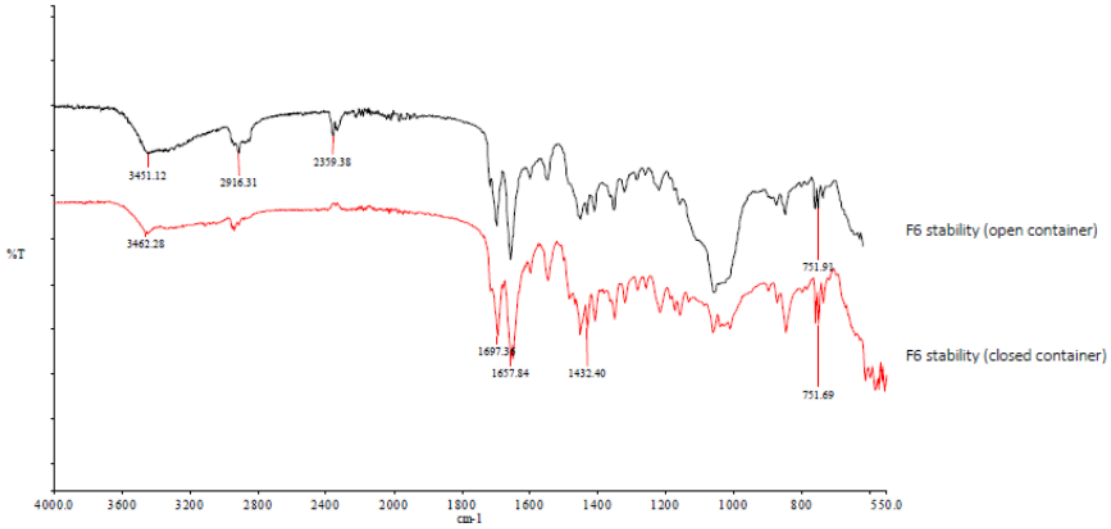


Figure 3-34: FTIR spectra of F6 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

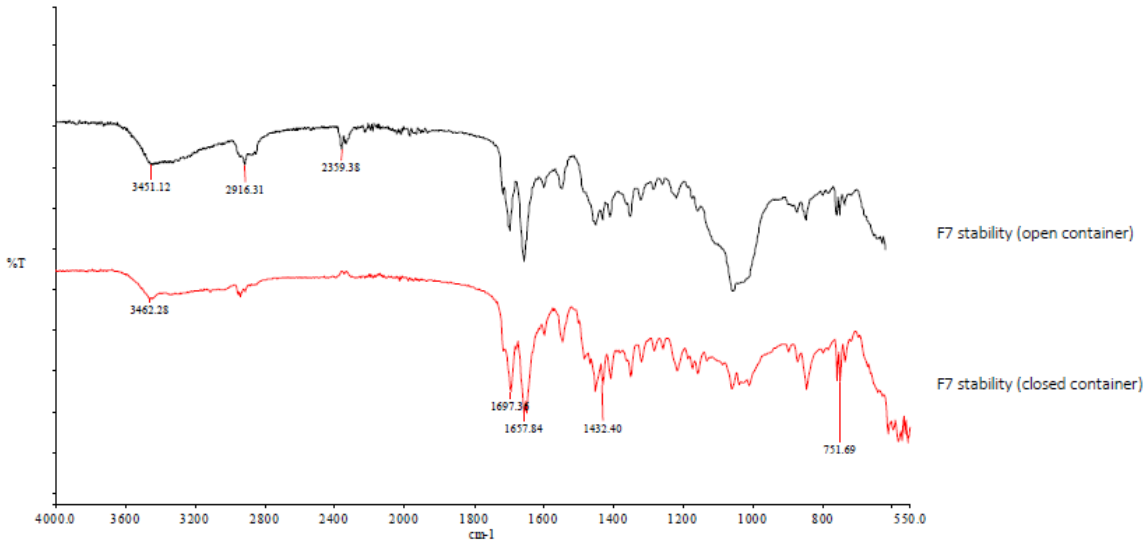


Figure 3-35: FTIR spectra of F7 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 3-1 or Table 2-7.

3.2 Evaluation of floating tablets

Tablets prepared from the granules were evaluated for tablet crushing strength, friability, weight uniformity, drug content uniformity, apparent density, porosity, floating capacity, swelling and erosion, dissolution, release data modeling, and stability testing. But, tablets prepared from powder mixtures were evaluated only for porosity, floating capacity, dissolution, and release data modeling, as these tablets had been compacted manually.

3.2.1 Tablet crushing strength, friability, weight uniformity, and drug content

A pharmaceutical dosage form must satisfy certain standards to claim it to be a quality product. Thus, the finished product quality characteristics related to its manufacturing process such as crushing strength, friability, weight uniformity, and drug content should be taken into account. Pharmacopoeias have laid down the specified limits within which the specification value should fall in order to be compliant as per the standards.

After granulation, tablets of the formulations F1 and F2 were prepared successfully at level A (49–54 N), and level B (54–59 N) of the targeted crushing strength as presented in Table 3-3. Both the formulations could not be prepared at the crushing strength level of 59–64 N; however, this level of crushing strength was achieved with tablets prepared from the powder mixture. It has been reported that the chemical composition of alginates affects their compression behaviour, where alginates with low guluronic acid content behave more elastically than alginates with low mannuronic acid content. In this study the ratio of mannuronic acid to guluronic acid was 1.56. Furthermore, the plasticity of potassium alginates is higher than that of sodium alginates; however, alginates deform elastically (Schmid and Picker-Freyer, 2009). Generally, the granulation process may enhance elastic recovery of alginate molecules after compression, which could explain the inability to prepare tablets of both the formulations F1 and F2 at level (C) of crushing strength after granulation.

Accordingly, the floating capacity, swelling, and drug release rate of drug-loaded matrix of F1 and F2 tablets were evaluated at two crushing strength levels (A and B) instead of A, B, and C.

Tablets of the formulations F3-F7 were successfully pressed automatically at levels A (49-54 N), B (54-59 N), and C (59-64 N) of crushing strength except those of the formulation F5 which were pressed manually. It has been reported in some studies that the crushing strength of tablets prepared from a mixture of two materials can be predicted from the crushing strength of tablets prepared from each of these materials as a linear relationship could be drawn for the composition of the mixture (Rubinstein and Jackson, 1987; Sheikh-Salem et al., 1988). In other studies, tablet crushing strength exceeds the crushing strength of tablets prepared from individual materials (Gren and Nyström, 1996; Olsson et al., 1998), or it becomes lower than that of the individual components (Sheikh-Salem et al., 1988; Leuenberger, 1982).

F3 and F4 formulations based on calcium carbonate were pressed successfully at all crushing strength levels and the good bonding capacity under compression of calcium carbonate (Mattsson and Nyström, 2000) and its role as filler in pharmaceutical formulations (Armstrong, 2009) could explain this. Although pressing sodium carbonate alone shows a good bonding capacity (Sonnergaard, 2006); tablets which contain sodium carbonate at 10% (w/w) (F5) could not be pressed automatically. Increasing the concentration to 20% (w/w) (F6) overcame this issue, and tablets were successfully pressed at levels A, B, and C of crushing strength. Generally, this suggests that compressibility of these floating formulations (F5 and F6) is dependent by the concentration of sodium carbonate. Tablets of F7 formulation without any gassing agent were successfully pressed at all required levels of crushing strength. However, the granulation process may enhance the elastic recovery of alginate molecules after compression, which could explain the inability to prepare tablets based on sodium bicarbonate as a gassing agent even at a higher level (59–64 N) of crushing strength following the granulation. In addition, it has been reported that sodium bicarbonate has a lower bonding capacity than sodium carbonate (Sonnergaard, 2006) and calcium carbonate (Mattsson and Nyström, 2000).

Hence, it is worth testing sodium carbonate and calcium carbonate as gassing agents as per this study, especially as the available information in the literature on using them within the floating tablets is inadequate.

Results of friability (%), average weight (g), and average drug content (mg) of prepared matrix tablets of the formulations F1-F7 are presented in Table 3-3. For the friability test, there were no signs of cracked, split, or broken tablets at the end of the test. Additionally, the friability results of the formulations F1, F2, F3, F6, and F7 fitted the (BP) limits, as the tablets had friability values < 1% (BP, 2015), however, the formulations F4 and F5 exceeded the BP limit of friability as results were (1.11% - 1.34%), and (1.14% - 1.16%) respectively. Generally, as the tablet crushing strength level increases, the mass loss percentage decreases in all the formulations. Consequently, using higher compression force can change the friability results to fit BP limits.

All prepared tablets of the formulations F1-F7 (Table 3-3) complied with BP specifications (BP, 2015) with respect to weight uniformity test. For content uniformity test (Table 3-3) results were in the acceptable range, indicating that all matrix tablets fitted the (BP) criteria in which each tablet drug content was between 85% and 115% of related average content (BP, 2015).

Table 3-3: Properties of pentoxifylline floating tablets of the formulations F1-F7.

Formulation	Crushing strength level	Crushing strength (N)[a]	Friability (%)	Tablet weight (g)[b]	Drug content (mg)[a]
F1	(A)	50.99 ± 0.27	0.80	0.297 ± 0.00	57.82 ± 1.63
	(B)	55.90 ± 0.33	0.60	0.292 ± 0.00	57.13 ± 0.64
F2	(A)	49.03 ± 0.24	0.88	0.318 ± 0.01	56.63 ± 0.97
	(B)	57.86 ± 0.31	0.66	0.306 ± 0.00	53.43 ± 1.45
F3	(A)	51.98 ± 0.16	0.96	0.305 ± 0.00	61.22 ± 0.57
	(B)	55.90 ± 0.24	0.94	0.302 ± 0.00	60.89 ± 0.93
	(C)	59.82 ± 0.17	0.82	0.302 ± 0.00	63.24 ± 1.51
F4	(A)	53.94 ± 0.40	1.34	0.343 ± 0.00	61.78 ± 1.28
	(B)	55.90 ± 0.34	1.28	0.342 ± 0.00	63.99 ± 1.57
	(C)	62.76 ± 0.23	1.11	0.343 ± 0.00	65.69 ± 1.53
F5	(A)	50.03 ± 0.27	1.16	0.299 ± 0.00	58.34 ± 1.81
	(B)	55.90 ± 0.69	1.15	0.300 ± 0.00	59.74 ± 2.13
	(C)	59.82 ± 0.85	1.14	0.298 ± 0.00	58.57 ± 2.90
F6	(A)	52.96 ± 0.80	0.89	0.315 ± 0.00	56.91 ± 2.12
	(B)	57.86 ± 0.35	0.57	0.335 ± 0.01	57.55 ± 1.89
	(C)	63.74 ± 0.44	0.56	0.349 ± 0.00	56.95 ± 1.77
F7	(A)	49.03 ± 0.52	0.79	0.296 ± 0.00	69.15 ± 0.80
	(B)	54.13 ± 0.36	0.57	0.296 ± 0.01	69.38 ± 1.15
	(C)	59.04 ± 0.23	0.47	0.305 ± 0.02	69.47 ± 0.76

Notes: [a]The data represents the mean ± SD of 10 determinations. [b]The data represents the mean ± SD of 20 determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations. For formulation composition, refer to Table 3-1 or Table 2-7.

3.2.2 Tablet apparent density and porosity

For floating drug delivery systems it is important to have a density < 1.004 g/cm^3 in order to initiate buoyancy on the release medium (Whitehead et al., 1998; Bardonnet et al., 2006). Upon water uptake, chains of hydrophilic polymers move apart from each other resulting in both weight and volume increases. Although, this will reduce the density of the swollen matrix, the rate of medium uptake depends upon the matrix porosity level. Therefore, the apparent density and porosity results of the tablets were used to evaluate the magnitude of the different formulation factors (crushing strength, the wet granulation, type and ratio of gas forming agents) on the prepared tablets.

The apparent density of the prepared tablets of the formulations F1-F7 were calculated by equation (3) (Chapter 2, section 2.2.6.2), and the results are shown in Figure 3-36 (for F1 and F2), Figure 3-37 (for F3 and F4), Figure 3-38 (for F5 and F6), and Figure 3-39 (for F7). Generally, increasing tablet crushing strength level increased significantly (p<0.05) the apparent density of all the tablets prepared from the powder mixture or the granules of the formulations F1, F2, F3, F4 and F7. However, the effect was not significant (P>0.05) for those of the formulations F5 and F6 except between the extreme margins of the crushing strength (levels A and C). This may be explained by the reduction in tablet thicknesses as particles became more adjacent to each other by increasing the compression force as shown in Table 3-4.

The granulation process caused a significant (P<0.05) decrease in tablet apparent density of F1 formulation at both crushing strength levels. In addition, a significant (P=0.001) decrease was noted in tablet apparent density results of F2 formulation prepared at crushing strength level (A); however, a non-significant (P=0.363) decrease was noted at level (B) of crushing strength. A non-significant (P>0.05) decrease in the apparent density results was observed in the formulations F6 and F7. In contrast, the granulation process caused a significant (P<0.05) increase in tablet apparent density of the formulations F3, F4, and F5 at all crushing strength levels.

For the formulations F1 and F2 (based on sodium bicarbonate gassing agent), as shown in Table 3-4, tablet thicknesses after the granulation process were increased in comparison to those before the granulation process which agree with the effect of the granulation process on alginate molecules elastic recovery after compression. This tablet thickness difference was reduced when sodium bicarbonate level was increased to 20% (w/w) (for F2 formulation) especially at crushing strength level (B). This indicates that the elastic recovery effect of sodium alginate (after the granulation process) was reduced. The high true density of sodium bicarbonate (Cable, 2009), which is 2.173 g/cm^3, in addition to the high compression pressure of level (B) may inverse the elastic recovery effect of the granulation process on the apparent density results of F2 formulation (Figure 3-36). The enhancement of sodium alginate molecules elastic recovery after compression following the granulation also explains the results of the formulation F7 (0% (w/w) gassing agent), where tablet thicknesses after granulation increased (Table 3-4) whilst the apparent densities decreased (Figure 3-39). This also explains the apparent density results of F6 (20% (w/w) sodium carbonate) (Figure 3-38).

The apparent density of F5 (10% (w/w) sodium carbonate) tablets (Figure 3-38) increased after the granulation. It has been reported that the amount of stress developed at the points of local deformation depend upon several factors such as physical properties of the material, force magnitude, rate of application, and contact time (Wray, 1992). F5 formulation was pressed manually after the granulation; therefore, the longer contact time between the granules and the punches of the tableting machine may overcome the alginate elastic recovery and explains the increase in the apparent density results.

The tablet thicknesses of F3 (10% (w/w)) and F4 (20% (w/w)) calcium carbonate based tablets decreased after the granulation (Table 3-4) which increased their apparent densities (Figure 3-37). This may be explained by the good compressibility of calcium carbonate that may overcome the effect of sodium alginate elastic recovery after compression following the granulation process; this also explains the benefits of using calcium carbonate in effervescent floating tablets.

Changing calcium carbonate concentration from 10% to 20% (w/w) significantly (P<0.05) increased the apparent density of all the tablets prepared from the powder mixture or the granules. Raising sodium carbonate concentration to 20% (w/w) significantly (P<0.05) increased the apparent densities of those tablets prepared from the powder mixture only. This may be explained by the high specific gravities of calcium carbonate and sodium carbonate which are 2.70 (Armstrong, 2009) and 2.53 (Hapgood, 2009) respectively, which also agrees with the results of sodium bicarbonate based tablets discussed earlier.

A non-significant (P>0.05) decrease in the apparent densities of tablets prepared from granules due to changing sodium carbonate concentration from 10% to 20% (w/w) was noted. As stated above, the manual pressing of F5 (10% (w/w) sodium carbonate) formulation could enhance the reduction of their tablet thicknesses with a higher ratio than that of F6 (20% (w/w) sodium carbonate) tablets which could explain this reduction in their densities.

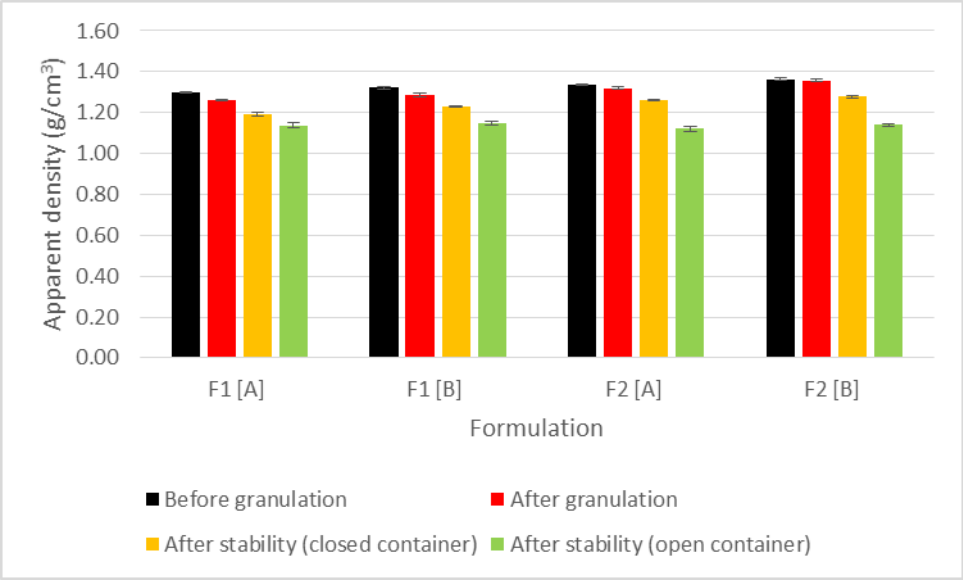


Figure 3-36: Apparent density of F1 and F2 tablets before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).
Note: The data represents the mean ± SD of six determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N).

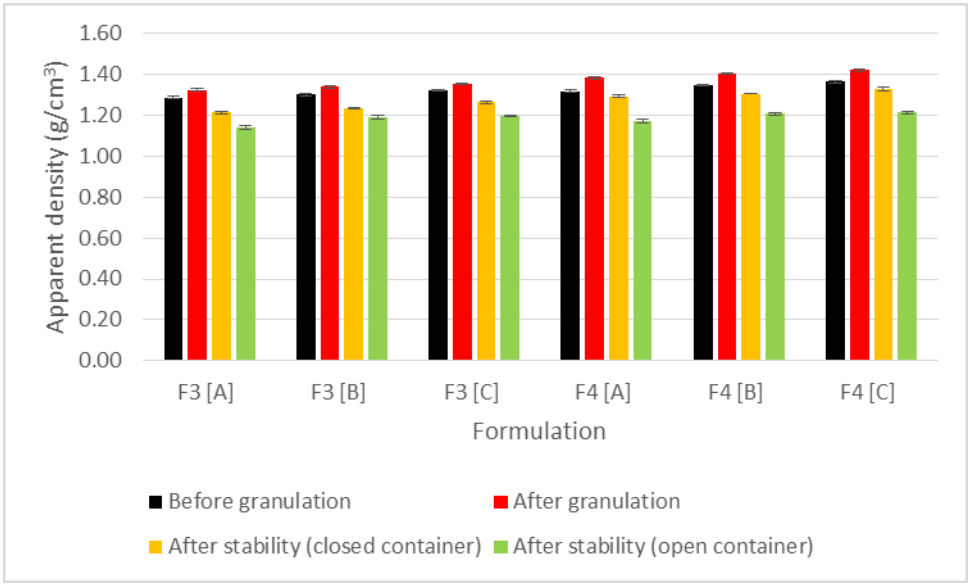


Figure 3-37: Apparent density of F3 and F4 tablets before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).
Note: The data represents the mean ± SD of six determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 3-1 or Table 2-7.

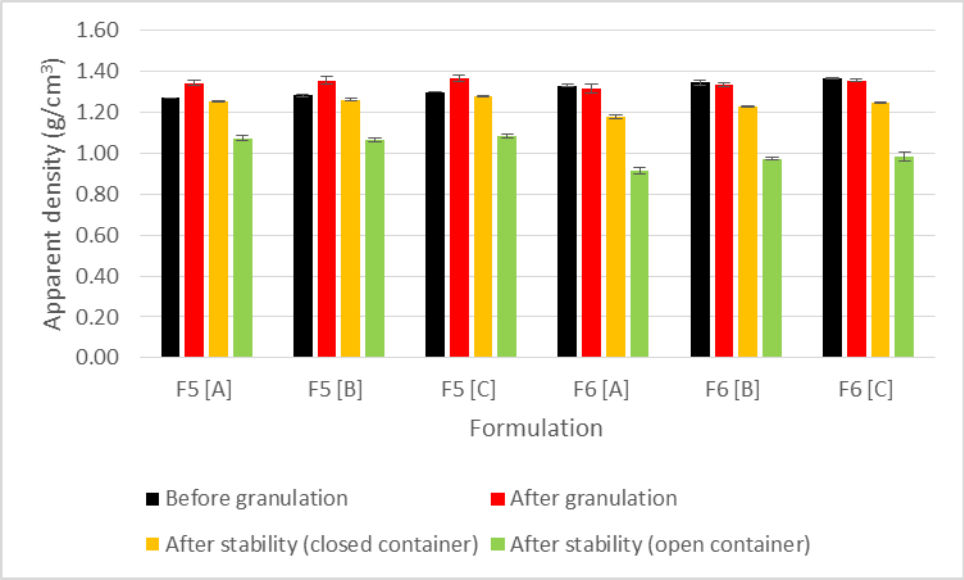


Figure 3-38: Apparent density of F5 and F6 tablets before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).
Note: The data represents the mean ± SD of six determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).

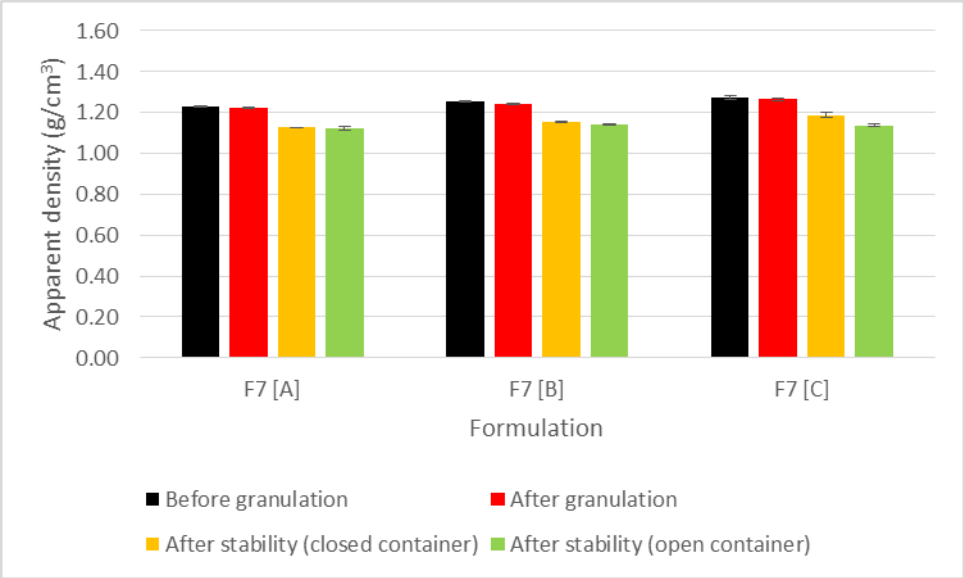


Figure 3-39: Apparent density of F7 tablets before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).
Note: The data represents the mean ± SD of six determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 3-1 or Table 2-7.

Table 3-4: F1-F7 tablets thickness before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Tablet thickness (cm)			
		Origin of prepared tablets			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F1	(A)	0.294 ± 0.01	0.303 ± 0.01	0.323 ± 0.01	0.326 ± 0.03
	(B)	0.289 ± 0.01	0.298 ± 0.02	0.315 ± 0.01	0.326 ± 0.02
F2	(A)	0322 ± 0.01	0.327 ± 0.00	0.345 ± 0.00	0.366 ± 0.01
	(B)	0.316 ± 0.01	0.318 ± 0.02	0.340 ± 0.02	0.357 ± 0.03
F3	(A)	0.299 ± 0.01	0.285 ± 0.02	0.317 ± 0.01	0.342 ± 0.03
	(B)	0.293 ± 0.01	0.282 ± 0.01	0.312 ± 0.01	0.336 ± 0.02
	(C)	0.290 ± 0.01	0.282 ± 0.01	0.307 ± 0.01	0.323 ± 0.02
F4	(A)	0.326 ± 0.01	0.311 ± 0.01	0.334 ± 0.02	0.369 ± 0.03
	(B)	0.319 ± 0.01	0.307 ± 0.01	0.331 ± 0.01	0.363 ± 0.04
	(C)	0.317 ± 0.01	0.304 ± 0.01	0.326 ± 0.03	0.357 ± 0.02
F5	(A)	0.298 ± 0.00	0.286 ± 0.01	0.332 ± 0.02	0.351 ± 0.01
	(B)	0.295 ± 0.00	0.283 ± 0.04	0.327 ± 0.02	0.350 ± 0.04
	(C)	0.292 ± 0.01	0.282 ± 0.04	0.327 ± 0.01	0.347 ± 0.03
F6	(A)	0.326 ± 0.01	0.329 ± 0.08	0.365 ± 0.02	0.421 ± 0.04
	(B)	0.322 ± 0.02	0.324 ± 0.01	0.354 ± 0.02	0.412 ± 0.02
	(C)	0.319 ± 0.01	0.320 ± 0.01	0.347 ± 0.01	0.405 ± 0.02
F7	(A)	0.305 ± 0.01	0.318 ± 0.02	0.342 ± 0.01	0.358 ± 0.02
	(B)	0.301 ± 0.01	0.313 ± 0.01	0.336 ± 0.01	0.353 ± 0.05
	(C)	0.297 ± 0.02	0.303 ± 0.01	0.326 ± 0.01	0.350 ± 0.01

Note: The data represents the mean ± SD. of three determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations. For formulation composition, refer to Table 3-1 or Table 2-7.

A statistical analysis of the tablets apparent density after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers was undertaken. Generally, storage in closed containers is reflective to the storage conditions of the packed pharmaceutical products; however, storage in open containers may apply further harsh conditions on the pharmaceutical dosage forms as they become in direct contact with an elevated level of heat and humidity which may accelerate degradation of unstable ingredients. Consequently, it is worth to study samples physical stability in both closed and open containers. As discussed earlier (Chapter 2, section 2.2.4), tablets were compacted manually using the powder mixtures and automatically using the granules. The good flow properties of the granules which facilitate their automatic pressing made them more suitable to benefit the pharmaceutical industry, therefore, only the tablets prepared from the granules were subjected to stability studies.

Tablet apparent densities after stability (in closed or open container) are presented in Figure 3-36 to Figure 3-39. The tablets apparent densities decreased significantly (P<0.001) in all the formulations (F1-F7) in either open or closed containers in comparison to the freshly prepared samples. This is also explained by the increase in tablets thicknesses after 3 months storage as presented in Table 3-4. It has been reported that the crushing strength, disintegration and dissolution rate of tablets could change with time as part of the aging process of pharmaceutical tablets (Lowenthal, 1972; Karehill and Nystrom, 1990; Babu and Pandit, 1999). Tablets stress relaxation after compression which depends upon the deformation mechanism could enhance this aging process (Hwang et al., 2001). Moreover, an elastically deformed material usually possesses a significant internal pressure following compression, and this internal pressure will be released over time (Rubinstein and Jackson, 1987). Consequently, during storage, this excess internal pressure may reach equilibrium with the external conditions such as temperature and humidity resulting in various physicomechanical characteristics. Hwang et al. (2001) studied tablet relaxation and physicomechanical stability of lactose, microcrystalline cellulose, and dibasic calcium phosphate directly compressed tablets by evaluating the percentage of change in thickness, crushing strength, and friability of freshly prepared tablets and those stored for one month at 25°C and 60% RH and 40°C and 75% RH.

In this work, the resulted change in the tablets thickness was used to evaluate the stress relaxation effect by calculating tablet apparent density values. The reduction of the apparent density results was higher in open containers than those of closed ones. A study by Aljaberi et al (2013) suggested that the direct exposure to a stressful humidity level (75% RH) causes a higher increase in tablet‘s dimensions when compared to those stored in closed containers.

Regarding porosity, tablet porosity percentages of the formulations F1-F7 are presented in Figure 3-40. Generally, increasing tablet crushing strength level decreased the porosity percentages of all the formulations F1-F7. This effect was significant (P<0.05) in F1 and F2 formulations and non-significant (P>0.05) in F3-F7 formulations except between the extreme levels of crushing strength (A and C). This reduction in the tablet porosity percentages may be explained by the tablet thickness results presented in Table 3-4, where increasing the tablet crushing strength level reduced the tablet thicknesses as particles became strongly bonding due to being closer which agrees with a previous study of effect of the tablet radial tensile strength to the tablet porosity (Sebahatu and Alderborn, 1999).

The granulation process decreased the tablet porosity significantly (P<0.05) in the formulations F1, F5, and F7, and non-significantly (P>0.05) in F2 formulation. In contrast, the porosity significantly increased (P<0.05) in the formulations F3 and F6, and non-significantly (P>0.05) in F4 formulation following the granulation process (Figure 3-40).

The effect of different treatment conditions on the production of cross-linked drug alginate granules has been reported by (Mukhopadhyay et al., 2008). This study demonstrated that increasing the water binder volume decreases porosity during the wet massing stage and this reduction in porosity could delay dissolution medium entrapment through the matrix at an early stage of the dissolution test. This may explain the results of F7 (0% w/w gassing agent) formulation where the granulation reduced the tablet porosity. However, tablet porosity of calcium carbonate based formulations (F3 and F4) increased after the granulation. This may be related to calcium carbonate insolubility in water (Armstrong, 2009) which could enhance the formation of voids between adjacent molecules during the wet massing stage with water.

In contrast, sodium carbonate as a gassing agent is a water-soluble material (Hapgood, 2009) which may form a homogenous mass with the hydrophilic polymeric (1:1) binary mixture of hydroxyethyl cellulose and sodium alginate during the wet massing process. This could explain the tablets porosity reduction at 10% (w/w) level for F5 formulation after the granulation. This complies with the results of the formulations F1 and F2 based on sodium bicarbonate which is also water-soluble (Cable, 2009). However, the significant (P<0.05) elevation in porosity results of F6 tablets could be explained by the hygroscopic properties of sodium carbonate, where one mole of sodium carbonate could gradually absorb one mole of water on exposure to air (Hapgood, 2009). Raising sodium carbonate concentration means more water molecules may be absorbed during the wet massing step and evaporated easily due to the drying step of the granulation process. Therefore the granules porosity will be increased. This agrees with the moisture content (%) results before and after the granulation (Table 3-2). The moisture content (%) for the formulations F5 (10% (w/w)) and F6 (20% (w/w)) based on sodium carbonate gassing agent were 5.70% ± 0.14 and 5.51% ± 0.12 before granulation and became 4.53% ± 0.19 and 4.11% ± 0.16 after the granulation respectively. Obviously, the moisture content (%) decreased in both formulations after the granulation, but more moisture lost was noted in F6 formulation based on 20% (w/w) sodium carbonate.

Increasing calcium carbonate concentration from 10% (w/w) (F3) to 20% (w/w) (F4) significantly (P<0.05) increased the porosity percentage of the tablets prepared either from the powder mixture or the granules (Figure 3-40). It has been reported that calcium carbonate mainly undergoes fragmentation when compressed (Roberts and Rowe, 1985); fragmentation establishes a large number of bonding points between calcium carbonate molecules during volume reduction, which will maintain the porosity of such tablets relatively high (Mattsson and Nyström, 2000). This may explain the increase in the tablet porosity results due to the change in calcium carbonate concentration in tablets prepared from either the powder mixture or the granules.

A significant (P<0.05) increase in porosity was noted when sodium carbonate concentration was raised from 10% (w/w) (F5) to 20% (w/w) (F6) in the tablets prepared from the granules, nonetheless, the porosity significantly (P<0.05) decreased for the tablets prepared from the powder mixture (Figure 3-40). Regarding the tablets prepared from the powder mixture, raising sodium carbonate concentration from 10% (w/w) (F5) to 20% (w/w) (F6) could enhance more voids between molecules being filled after compression, which may reduce the porosity. This also conforms to the results of sodium bicarbonate based tablets as increasing the level of sodium bicarbonate from 10% (w/w) (F1) to 20% (w/w) (F2) significantly (P<0.05) decreased all the tablet porosity results prepared from the powder mixture or the granules. However, the significant (P<0.05) increase in the porosity values of the tablets prepared from the granules may be explained by the hygroscopic properties of sodium carbonate as discussed earlier.

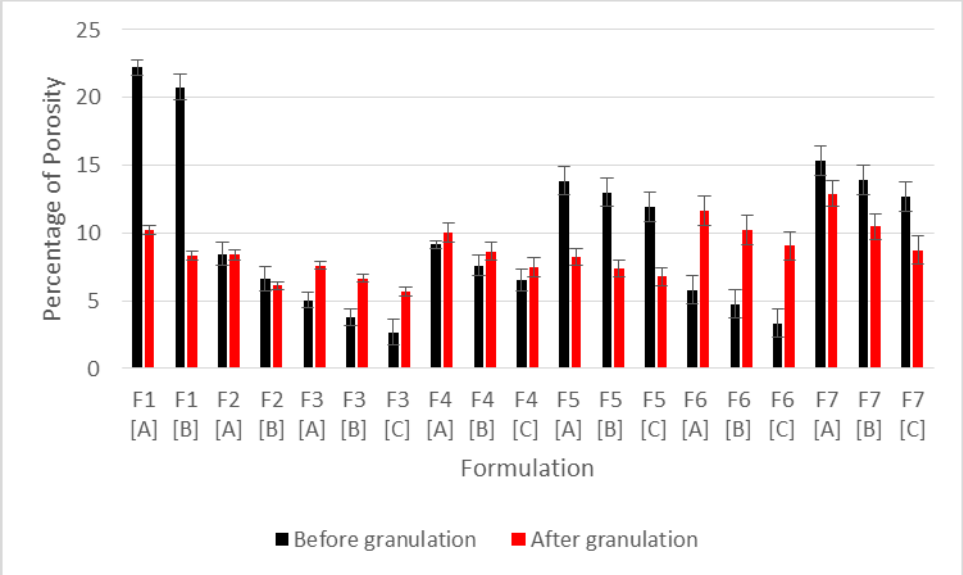


Figure 3-40: Porosity percentage of the formulations F1-F7 before and after granulation.
Note: The data represents the mean ± SD. of three determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations.
For formulation composition, refer to Table 3-1 or Table 2-7.

3.2.3 Tablet floating capacity

Floating drug delivery systems, as shown in (Figure 3-41), aim to maintain floating for a long period of time on the release medium of the stomach without affecting the gastric emptying time. Normally in human, the gastric emptying of large single unit dosage forms is changeable in the fasted state. It depends on the time of arrival in the stomach in relation to activity of inter digestive myloelectric cycle, but a longer time is required for the gastric emptying in the fed conditions. All undigested materials are normally emptied out of the stomach and down the small intestine at the end of the gastric emptying process (Wilson and Washington, 1989)**.** It is important for floating tablets to avoid premature sweeping from their major absorption zone of the stomach and upper intestine, which could be managed by achieving the least possible lag time, and longer floating duration.

All the tablets (F1-F7) were tested for the floating capacity under the same conditions and using the same apparatus for the *in vitro* studies. F7 tablets had no floating capacity, as they do not contain any gassing agent. Sodium bicarbonate, calcium carbonate and sodium carbonate as gassing agents enhanced the floating behaviour of the formulated tablets. Carbon dioxide is generated by reaction with the acidic dissolution medium (0.1 M HCl) and entrapped in the formed gel layer around the swollen tablets. Figure 3-42 reveals the floating of F4 tablets prepared at 49–54 N crushing strength, as an example, a floating lag time was ~ 7 min and tablets kept floating for > 24 h. Table 3-5 and Table 3-6 represent all the prepared tablets floating lag time and floating duration results respectively.

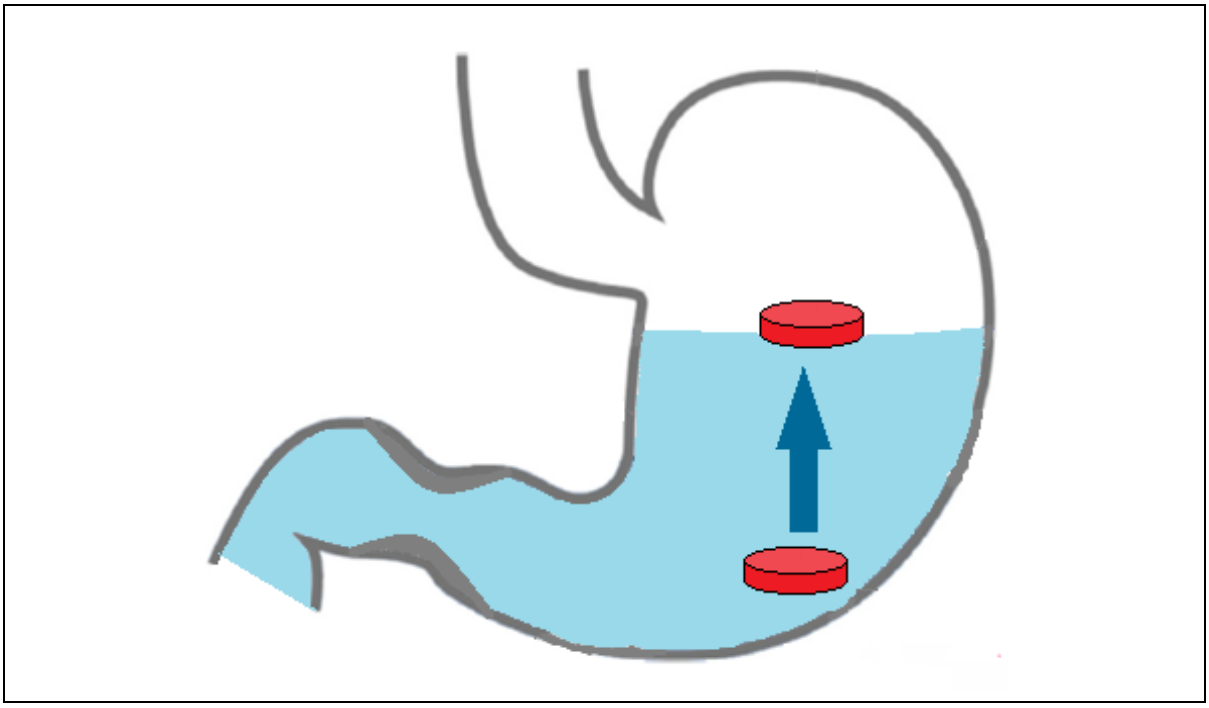
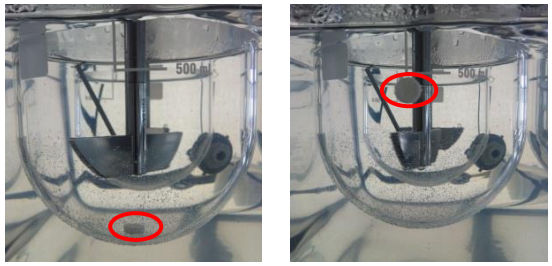


Figure 3-41: Schematic presentation of gastroretentive floating system.



At zero, initial, time After floating

Figure 3-42: Floating process of F4 tablet prepared at 49–54 N crushing strength (marked with a circle) during drug release.

Table 3-5: Floating lag-time of the formulations F1-F7 at different crushing strength levels before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Floating lag time (min)			
		Origin of prepared tablet			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F1	(A)	0.84 ± 0.08	6.54 ± 1.19	2.14 ± 0.13	3.51 ± 1.31
	(B)	1.81 ± 0.25	9.78 ± 1.77	5.91 ± 1.68	4.91 ± 1.72
F2	(A)	0.44 ± 0.03	4.13 ± 0.35	2.17 ± 0.24	0.48 ± 0.04
	(B)	0.92 ± 0.05	4.48 ± 0.67	2.42 ± 0.04	1.06 ± 0.39
F3	(A)	0.32 ± 0.07	21.81 ± 4.00	7.49 ± 1.19	5.40 ± 0.44
	(B)	0.81 ± 0.03	24.17 ± 1.62	17.06 ± 4.94	28.18 ± 0.31
	(C)	7.19 ± 0.57	27.46 ± 4.42	23.92 ± 4.81	30.33 ± 1.86
F4	(A)	0.21 ± 0.04	6.93 ± 1.03	4.18 ± 0.58	6.71 ± 0.18
	(B)	0.26 ± 0.03	9.99 ± 1.36	5.57 ± 0.85	6.82 ± 0.24
	(C)	0.31 ± 0.01	13.11 ± 1.38	6.65 ± 0.71	7.69 ± 1.83

Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations.

Table 3-5 (continued): Floating lag-time of the formulations F1-F7 at different crushing strength levels before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Floating lag time (min)			
		Origin of prepared tablet			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F5	(A)	1.88 ± 0.65	6.95 ± 0.91	9.08 ± 0.84	0.41 ± 0.44
	(B)	3.46 ± 0.21	7.43 ± 0.70	10.82 ± 0.45	0.91 ± 0.62
	(C)	3.74 ± 0.21	10.09 ± 0.96	12.72 ± 1.06	1.55 ± 0.21
F6	(A)	4.20 ± 0.73	8.27 ± 1.25	9.49 ± 0.65	0.19 ± 0.04
	(B)	5.44 ± 1.33	11.09 ± 1.19	11.73 ± 1.12	0.20 ± 0.02
	(C)	7.19 ± 0.24	12.38 ± 1.86	12.83 ± 1.55	0.20 ± 0.02
F7	(A)	Complete disintegration (within 30 min)	No floating	No floating	No floating
	(B)	No floating	No floating	No floating	No floating
	(C)	No floating	No floating	No floating	No floating

Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations.

Table 3-6: Floating duration of the formulations F1-F7 at different crushing strength levels before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Total floating duration (h)			
		Origin of prepared tablet			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F1	(A)	> 12	> 8	> 24	> 24
	(B)	> 12	> 8	> 24	> 24
F2	(A)	> 24	> 24	> 24	> 24
	(B)	> 24	> 24	> 24	> 24
F3	(A)	Complete disintegration (within 30 min)	> 5	> 8	> 8
	(B)	Complete disintegration (within 30 min)	> 5	> 8	> 8
	(C)	> 4	> 8	> 12	> 8
F4	(A)	Complete disintegration (within 30 min)	> 24	> 24	> 24
	(B)	Complete disintegration (within 30 min)	> 24	> 24	> 24
	(C)	Complete disintegration (within 30 min)	> 24	> 24	> 24

Notes: The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations. For formulation composition, refer to Table 3-1 or Table 2-7.

Table 3-6 (continued): Floating duration of the formulations F1-F7 at different crushing strength levels before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Total floating duration (h)			
		Origin of prepared tablet			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F5	(A)	> 12	> 12	> 24	> 24
	(B)	> 12	> 12	> 24	> 24
	(C)	> 12	> 12	> 24	> 24
F6	(A)	> 24	> 24	> 24	> 24
	(B)	> 24	> 24	> 24	> 24
	(C)	> 24	> 24	> 24	> 24
F7	(A)	Complete disintegration (within 30 min)	No floating	No floating	No floating
	(B)	No floating	No floating	No floating	No floating
	(C)	No floating	No floating	No floating	No floating

Notes: The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations. For formulation composition, refer to Table 3-1 or Table 2-7.

Increasing the crushing strength level of the floating tablets (F1-F6) increased the floating lag time results. Regarding the formulations prepared from the powder mixture, a significant (P<0.05) increase in the floating lag time was noted for F1 and F2 formulations. A non-significant (P>0.05) effect was shown in all the other formulations except those of F3 where a significant (P<0.05) increase was noted at level C of crushing strength. Additionally, a non-significant (P>0.05) increase in the lag time results was seen in all the floating tablets (F1-F6) prepared from granules, except between the extreme margins of crushing strength (level A and C) of F3-F6 tablets (Table 3-5). These results could be explained by the porosity results (Section 3.2.2) where reducing the tablet porosity, as a result of increased compaction force, delayed the penetration of the acidic medium and hence delayed the gas generation process.

The granulation process caused a significant (P<0.05) increase in the floating lag time of all the tablet (F1-F6) compared to that of the tablets prepared from the powder mixture before the granulation (Table 3-5). A complete disintegration effect (within 30 min) was seen in the tablets prepared from the powder mixture based on calcium carbonate as a gassing agent (F3 and F4). These tablets rapidly moved in an upward motion and disintegrated on the surface of the dissolution medium. All the tablets based on sodium bicarbonate (F1 and F2) or sodium carbonate (F5 and F6) as a gassing agent either prepared from the powder mixture or the granules did not show any disintegration behaviour. This disintegration behaviour may be explained by the stronger effervescent activity of calcium carbonate compared to sodium bicarbonate and sodium carbonate, which ruptured the tablet structure of the formulations F3 and F4 prepared from powder mixture (Table 3-5). During the granulation process, liquid bridges of adhesives such as hydroxyethyl cellulose are formed between particles during the wet massing step and these harden due to the drying step (Summers and Aulton, 2007). This could make the internal structure of the tablets much more resistant to the disintegration effect of calcium carbonate effervescent reaction, and provide sufficient time for swelling and gel layer formation.

It has been reported that carbonates could generate an alkaline microenvironment for pH sensitive polymers to initiate gel formation (Deshpande et al., 1997). The absence of the disintegration behaviour for F5 and F6 tablets prepared from powder mixture could be explained by the better ability of sodium carbonate compared to calcium carbonate to provide a suitable microenvironment for the polymer to start gelling as 1% (w/v) aqueous solution of sodium carbonate generates a pH of 11.4 at 25°C (Hapgood, 2009) while 10% (w/v) aqueous dispersion of calcium carbonate produces a pH of 9.0 (Armstrong, 2009).

The increase in the lag time results of F1 and F2 (10% and 20% (w/w) sodium bicarbonate respectively), and F5 (10% (w/w) sodium carbonate) tablets after the granulation (Table 3-5) may be due to the reduction in the porosity (Section 3.2.2). Although the porosity level of F6 (20% (w/w) sodium carbonate) formulation increased following the granulation process, its floating lag time also increased. The increase in the porosity level may enhance rapid contact between the gassing agent and the acidic medium, but it also could accelerate the escape of liberated gas bubbles from the matrix structure before the formation of a coherent gel layer around the tablet, which may delay the floating process.

Changing sodium bicarbonate concentration from 10% (w/w) (F1) to 20% (w/w) (F2) caused a significant (P<0.05) decrease in the lag time data of the tablets prepared from the powder mixture at both crushing strength levels. However, the reduction in the lag time values was not significant (P>0.05) in the tablets prepared from the granules. Increasing calcium carbonate concentration from 10% (w/w) (F3) to 20% (w/w) (F4) in tablets prepared from the powder mixture decreased the lag time non-significantly (P>0.05) except at level C of crushing strength. Moreover, a significant (P<0.05) reduction in the floating lag time was noted in the tablets prepared from the granules when calcium carbonate level was increased from 10% to 20% (w/w). Increasing the gassing agent content available for an acidic medium enhanced the efficiency of the effervescent reaction, which was represented by a shorter floating lag time. Changing sodium carbonate concentration from 10% (F5) to 20% (w/w) (F6), increased the lag time non-significantly (P>0.05) in all the tablets.

The ability of sodium carbonate to generate an alkaline microenvironment to accelerate swelling and gel formation may reduce the dissolution medium entrapment rate and the quantity of acidic medium available for the effervescent reaction. Moreover, raising sodium carbonate level to 20% (w/w) increased tablets density (Section 3.2.2), and more time was taken for the floating process.

Regarding the floating duration (Table 3-6), although, F1 tablets prepared from the powder mixture floated for > 12 h, there were 4 h reduction in their floating duration after the granulation process. In addition, there was no difference in the floating duration of F2 formulation before and after the granulation, where they floated for > 24 h. It is clear that 20% (w/w) concentration was more effective than 10% (w/w) concentration to maintain tablets on the surface of the dissolution medium for a longer duration of time.

As stated above, tablets based on calcium carbonate as a gassing agent of the formulations F3 and F4 prepared from the powder mixture showed complete disintegration behaviour within short time (30 min) after floating. However, following the granulation process, the tablets of F3 (10% (w/w)) formulation floated for > 5 h, while F4 (20% (w/w)) formulation floated for > 24 h due to the high gassing agent reservoir available for the floating process. The granulation process did not cause any difference in the floating duration results of F5 and F6 tablets based on sodium carbonate as a gassing agent, as > 12 h and > 24 h were reported, respectively. This may be related to the absence of the disintegration effect due to the ability of sodium carbonate to generate an alkaline microenvironment to accelerate gel formation; however the longer floating duration could be related to the high gassing agent reservoir during the test for F6.

Regarding stability studies, the effect of storage at 40°C ± 2°C and 80% ± 5% RH for 3 months on the tablets floating lag time and floating duration has been evaluated and presented in Table 3-5 and Table 3-6 respectively. The floating lag time results of both the formulations based on sodium bicarbonate F1 (10% (w/w) and F2 (20% w/w) decreased after storage in closed and open containers. In closed containers, the effect was significant (P<0.05) for F1 tablets at both crushing strength levels, however it was not significant (P>0.05) for F2 tablets. Furthermore, in open containers, a significant (P<0.05) effect was only noted for F1 tablets at crushing strength level (B) and F2 tablets at crushing strength level (A). The floating lag time results of the tablets based on 10% (w/w) calcium carbonate as a gassing agent (F3) in closed containers decreased at all crushing strength levels. The effect was non-significant (P>0.05) except at level A of crushing strength. In contrast, storage in open containers increased the floating lag time non-significantly (P>0.05) in comparison with freshly prepared ones. But, at level A of crushing strength the floating lag time was significantly (P<0.05) decreased. For F4 (20% (w/w) calcium carbonate) tablets, the floating lag time non-significantly decreased (P>0.05) after storage in either closed or open containers at all crushing strength levels. An exception was reported at level C of crushing strength in open containers where the effect was significant (P<0.05) (Table 3-5).

The decrease in floating lag time may be explained by the increase in the tablet thicknesses due to the aging process which facilitated dissolution medium entrapment at early stages of the dissolution process. This means rapid contact between the gassing agent and the acidic medium to start the effervescent and the floating processes. For calcium carbonate based tablets, the reduction in the lag time results was higher in closed containers than in open ones. The storage in open containers caused a direct exposure to a stressful humidity level (80% RH) which caused a higher increase in tablets' dimensions when compared to those stored in closed containers (Table 3-4). Even calcium carbonate has a higher effervescent activity; it has less ability to generate an alkaline microenvironment. Therefore, this may lead to escape of generated carbon dioxide bubbles at early stages of contact with the acidic medium and delay the floating process which explains the higher reduction in the floating lag time values in closed containers than that in open ones.

The lag time results of the formulations F5 and F6 based on sodium carbonate non-significantly (P>0.05) increased after a storage in closed containers. Conversely, a significant (P<0.05) decrease was noted after storage in the open ones. This increase in the lag time results of the tablets of F5 and F6 formulation may be related to the high hygroscopic properties of sodium carbonate (Section 3.2.2). The relatively high moisture level during the storage may decrease the concentration of sodium carbonate molecules available for the effervescent reaction at the commencement of the dissolution test which was reflected by the increase in the floating lag time results. Even storage in open containers stressfully caused a direct exposure to humidity, however the lag time results were sharply decreased. This could be explained by the sharp reduction in their apparent density results at levels A, B, and C of crushing strength where 0.92, 0.97, and 0.98 g/cm^3 were respectively reported (Figure 3-38) which enhanced rapid floating.

Additionally, in both closed and open containers, the floating duration was sharply increased from > 8 h to > 24 h for F1 formulation (10% (w/w) sodium bicarbonate); but, it did not change for F2 formulation (20% (w/w) sodium bicarbonate) where results remained > 24 h. Additionally, the floating duration was increased from > 5 h to > 8 h for F3 (10% (w/w) calcium carbonate) tablets and sharply increased from > 12 h to > 24 h for F5 (10% (w/w) sodium carbonate) tablets after storage in either closed or open containers. Yet, the floating duration of the formulations F4 (20% (w/w) calcium carbonate) and F6 (20% (w/w) sodium carbonate) did not change after the storage and they continued to float for > 24 h (Table 3-6). This agrees with the tablet relaxation behaviour during the storage which could enhance faster dissolution medium entrapment through the dilated inter-particulate voids of the relaxed tablet structure. This enhanced a rapid reaction with the superficial gassing agent molecules and shortened the lag time results of the formulations F1-F6. However, the gassing agent was also uniformly distributed all over the tablet matrix. Consequently, a sufficient deep penetration of the acidic medium through the relaxed matrix voids would be expected to make a contact with the deeply impeded gassing agent molecules. Extra bubbles of carbon dioxide would be generated to maintain the floating process for longer floating time duration. Moreover, 20% (w/w) of the gassing agents was already enough for the tablets to float > 24 h.

3.2.4 Swelling and erosion studies

The hydration layer plays a key role in the controlled drug release of gel forming tablets. Also, drug solubility plays a major role in the release mechanism. Water soluble drugs are released by diffusion through the formed gel layer, nonetheless, for poor water-soluble drugs, matrix erosion is considered as the rate limiting step for the drug release. Since the designed floating tablets based on gel forming polymeric mixture (hydroxyethyl cellulose and sodium alginate), it was important to evaluate swelling and erosion data. Swelling studies were conducted according to the method described earlier (Chapter 2, section 2.2.6.4). Results were utilized to make a correlation with the drug release rate and the release mechanism. Only the tablets prepared from the granules were subjected to swelling studies due to the good flow properties that facilitate their automatic pressing by the single-punch tableting machine which made them more suitable to benefit the pharmaceutical industry.

The % of dissolution medium uptake (DMU) for all the tablets prepared from the granules (F1-F7) in 0.1 M HCl medium was calculated by equation (5) (Chapter 2, section 2.2.6.4), and data is presented in Figure 3-43 to Figure 3-46**.** For all the tablets the percentage of dissolution medium uptake (DMU), in 0.1 M HCl medium, showed a continuous increase until 12 h of the experiment time except for the control tablets (F7) where the increase continued till 8 h only. Increasing the tablet crushing strength in all the formulations (F1-F7) did not cause a significant (P>0.05) effect in the swelling rate results at majority of the time points. Viridén et al. (2009) showed that the tablet strength had only a small effect on the swelling rate of hydrophilic tablets. Tablets of F2 formulation showed a significant (P<0.05) decrease in DMU (compared to F1 formulation) at most of the time points (Figure 3-43). When a tablet floats on the dissolution medium, its upper surface does not come in contact with the medium, while other surfaces are placed under the dissolution medium surface. Once it sinks after a period of time, all surfaces of this tablet becomes completely available for DMU. Accordingly, the surface area available for water uptake and the floating duration could explain the lower swelling rate of F2 tablets in comparison with F1 tablets. As stated previously, tablets of F2 formulation floated for > 24 h while F1 tablets floated for only > 8 h and then sank for the rest of the experiment time.

This means that the upper tablet surface of F1 formulation became available for DMU after sinking and the tablet showed higher swelling rate by the end of the experiment. As presented in Figure 3-46, F7 control tablets that remained under the surface of the dissolution medium throughout the experiment time showed an almost similar swelling rate profile of those of F1 tablets (Figure 3-43) and the difference was not significant (P>0.05) at majority of the time points. Nevertheless, F2 tablets showed a significant (P<0.05) lower swelling rate results (Figure 3-43) than those of F7 tablets at larger part of the time points.

Raising calcium carbonate levels from 10% (w/w) (F3) to 20% (w/w) (F4) caused a significant (P<0.05) decrease in the tablet swelling at most of the time points (Figure 3-44). However, increasing sodium carbonate level did not cause a significant (P>0.05) effect on the swelling of F5 and F6 tablets at majority of the time points (Figure 3-45). F4 tablets floated for > 24 h while F3 tablets floated for only > 5 h. This means that the upper tablet surface of F3 sample became available for DMU after sinking and the tablet showed great swelling by the end of the experiment. Although, tablets of F5 (10% (w/w)) and F6 (20% (w/w)) formulations, based on sodium carbonate as a gassing agent, floated for > 12 and > 24 h respectively (Table 3-6), the DMU results were almost the same. Data of the formulations F5 and F6 (Figure 3-45) showed a continuous increase in swelling rate until 12 h only which could explain the absence of a significant (P>0.05) difference between the formulations F5 and F6 at bulk of the time points.

Pentoxifylline control tablets of F7 formulation (Figure 3-46) that remained under the surface of the dissolution medium for the entire period of the experiment and demonstrated a significantly (P<0.05) higher swelling rate profile compared to the formulations F3 and F4 based on calcium carbonate as a gassing agent at most of the time points. However, this difference was not significant (P>0.05) in comparison to the formulations F5 and F6 which were based on sodium carbonate at larger part of the time points. Sodium carbonate is a stronger alkaline material than calcium carbonate (Section 3.2.3) which may explain the ability of the formulations F5 and F6 to swell at an almost similar rate to F7 formulation even after the long period of floating. Figure 3-47 reveals images of F4 and F7 tablets prepared at 49-54 N crushing strength (as examples) during their swelling characterization test for 24 h.

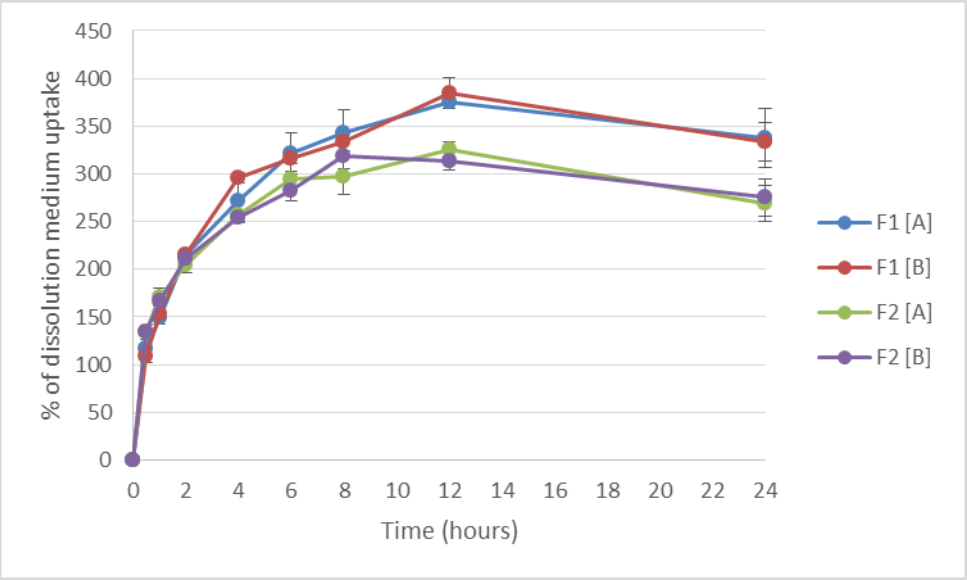


Figure 3-43: Percentage of medium uptake for the formulations F1 and F2 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N).

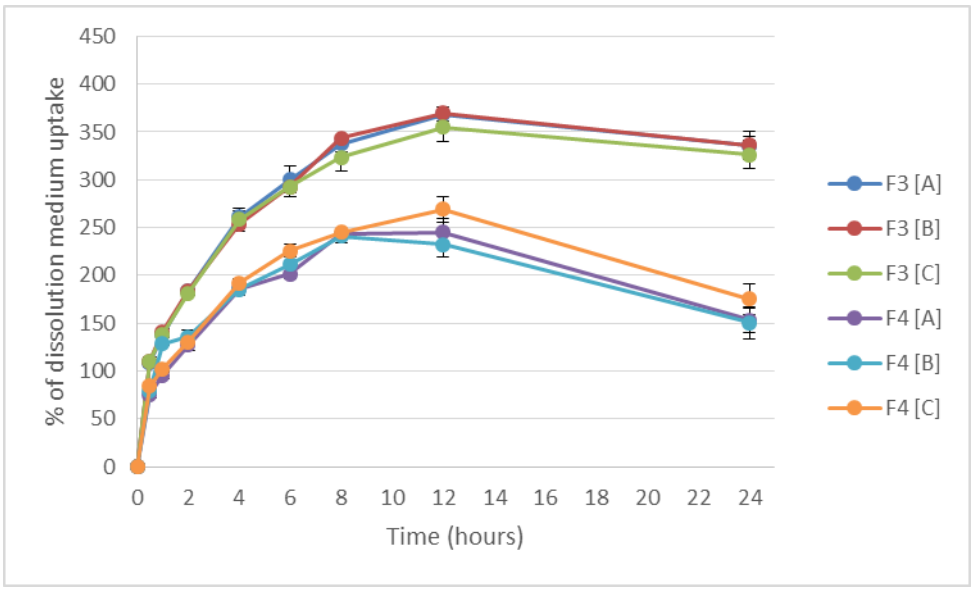


Figure 3-44: Percentage of medium uptake for the formulations F3, and F4 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 3-1 or Table 2-7.

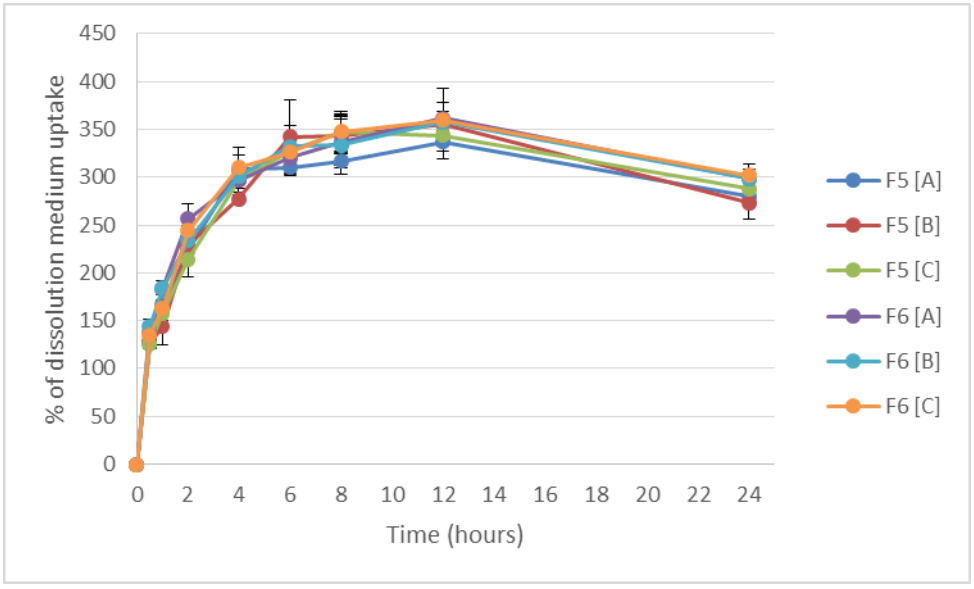


Figure 3-45: Percentage of medium uptake for the formulations F5, and F6 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).

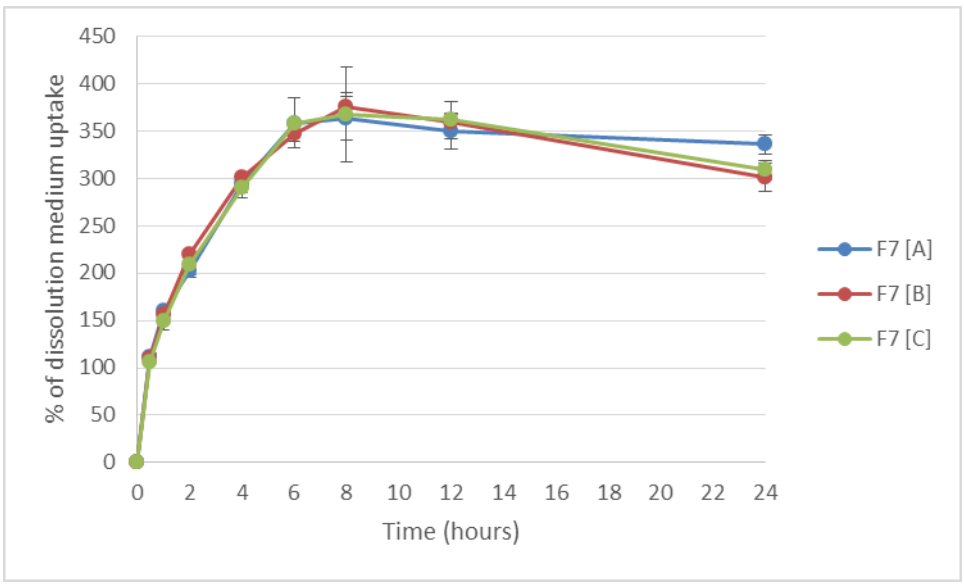


Figure 3-46: Percentage of medium uptake for F7 formulation (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 3-1 or Table 2-7.

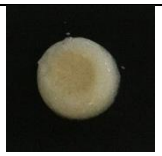
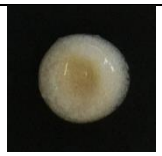
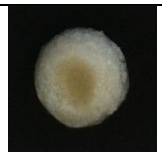
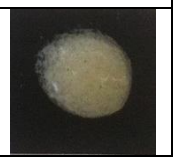
Time (hours)	0	2	4	8	12	24
F4						
F7						

Figure 3-47: Images of F4 and F7 tablets during their swelling for 24 hours. For formulation composition, refer to Table 3-1 or Table 2-7.

Regarding erosion studies, they were accomplished according to the method described earlier (Chapter 2, section 2.2.6.4). Only the tablets prepared from the granules were subjected to erosion studies due to the good flow properties that facilitate their automatic pressing by the single-punch tableting machine. The % of mass loss for all the tablets was calculated by equation (6) (Chapter 2, section 2.2.6.4). Figure 3-48 to Figure 3-51 represent the percentage of the mass loss of all the tablets (F1-F7) prepared from the granules where all the tablets showed gradual loss in their masses up to almost half of their original weight at the end of 24 h. Increasing crushing strength levels did not cause a significant (P>0.05) effect on the mass loss values of all the formulations (F1-F7) at majority of the time points. Increasing the gassing agent concentration of sodium bicarbonate (Figure 3-48), calcium carbonate (Figure 3-49) and sodium carbonate (Figure 3-50) from 10% to 20% (w/w) significantly (P<0.05) increased the mass loss values at most of the time points. Pentoxifylline control tablets (F7) demonstrated the lowest mass loss percentage profile as shown in (Figure 3-51) and their results were significantly (P<0.05) lower than all the other formulations at larger part of the time points. This may be explained by the higher effervescent effect due to the higher gassing agent level, which liberates more carbon dioxide bubbles. This means more mass loss from the tablet matrix due to the effervescent process.

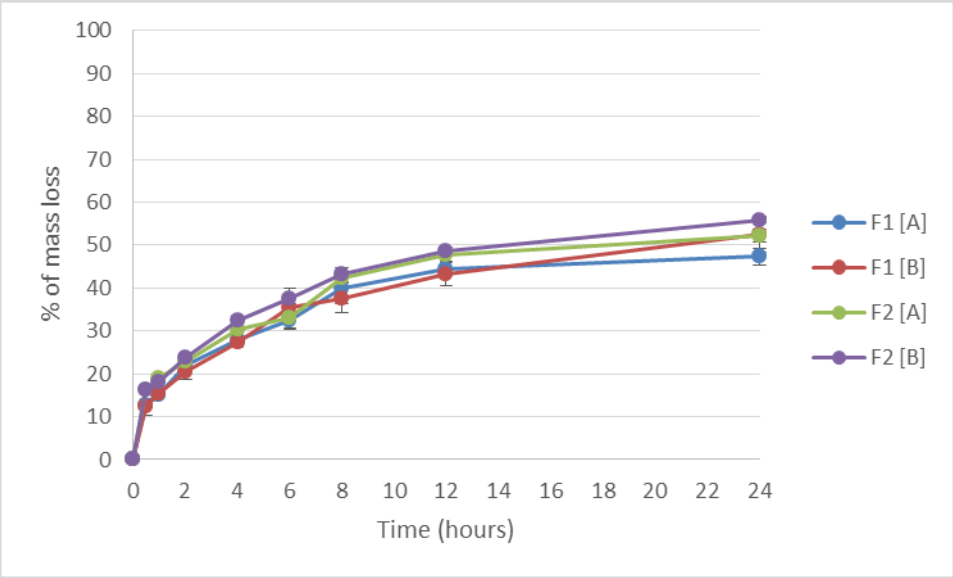


Figure 3-48: Percentage of mass loss for the formulations F1 and F2 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N).

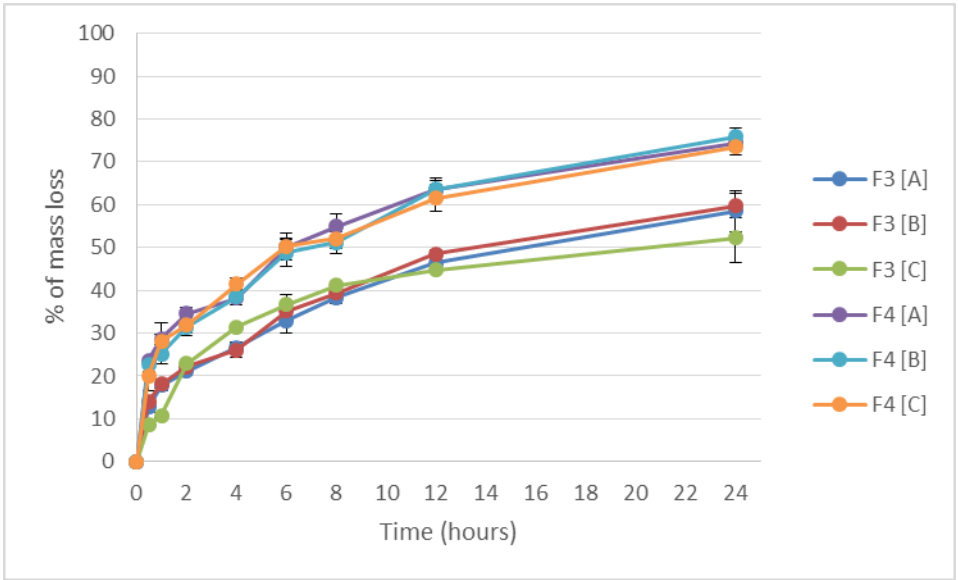


Figure 3-49: Percentage of mass loss for the formulations F3, and F4 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 3-1 or Table 2-7**.**

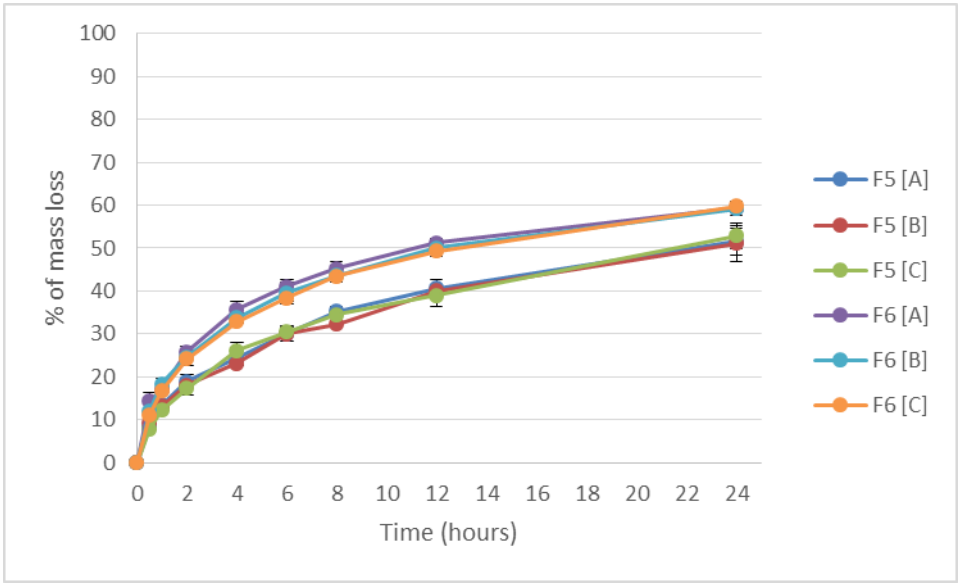


Figure 3-50: Percentage of mass loss for the formulations F5, and F6 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).

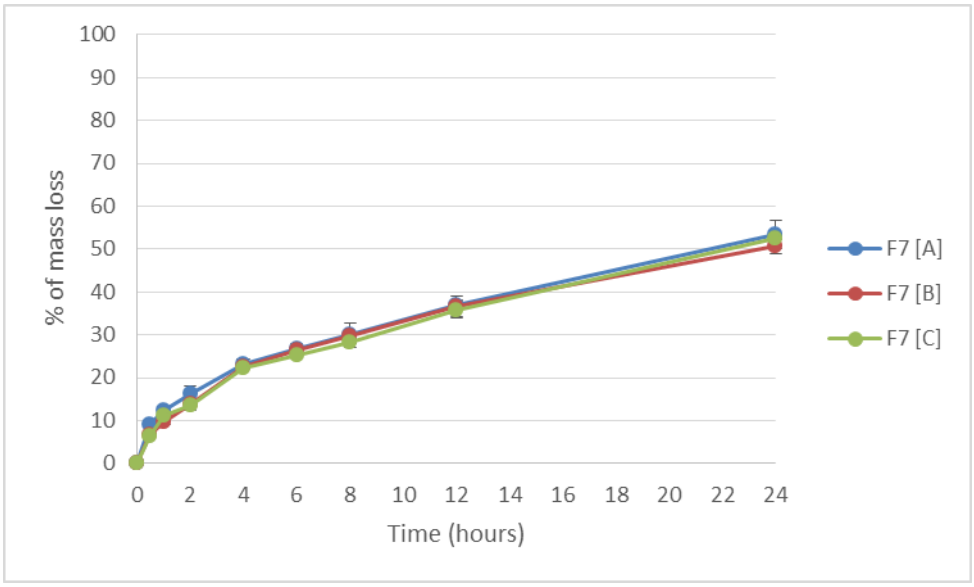


Figure 3-51: Percentage of mass loss for F7 formulation (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 3-1 or Table 2-7.

3.2.5 *In vitro* drug release studies

In vitro drug release study is an important analytical method to investigate and develop product behaviour during various stages of new drug product development. Moreover, the resulted release profile can reveal essential information regarding the release mechanism and kinetics, enabling a rational and scientific approach to drug product development. Dissolution profiles of all the tablets (F1-F7) prepared from the powder mixtures are presented in Figure 3-52 to Figure 3-55.

Statistically, the tablets of F1 (10% (w/w) sodium bicarbonate) and F2 (20% (w/w) sodium bicarbonate) showed a significant (P<0.05) decrease in their drug release rate when their crushing strength level increased from level (A) to level (B) at majority of the time points (Figure 3-52). Additionally, a significant (P<0.05) difference was found between the release profiles of pentoxifylline control tablets (F7) at different crushing strength levels at most of the time points (Figure 3-55). The tablets of F3 (10%) and F4 (20%) based on calcium carbonate as a gassing agent showed only a small difference between their drug release rate due to their complete disintegration. An exception was noted in those of F3 at level C of crushing strength where a significant (P<0.05) slower release rate occurred up to 12 h at bulk of the time points (Figure 3-53). The tablets of F5 and F6 which contained sodium carbonate as a gassing agent did not disintegrate and the difference between their drug release rate was not significant (P>0.05) at larger part of the time points (Figure 3-54).

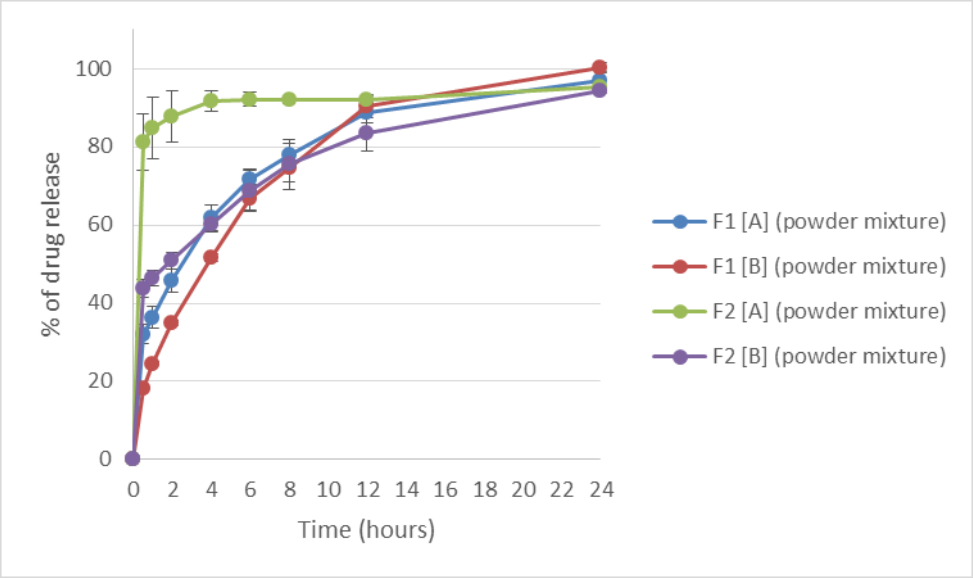


Figure 3-52: Percentage of drug release of F1 and F2 floating tablets pressed at levels (A) and (B) of crushing strength in 0.1 M HCl medium before granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

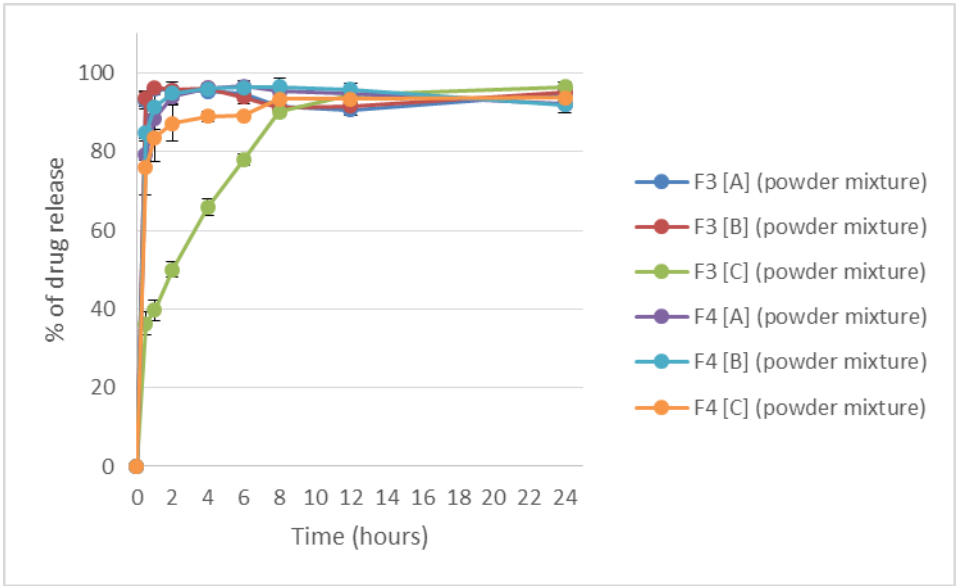


Figure 3-53: Percentage of drug release of F3, and F4 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium before granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 3-1 or Table 2-7

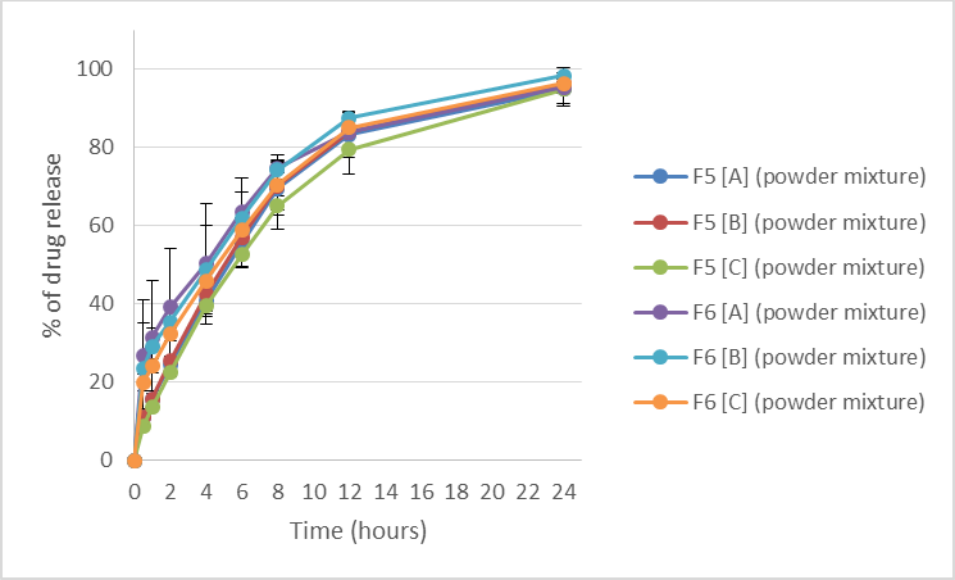


Figure 3-54: Percentage of drug release of F5, and F6 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium before granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

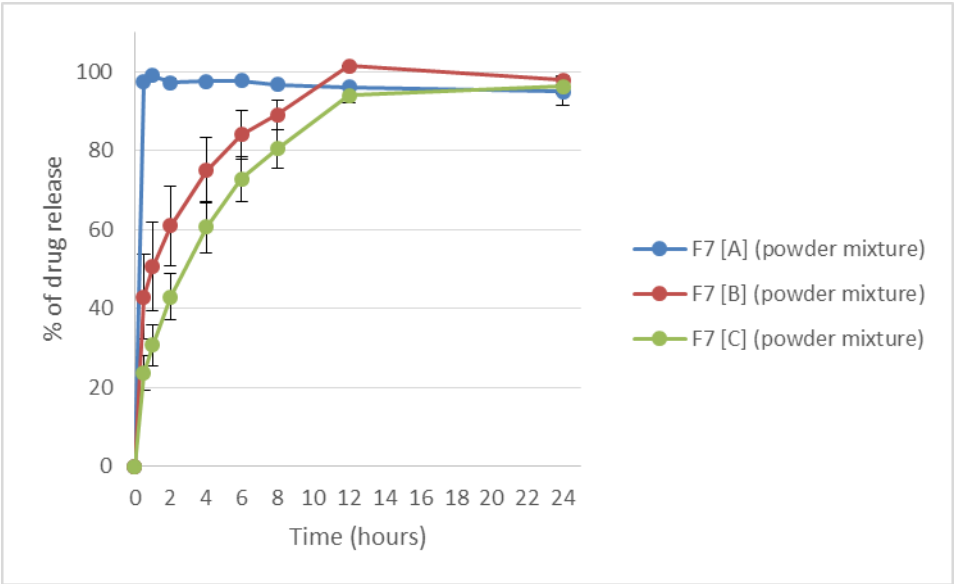


Figure 3-55: Percentage of drug release of F7 control tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium before granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 3-1 or Table 2-7.

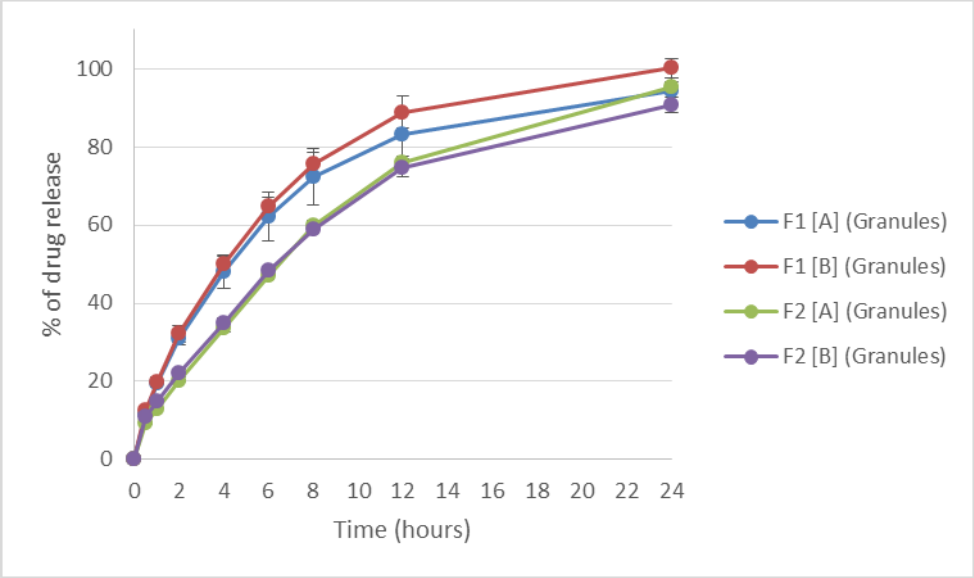


Figure 3-56: Percentage of drug release of F1, and F2 floating tablets pressed at levels (A), and (B) of crushing strength in 0.1 M HCl medium after granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49-54 N) and B (54-59 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

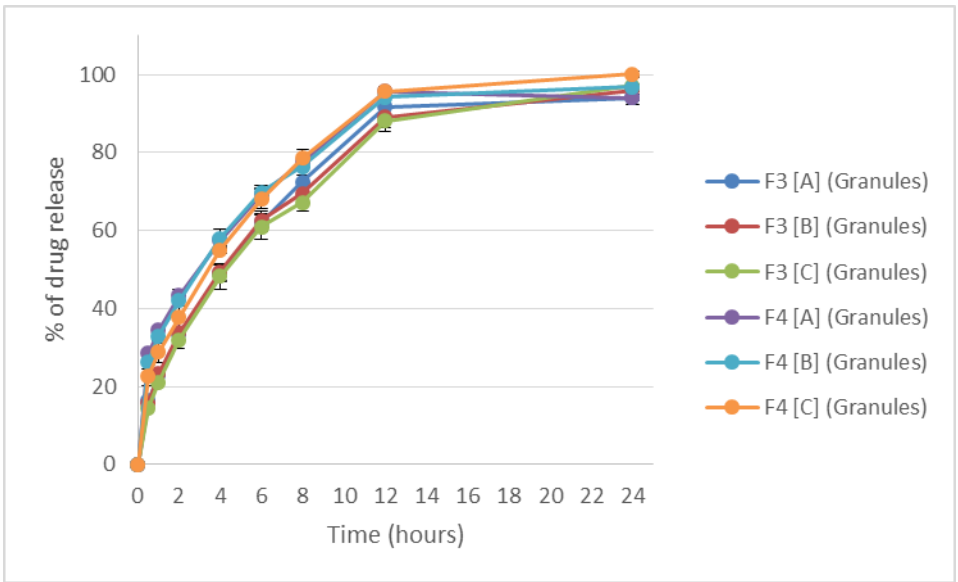


Figure 3-57: Percentage of drug release of F3, and F4 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 3-1 or Table 2-7

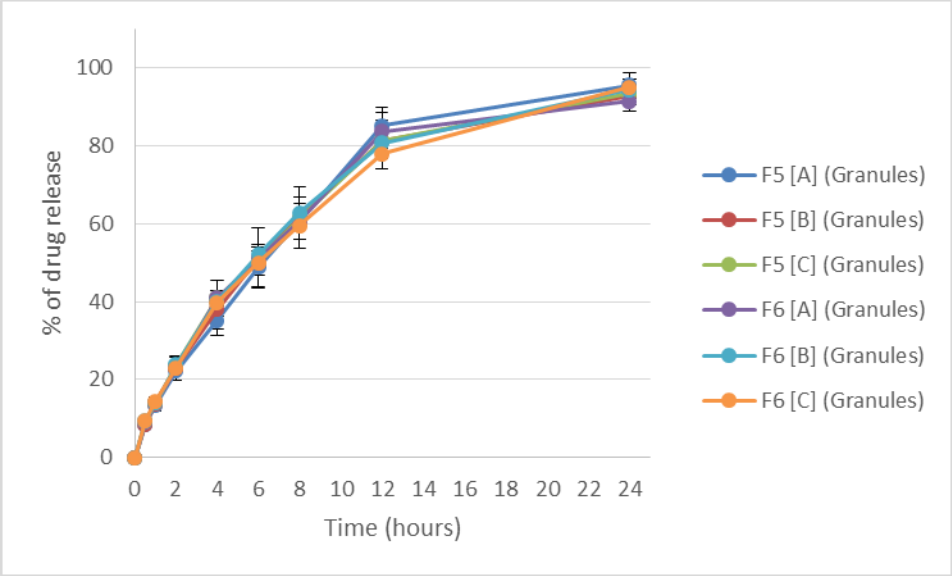


Figure 3-58: Percentage of drug release of F5, and F6 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

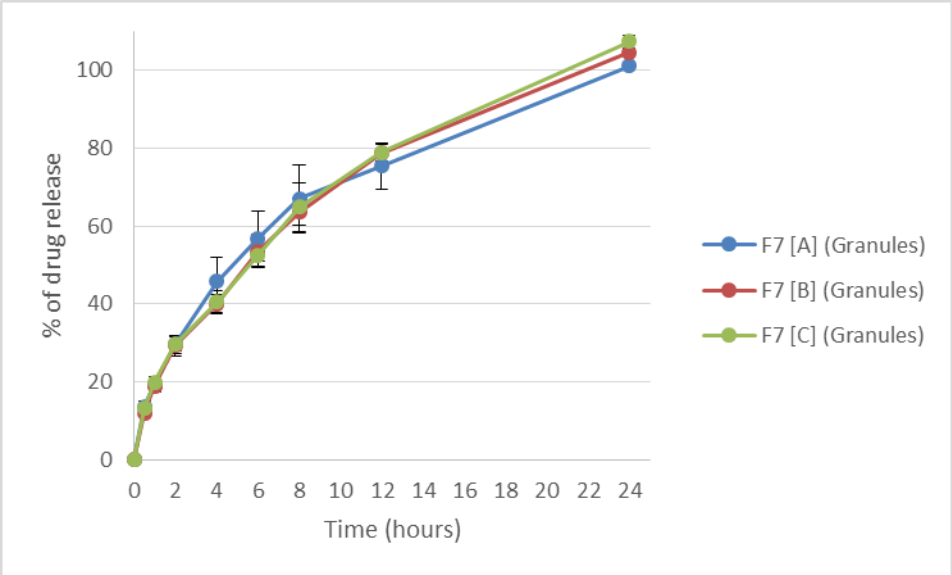


Figure 3-59: Percentage of drug release of F7 control tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after granulation.
Notes**:** The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 3-1 or Table 2-7.

Although Liew et al (2006) proposed that both gel layer generation around a matrix tablet as well as the gel layer porosity can control the drug release process, but not the dry matrix porosity; however, Mandal et al (2009) reported a significant difference in drug release from highly compressed tablets, indicating that there is a limit of crushing strength above which the porosity of a dry matrix will affect the penetration of the dissolution medium inside the tablet. This agrees with the porosity results of F1, F2, and F7 tablets (Section 3.2.2), where increasing the compression force made the powder mixture particles closer to each other and reduced the porosity percentage significantly (P<0.05). Therefore, the penetration of the dissolution medium into the matrix to dissolve pentoxifylline was more difficult, and the drug release process was delayed. Calcium carbonate may show higher effervescent behaviour compared to sodium carbonate (Section 3.2.3), but the ability of sodium carbonate to generate an alkaline microenvironment to accelerate swelling and gel formation is better than that of calcium carbonate. Thus, an insufficient gel layer formation may lead to partial or complete tablet disintegration in case of calcium carbonate based tablets.

The drug release rate of (F1-F7) tablets prepared from the granules is shown in Figure 3-56 to Figure 3-59. Increasing the tablets crushing strength level in all the formulations (F1-F7) caused a non-significant (P>0.05) difference in their drug release rate at majority of the time points. This comes in agreement with DMU results (Section 3.2.4) where the tablet strength had only a small effect on the tablets swelling rate behaviour. In addition, Ebube and Jones (2004) concluded a minimal effect of compression force on acetaminophen release rate from either hydroxypropylmethyl cellulose or hydroxypropyl cellulose matrices prepared from granules. Consequently, this gives an advantage to control other formulation parameters such as high friability percentages by raising the compression force without disturbing the drug release rate.

The effect of the granulation process on the drug release rate from the formulations F1-F7 reveals that the granulation extended the drug release rate of all the prepared tablets. A significant (P<0.05) decrease at larger part of the time points was noted in the release profiles in both the formulations F1 and F2 except at level (B) of crushing strength for F1 formulation which was not significant (P>0.05) at bulk of the time points. Additionally, the granulation effect was significant (P<0.05) in the formulations F3, F4, and F7, yet, it was not significant (P>0.05) in the formulations F5 and F6 at most of the time points. A lower standard deviation (SD) values were reported for the formulations F5, F6, and F7 following the granulation which reveals a homogenous drug release rate in comparison with tablets prepared from the powder mixtures.

The granulation process enhanced the internal structure resistance of the formulations F3 and F4 to rupture due to calcium carbonate effervescent behaviour and gave enough time for swelling and gel layer formation to control the drug release process. Results of the tablets based on sodium bicarbonate as a gassing agent (F1 and F2) and the control tablets (F7) may be explained by results of Mukhopadhyay et al. (2008) study where increasing the water binder volume decreased the porosity during the wet massing stage, and this reduction decreased the dissolution medium entrapment rate through the matrix at an early stage of the dissolution test, which decreased the drug release process. The insignificant (P>0.05) effect of the granulation process on F5 and F6 tablets at most of the time points may be explained by the high alkalinity of sodium carbonate as a gassing agent which may explain the ability of the tablets either before or after the granulation to swell at a similar rate. Although the porosity of F6 formulation increased after the granulation as discussed earlier (Section 3.2.2), it has been proposed that dissolution medium can pass through tablet surface pores to initiate gel layer formation through the swelling process (Alderman, 1984). Within the formed gel blocks, the liquid can fill pores in less than 15 min, after which water can be primarily transported through the created coherent gel layer (Bajwa et al., 2006). Accordingly, swelling rate may control the drug release rate and explain the insignificant (P>0.05) effect of granulation.

Increasing the concentration of sodium bicarbonate from 10% to 20% (w/w) increased significantly (P<0.05) the drug release rates of the formulations prepared from the powder mixture at majority of the time points (Figure 3-52). More pore formation in the wet matrix structure due to the effervescent process and the liberation of more carbon dioxide bubbles explains the higher drug release rate. In contrast, increasing sodium bicarbonate concentration significantly (P<0.05) decreased the drug release rate of the formulations prepared from the granules at bulk of the time points (Figure 3-56). This conforms to the DMU results (Section 3.2.4), where the swelling rate of F1 formulation was higher than that of F2 (Figure 3-43). Accordingly, a higher swelling rate indicates more dissolution medium entrapment in the matrix structure, which may dissolve and release more drug molecules. A non-significant (P>0.05) effect of raising the concentration of calcium carbonate as a gassing agent on the drug release rate of the tablets prepared from the powder mixture at larger part of the time points was noted except at level C of crushing strength as shown in (Figure 3-53). This may be explained by the complete disintegration behaviour of the tablets (within 30 min). However, the effect was significant (P<0.05) in the tablets prepared from the granules at majority of the time points (Figure 3-57). Increasing calcium carbonate concentration from 10% to 20% (w/w) increased pore formation in the formed gel layer around the tablets due to the entrapped gas bubbles, and this caused a higher drug release rate. Increasing sodium carbonate concentration produced a non-significant (P>0.05) increase in the rate of drug release from the tablets prepared either from the powder mixture (Figure 3-54) or the granules (Figure 3-58) at most of the time points. This agrees with the effect of sodium carbonate alkalinity on the swelling behaviour of tablets (Section 3.2.4).

The effect of adding a gassing agent on the drug release rate of the tablets prepared from the powder mixture or the granules was evaluated by comparing F7 (0% w/w gassing agent) results with all the other formulations. As presented in Figure 3-55 and Figure 3-59, pentoxifylline control tablets (F7) prepared from the powder mixture or the granules respectively, showed a drug release rate almost similar (P>0.05) to that of F1 formulation, but significantly (P<0.05) higher than that of F2 formulation at bulk of the time points.

This also agrees with the swelling study results (Section 3.2.4), where the swelling rate of F7 formulation (Figure 3-46) was almost similar (P>0.05) to that of F1 formulation and significantly (P<0.05) higher than that of F2 formulation at majority of the time points (Figure 3-43). Adding calcium carbonate at both concentrations caused a higher drug release rate due to liberation of carbon dioxide bubbles. Generally, the effect was significant (P<0.05) at larger part of the time points for the tablets prepared from the powder mixture following the disintegration behaviour in most of F3 and F4 tablets (Figure 3-53) except at level A of crushing strength where F7 tablets also showed complete disintegration (Figure 3-55). For the tablets prepared from the granules, the effect was not significant (P>0.05) at 10% (w/w) (F3) but significant (P<0.05) at 20% (w/w) (F4) of calcium carbonate (Figure 3-57) compared to F7 tablets (Figure 3-59) at most of the time points. In contrast, adding sodium carbonate (gassing agent) at 10% (F5) and 20% (w/w) (F6) decreased the release rate compared to that of pentoxifylline control tablets (F7) of both the powder mixture (Figure 3-54 and Figure 3-55) and the granules origin (Figure 3-58 and Figure 3-59) respectively. Generally, the effect was not significant (P>0.05) at majority of the time points except for the tablets prepared from the powder mixture at level A of crushing strength where F7 tablets showed complete disintegration behaviour (within 30 min). Although, the tablets of the formulations F5 and F6 floated for > 12 and > 24 h respectively (Table 3-6); their DMU results (Section 3.2.4) were almost similar to that of F7 formulation due to the alkalinity of sodium carbonate which may explain the non-significant (P>0.05) difference in their drug release rate.

Regarding the stability studies, storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed containers slightly (P>0.05) decreased the drug release rate of all the tablets of F1 (Figure 3-60) and F2 (Figure 3-61) formulations in comparison with the freshly prepared tablets at majority of the time points. However, storage in open containers increased the drug release rate non-significantly (P>0.05) for F1 tablets and significantly (P<0.05) for F2 tablets at both crushing strength levels at most of the time points. The *in vitro* drug release results of the stability studies in open containers agrees with the reduction in the lag time results after storage (Section 3.2.3) where the dissolution medium easily penetrated the relaxed tablet matrices to dissolve the drug and release it at a higher rate in comparison to the freshly prepared tablets.

Storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed containers caused a decrease in the drug release rate of tablets based on calcium carbonate (gassing agent) as presented in Figure 3-62 and Figure 3-63. Although the effect was not significant (P>0.05) at bulk of the time points for F3 (10% (w/w) calcium carbonate) formulation, it was significant (P<0.05) for F4 (20% (w/w) calcium carbonate) formulation at majority of the time points. Storage for three months in the open containers caused a significant (P<0.05) increase in the drug release rate of F3 (10% (w/w) calcium carbonate) formulation at larger part of the time points. A significant (P<0.05) decrease in the *in vitro* drug release results of F4 (20% (w/w) calcium carbonate) formulation at bulk of the time points was noted except at level C of crushing strength where the effect was not significant (P>0.05) at most of the time points. These results support the later proposal (Section 3.2.6) that the *in situ* ability of anionic alginate molecules to form a gel in the presence of multivalent cations such as calcium ions in aqueous medium especially under a relatively high moisture level during storage will generate an insoluble gel that may decrease the drug release rate. Nevertheless, the cross linking process with 10% (w/w) (F3) calcium carbonate may be insufficient to overcome the increase in the tablets dimensions due to tablet aging behaviour.

The stability drug release rate of sodium carbonate (gassing agent) formulations (F5, 10% (w/w) and F6, 20% (w/w)) were presented in Figure 3-64 and Figure 3-65 respectively. Storage for three months in either closed or open containers significantly increased (P<0.05) the *in vitro* drug release rate of both F5 and F6 at all crushing strength levels at bulk of the time points. An exception was reported at the lower gassing agent concentration (F5) in the closed containers where the effect was not significant (P>0.05) at majority of the time points.

For F7 formulation (0% gassing agent), a significant (P<0.05) increase in the drug release rate was reported at levels A, B, and C of crushing strength at larger part of the time points (Figure 3-66). This increase in the drug release rate of F5, F6, and F7 tablets may be explained by the tablet relaxation during the storage process which enhanced more entrapment of the dissolution medium in the matrices, leading to dissolve more pentoxifylline molecules and generating higher dissolution profiles.

Generally, tablets stored in the closed containers showed an increase in their dimensions; still a lower change in their drug release rate was noted in comparison to those stored in the open containers. This may indicate a better physical stability of such formulations in closed containers rather than under the harsh storage conditions (open containers). Generally, solid oral dosage forms, such as tablets, needs protection from moisture, and sometimes from light or reactive gases. Because moisture may enhance the drug substance decomposition rate or the dissolution rate of the dosage form, a typical container closure system for such drug products should have low moisture permeation rate such as plastic bottle with a screw-on or snap-off closure or a flexible packaging system, like a pouch or a blister package. Essentially, a suitable eye-catching label to direct patients for good practice should be recommended for floating tablet formulations.

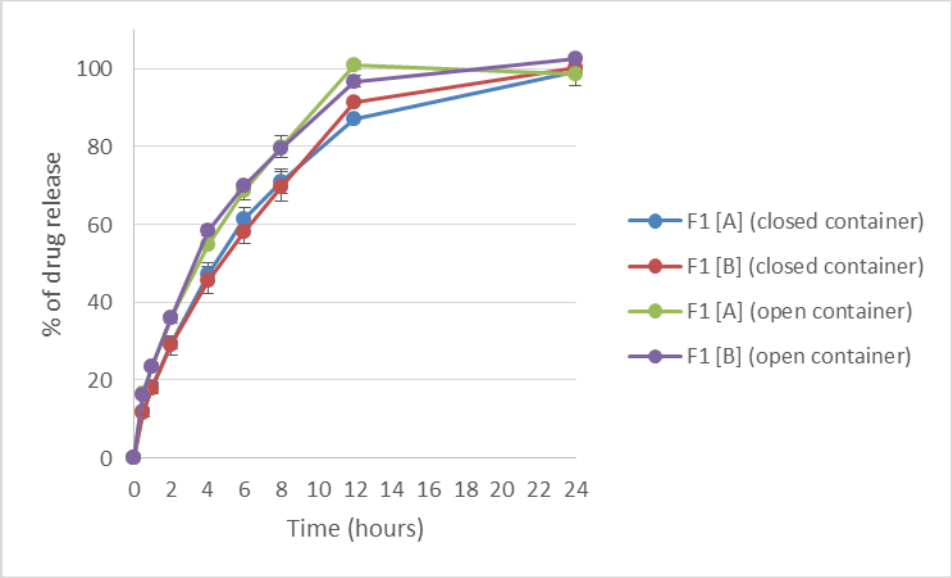


Figure 3-60: Percentage of drug release of F1 floating tablets pressed at levels (A) and (B) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

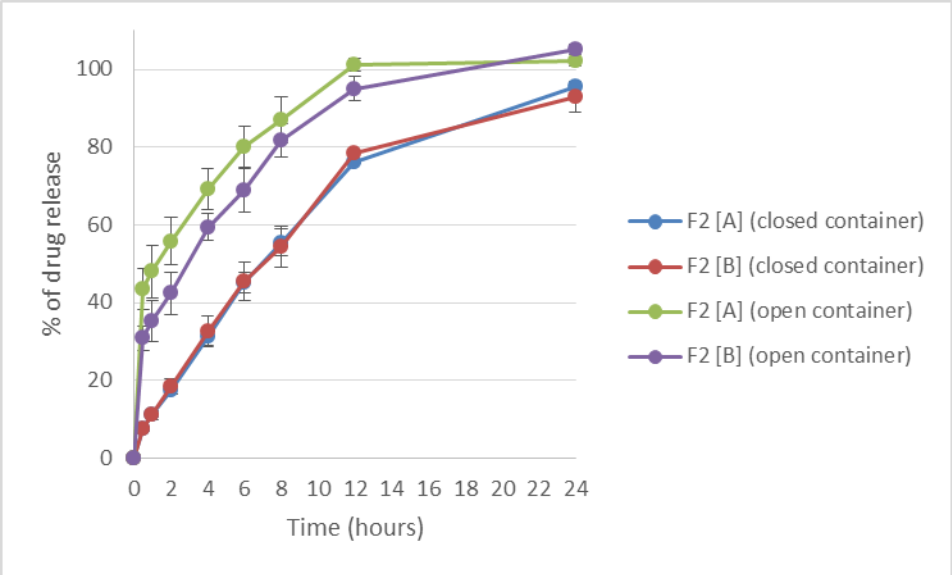


Figure 3-61: Percentage of drug release of F2 floating tablets pressed at levels (A) and (B) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 3-1 or Table 2-7.

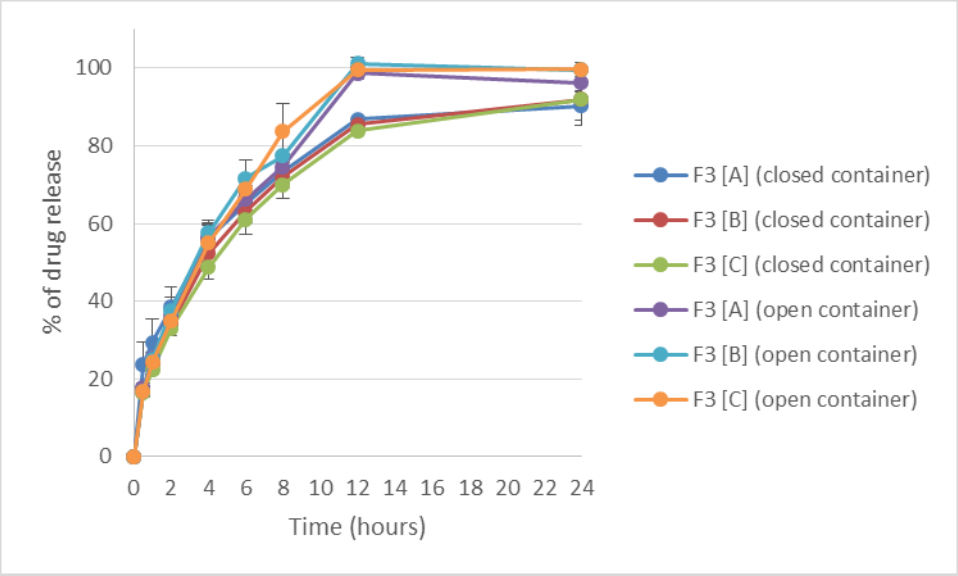


Figure 3-62: Percentage of drug release of F3 floating tablets pressed at levels (A) and (B) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

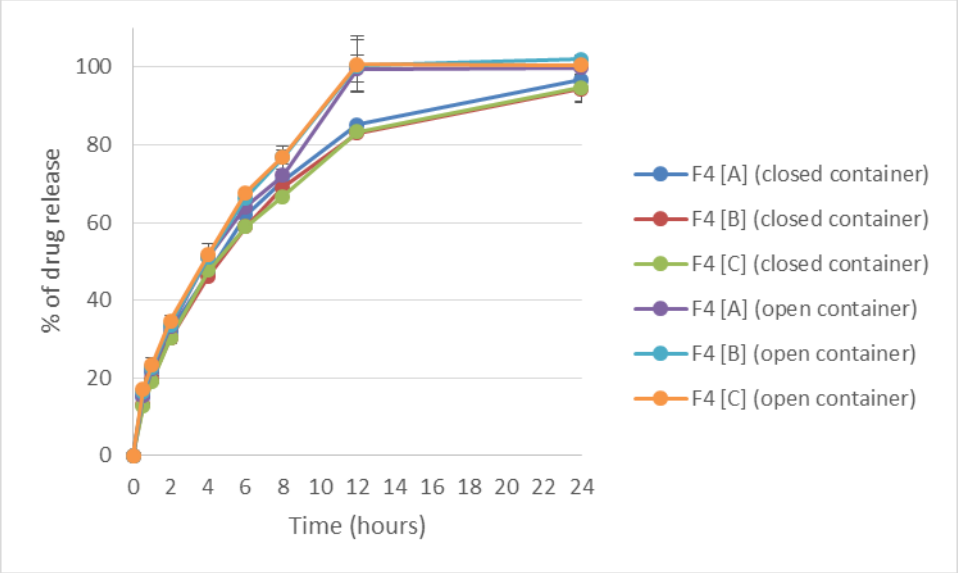


Figure 3-63: Percentage of drug release of F4 floating tablets pressed at levels (A) and (B) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 3-1 or Table 2-7.

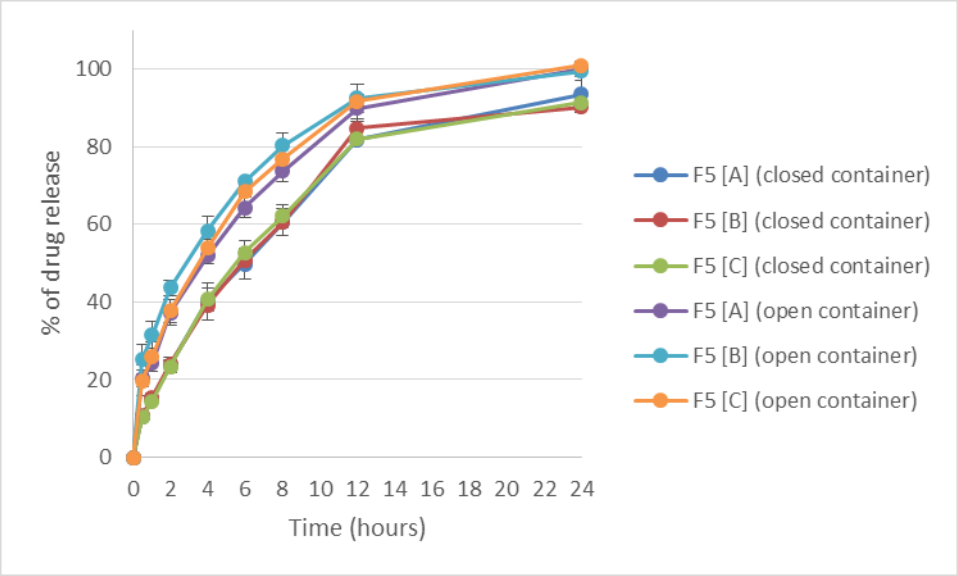


Figure 3-64: Percentage of drug release of F5 floating tablets pressed at levels (A) and (B) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

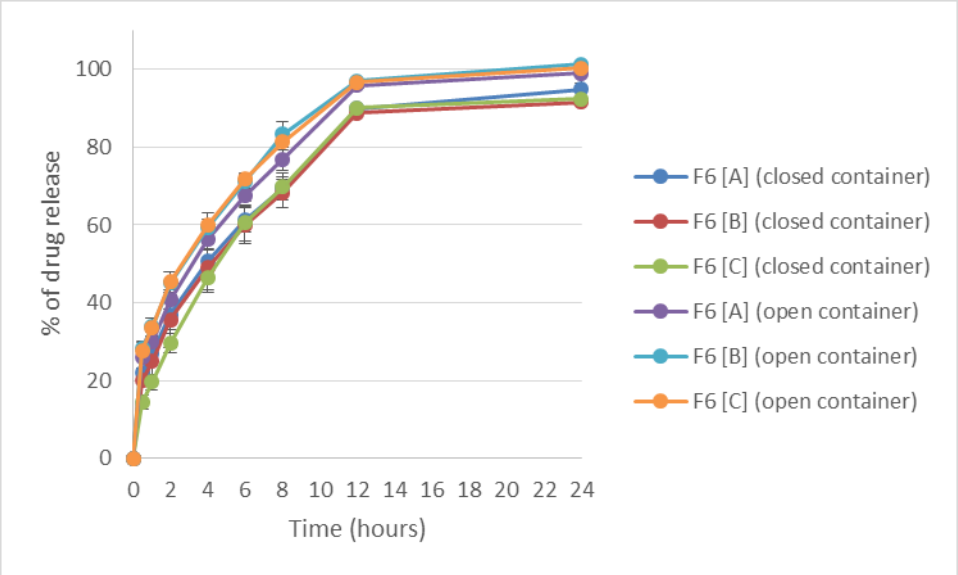


Figure 3-65: Percentage of drug release of F6 floating tablets pressed at levels (A) and (B) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 3-1 or Table 2-7.

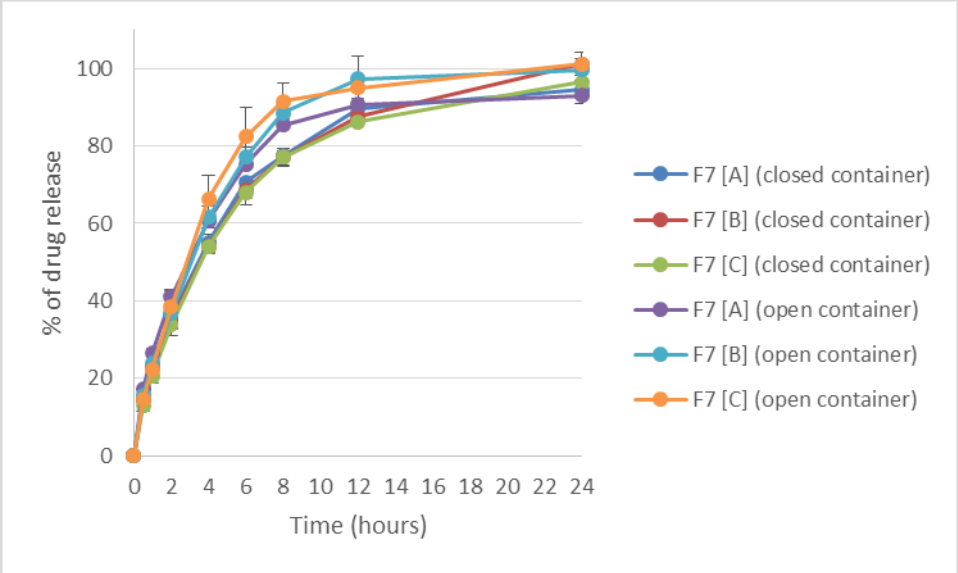


Figure 3-66: Percentage of drug release of F7 control tablets pressed at levels (A) and (B) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 3-1 or Table 2-7.

Regarding the ICH (Q6A), any change in the qualitative characteristics of the dosage form, such as the colour, during storage should be investigated appropriately (ICH, 1999). The morphological changes due to storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers had been observed (Figure 3-67). Pictures of the tablets based on sodium bicarbonate (F1 and F2) gave an impression that the tablets became pink and spotted after the storage, however they were not. Pictures were taken at different time intervals during the study and it was difficult to have the same quality of the pictures at each time interval. Additionally, no change in the tablets colour of the formulations based on calcium carbonate (F3 and F4) was observed after the storage neither in the closed nor in the open containers. This agrees with earlier results of DSC (Section 3.1.2) and FTIR (Section 3.1.3) that confirmed stability of pentoxifylline in the formulations F1-F4 after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers. In contrast, small spots with brown colour were shown on the surface of F5 (10% sodium carbonate) and F6 (20% sodium carbonate) tablets only after storage in open containers. Although, both DSC (Section 3.1.2) and FTIR results (Section 3.1.3) indicates stability of pentoxifylline in such formulations, this is not acceptable and needs further investigations in the future using a specific stability-indicating assay method such as HPLC to determine the drug content and any possible degradation products.

Formulation	Freshly prepared tablets	Tablets after storage at 40°C ± 2°C and 80% ± 5% RH	
		Closed container	Open container
F1			
F2			
F3			
F4			
F5			
F6			
F7			

Figure 3-67: Pictures of F1-F7 tablets freshly prepared and after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 3-1or Table 2-7.

3.2.6 Release data modeling and analysis

Hydrophilic polymers such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methylcellulose, sodium carboxymethyl cellulose, and alginates are commonly used to fabricate three dimensional networks (matrices) to extend the drug release. Within these systems, drug and other substances like excipients required for the formulation are embedded (Kydonieus, 1992; Wise, 2000). On contact with aqueous media, water penetrates the polymer network inducing stresses within the matrix polymer causing relaxation shown as swelling by converting the hydrated polymer from a glassy state (or crystalline phase) to a rubbery state (Kararli et al., 1990; Ju et al., 1995; Linder et al., 1996). The resulted gel layer will control further diffusion of water into the matrix as well as diffusion of the drug out of the matrix. With time, this gel layer will dissolve (erode) in the medium by slow disentanglement of the polymer chains. After erosion, the new matrix surface will again be hydrated to form a new gel layer. In general, polymer dissolution (erosion) and diffusion of drug molecules across the gel layer have been identified as the rate-controlling mechanisms (Li and Jasti, 2006).

Presence of cross-links between the polymeric chains enhances swelling of the network and delays its dissolution in the liquid medium. In case of strong cross-links between polymeric chains, covalent bonds are present, and the network is not modifying with time. However, in case of weak cross-links, van der Waals, dipole–dipole, hydrophobic and hydrogen bonding exist; and this kind of network can easily undergo erosion due to polymer-polymer junction weakness. Further complicated situation is present in matrices based on two different polymers as two interpenetrating structures (networks) are created. Normally, these systems are created by an early swelling of a monomer and reacting to form a second intermeshing network structure (Aso et al. 1999, Xuequan et al., 2000).

Matrices can be classified regarding their porosity into macroporous, microporous and non-porous systems. In macroporous and microporous systems, drug diffusion occurs essentially through pores ranging in size between 0.1-1 mm and between 50-200 Å respectively. Conversely, in non-porous systems drug molecules diffuse through network meshes as only the polymeric phase exists and no pores are present (Kydonieus, 1992).

Figure 3-68 represent polymer swelling/erosion and drug delivery process from matrix systems. During the drug release process, eroding, swelling, and diffusion fronts can be shown (Lee and Kim, 1991). The eroding front separates the release environment (dissolution medium) from the matrix. Position of the eroding front depends on hydrodynamic conditions of the release environment and on cross-linking strength of the matrix. It moves outwards when swelling kinetics is predominant on the erosion process, and moves inwards in the opposite situation. The swelling front separates the swollen matrix layer from the dry glassy core. It moves inward with a speed depends on the viscoelastic properties of the polymer / solvent couple of non-porous matrices, while it depends additionally on matrix porosity for porous systems.

Drug release kinetics can be influenced by drug / polymer ratio, drug distribution inside the matrix, drug dissolution / diffusion characteristics, polymer swelling and erosion characteristics, and system geometry (Conte et al., 1988; Colombo et al., 1999). Drug solubility plays a major role in the release mechanism. Soluble drugs are released by diffusion through the formed gel layer, while insoluble drug release is done by erosion followed by dissolution and diffusion of drug molecules.

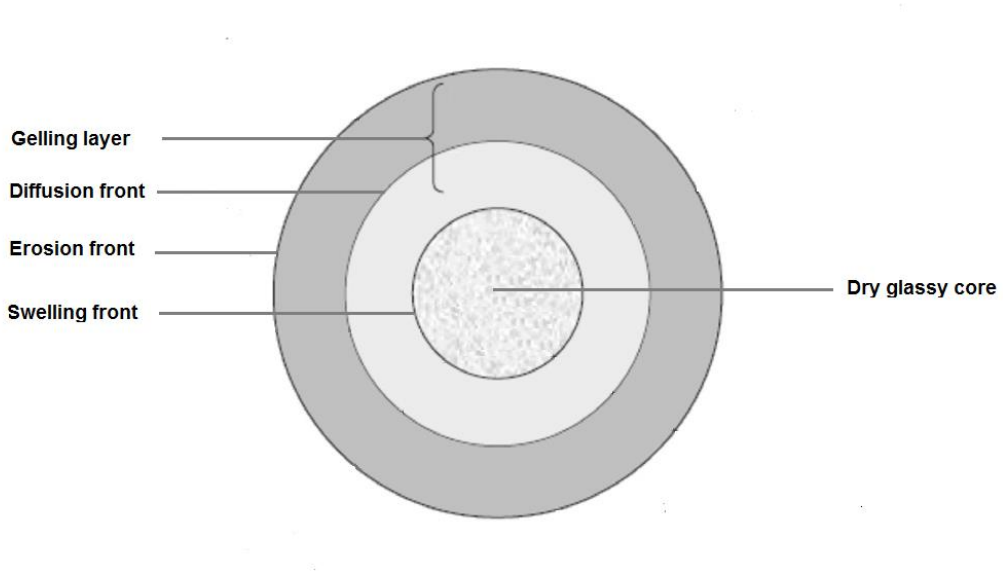


Figure 3-68: Polymer swelling/erosion and drug delivery process from matrix systems (Lopes et al., 2005)

Extended drug release systems such as matrices are able to control drug release rate and its duration of action by maintaining drug concentration in the blood or in targeted tissues at a desired level as long as possible (Langer and Wise, 1984, Robinson and Lee, 1987). Newly developed pharmaceutical products are extensively evaluated by the pharmaceutical industry and the registration authorities to ensure that drug release / dissolution occurs in an appropriate manner (Costa and Sousa Lobo, 2001). Drug is released continuously from most oral sustained drug release systems in a linear or non-linear release fashion (Bussemer and Bodmeier, 2003) as drug cristallinity, polymorphic form, particle size, solubility and amount in the dosage form can influence the release kinetics (Salomon and Doelker, 1980; El-Arini and Leuenberger, 1995). Thus, the quantitative analysis of the drug release data obtained from *in vitro* dissolution tests is easier when mathematical models are applied. This approach enables prediction of the drug delivery system release kinetics and consequently has a very important role in the drug delivery systems optimisation. Well-defined drug release kinetics is required in order to supply the drug maintenance dose to achieve the desired therapeutic level (Grassi and Grassi, 2005). In this work, zero order, first order, Hixson-Crowell, Higuchi, and Korsmeyer–Peppas mathematical release models were used to describe drug release process from the designed floating systems.

Pharmaceutical dosage forms that do not disaggregate (assuming that area does not change) and release the drug slowly can be represented by zero order models. This model can be used to describe the drug dissolution of some transdermal systems, as well as matrix tablets with low soluble drugs, coated forms, and osmotic systems (Varelas et al., 1995). The same amount of drug by unit of time can be achieved by this order of release and it is the ideal method of drug release in order to achieve a pharmacological prolonged action (Costa and Sousa Lobo, 2001). Release of water-soluble drugs loaded in porous matrices can be fitted into first order release model in which the drug is released in a way that is proportional to the amount of drug remaining in its interior (Costa and Sousa Lobo, 2001). Higuchi (1963) developed another mathematical model using an equation to describe the drug release from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.

Several types of modified release pharmaceutical dosage forms can be fitted into this model such as some transdermal systems (Costa et al., 1996) and matrix tablets with water soluble drugs (Desai et al., 1966a,b; Schwartz et al., 1968a,b). The Hixson-Crowell model is a cube root law describes the drug release from delivery systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931). Korsmeyer-pepas model is used to describe the release of polymeric pharmaceutical dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved (Korsmeyer et al., 1983). Drug release mechanism could be predicted from values of exponent (*n*). For a cylindrical tablet, a value of $n \leq 0.45$ indicates Case I transport or Fickian release (release by diffusion), $0.45 < n < 0.89$ indicates anomalous or non-Fickian release (release by diffusion and polymer relaxation), $n = 0.89$ indicates Case II transport (release by polymer erosion and zero-order kinetics), and $n > 0.89$ indicates Super Case II transport (release by polymer erosion) (Peppas, 1985; Mura et al., 1995).

Table 3-7 summarizes the release rate constants (*k*), and correlation coefficients (R^2) calculated after fitting the release profiles of the formulations F1-F7 into zero order, first order, Hixson-Crowell, and Higuchi drug release mathematical models. Due to the rapid dissolution profiles of the tablets prepared from the powder mixtures at levels A of crushing strength of F2 (Figure 3-52), at levels A and B of F3 (Figure 3-53), at levels A, B, and C of F4 (Figure 3-53), and at level A of F7 (Figure 3-55) their profiles were excluded from Table 3-7 evaluation.

The *in vitro* drug release rate of the formulations F1-F7 were best explained by first order, Hixson-Crowell, and Higuchi‘s equations, as greater than 0.98 linearity (R^2) values were obtained. Results indicates a concentration dependent drug release process and a change in diameter and surface area of the matrices with the progressive dissolution process as a function of time. Additionally, the release of pentoxifylline from the evaluated floating matrices (F1-F7) as a square root of time dependent process was based on Fickian diffusion.

The drug release data were fitted into Korsmeyer–Peppas equation (Equation 11, chapter 2, section 2.2.6.6), which describes the drug release from polymeric systems, to evaluate the effect of different variables such as tablet crushing strength, the granulation process, and gassing agent concentration on the drug release mechanism of the prepared tablet (F1-F7).

Table 3-7: Release rate constants (k), and correlation coefficients (R^2) calculated after fitting the release profiles of F1-F7 into of zero order, first order, Hixson-Crowell, and Higuchi drug release mathematical models.

Formulation	Origin of prepared tablets	Crushing strength Level	Drug release mathematical model							
			Zero order		First order		Hixson-Crowell		Higuchi	
			R^2	K_0 ($mg*h^{-1}$)	R^2	K_1 (h^{-1})	R^2	K_{HC} ($mg^{1/3}*h^{-1}$)	R^2	K_H ($mg^{1/2}*h^{-1}$)
F1	Powder	(A)	0.9363	5.0306	0.9988	0.1564	0.9905	0.1617	0.9925	21.582
		(B)	0.9569	6.3404	0.9885	0.1810	0.9982	0.1908	0.9974	26.974
	Granules	(A)	0.9350	6.3000	0.9980	0.1451	0.9860	0.1670	0.9930	27.050
		(B)	0.9440	6.7200	0.9970	0.1773	0.9960	0.1920	0.9960	28.760
F2	Powder	(A)	0.6237	0.8232	0.6670	0.0712	0.6539	0.0533	0.7917	3.865
		(B)	0.9719	3.5910	0.9985	0.1092	0.9952	0.1153	0.9923	15.120
	Granules	(A)	0.9870	5.9810	0.9930	0.1152	0.9980	0.1410	0.9870	24.910
		(B)	0.9850	5.6540	0.9960	0.1082	0.9990	0.1330	0.9900	23.610

The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations. For formulation composition, refer to Table 3-1 or Table 2-7. Figure 3-69 shows the release kinetic plots with equations.

Table 3-7 (continued): Release rate constants (k), and correlation coefficients (R^2) calculated after fitting the release profiles of F1-F7 into of zero order, first order, Hixson-Crowell, and Higuchi drug release mathematical models.

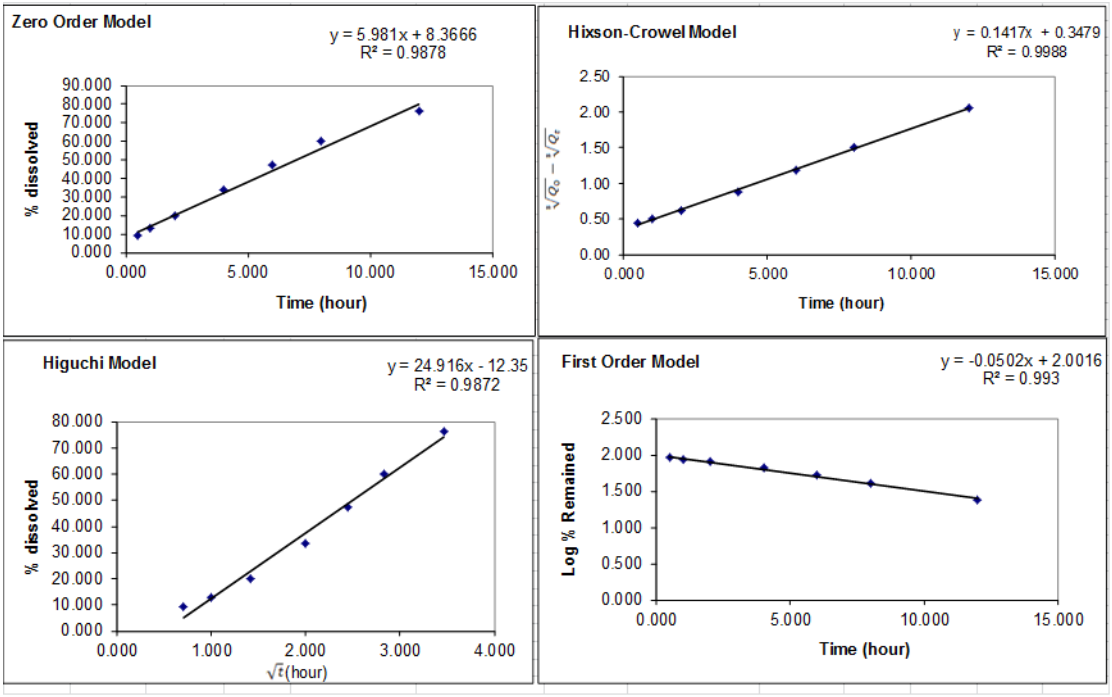
Formulation	Origin of prepared tablets	Crushing strength Level	Drug release mathematical model							
			Zero order		First order		Hixson-Crowell		Higuchi	
			R^2	K_0 ($mg*h^{-1}$)	R^2	K_1 (h^{-1})	R^2	K_{HC} ($mg^{1/3}*h^{-1}$)	R^2	K_H ($mg^{1/2}*h^{-1}$)
F3	Powder	(A)	0.5492	-0.3801	0.5058	-0.0560	0.5199	-0.0349	1.0000	1.000
		(B)	0.5623	-0.3834	0.5172	-0.0617	0.5337	-0.0376	0.4637	-1.450
		(C)	0.9193	5.4102	0.9832	0.2229	0.9760	0.2061	0.9795	23.270
	Granules	(A)	0.9768	6.4900	0.9632	0.1891	0.9933	0.1968	0.9985	27.342
		(B)	0.9671	6.2208	0.9803	0.1670	0.9938	0.1802	0.9986	26..34
		(C)	0.9682	6.2580	0.9718	0.1614	0.9912	0.1768	0.9973	26.466
F4	Powder	(A)	0.3708	0.9083	0.3764	0.0949	0.3823	0.0658	0.5424	4.578
		(B)	0.4099	0.6645	0.4778	0.0903	0.4577	0.0580	0.5787	3.290
		(C)	0.6909	1.2145	0.8202	0.1004	0.7843	0.0808	0.8178	5.506
	Granules	(A)	0.9781	5.7699	0.9311	0.2250	0.9829	0.2085	0.9977	24.283
		(B)	0.9657	5.8074	0.9552	0.2054	0.9901	0.1987	0.9984	24.604
		(C)	0.9730	6.3913	0.9450	0.2351	0.9909	0.2215	0.9978	26.969

The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations. For formulation composition, refer to Table 3-1 or Table 2-7. Figure 3-69 shows the release kinetic plots with equations.

Table 3-7 (continued): Release rate constants (k), and correlation coefficients (R^2) calculated after fitting the release profiles of F1-F7 into of zero order, first order, Hixson-Crowell, and Higuchi drug release mathematical models.

Formulation	Origin of prepared tablets	Crushing strength Level	Drug release mathematical model							
			Zero order		First order		Hixson-Crowell		Higuchi	
			R^2	K_0 ($mg*h^{-1}$)	R^2	K_1 (h^{-1})	R^2	K_{HC} ($mg^{1/3}*h^{-1}$)	R^2	K_H ($mg^{1/2}*h^{-1}$)
F5	Powder	(A)	0.9722	6.5091	0.9943	0.1462	0.9974	0.1691	0.9918	27.394
		(B)	0.9674	6.5549	0.9964	0.1492	0.9979	0.1718	0.9939	27.686
		(C)	0.9705	6.3234	0.9983	0.1303	0.9980	0.1557	0.9954	26.686
	Granules	(A)	0.9968	6.5989	0.9523	0.1490	0.9831	0.1712	0.9818	27.290
		(B)	0.9849	6.3283	0.9864	0.1333	0.9983	0.1578	0.9950	26.505
		(C)	0.9804	6.2525	0.9848	0.1327	0.9963	0.1565	0.9955	26.255
F6	Powder	(A)	0.9627	5.1328	0.9944	0.1343	0.9913	0.1483	0.9906	21.695
		(B)	0.9780	5.6887	0.9884	0.1557	0.9979	0.1680	0.9912	23.864
		(C)	0.9800	5.8058	0.9910	0.1446	0.9993	0.1615	0.9934	24.358
	Granules	(A)	0.9848	6.4070	0.9687	0.1416	0.9900	0.1643	0.9919	26.794
		(B)	0.9784	6.2527	0.9926	0.1315	0.9994	0.1559	0.9969	26.300
		(C)	0.9789	5.9492	0.9922	0.1195	0.9979	0.1443	0.9963	25.010
F7	Powder	(A)	0.6161	-0.1697	0.4580	-0.0707	0.5119	-0.0311	0.5679	-0.679
		(B)	0.9280	4.9154	0.9327	0.3222	0.8799	0.3822	0.9924	21.187
		(C)	0.9352	6.1052	0.9858	0.2126	0.9970	0.2069	0.9946	26.236
	Granules	(A)	0.9313	5.5089	0.9873	0.1124	0.9734	0.1355	0.9910	23.680
		(B)	0.9718	5.7306	0.9963	0.1207	0.9973	0.1434	0.9974	24.192
		(C)	0.9749	5.6694	0.9950	0.1207	0.9971	0.1430	0.9958	23.880

The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations. For formulation composition, refer to Table 3-1 or Table 2-7. Figure 3-69 shows the release kinetic plots with equations.



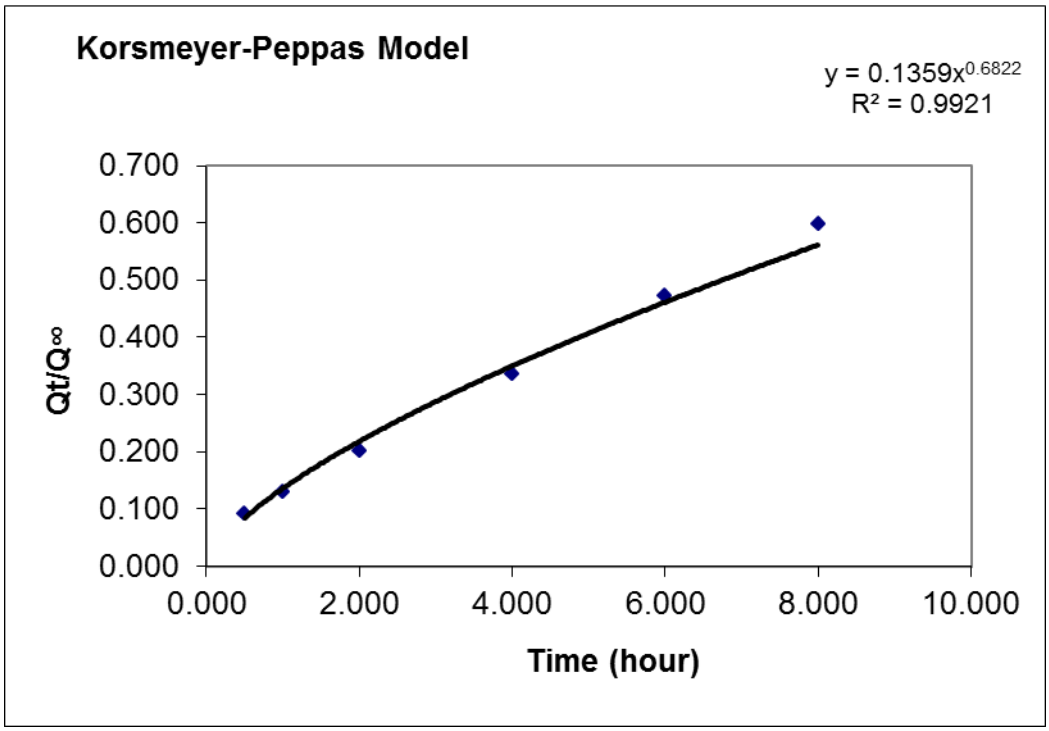


Figure 3-69: Mathematical model plots of F2 floating tablets (as an example) pressed at level (A) of crushing strength in 0.1 M HCl medium after granulation.

As shown in Table 3-8, drug release results of F1-F7 tablets fitted into Korsmeyer–Peppas equation as correlation coefficients (R^2) greater than 0.98 were obtained in most cases except for those tablets prepared from the powder mixture of F1 formulation (10% (w/w) sodium bicarbonate) at crushing strength level (A), F2 formulation (20% (w/w) sodium bicarbonate) at crushing strength level (B), and F3 formulation (10% (w/w) calcium carbonate) at crushing strength level (C) where (R^2) values were 0.9710, 0.9459, and 0.9392 respectively. There were insufficient data points on the release profile ≤ 60% drug release in order to provide accurate values for tablets prepared from the powder mixture of F2 (Figure 3-52), F3, F4 (Figure 3-53), and F7 (Figure 3-55) due to their rapid drug release rate.

The values of release rate constant (K_P) conforms to the *in vitro* drug release results discussed earlier (Section 3.2.5). Generally, increasing tablet crushing strength showed a decrease in K_P values of the tablets prepared from the powder mixture but slightly changed those of the granules origin. This complies with *in vitro* drug release studies, where increasing the compression force made the powder mixture particles closer to each and reduced the porosity percentage values. This also delayed penetration of the dissolution medium into the matrix to dissolve the drug, which decreased the drug release rates.

The granulation process decreased the release rate constant (K_P) of all the formulations (F1-F7). This agrees with previous discussion for the effect of the granulation process on the drug release process (Section 3.2.5), where the granulation decreased porosity during the wet massing stage, and this reduction delayed the dissolution medium entrapment through the matrix at an early stage of the dissolution test, and decreased the drug release rate.

It has been noted that as sodium bicarbonate concentration increased from 0% to 20% (w/w), drug release rate (K_p) decreased in all the tablets prepared from the granules. This complies with the drug release rate (Section 3.2.5) as increasing sodium bicarbonate concentration increased the floating duration, which decreased the available surface area of tablets for DMU. Consequently, a lower swelling rate was obtained (Section 3.2.4), which means less dissolution medium entrapment in matrix tablet bodies, which was presented by reduction in the drug release rate.

Regarding the other formulations (F3-F6), increasing gassing agent concentration from 0% (w/w) to 20 % (w/w) increased K_P values of all the tablets except those based on sodium carbonate as a gassing agent (F5 and F6) prepared from the powder mixture or the granules which obeys with the drug release rate discussed earlier (Section 3.2.5).

The effect of the tablet crushing strength, the granulation process, and the gassing agent concentration on the drug release mechanism of the prepared tablet (F1-F7) was also evaluated through the release exponent (*n*) values. As shown in Table 3-8, increasing tablet crushing strength for F1 formulation prepared from powder mixture changed the release exponent (*n*) values from 0.2532 to 0.5057. This indicates a change in the mechanism of the drug release from Fickian to non-Fickian, which means involvement of polymer swelling or relaxation in the release process beside drug diffusion. However, the results of F2 formulation were not clear regarding release kinetics due to the insufficient data points at level (A) of crushing strength. Changing the crushing strength level in the tablets prepared from the granules slightly changed the exponent (*n*) values in both the formulations F1 and F2, where values were in the range of 0.5799 - 0.6822, which indicates anomalous or non-Fickian release mechanism. Regarding the formulations F3-F7, changing the crushing strength level slightly changed (*n*) values but without changing the release mechanism of all the prepared tablets. An exception was noted in those of F7 (0% gassing agent) formulation prepared from the powder mixture where (*n*) values indicates a change from Fickian to non-Fickian release. This reveals involvement of polymer swelling or relaxation in the release beside drug diffusion.

Generally, as presented in Table 3-8, the granulation process changed the exponent (*n*) values for both the formulations F1 and F2 at both crushing strength levels from Fickian to a non-Fickian release mechanism, which suggests the involvement of polymer relaxation in the release process in addition to drug diffusion.

Effect of the granulation process on the release kinetics of F3, F4 and F7 tablets was not clear because of insufficient data points. For the tablets based on sodium carbonate as a gassing agent (F5 and F6), the granulation process changed the drug release mechanism only for F6 (20% (w/w) sodium carbonate) formulation from Fickian to non-Fickian release, however the release mechanism for F5 (10% (w/w) sodium carbonate) formulation remained non-Fickian release.

The effect of increasing the gassing agent concentration from 0% to 20% (w/w) on the release kinetics was not clear in the tablets prepared from the powder mixture due to the insufficient data points. However, for the tablets prepared from the granules the effect was much clearer. It was noted that at the absence of a gassing agent, the drug release was through diffusion and polymer relaxation (non-Fickian release). The addition of gassing agents (sodium bicarbonate, calcium carbonate, or sodium carbonate) slightly increased the exponent (*n*) values, which reveals a little more contribution of polymer relaxation and erosion to release mechanism (Jiménez-Martinez et al., 2008). This may be related to the movement of generated carbon dioxide bubbles from internal to peripheral sides of floating tablets, which increased the mass loss or polymer erosion behaviour. The release mechanism did not change on the addition of gassing agents, but, adding calcium carbonate at 20% (w/w) level changed the release mechanism to diffusion mechanism (Fickian release). This may be explained by the *in situ* ability of the anionic alginate molecules to form a gel in the presence of multivalent cations such as calcium ions in aqueous medium, which fit in to the guluronate block structure like eggs in an egg box (Gacesa, 1988; Grant et al., 1973). In addition, theophylline release from polymeric matrices contained calcium ions was studied by Nokhodchi and Tailor (2004). They proposed that when calcium ions concentration increases the drug release rate increases to an optimum level before declining due to insufficient calcium ions being available to cross-link with the anionic alginate molecules to form an insoluble gel. This explain the change in the drug release mechanism from diffusion and polymer relaxation (F3) to diffusion only (F4) which may be due to better and stronger gel formation.

Table 3-8: Korsmeyer-Peppas kinetic parameters of the formulations F1-F7 pentoxifylline tablet formulations.

Formulation	Origin of prepared tablets	Crushing strength Level	Korsmeyer-Pepas		
			R^2	n	K_p (h^{-n})
F1	Powder	(A)	0.9710	0.2532	0.3809
		(B)	0.9969	0.5057	0.2512
	Granules	(A)	0.9989	0.5799	0.1907
		(B)	0.9990	0.6690	0.1990
F2	Powder	(A)	N.A	N.A	N.A
		(B)	0.9459	0.1503	0.4747
	Granules	(A)	0.9921	0.6822	0.1359
		(B)	0.9907	0.6113	0.1566
F3	Powder	(A)	N.A	N.A	N.A
		(B)	N.A	N.A	N.A
		(C)	0.9392	0.2310	0.4161
	Granules	(A)	0.9993	0.5280	0.2336
		(B)	1	0.5441	0.2319
		(C)	0.9995	0.5800	0.2144
F4	Powder	(A)	N.A	N.A	N.A
		(B)	N.A	N.A	N.A
		(C)	N.A	N.A	N.A
	Granules	(A)	0.9910	0.3355	0.3522
		(B)	0.9927	0.3768	0.3342
		(C)	0.9880	0.4202	0.2949
F5	Powder	(A)	0.9929	0.6470	0.1662
		(B)	0.9944	0.6656	0.1673
		(C)	0.9982	0.7289	0.1410
	Granules	(A)	0.9995	0.7032	0.1359
		(B)	0.9997	0.7210	0.1397
		(C)	0.9969	0.7083	0.1458
F6	Powder	(A)	0.9899	0.3012	0.3246
		(B)	0.9881	0.3458	0.2928
		(C)	0.9835	0.4379	0.2534
	Granules	(A)	0.9980	0.7116	0.1452
		(B)	0.9972	0.7005	0.1481
		(C)	0.9979	0.6739	0.1487
F7	Powder	(A)	NA	NA	NA
		(B)	0.9986	0.2511	0.5098
		(C)	0.9963	0.4564	0.3163
	Granules	(A)	0.9985	0.5859	0.1994
		(B)	0.9961	0.5889	0.1855
		(C)	0.9980	0.5457	0.1968

Notes: N.A: There are insufficient data points on the release profiles ≤ 60% drug release in order to provide accurate values. The compression force of the prepared tablets was adjusted to give two crushing strength levels: A (49–54 N), and B (54–59 N) for F1 and F2 formulations, and three crushing strength levels: A (49–54 N), B (54–59 N), and C (59-64 N) for F3-F7 formulations. For formulation composition, refer to Table 3-1 or Table 2-7.

3.3 Conclusions

In this chapter, floating tablets of pentoxifylline were prepared using a (1:1) ratio of hydroxyethyl cellulose and sodium alginate polymeric mixture based on sodium bicarbonate, calcium carbonate or sodium carbonate gas forming agent. The granulation process may enhance elastic recovery of alginate molecules after compression, which explains the inability to prepare tablets of both the formulations F1 (10% (w/w) sodium bicarbonate) and F2 (20% (w/w) sodium bicarbonate) at 59-64 N, (level C), crushing strength after the granulation. All the prepared tablets (F1-F7) through the granulation showed acceptable physical properties via complying with the BP requirements of friability, weight and drug content uniformity. The results of the formulations F4 (20% (w/w) calcium carbonate) and F5 (10% (w/w) sodium carbonate) exceeded the BP limit of friability (< 1%), however, as the tablet crushing strength level increased as the mass loss percentage decreased. Increasing the compression force showed negligible influence on the drug release rate after the granulation. This gives an advantage to control the other formulation parameters such as high friability percentages by raising the compression force without disturbing the drug release rate.

The effect of the granulation process on the drug release rate from all the formulations F1-F7 reveals that the granulation extended the drug release rate of all the prepared tablets. Increasing the concentration of the gassing agent decreased the floating lag time results of the tablets based on sodium bicarbonate or calcium carbonate due to the higher effervescent efficiency. In contrast, the lag time results increased in the tablets based on sodium carbonate due to increasing the tablets apparent densities. Raising sodium bicarbonate concentration in the tablets prepared after the granulation increased the floating duration which decreased the available surface area for the dissolution medium uptake. Consequently, a decrease in the swelling and the drug release rates were noted. In contrast, an increase in the drug release rate was noted in calcium carbonate based tablets when its concentration was increased due to the amplified pore formation in the generated gel layer around the tablets.

However, sodium carbonate, regardless its concentration, generated an alkaline microenvironment which accelerated the swelling and the gel formation rate. Hence, altering sodium carbonate concentration did not change the drug release rate from the prepared tablets.

The drug release rate of all the formulations (F1-F7) fitted into non-Fickian release mechanism except F4 tablets, containing 20% (w/w) calcium carbonate as a gassing agent, which fitted into Fickian release mechanism due to the *in situ* ability of the anionic alginate molecules to be cross linked in the presence of enough concentration of calcium ions. The tablets could float on the surface of dissolution medium and sustain the drug release over 24 h. F4 tablets prepared with 20% (w/w) calcium carbonate showed satisfactory results with respect their quality control tests, floating lag time, total floating duration, swelling ability, and sustained drug release rate. Stability studies point to suitability of closed containers for such formulations. Generally, from the results, calcium carbonate was the most effective gassing agent to produce efficient floating tablets and this can add to the pharmaceutical filed as there is sparse literature about calcium carbonate application in floating gastroretentive drug delivery systems. Therefore, calcium carbonate containing formulation, F4, was chosen for preliminary *in vivo* studies (Chapter 5).

In the following chapter (Chapter 4), another model drug, cefalexin monohydrate, which can be better to benefit from the gastroretentive systems, was loaded in floating tablet dosage forms using the gassing agents used with pentoxifylline floating tablets.

Chapter Four: Evaluation of the effect of sodium bicarbonate, calcium carbonate, and sodium carbonate as gassing agents on cefalexin monohydrate floating tablets

In this chapter, tablets based on a gel forming polymeric mixture of (1:1) ratio of hydroxyethyl cellulose and sodium alginate, and a gassing component based on sodium bicarbonate, calcium carbonate or sodium carbonate were developed and evaluated as an effervescent gastroretentive drug delivery system. Cefalexin monohydrate was used as a model drug since it has a short half-life of approximately 1 h (Davies and Holt, 1972). Consequently, it is suitable for sustained drug delivery. Still, its instability at intestinal pH and its narrow absorption window at the upper gastrointestinal tract (GIT) made it ideal model drug for the gastroretentive delivery systems but not the ordinary sustained release delivery systems (Yin et al., 2013). The variables that may affect drug release and floating properties were evaluated, such as the wet granulation (to compare effects of powders versus those of granules), and type and ratio of the gas forming agent.

In order to increase the challenge level over the designed floating tablets, the (1:1) binary mixture of hydroxyethyl cellulose and sodium alginate content was reduced by almost 36% (w/w) in cefalexin monohydrate tablets compared to pentoxifylline tablets (Chapter 3) due to the change in their drug content. In chapter 3, the dose of pentoxifylline was only 60 mg to evaluate the designed floating tablets, but in this chapter cefalexin monohydrate dose was raised up to 250 mg.

4.1 Evaluation of the prepared powders and granules (pre-compression characterisation)

All the prepared powder mixtures and granules of the formulations F8-F14 were evaluated for flowability CI index, moisture content percentage, DSC, and FTIR. The formulations F8-F14 compositions are presented in Table 4-1 (and also Table 2-8).

Table 4-1: Composition of prepared F8-F14 tablets

Ingredients/Formulation	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)
Cefalexin monohydrate	250	250	250	250	250	250	250
Hydroxyethyl cellulose	68.8	68.8	68.8	68.8	68.8	68.8	68.8
Sodium alginate	68.8	68.8	68.8	68.8	68.8	68.8	68.8
Sodium bicarbonate	42.6	96.8					
Calcium carbonate			42.6	96.8			
Sodium carbonate					42.6	96.8	
Magnesium stearate (0.5%)	2.2	2.4	2.2	2.4	2.2	2.4	1.9
Total weight	432.4[a]	486.8[a]	432.4[a]	486.8[a]	432.6[a]	486.8[a]	389.5

[a] Difference in weight was due to raising gassing agent content from 10% to 20% (w/w).

Note: number of moles of the gassing agents used in the formulations is 5.1×10^{-4} (F8), 11.5×10^{-4} (F9), 4.3×10^{-4} (F10), 9.7×10^{-4} (F11), 4.0×10^{-4} (F12), and 9.1×10^{-4} (F13).

4.1.1 Flowability and moisture content for powders and granules

The results of the moisture content and the CI value of the formulations F8-F14 before and after granulation are shown in Table 4-2. The granulation process caused a significant (P<0.05) decrease in the percentage of the moisture content of all the formulations except F13 where p=0.380.

Moreover, CI decreased following the granulation in all the formulations (F8-F14, Table 4-2) which reveals better flow properties of the granules compared to the powder mixture (Gaisford, 2013). The effect was significant (P<0.05) in the formulations based on sodium bicarbonate (F8 and F9) and sodium carbonate (F12 and F13) as gassing agents, but not significant (P>0.05) in all the other formulations (F10, F11, and F14).

The water solubility of sodium bicarbonate (Chapter 3, section 3.2.2) could enhance formation of a homogenous mass with the hydrophilic polymeric binary mixture of hydroxyethyl cellulose and sodium alginate during the wet massing process. This could assist agglomeration techniques of the granulation process where fine solid particles are converted into larger ones by mixing them in the presence of water binding liquid. This acts in accordance with the significant (P<0.05) decrease in CI results of F12 and F13 based on sodium carbonate as a gassing agent which is also water-soluble (Chapter 3**,** section 3.2.2). Additionally, this may explain the non-significant (P>0.05) effect of the granulation process on the formulations F10 and F11 based on calcium carbonate which is less water-soluble (Chapter 3**,** section 3.2.2). Hamed et al. (2005) proposed that changing proportions of water soluble excipients in formulations could significantly modify granules' properties which may explain the absence of significant effect of the granulation on the CI results of cefalexin monohydrate control formulation (F14).

Table 4-2: Moisture content and Carr's index with statistical analysis (*p*-value) results of the formulations F8-F14 before and after granulation.

Test	Formulation	Origin of prepared tablets		*P*-value
		Powder mixture	Granules	
Moisture content (%)	F8	6.25 ± 0.20	4.36 ± 0.13	0.001
	F9	5.68 ± 0.12	4.95 ± 0.16	0.013
	F10	6.74 ± 0.08	5.31 ± 0.42	0.023
	F11	5.97 ± 0.17	4.28 ± 0.08	0.001
	F12	6.80 ± 0.12	5.09 ± 0.13	0.004
	F13	6.17 ± 0.17	6.02 ± 0.11	0.380
	F14	7.20 ± 0.14	5.02 ± 0.26	0.001
Carr's Index (CI) (%)	F8	43.09 ± 0.78	23.67 ± 0.32	0.001
	F9	38.37 ± 1.87	22.34 ± 0.57	0.003
	F10	37.14 ± 4.89	30.97 ± 1.09	0.194
	F11	38.79 ± 1.83	33.97 ± 0.31	0.052
	F12	39.89 ± 1.54	28.02 ± 1.10	0.016
	F13	40.39 ± 2.26	18.92 ± 1.48	0.001
	F14	37.46 ± 4.29	31.72 ± 1.70	0.066

Note: The data represents the mean ± SD of three determinations.
For formulation composition, refer to Table 4-1 or Table 2-8.

4.1.2 Differential scanning calorimetry (DSC)

The compatibility of cefalexin monohydrate with excipients within the formulations F8-F14 before and after the granulation was studied using DSC. Cefalexin melting point and decomposition temperature was not clearly defined in literature. El-Shattawy et al. (1982) reported that cefalexin showed exothermic peaks at 178°C and at 198°C when it decomposed. Also, Doadrio et al. (2004) presented that samples containing cefalexin had an endothermic melting peak at 50°C and an exothermic decomposition peak at 200°C. However, Agnihotri, et al. (2006) stated that for pure cefalexin, an endothermic peak appeared at 194°C due to the melting of the drug. Recently, Chuong et al., (2016) concluded that the melting of cefalexin is atypical, and cefalexin monohydrate had ability to absorb energy from 31.5 to 121.9°C to permit both free and bound water to evaporate, and more enthalpy to assist degradation ranging from 176.2 to 200.3°C.

As shown in Figure 4-1, pure cefalexin monohydrate showed a broad endothermic peak at about 102.72˚C due to water evaporation, and a sharper positive transition (heat release) at 192.57˚C due to the drug degradation. Sodium alginate had a broad endothermic peak around 114.24˚C and two exothermic peaks at 212.89˚C and 240.02˚C (Chapter 3, Figure 3-2). Hydroxyethyl cellulose, sodium bicarbonate, and sodium carbonate showed endothermic peaks at about 94.88˚C (Chapter 3, Figure 3-3), 145.81˚C (Chapter 3, Figure 3-5), and 85.80˚C (Chapter 3, Figure 3-7) respectively. However, calcium carbonate as a gassing agent did not show any thermal activity as presented in (Chapter 3, Figure 3-6). Figure 4-2 and Figure 4-3 show DSC thermograms of placebo powder mixtures and placebo granules samples of F12 and F13 formulations respectively.

The DSC thermograms of the powder mixture and the granules of the formulations F8-F14 are shown in Figure 4-4 to Figure 4-10 respectively. A slight shift was noted in the drug exothermic peak to a lower temperature in the powder mixture samples (192.26˚C, 192.34˚C, 192.07˚C, and 192.15˚C), and to a higher temperature in the granules samples (194.35˚C, 194.68˚C, 194.42˚C and 193.95˚C) of the formulations F8 (Figure 4-4) and F9 (Figure 4-5) based on sodium bicarbonate as a gassing agent and the formulations F12 (Figure 4-8) and F13 (Figure 4-9) based on sodium carbonate respectively. Additionally, the DSC thermograms of the powder mixtures and the granules of F10, F11 (based on calcium carbonate), and the control formulation (F14) are shown in Figure 4-6, Figure 4-7, Figure 4-10 respectively. A slight shift in the drug exothermic peak to a lower temperature in the powder mixture samples (192.24˚C, 192.52˚C, and 191.94˚C), and the granules samples (191.91˚C, 191.66˚C, and 191.24˚C) was noted in the formulations F10, F11, and F14 respectively. This could be due to minor morphological changes of cefalexin monohydrate that took place after physical mixing and the granulation process (Agnihotri et al., 2006).

An overlapping between the broad endothermic peaks of cefalexin monohydrate, and the binary polymeric mixture (hydroxyethyl cellulose and sodium alginate) was shown at about 103.34˚C, 106.15˚C, 102.74˚C, 100.18˚C, 104.28˚C, 103.15˚C, and 106.27˚C for the powder mixture samples and a round 99.20˚C, 97.61˚C, 103.13˚C, 101.93˚C, 115.77˚C, 106.06˚C, and 104.43˚C for the granules samples of the formulations F8-F14 respectively.

The gassing agent (sodium bicarbonate) endothermic peak was noted at 156.62˚C, and 154.81˚C for the powder mixture samples and at 153.34˚C and 151.40˚C for the granules samples of the formulations F8 and F9 respectively. However, the gassing agent (calcium carbonate) was not involved in the thermal changes of the formulations F10 and F11 as it did not show any thermal activity as discussed earlier. Regarding F12 and F13 formulations based on sodium carbonate, thermograms presented more thermal activities especially after the granulation process. The endothermic peaks presented at 101.30˚C, 142.69˚C for F12 granules (Figure 4-8) and at 136.92˚C for F13 granules (Figure 4-9) were not related to the drug-excipient interactions. These thermal activities were related to the physical interaction between the formulation excipients as shown in Figure 4-2 for F12 and Figure 4-3 for F13 placebo samples. Moreover, sodium alginate exothermic peak noted at 205.40˚C for F12 and at 205.72˚C for F13 granules samples was related to the formulation excipients interactions.

Moreover, these thermal changes were not due to the gassing agents (sodium bicarbonate, calcium carbonate, or sodium carbonate) as the thermogram of cefalexin monohydrate with the excipients in the control formulation (F14) before and after the granulation displayed a slight decrease in the drug exothermic peak, from 192.57˚C (Figure 4-1), to 191.94˚C and 191.24˚C in the powder mixture and the granules samples respectively. Additionally, a broad endothermic peak due to overlapping between the endothermic peaks of the drug and the hydrophilic polymers was noted at 106.27˚C and 104.43˚C (Figure 4-10).

No additional thermal changes were reported in the DSC thermograms of the formulations F8-F14, but results obtained with DSC should always be confirmed with other tests, like IR, to avoid misleading conclusions (Chapter 3, section 3.1.2). The FTIR spectra (Section 4.1.3) confirmed presence of cefalexin monohydrate characteristic bands for the formulations F8-F14 indicating absence of incompatibility between the drug, the gassing agents (sodium bicarbonate, calcium carbonate, or sodium carbonate) and the formulation excipients (hydroxyethyl cellulose, sodium alginate, and magnesium stearate).

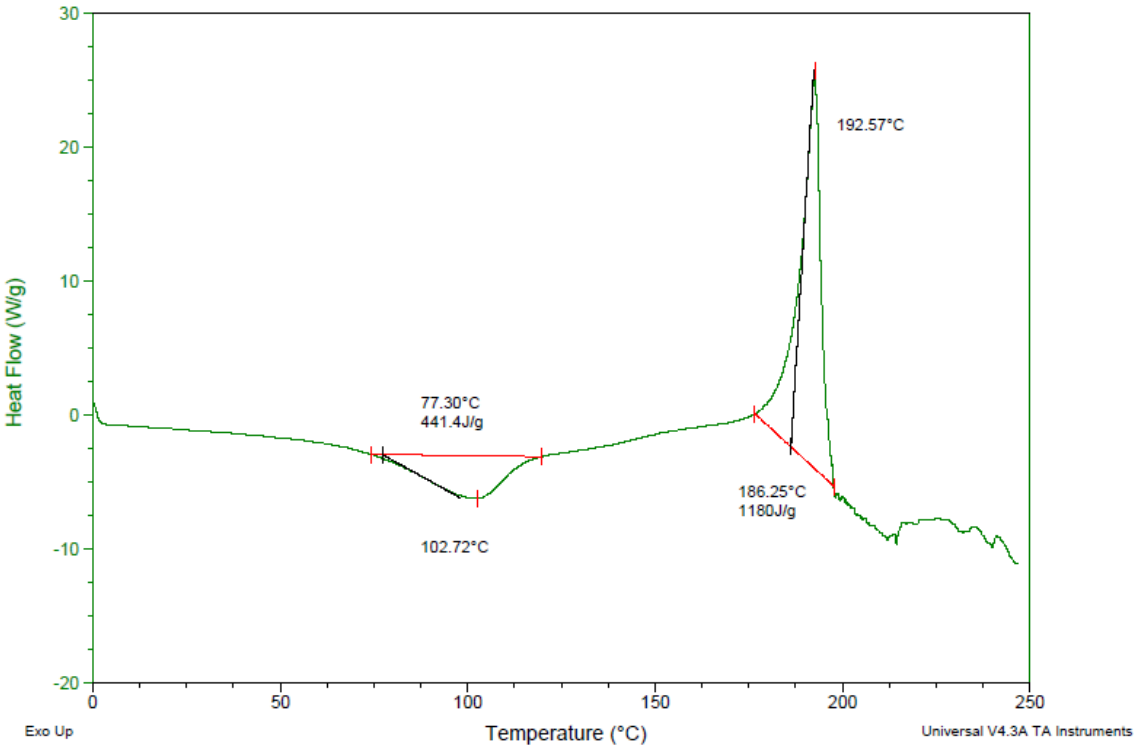


Figure 4-1: DSC thermogram of pure cefalexin monohydrate.

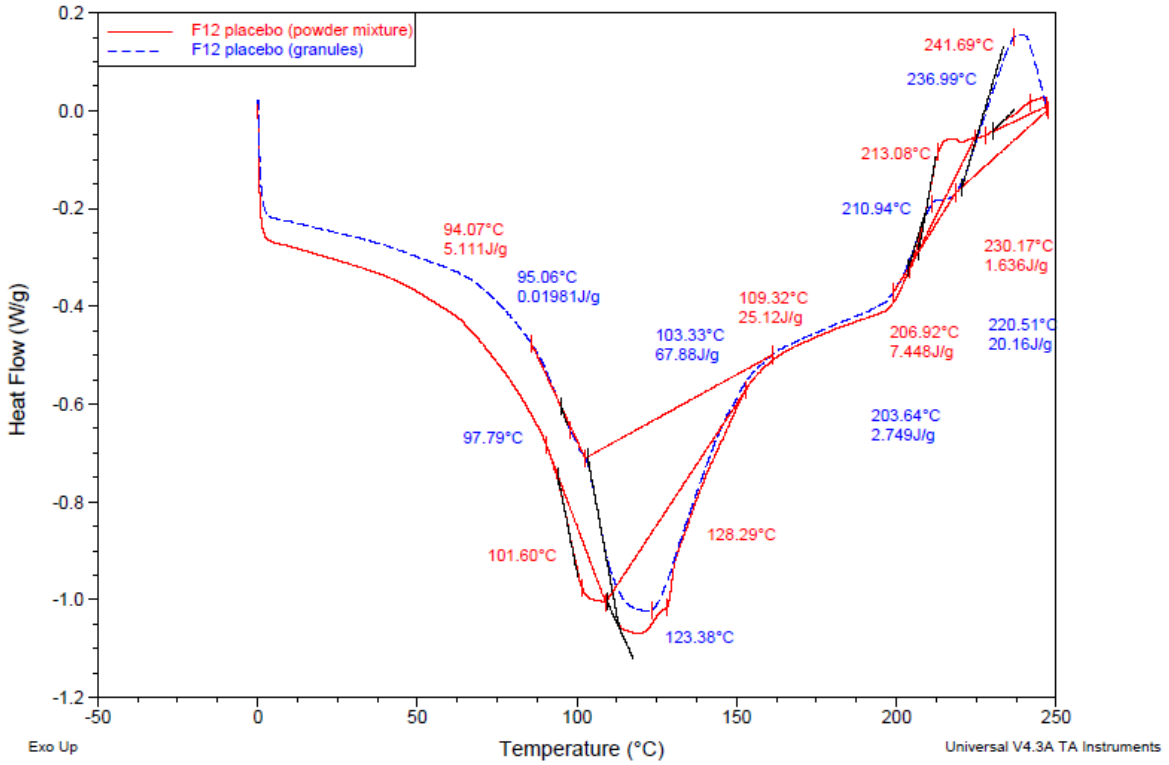


Figure 4-2: DSC thermogram of F12 formulation placebo powder mixture and placebo granules.
For formulation composition, refer to Table 4-1 or Table 2-8.

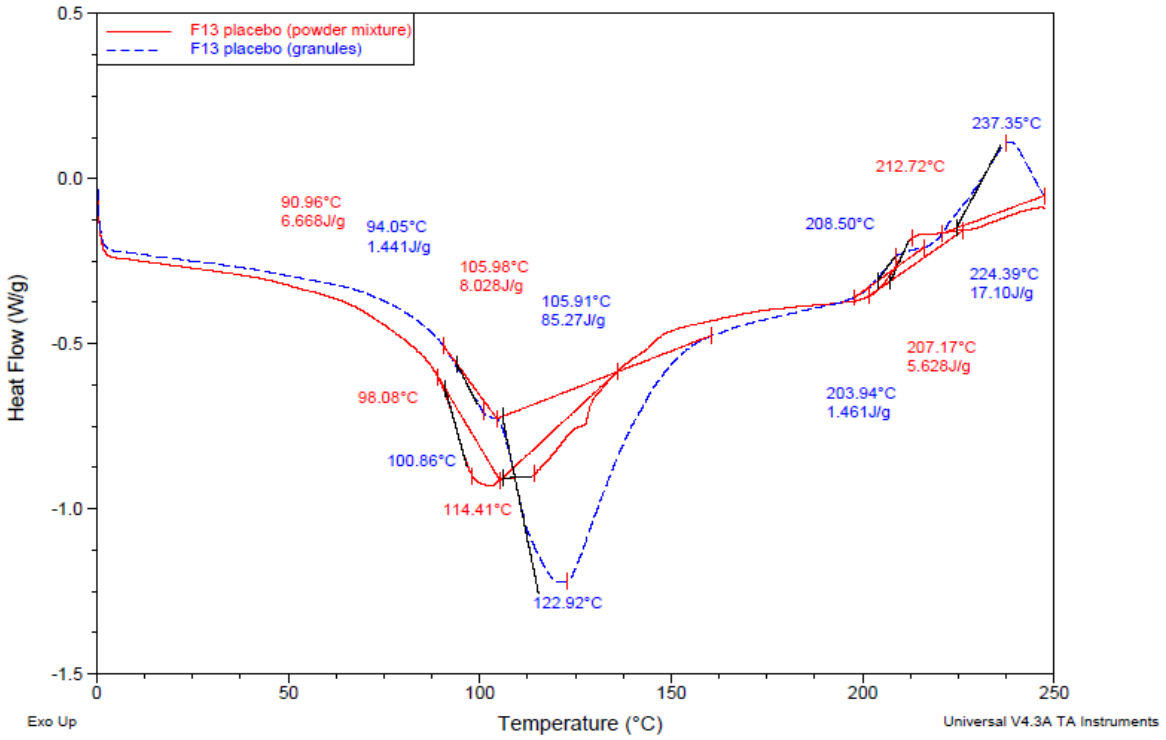


Figure 4-3: DSC thermogram of F13 formulation placebo powder mixture and placebo granules.

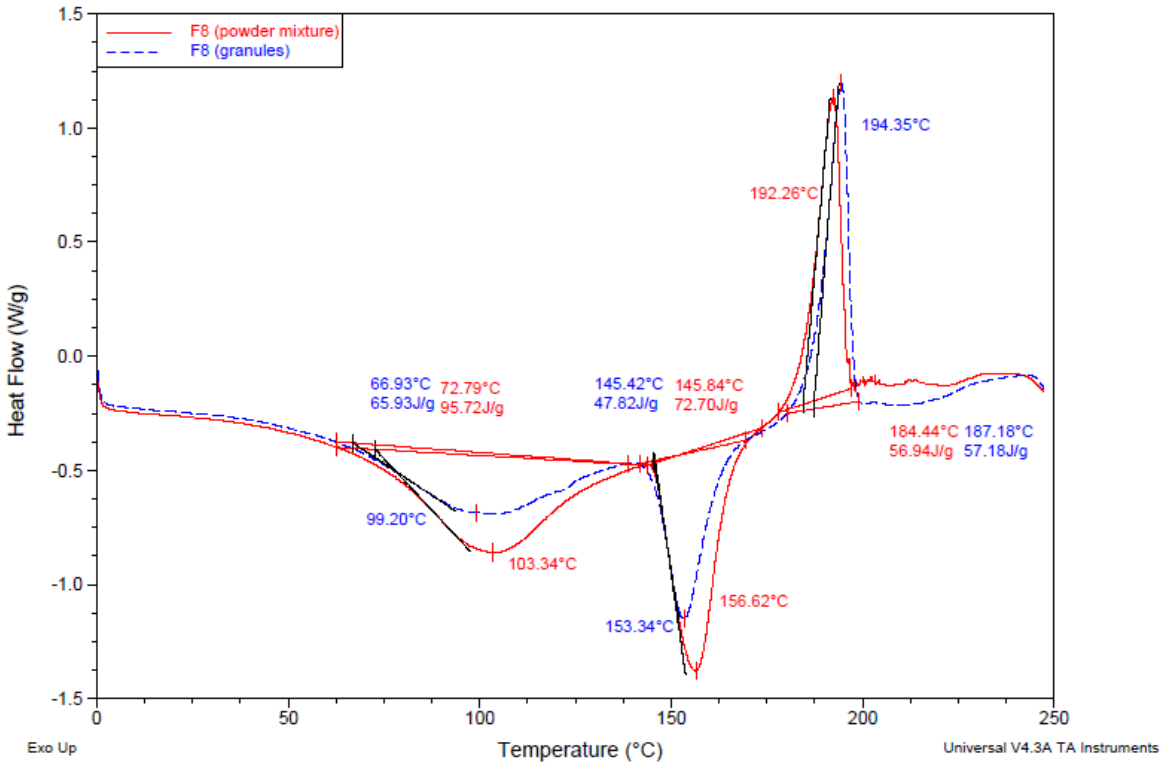


Figure 4-4: DSC thermograms of F8 powder mixture and F8 granules.
For formulation composition, refer to Table 4-1 or Table 2-8.

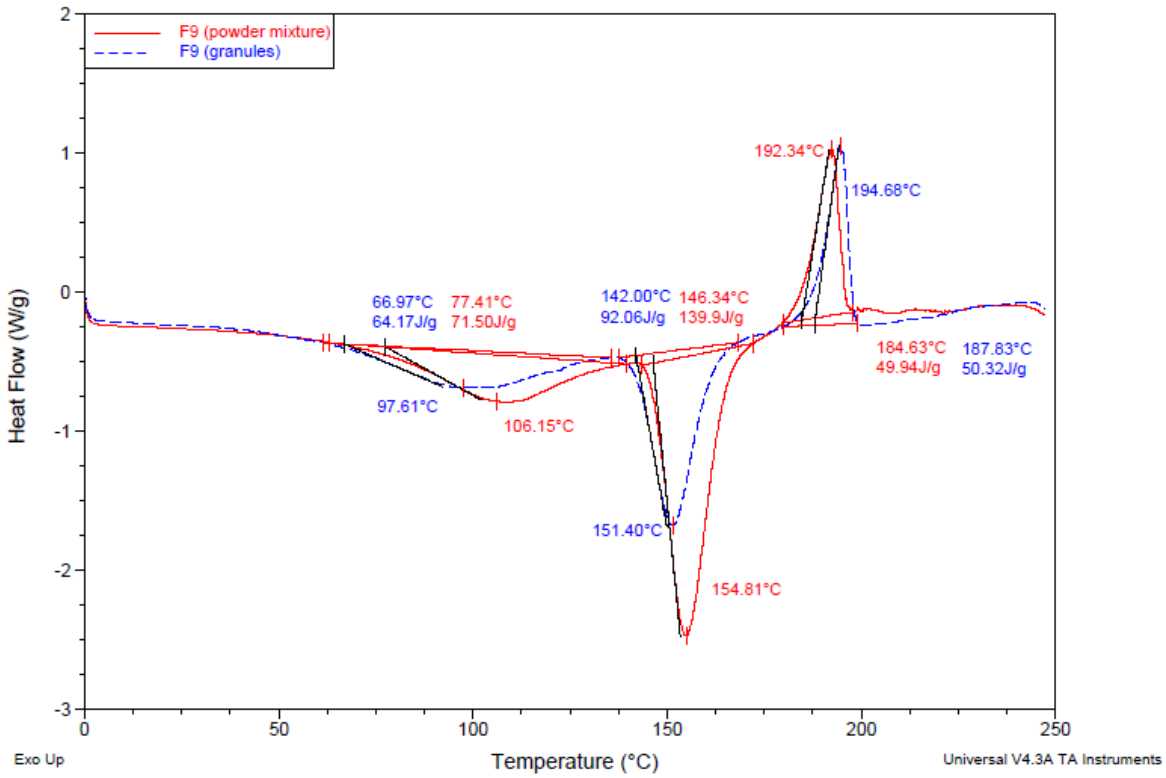


Figure 4-5: DSC thermograms of F9 powder mixture and F9 granules.

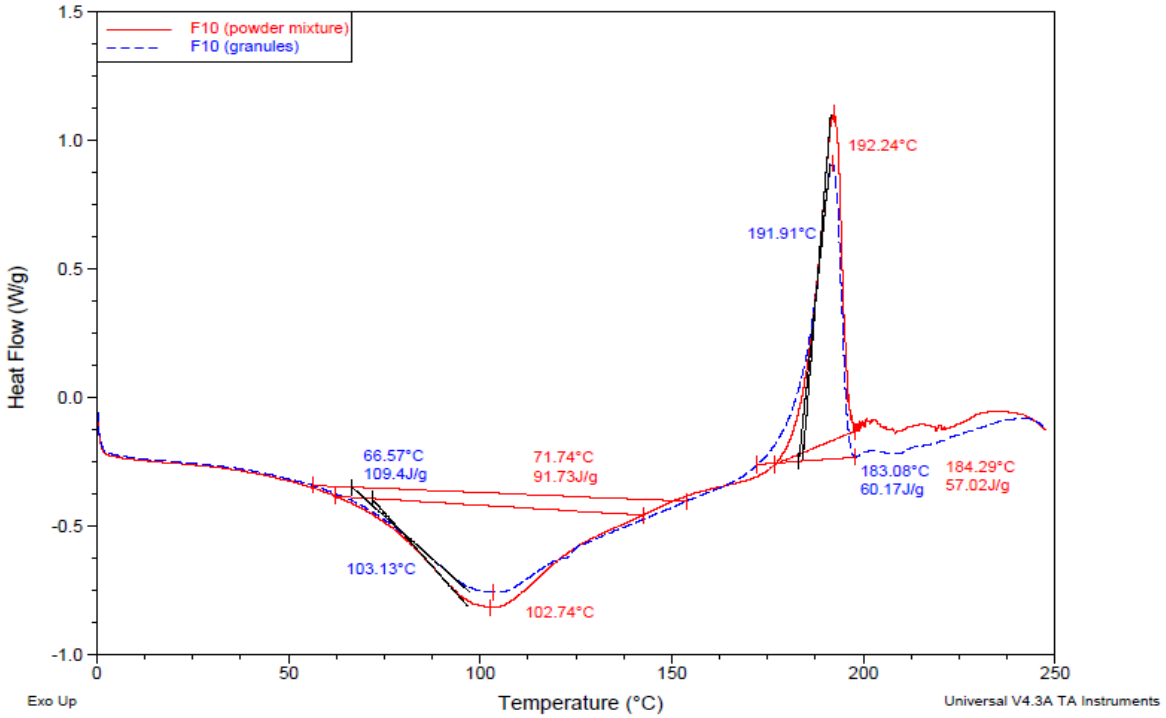


Figure 4-6: DSC thermograms of F10 powder mixture and F10 granules. For formulation composition, refer to Table 4-1 or Table 2-8.

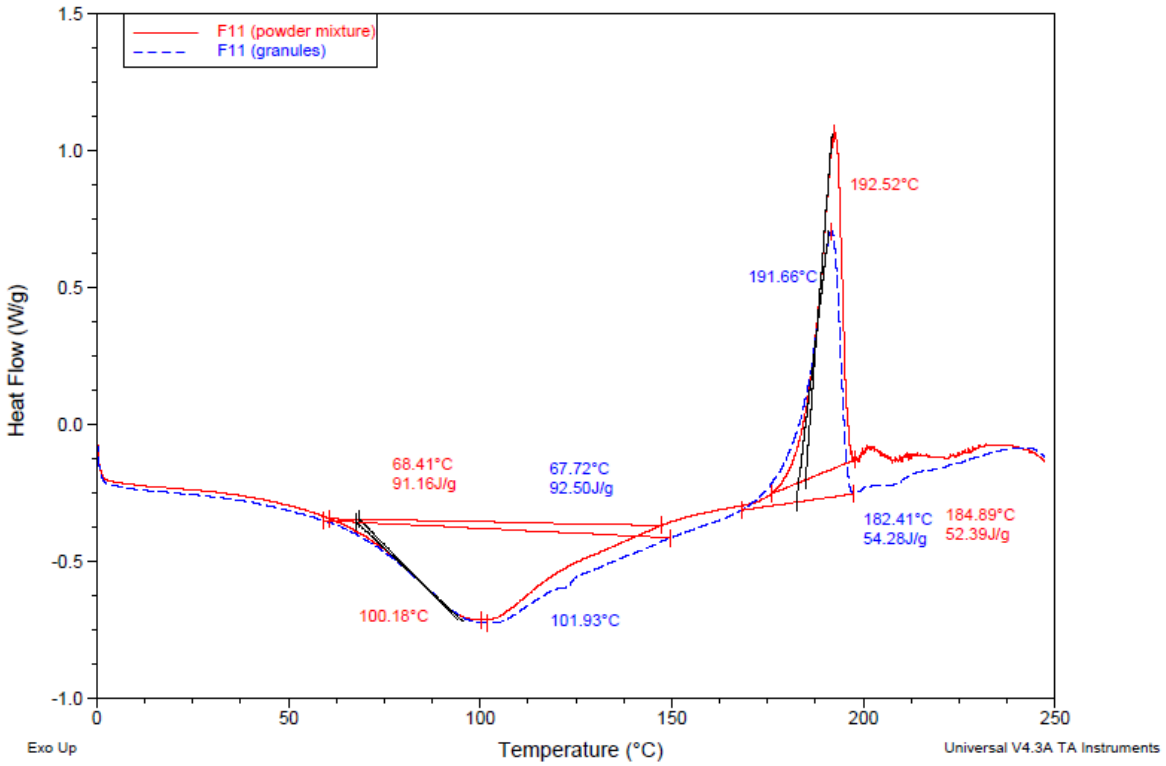


Figure 4-7: DSC thermograms of F11 powder mixture and F11 granules.

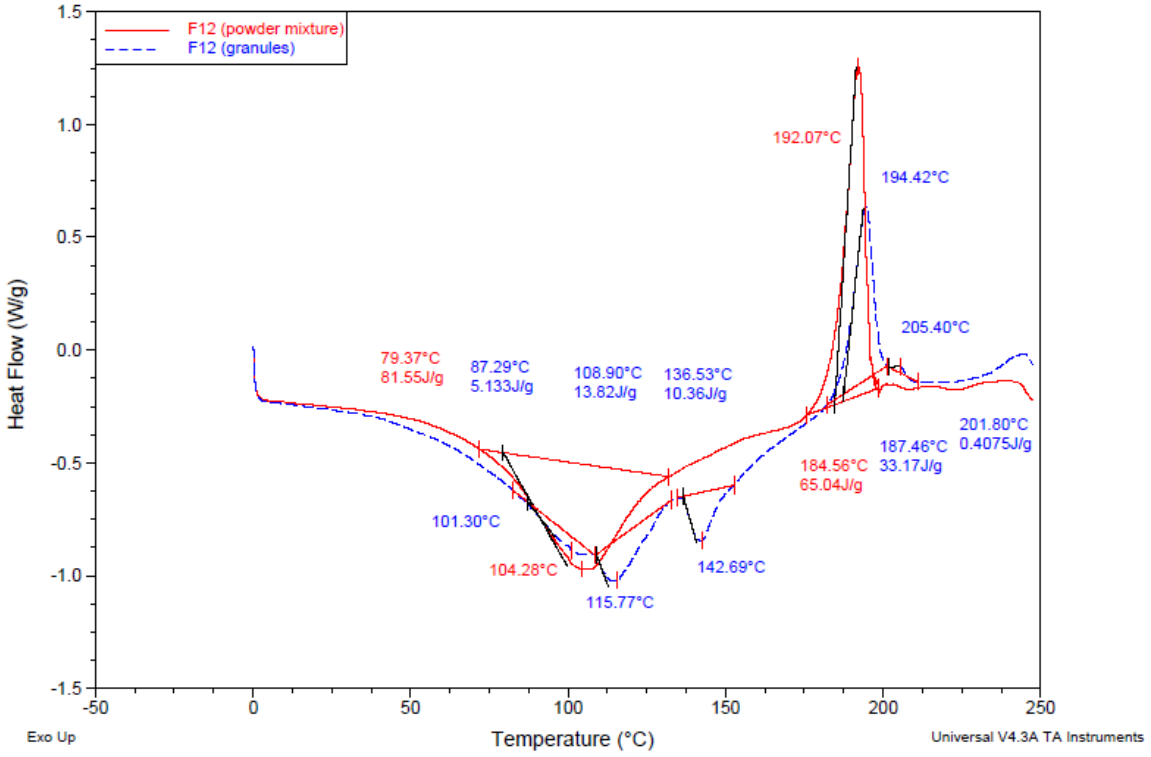


Figure 4-8: DSC thermograms of F12 powder mixture and F12 granules. For formulation composition, refer to Table 4-1 or Table 2-8.

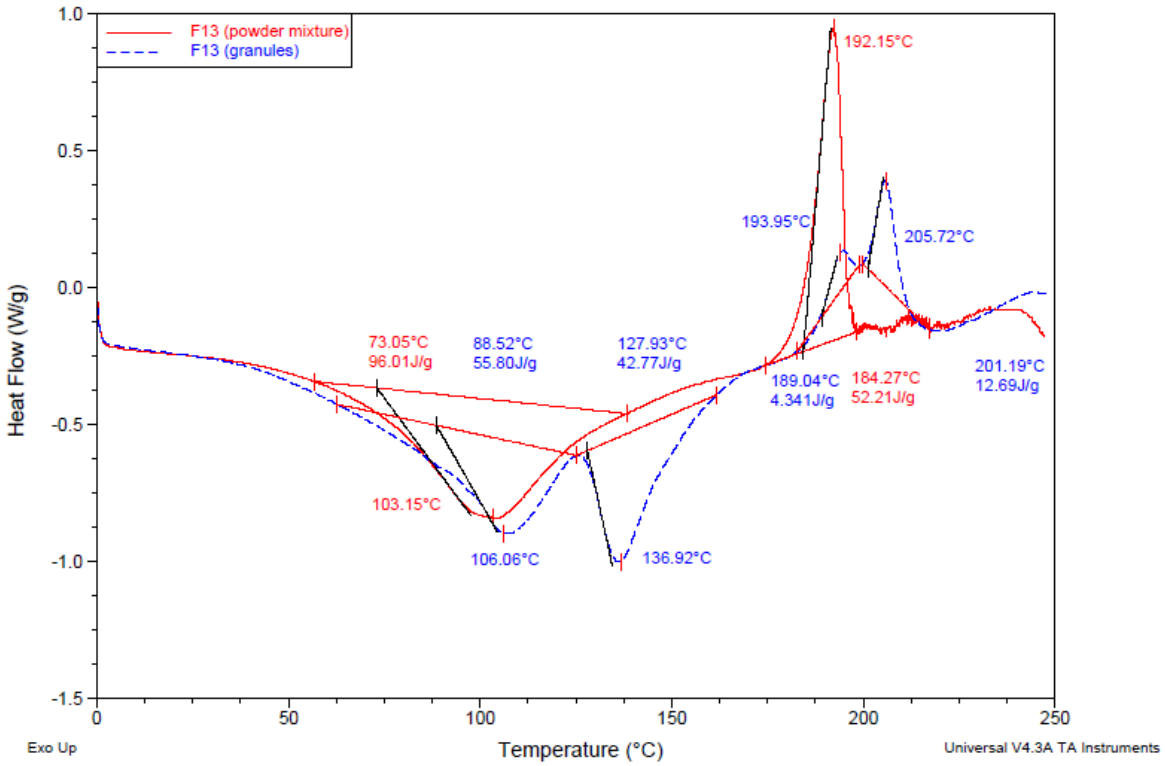


Figure 4-9: DSC thermograms of F13 powder mixture and F13 granules.

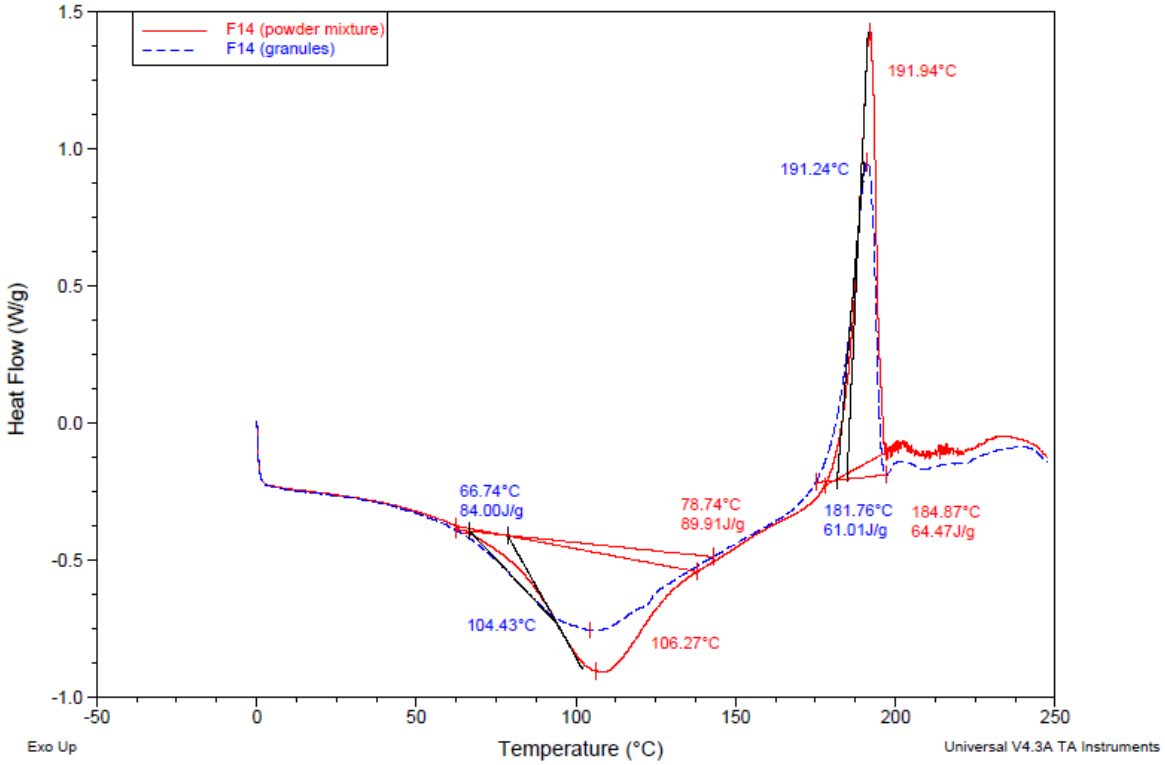


Figure 4-10: DSC thermograms of F14 powder mixture and F14 granules. For formulation composition, refer to Table 4-1 or Table 2-8.

The granules of all the formulations (F8-F14) were stored for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers and evaluated by DSC to investigate possible effects of the stressed conditions on the drug. Figure 4-11 to Figure 4-17 represent DSC thermograms of F8-F14 stability samples.

For the closed container stability samples, all characteristic peaks of cefalexin monohydrate and excipients used in the formulations F8-F14 showed almost similar thermal behaviour in comparison with the related freshly prepared granules (Figure 4-4 to Figure 4-10). The exothermic peak of cefalexin monohydrate was presented at 192.46°C, 196.45°C, 192.09°C, 192.03°C, 196.79°C, 196.03°C, and 191.31°C, and the overlapping endothermic peak of the drug and the hydrophilic polymers was noted at 120.45°C, 107.75°C, 102.71°C, 97.94°C, 110.67°C, 110.82°C, and 106.60°C for the formulations F8-F14 respectively (Figure 4-11 to Figure 4-17). Moreover, the endothermic peak of sodium bicarbonate and sodium carbonate gassing agents was shown at 170.52°C, 160.22°C, 142.18°C and 141.10°C for the formulations F8 (Figure 4-11), F9 (Figure 4-12), F12 (Figure 4-15) and F13 (Figure 4-16) respectively.

Similar behaviour was reported in the open container stability samples of the formulations F10 (Figure 4-13) and F11 (Figure 4-14) based on calcium carbonate gassing agent, and the control formulation (F14) (Figure 4-17) with exothermic degradation peak presented at 191.90°C, 192.08°C, and 190.77°C, and overlapping endothermic peak at 103.13°C, 100.85°C, and 113.26°C respectively. This represents the stability indicating effect of calcium carbonate. Thermogram of open container stability sample of F8 (10% (w/w) sodium bicarbonate) showed the drug exothermic peak and the endothermic overlapping peak of the drug and the polymeric mixture with lower peaks intensity. Moreover, a complete disappearance of the characteristic endothermic peak of sodium bicarbonate was noted (Figure 4-11). In contrast, as shown in Figure 4-12, thermogram of F9 (20% (w/w) sodium bicarbonate) open container sample showed complete disappearance of the drug exothermic peak and sharp reduction in the endothermic peak of sodium bicarbonate, however the overlapping endothermic peak was still present.

Thermograms of sodium carbonate based formulations (F12 (Figure 4-15) and F13 (Figure 4-16)) stored in open container at 40°C ± 2°C and 80% ± 5% RH showed complete disappearance of both the drug exothermic peak and the endothermic peak of sodium carbonate, however the overlapping endothermic peak was still present.

The changes in the thermal behaviour of sodium carbonate in the open container stability samples agrees with its water solubility (Chapter 3, section 3.2.2) where direct exposure to the stressful humidity level (80%) for 3 months caused complete loss of its crystallinity where an increase in the matrix microenvironment pH resulted in degradation of cefalexin monohydrate as noted in the FTIR results (Section 4.1.3). Nevertheless, calcium carbonate insolubility in water (Chapter 3, section 3.2.2) and absence of the gassing agent in the control formulation explain the physical stability of cefalexin monohydrate in the formulations F10 (10% (w/w) calcium carbonate), F11 (20% (w/w) calcium carbonate), and F14 stored under same stressful conditions.

Generally, the results of DSC suggest dependency of cefalexin monohydrate physical stability in open containers for 3 months at 40°C ± 2°C and 80% ± 5% RH on the gassing agent water solubility and the resulted matrix microenvironment pH. Thus, better physical stability of cefalexin monohydrate loaded in sodium bicarbonate or sodium carbonate floating tablets for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed containers than that in open ones was noted. This suggests that, all cefalexin monohydrate floating systems based on such gas forming agents should be packaged by pharmaceutical companies in tightly closed containers with an eye-catching label to direct patients for good practice.

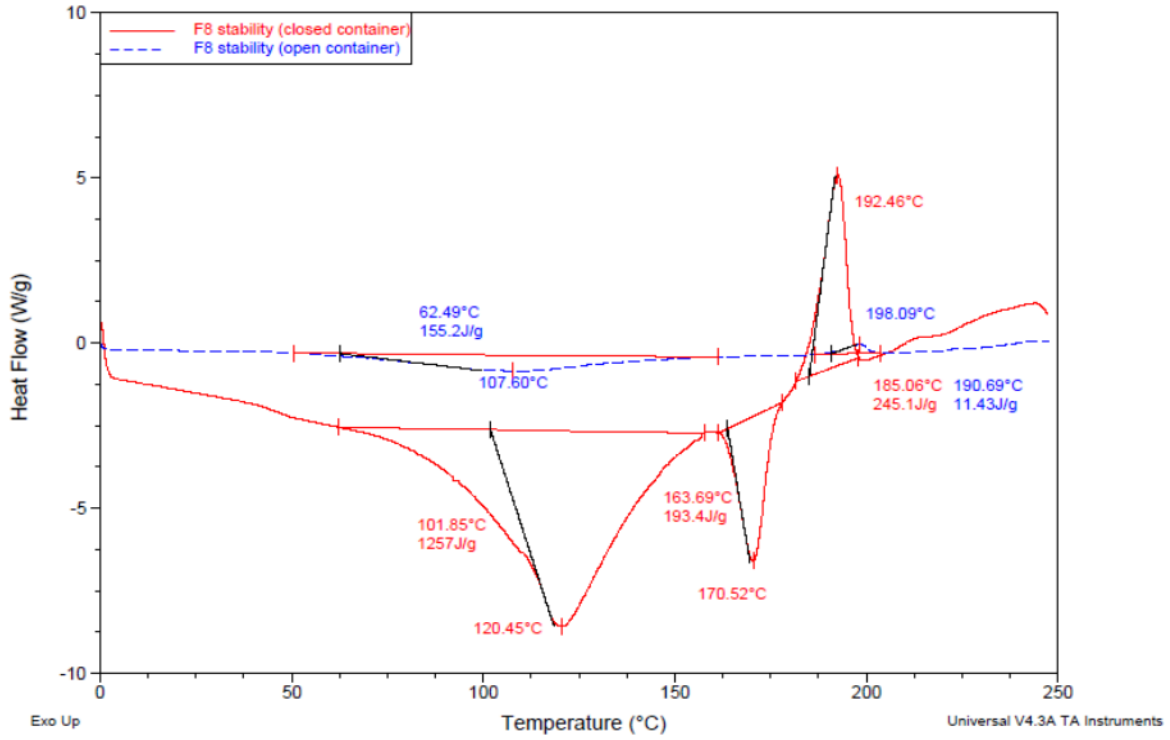


Figure 4-11: DSC thermograms of F8 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

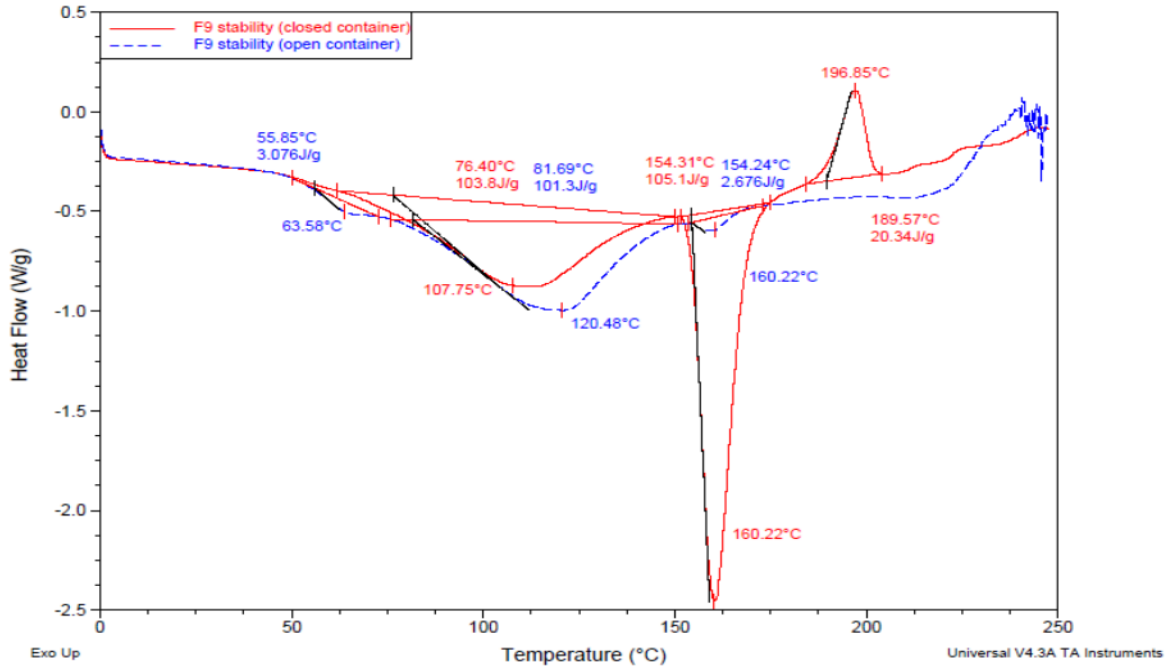


Figure 4-12: DSC thermograms of F9 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 4-1 or Table 2-8.

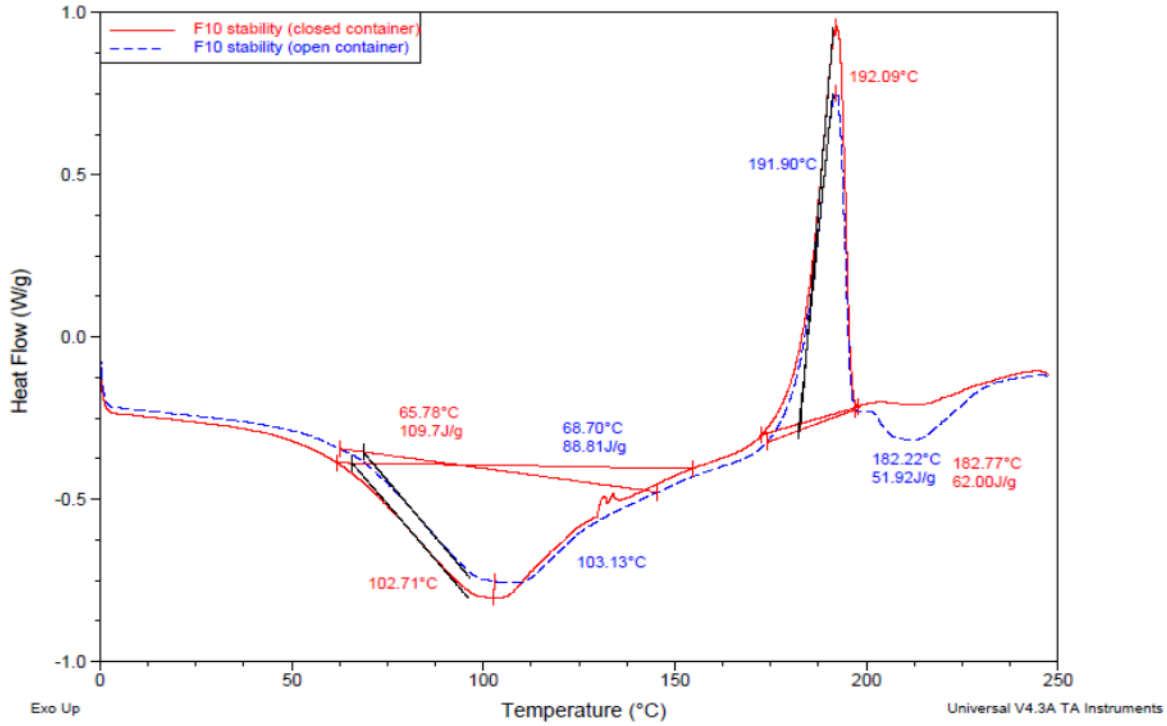


Figure 4-13: DSC thermograms of F10 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

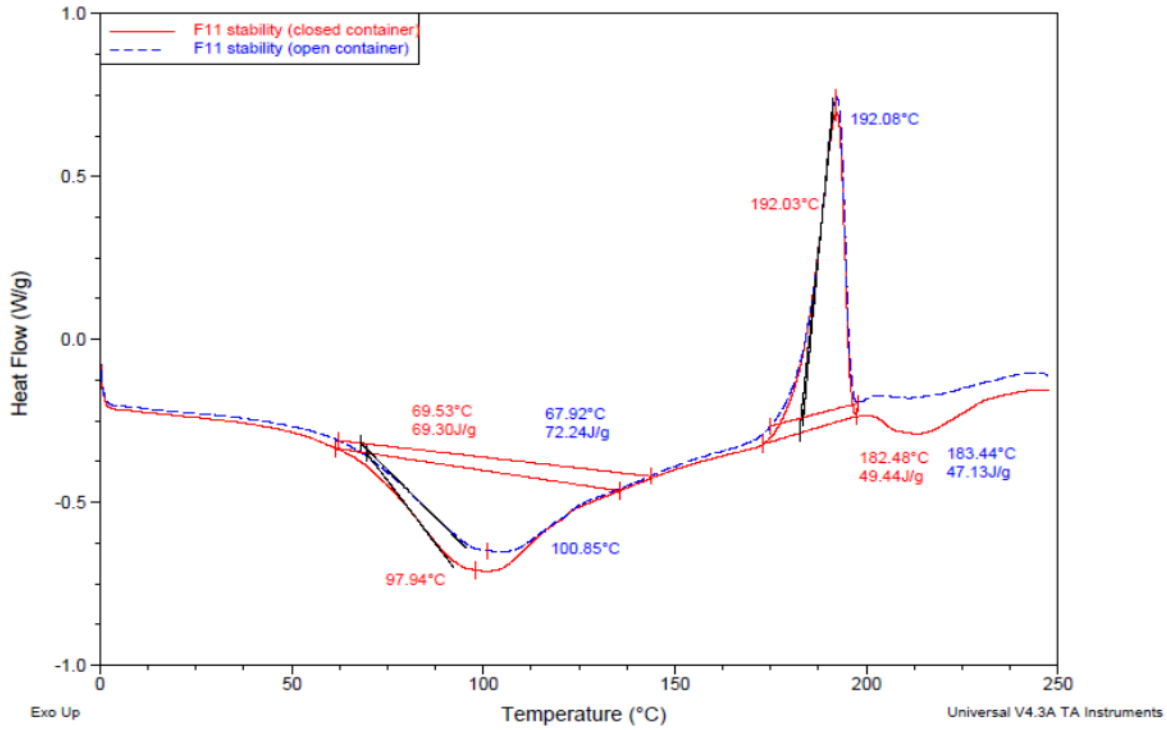


Figure 4-14: DSC thermograms of F11 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 4-1 or Table 2-8.

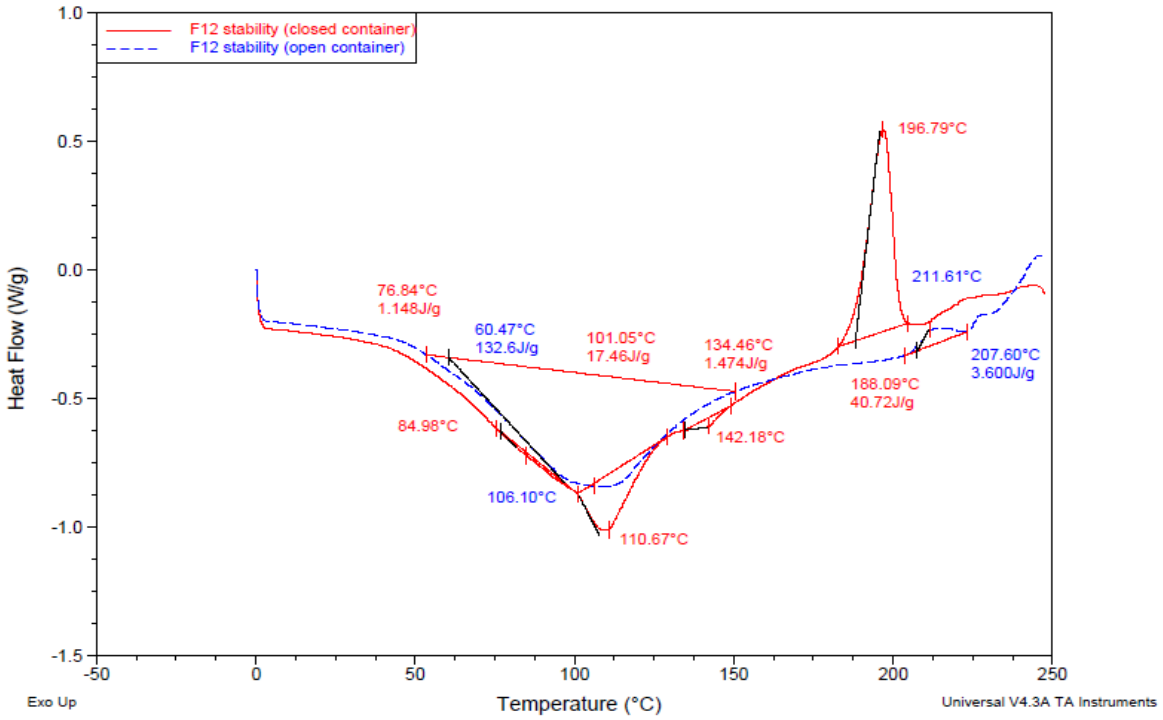


Figure 4-15: DSC thermograms of F12 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

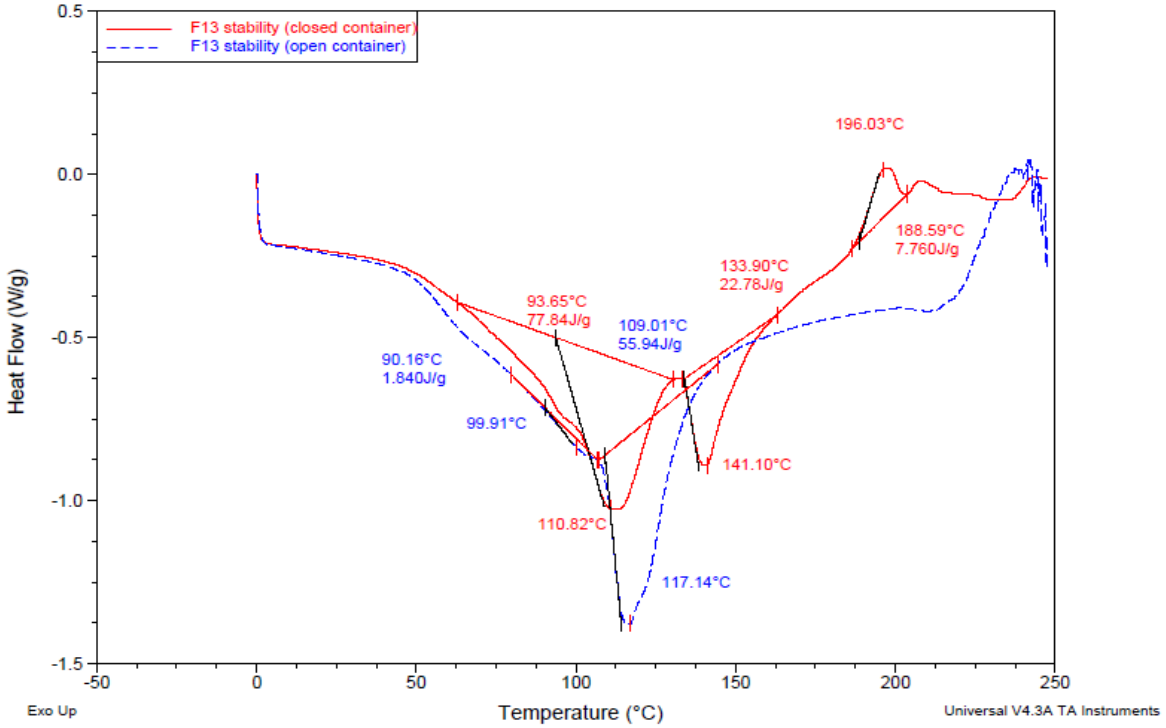


Figure 4-16: DSC thermograms of F13 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 4-1 or Table 2-8.

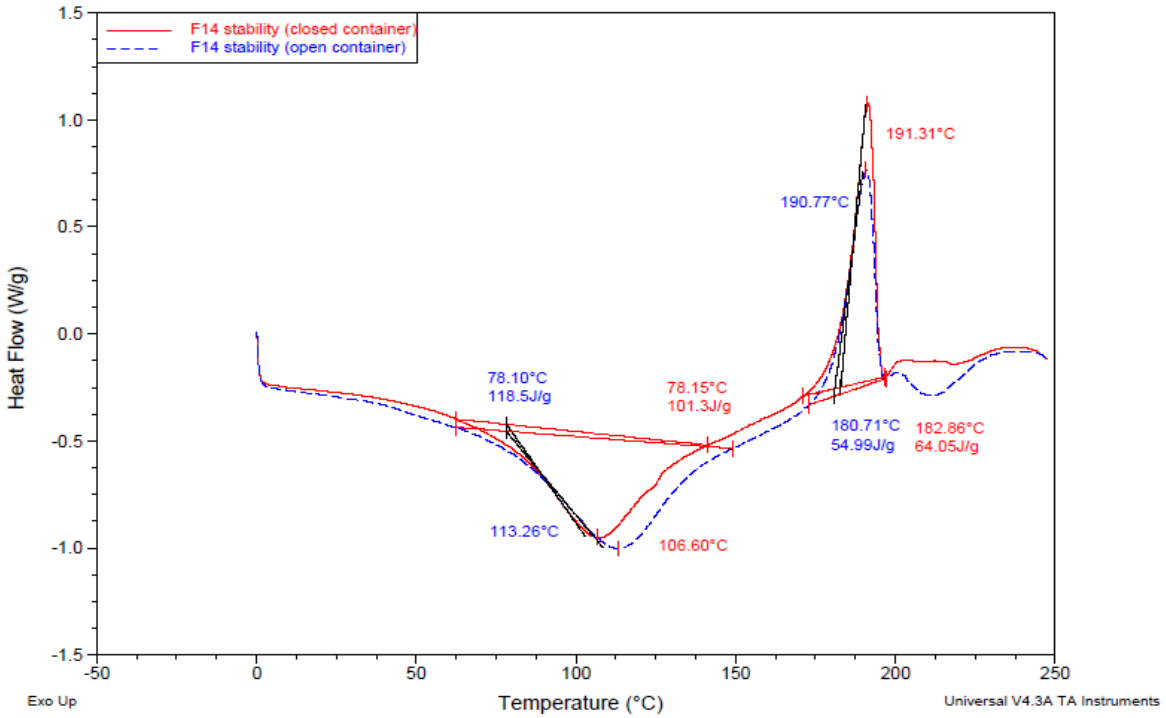


Figure 4-17: DSC thermograms of F14 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 4-1 or Table 2-8.

4.1.3 Fourier-transform infrared spectroscopy (FTIR)

The Fourier-transform infrared spectroscopy was used to study the compatibility of cefalexin monohydrate with excipients (hydroxyethyl cellulose, sodium alginate, sodium bicarbonate, calcium carbonate, sodium carbonate, and magnesium stearate) within the formulations F8-F14 before and after the granulation. Figure 4-18 to Figure 4-24 represent the IR spectra of pure cefalexin monohydrate, the powder mixtures, and the granules of all the formulations F8-F14. The spectrum of cefalexin monohydrate shows characteristic bands at 3037 and 1280 cm^{-1} for carboxylic acid –O–H, and carboxylic acid –C–O stretching mode respectively. Bands presented at 1803 and 1686 cm^{-1} are due to the four-membered lactam –C=O and secondary amide –C=O stretching mode respectively. Bending of both primary amide $–NH_2$, and secondary amide –N–H as well as secondary amide –C–N stretching are shown at 1578 cm^{-1}. In addition bands at 1454 and 953 cm^{-1} are for carboxylic acid –C–O–H in and out of plan bending respectively (Stuart, 2004, Agnihotri et al., 2006).

The drug peaks were also presented at the same wave numbers in the spectra of the drug-loaded powder mixtures and granules of all the formulations F8 F14. A slight shift in the bands due the four-membered lactam –C=O and secondary amide –C=O stretching mode were noted at 1753 and 1687 cm^{-1} respectively, and the bending of both primary amide $–NH_2$, and secondary amide –N–H as well as secondary amide –C–N stretching were shifted to 1572 cm^{-1}. Characteristic peaks representing primary amide $–NH_2$ asymmetric and symmetric stretching modes were shown only in the granules of F8 and F9 formulations near 3671, 2985, and 2900 cm^{-1}. The IR peak at 2358 cm^{-1} was due to carbon dioxide (Stuart, 2004). Accordingly, FTIR results suggest the absence of incompatibility between the drug and the formulation excipients.

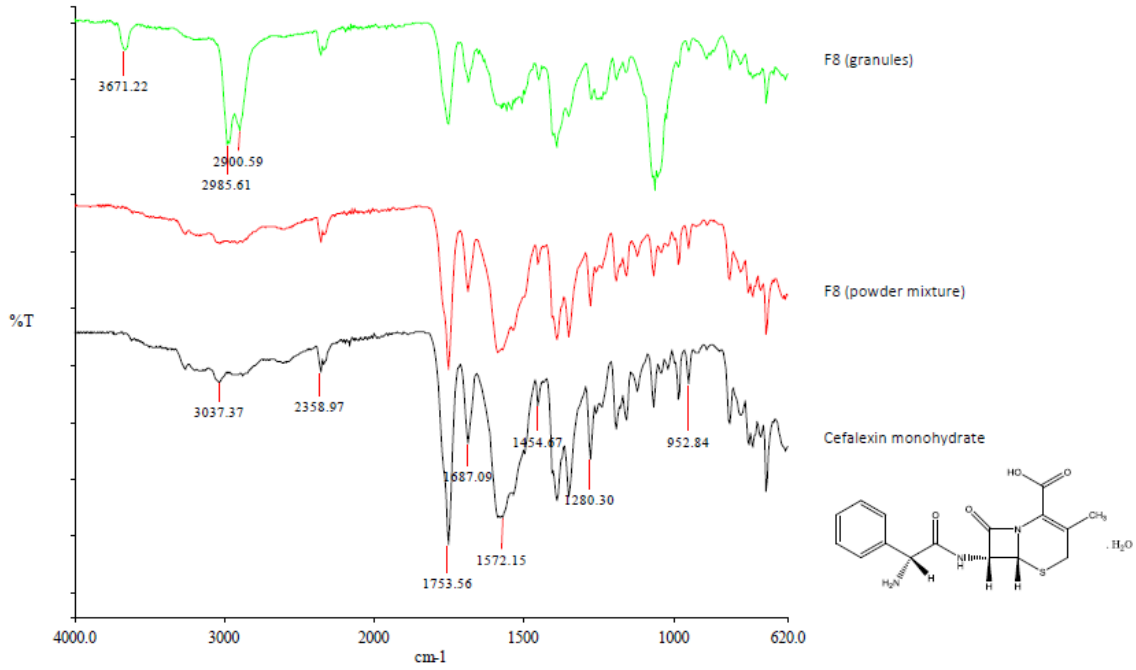


Figure 4-18: FTIR spectra of pure cefalexin monohydrate, F8 powder mixture and F8 granules.

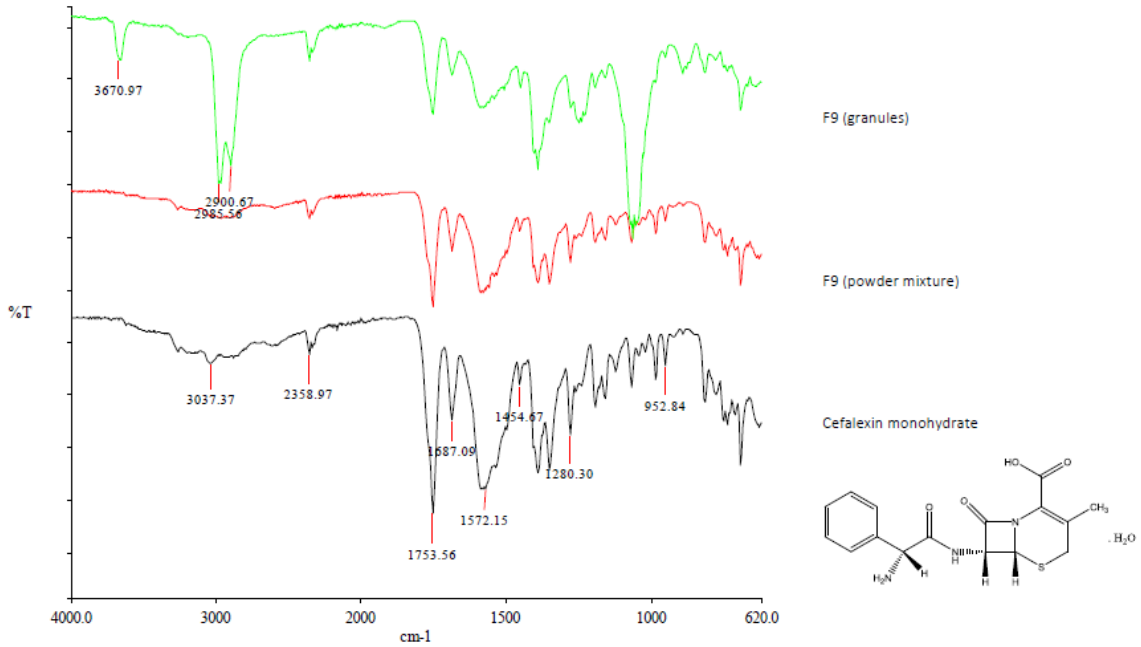


Figure 4-19: FTIR spectra of pure cefalexin monohydrate, F9 powder mixture and F9 granules.
For formulation composition, refer to Table 4-1 or Table 2-8.

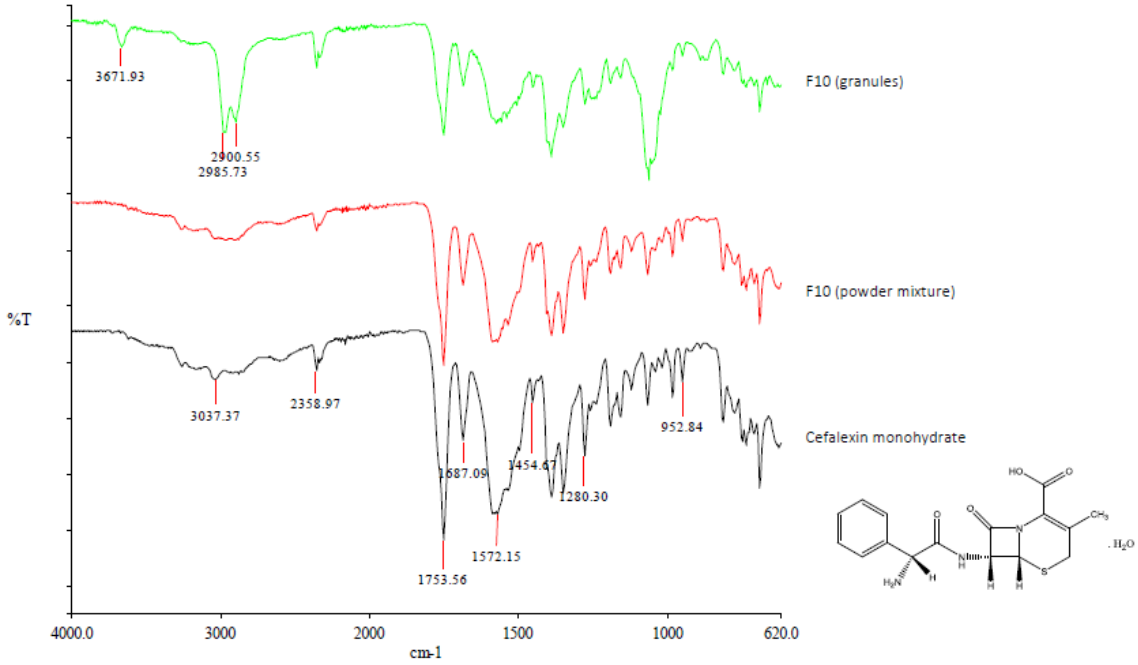


Figure 4-20: FTIR spectra of pure cefalexin monohydrate, F10 powder mixture and F10 granules.

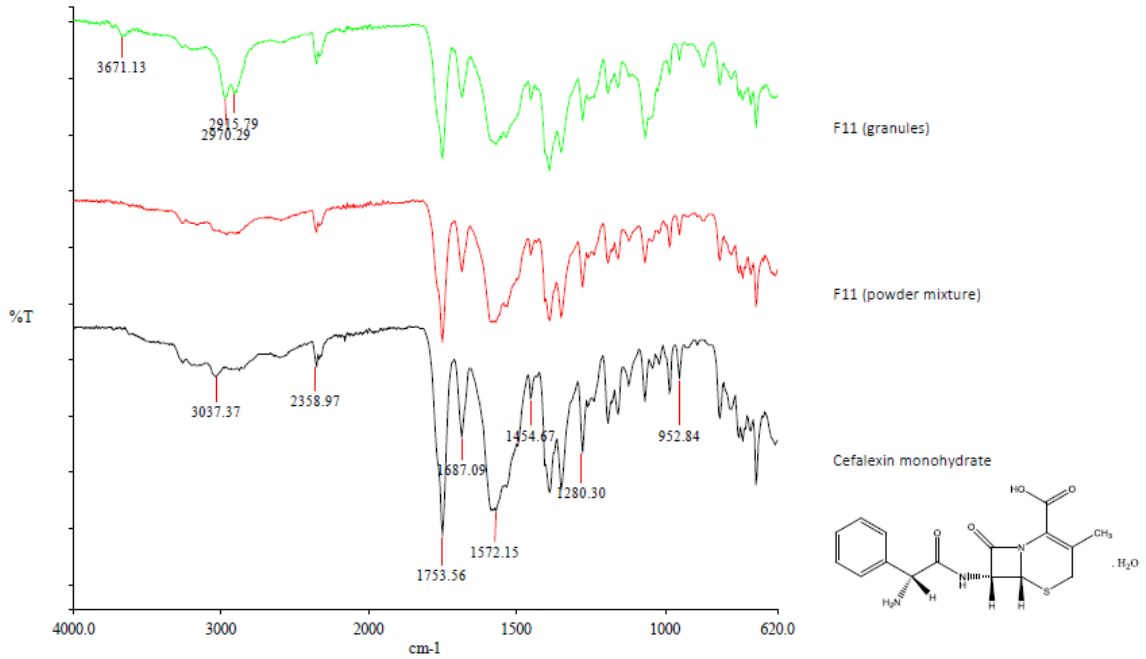


Figure 4-21: FTIR spectra of pure cefalexin monohydrate, F11 powder mixture and F11 granules.
For formulation composition, refer to Table 4-1 or Table 2-8.

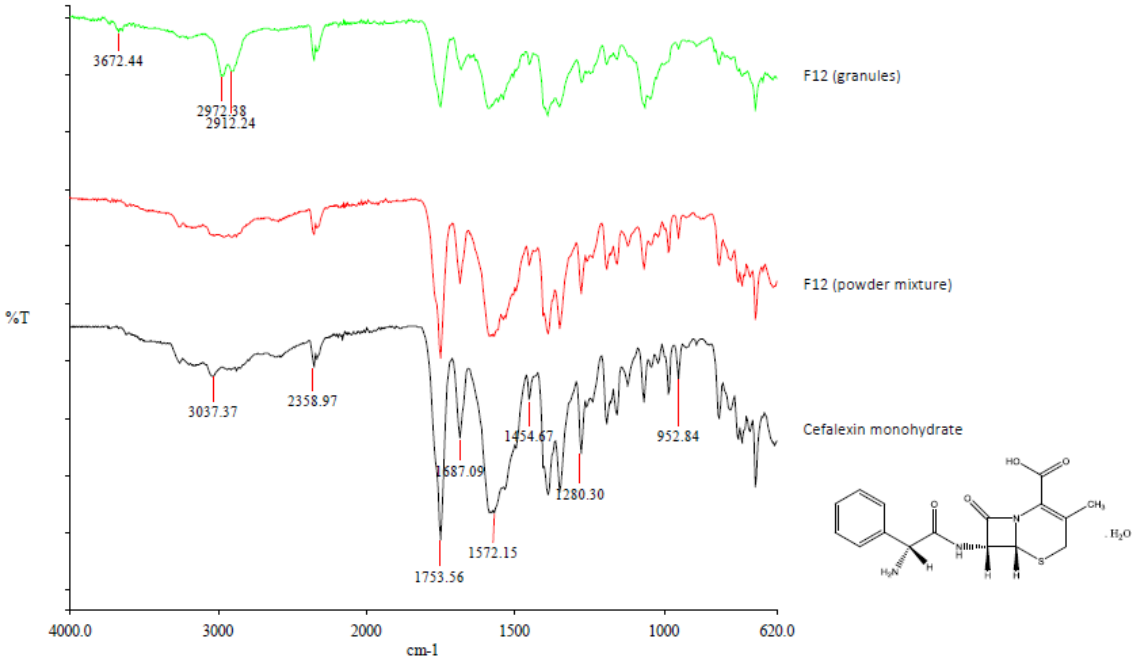


Figure 4-22: FTIR spectra of pure cefalexin monohydrate, F12 powder mixture and F12 granules.

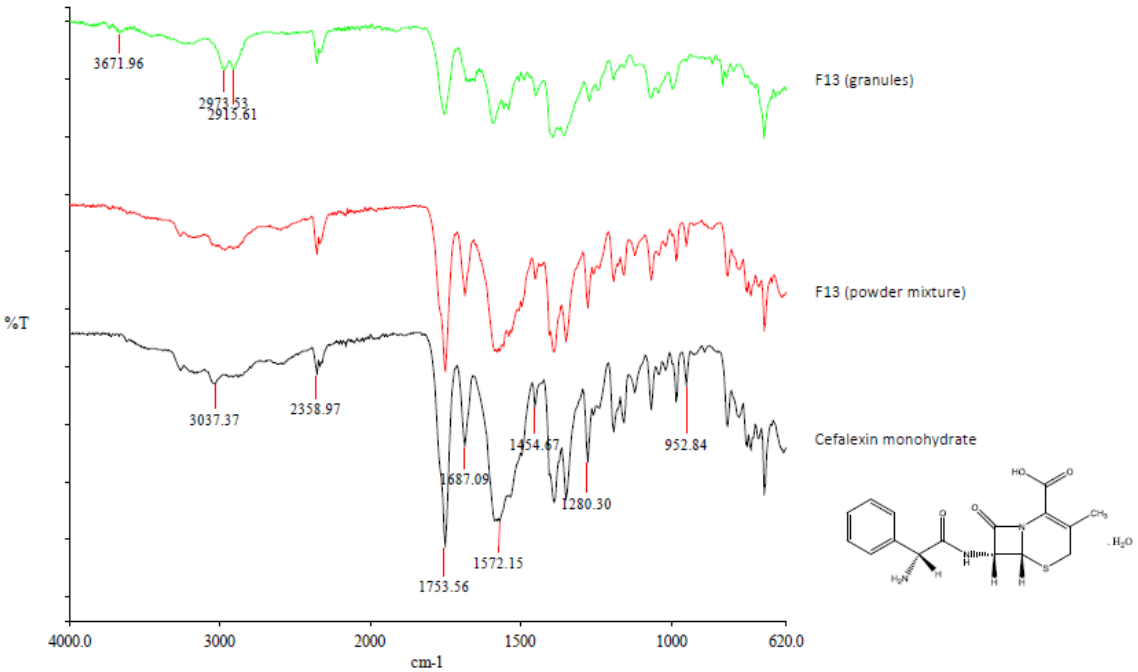


Figure 4-23: FTIR spectra of pure cefalexin monohydrate, F13 powder mixture and F13 granules.
For formulation composition, refer to Table 4-1 or Table 2-8.

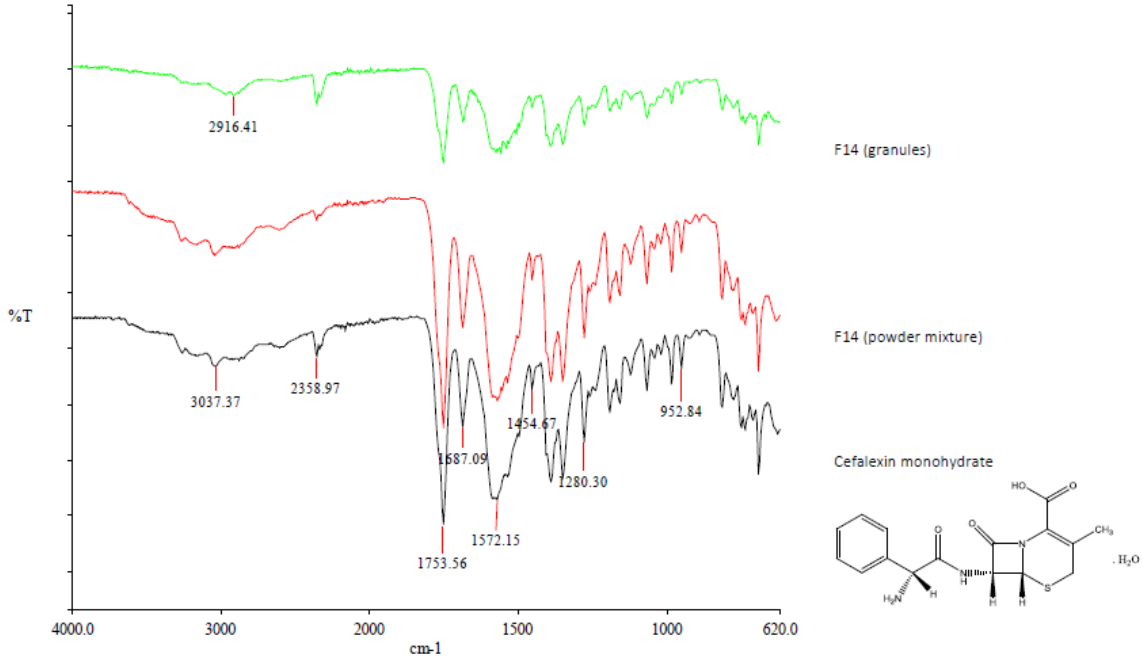


Figure 4-24: FTIR spectra of pure cefalexin monohydrate, F14 powder mixture and F14 granules.
For formulation composition, refer to Table 4-1 or Table 2-8**.**

The granules of all the formulations (F8-F14) were stored for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers and evaluated by FTIR to investigate possible effects of the stressed conditions on the drug. Figure 4-25 to Figure 4-31 represent after the storage (in closed or open containers) IR spectra of F8-F14 granules respectively. Generally, the drug characteristic bands of the stability samples (in closed or open containers) were presented at almost the same wave numbers of the freshly prepared granules of the formulations F8-F14 (Figure 4-18 to Figure 4-24). Cefalexin monohydrate characteristic bands were presented at 3040–3368 cm^{-1} and 1249–1280 cm^{-1} for carboxylic acid –O–H, and carboxylic acid –C–O stretching mode respectively. Bands presented at 1753–1755 cm^{-1} and 1654–1688 cm^{-1} were due to the four-membered lactam –C=O and secondary amide –C=O stretching mode respectively. Bending of both primary amide $–NH_2$, and secondary amide –N–H as well as secondary amide –C–N stretching were shown at 1570–1598 cm^{-1}. In addition bands at 1450–1491 cm^{-1} and 862–1004 cm^{-1} were for carboxylic acid –C–O–H in and out of plan bending respectively (Figure 4-25 to Figure 4-31). For F9 (20% (w/w) sodium bicarbonate) open container samples the four-membered lactam –C=O band was completely disappeared (Figure 4-26).

As discussed earlier (Section 4.1.2), the change in the formulation F8 (disappearance of sodium bicarbonate melting peak) in the open container stability samples agrees with sodium bicarbonate water solubility (Chapter 3, section 3.2.2) where direct exposure to the stressful humidity level (80%) for 3 months caused complete (Figure 4-11) or incomplete (Figure 4-12) loss of sodium bicarbonate crystallinity depending upon its reservoir (10% or 20% (w/w)). This may increase the pH of the matrix microenvironment in a concentration dependent rhythm and may cause degradation for cefalexin monohydrate which was represented by the loss of the four-membered lactam –C=O band (Figure 4-26). This also complies with the results of the open container samples of sodium carbonate based formulations (F12 and F13), which is water soluble, where the four-membered lactam –C=O band was completely disappeared (Figure 4-29 and Figure 4-30 respectively). On the other hand, FTIR data (Figure 4-27 and Figure 4-28) confirm the physical stability of the drug within F10 and F11 calcium carbonate as a gas forming agent in the gastroretentive drug delivery systems with cefalexin monohydrate as well as with pentoxifylline (Chapter 3, section 3.1.3).

Overall, the results of the FTIR suggest better physical stability of cefalexin monohydrate floating tablets for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed containers rather than that in open ones. Still, cefalexin monohydrate physical stability in open containers for 3 months at 40°C ± 2°C and 80% ± 5% RH is suggested to be reliant on the gassing agent water solubility and the resulted matrix microenvironment pH.

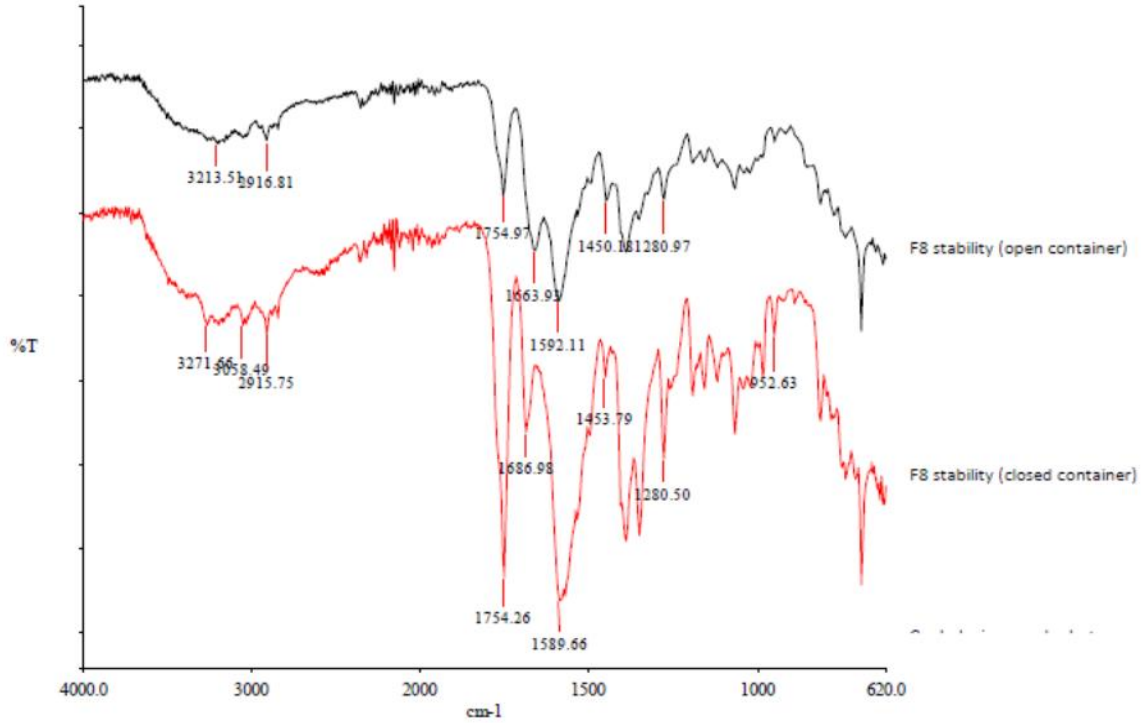


Figure 4-25: FTIR spectra of F8 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 4-1 or Table 2-8.

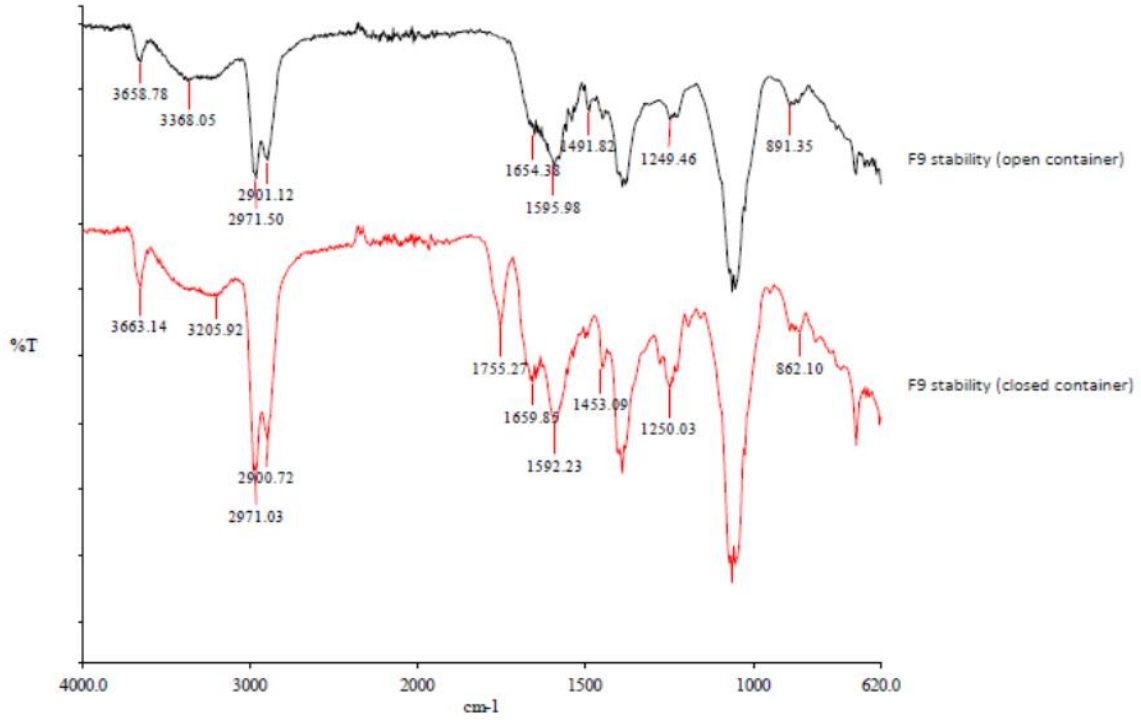


Figure 4-26: FTIR spectra of F9 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

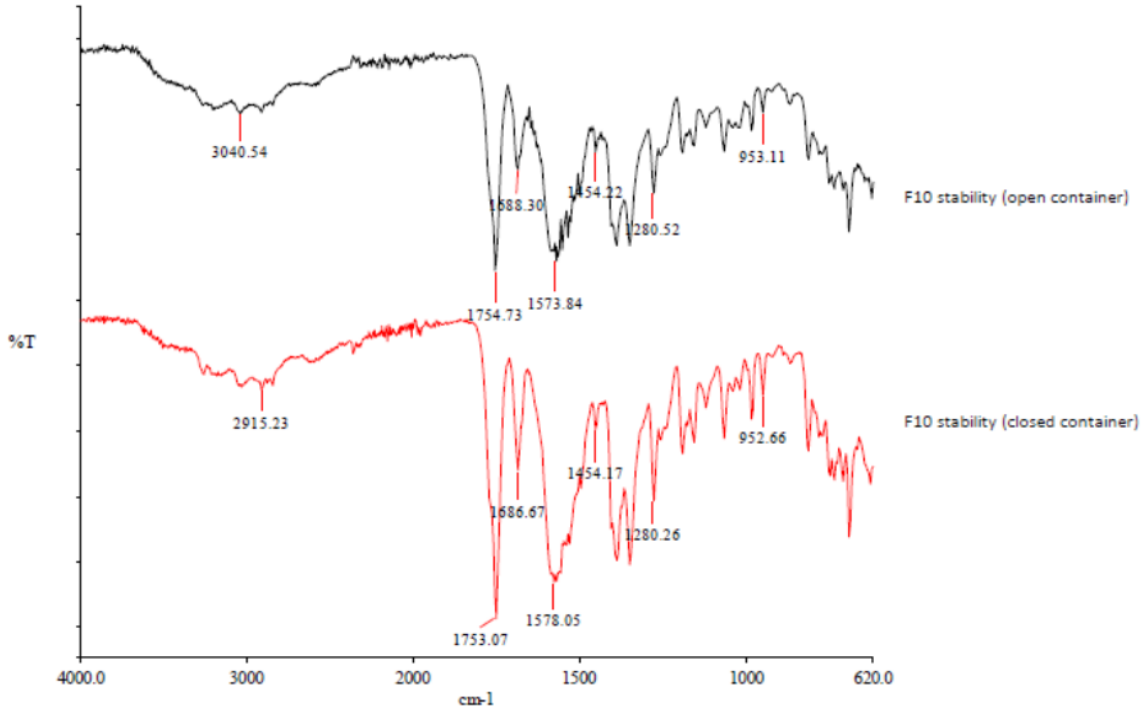


Figure 4-27: FTIR spectra of F10 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 4-1 or Table 2-8.

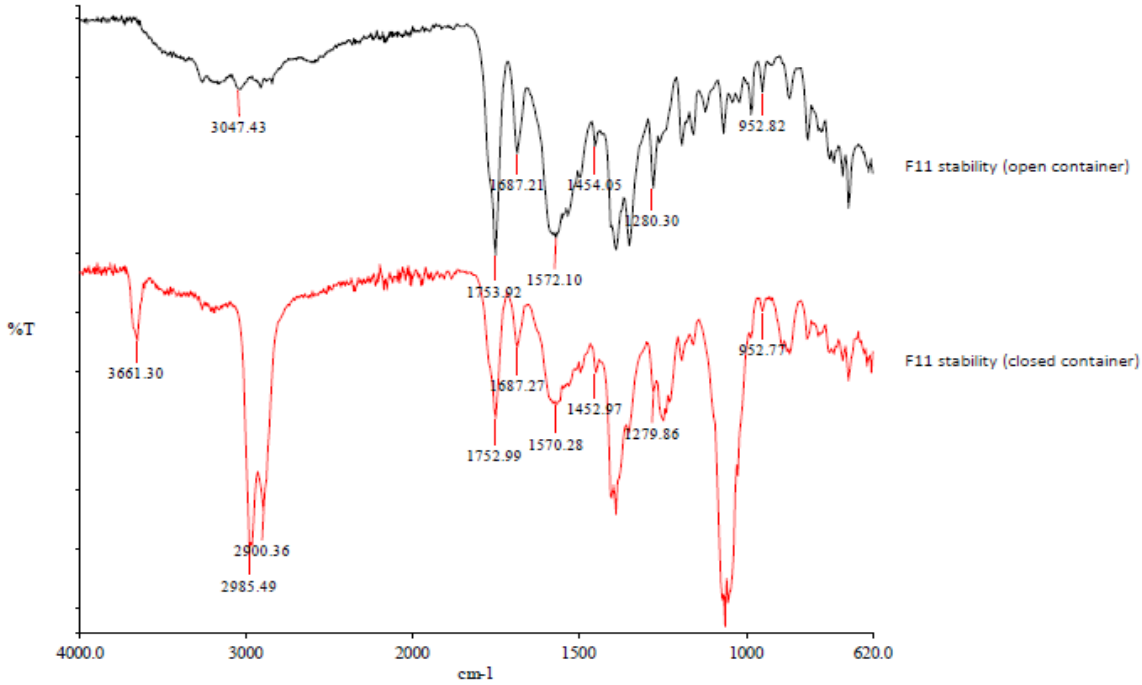


Figure 4-28: FTIR spectra of F11 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

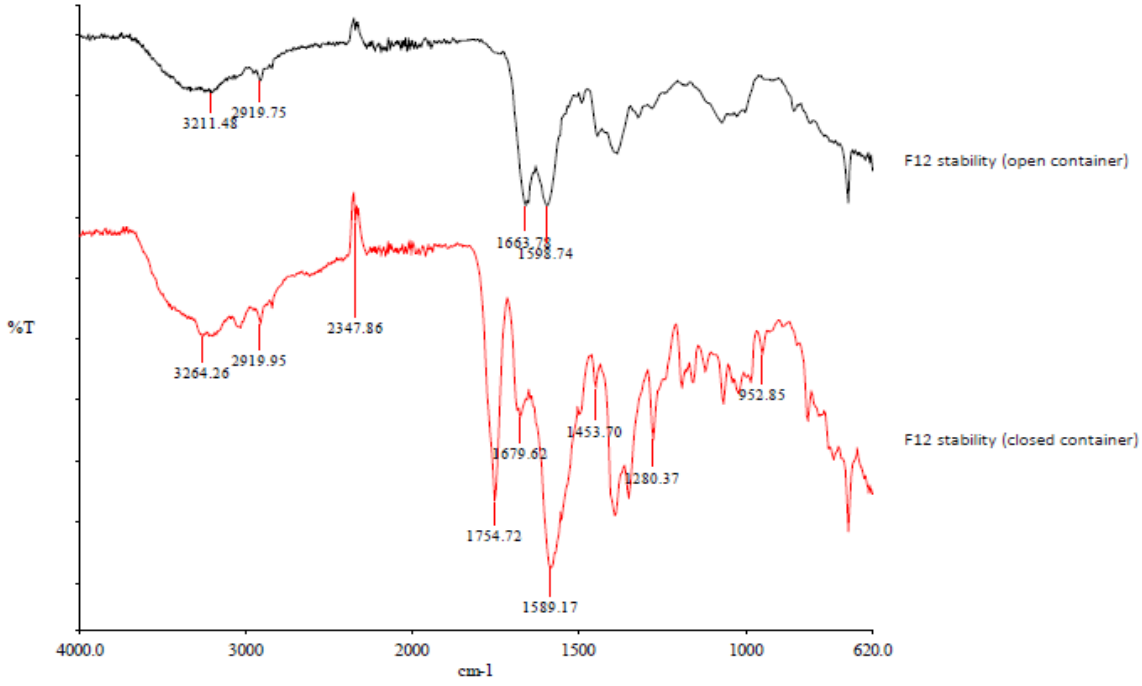


Figure 4-29: FTIR spectra of F12 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 4-1 or Table 2-8.

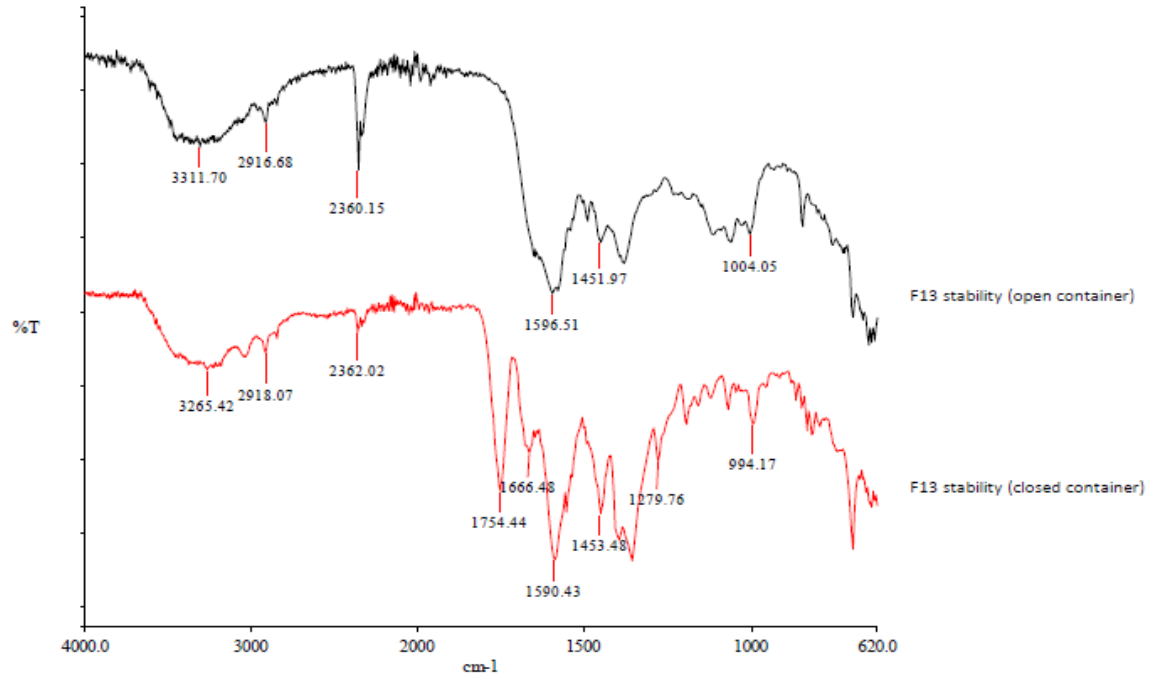


Figure 4-30: FTIR spectra of F13 granules and storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.

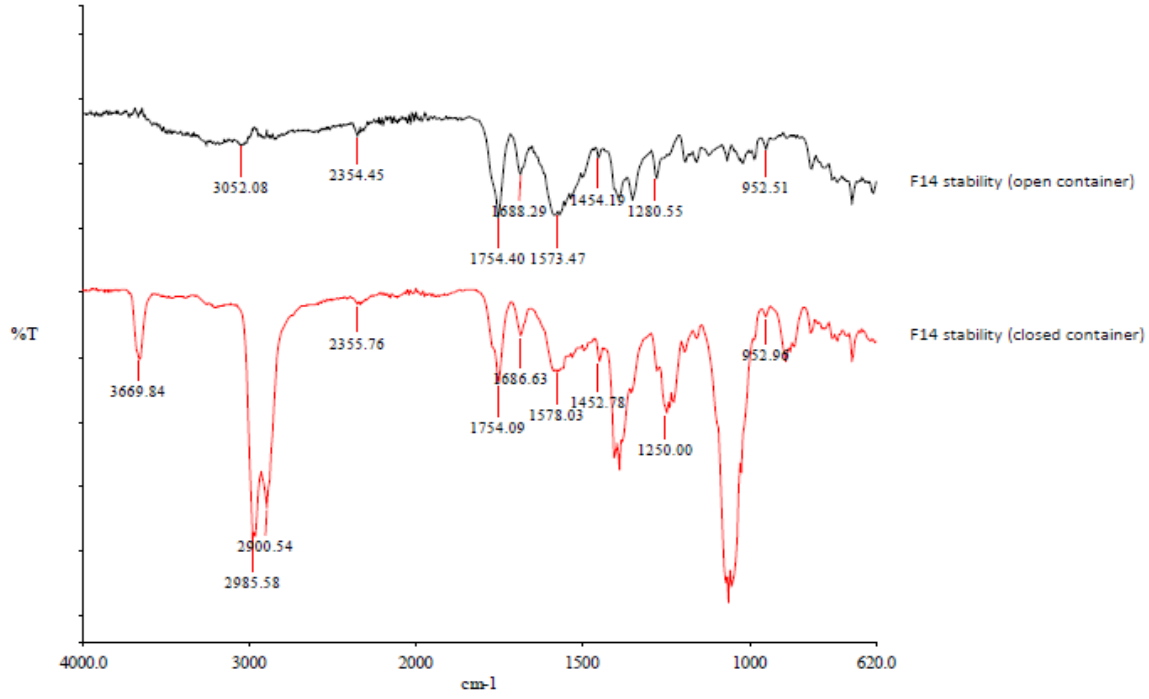


Figure 4-31: FTIR spectra of F14 granules after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 4-1 or Table 2-8.

4.2 Evaluation of floating tablets

Tablets prepared from the granules were evaluated for tablet crushing strength, friability, weight uniformity, drug content uniformity, apparent density, porosity, floating capacity, swelling and erosion, dissolution, release data modeling, and stability testing. Tablets prepared from the powder mixtures were evaluated only for porosity, floating capacity, dissolution, and release data modeling, as these tablets had been compacted manually.

4.2.1 Tablet crushing strength, friability, weight uniformity, and drug content

All the prepared tablets' results of crushing strength (N), friability (%), average weight (g), and average drug content (mg) are presented in Table 4-3. All the tablets of the formulations F8-F14 were successfully pressed automatically at levels A (49-54 N), B (54-59 N), and C (59-64 N) of crushing strength.

For the friability test, although there were no signs of cracked, split, or broken tablets at the end of the test, results at 59-64 N crushing strength were 1.10% (F8), 1.67% (F9), 1.10% (F10), 1.67% (F11), and 1.23% (F14) which did not fit the (BP) limit, as the friability values were slightly more than 1% (BP, 2015). However, the results of both F12 and F13 formulations fit the BP limit of friability except at level A of crushing strength (Table 4-3). Generally, as the tablet crushing strength level increased as the friability percentage decreased in all the formulations. Consequently, formulators can use higher compression force to change the friability results to fit the BP limit (< 1%). All the prepared tablets of the formulations F8-F14 (Table 4-3) complied with BP specifications (BP, 2015) with respect to weight uniformity test. With regards to content uniformity test, Table 4-3, results were in the acceptable range, indicating that all matrix tablets fitted the (BP) criteria in which each tablet drug content was between 85% and 115% of related average content (BP, 2015).

Table 4-3: Properties of cefalexin monohydrate floating tablets of the formulations F8-F14.

Formulation	Crushing strength level	Crushing strength (N)[a]	Friability (%)	Tablet weight (g)[b]	Drug content (mg)[a]
F8	(A)	50.99 ± 0.61	3.68	0.439 ± 0.01	273.13 ± 5.11
	(B)	56.88 ± 0.79	2.16	0.455 ± 0.01	232.04 ± 6.67
	(C)	63.74 ± 0.81	1.10	0.457 ± 0.01	280.61 ± 5.92
F9	(A)	50.99 ± 0.45	3.44	0.518 ± 0.01	274.03 ± 5.49
	(B)	57.86 ± 0.49	2.03	0.526 ± 0.00	272.91 ± 5.47
	(C)	62.76 ± 0.69	1.67	0.523 ± 0.01	273.55 ± 6.39
F10	(A)	50.99 ± 0.61	3.68	0.439 ± 0.01	273.13 ± 5.11
	(B)	56.88 ± 0.79	2.16	0.455 ± 0.01	232.04 ± 6.67
	(C)	63.74 ± 0.81	1.10	0.457 ± 0.01	280.61 ± 5.91
F11	(A)	50.99 ± 0.45	3.44	0.518 ± 0.01	274.03 ± 5.49
	(B)	57.86 ± 0.49	2.03	0.526 ± 0.00	272.91 ± 5.47
	(C)	62.76 ± 0.69	1.67	0.523 ± 0.01	273.55 ± 6.39
F12	(A)	50.01 ± 0.20	1.02	0.468 ± 0.01	277.77 ± 7.84
	(B)	56.88 ± 0.18	0.85	0.472 ± 0.00	280.93 ± 8.53
	(C)	63.74 ± 0.28	0.69	0.464 ± 0.01	283.40 ± 8.21
F13	(A)	49.03 ± 0.21	1.11	0.515 ± 0.01	287.99 ± 4.98
	(B)	54.92 ± 0.22	0.96	0.518 ± 0.01	285.07 ± 6.30
	(C)	60.80 ± 0.25	0.85	0.520 ± 0.01	284.18 ± 8.02
F14	(A)	49.03 ± 0.36	1.50	0.420 ± 0.01	273.78 ± 8.59
	(B)	54.92 ± 0.24	1.33	0.423 ± 0.00	273.98 ± 9.15
	(C)	63.74 ± 0.30	1.23	0.417 ± 0.00	269.32 ± 8.44

Notes: [a]The data represents the mean ± SD of 10 determinations. [b]The data represents the mean ± SD of 20 determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). For formulation composition, refer to Table 4-1 or Table 2-8.

4.2.2 Tablet apparent density and porosity

In order to evaluate the magnitude of different formulation factors (crushing strength, the wet granulation, type and ratio of gas forming agents) on the prepared tablets the apparent density and porosity results of the tablets were used. The apparent density of all the prepared tablets F8-F14 were calculated by equation (3) (Chapter 2, section 2.2.6.2), and the results are shown in Figure 4-32 to Figure 4-35 respectively. Generally, increasing the tablet crushing strength level in the tablets prepared from the powder mixtures of F8-F13, significantly (P<0.05) increased their apparent density results. Exceptionally, the effect was not significant (P>0.05) between the crushing strength levels A and B of F8, F10, F12, and F13 tablets, and between the crushing strength levels B and C of F9 and F11 tablets where the effect was not significant (P>0.05). Neither the effect was significant (P>0.05) for F14 tablets between all the crushing strength levels. For the tablets prepared from the granules, changing the crushing strength level increased tablet apparent density. Mostly the effect was significant (P<0.05) in all the formulations except for F12 tablets (at all crushing strength levels), for tablets of F8 and F10 (at levels B and C), and for F9 and F13 tablets (at levels A and B) where P>0.05. This agrees with the reduction in the tablet thicknesses (Table 4-4) as particles became more adjacent to each other by increasing the compression force. Also, these results are similar to that of pentoxifylline tablets (Chapter 3, section 3.2.2) based on sodium bicarbonate (F1 and F2), calcium carbonate (F3 and F4), sodium carbonate (F5 and F6), and the control ones (F7).

The granulation process decreased significantly (P<0.001) the apparent density values of all the prepared tablets of the formulations F8-F14 (Figure 4-32 to Figure 4-35 respectively). These results were similar to the related apparent density results of pentoxifylline floating tablet F1, F2 (10% and 20% (w/w) sodium bicarbonate respectively), F6 (20% (w/w) sodium carbonate), and F7 (the control tablets) (Chapter 3, section 3.2.2) where the enhancement of sodium alginate elastic recovery after compression following the granulation explains their apparent density reduction as the tablet thicknesses after the granulation increased (Chapter 3, Table 3-4).

It is clear that the drug content was increased from 60 mg of pentoxifylline (F1-F7) to 250 mg of cefalexin monohydrate (F8-F14), and the binary (1:1) mixture level of hydroxyethyl cellulose and sodium alginate was kept at almost 140 mg (Chapter 2**,** For formulation composition, refer to Table 2-7 and Table 2-8) in all the formulations (F1-F14). Although, this should decrease the elastic recovery effect of alginate following the granulation because the polymeric content was reduced by almost 36% (w/w), Kaneniwa et al. (1984) reported that pressing cefalexin powder with small diameter punch (0.7 cm) showed greater elastic behaviour than pressing it with larger diameter one (2.0 cm). This suggests additional elastic recovery effect to that of sodium alginate as the tablet thicknesses of the formulations F8-F14 increased after the granulation (Table 4-4).

Changing the concentration of the gassing agent (sodium bicarbonate (Figure 4-32), calcium carbonate (Figure 4-33), or sodium carbonate (Figure 4-34)) from 10% (w/w) to 20% (w/w) significantly (P<0.05) increased the apparent density results of all the tablets either prepared from the powder mixtures or the granules. An exception was noted in the tablets prepared from the powder mixture of the formulations based on sodium bicarbonate at level C of crushing strength where the effect was not significant (P>0.05) (Figure 4-32). The high specific gravity of sodium bicarbonate (2.173 g/cm^3), calcium carbonate (2.70 g/cm^3) and sodium carbonate (2.53 g/cm^3) may explain such increased density results which also agree with the related results of pentoxifylline floating tablets based on same gassing agents. An exception was noted in pentoxifylline floating tablets prepared from the granules where increasing sodium carbonate concentration from 10% (w/w) (F5) to 20% (w/w) (F6) decreased the apparent density results. This may be explained by the manual pressing of F5 tablets that enhanced higher reduction of their tablet thicknesses in comparison with the automatically pressed F6 tablets (Chapter 3, section 3.2.2).

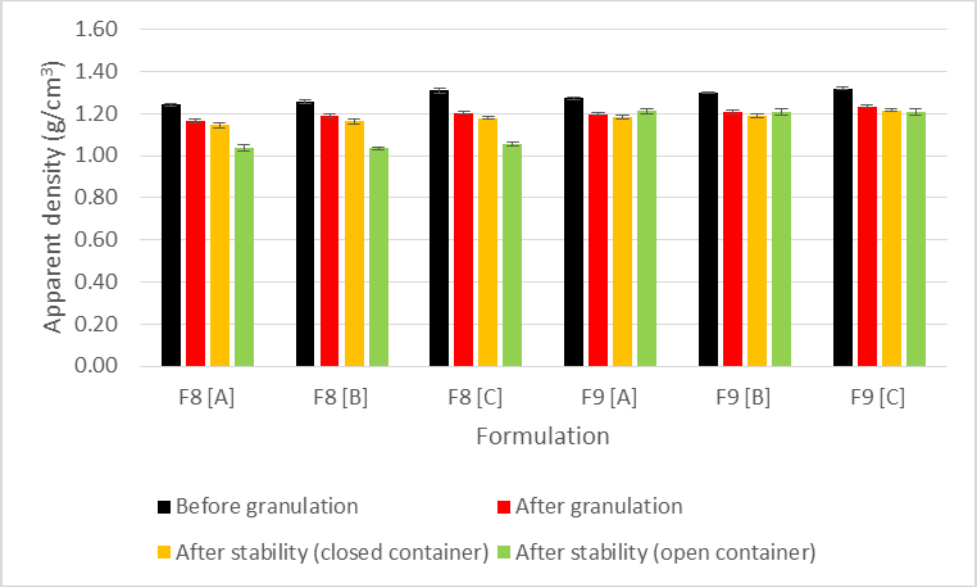


Figure 4-32: Apparent density of F8 and F9 tablets before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).
Note: The data represents the mean ± SD of six determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).

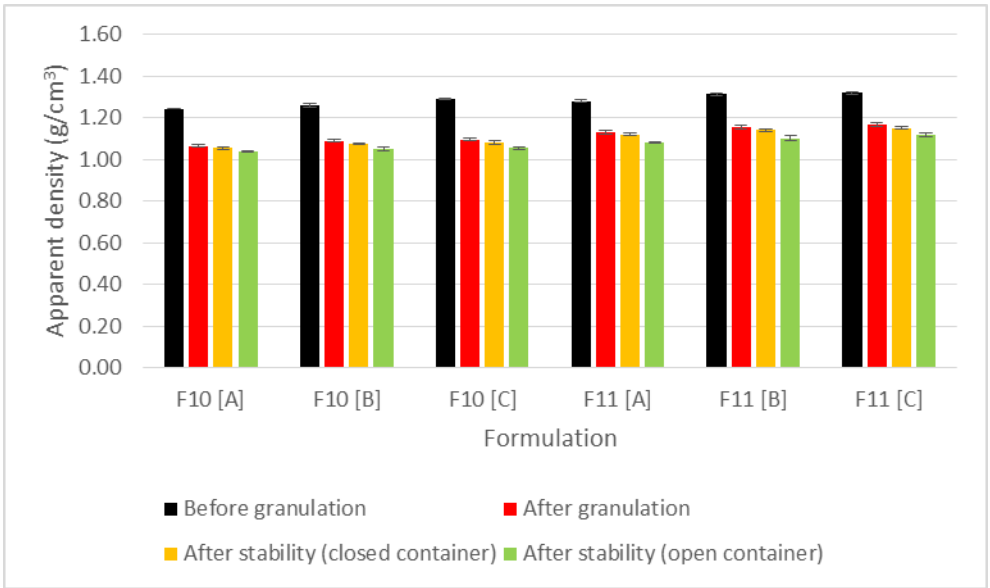


Figure 4-33: Apparent density of F10 and F11 tablets before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).
Note: The data represents the mean ± SD of six determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 4-1 or Table 2-8.

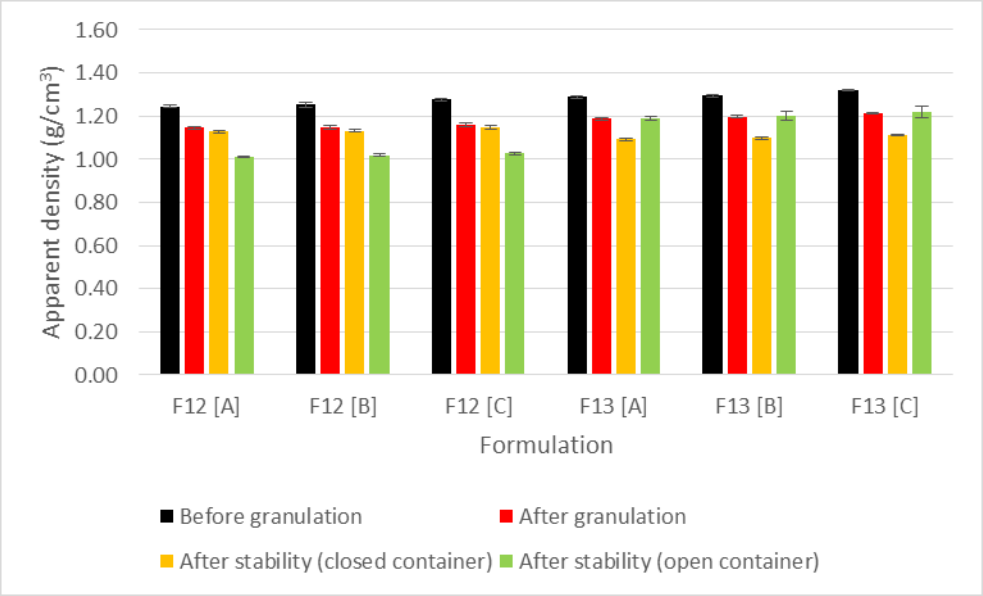


Figure 4-34: Apparent density of F12 and F13 tablets before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).
Note: The data represents the mean ± SD of six determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).

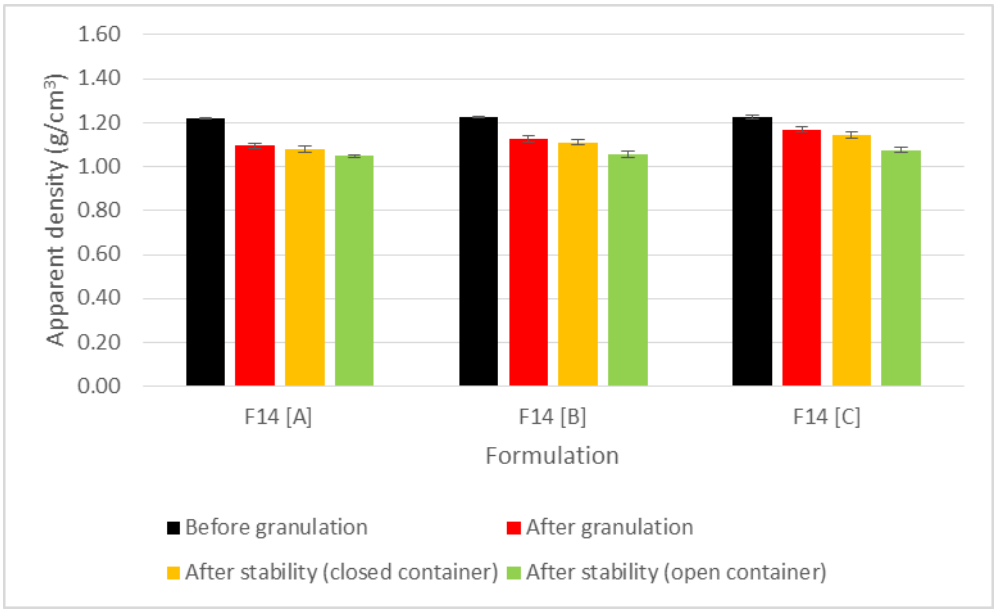


Figure 4-35: Apparent density of F14 tablets before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).
Note: The data represents the mean ± SD of six determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 4-1 or Table 2-8.

Table 4-4: F8-F14 tablets thickness before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Tablet thickness (cm)			
		Origin of prepared tablets			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F8	(A)	0.482 ± 0.00	0.507 ± 0.03	0.513 ± 0.02	0.550 ± 0.01
	(B)	0.471 ± 0.01	0.500 ± 0.02	0.509 ± 0.04	0.549 ± 0.03
	(C)	0.467 ± 0.03	0.496 ± 0.01	0.505 ± 0.01	0.537 ± 0.03
F9	(A)	0.533 ± 0.01	0.559 ± 0.03	0.565 ± 0.02	0.550 ± 0.06
	(B)	0.521 ± 0.01	0.552 ± 0.02	0.558 ± 0.02	0.550 ± 0.05
	(C)	0.517 ± 0.01	0.543 ± 0.02	0.549 ± 0.03	0.547 ± 0.09
F10	(A)	0.483 ± 0.01	0.552 ± 0.01	0.557 ± 0.01	0.571 ± 0.01
	(B)	0.469 ± 0.01	0.545 ± 0.01	0.550 ± 0.00	0.565 ± 0.04
	(C)	0.463 ± 0.01	0.544 ± 0.01	0.550 ± 0.01	0.562 ± 0.01
F11	(A)	0.531 ± 0.01	0.589 ± 0.01	0.594 ± 0.01	0.612 ± 0.03
	(B)	0.519 ± 0.01	0.576 ± 0.01	0.582 ± 0.01	0.602 ± 0.03
	(C)	0.516 ± 0.00	0.566 ± 0.01	0.572 ± 0.01	0.593 ± 0.02
F12	(A)	0.481 ± 0.01	0.521 ± 0.02	0.528 ± 0.02	0.559 ± 0.02
	(B)	0.472 ± 0.01	0.520 ± 0.01	0.525 ± 0.01	0.560 ± 0.02
	(C)	0.470 ± 0.00	0.516 ± 0.01	0.522 ± 0.02	0.558 ± 0.05
F13	(A)	0.531 ± 0.01	0.568 ± 0.02	0.620 ± 0.01	0.638 ± 0.06
	(B)	0.526 ± 0.00	0.559 ± 0.01	0.611 ± 0.01	0.631 ± 0.15
	(C)	0.517 ± 0.01	0.554 ± 0.01	0.606 ± 0.02	0.625 ± 0.15
F14	(A)	0.443 ± 0.02	0.490 ± 0.01	0.499 ± 0.01	0.523 ± 0.04
	(B)	0.441 ± 0.03	0.485 ± 0.01	0.491 ± 0.02	0.517 ± 0.02
	(C)	0.437 ± 0.01	0.471 ± 0.02	0.481 ± 0.03	0.503 ± 0.02

Note: The data represents the mean ± SD. of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 4-1 or Table 2-8.

Tablets apparent density after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers was analysed statistically. Figure 4-32 to Figure 4-35 show tablets apparent densities of the formulations F8-F14 respectively after stability studies in closed or open containers. Generally, the tablets apparent density of all the formulations F8-F14 decreased after storage at 40°C ± 2°C and 80% ± 5% RH in both closed and open containers.

A significant (P<0.05) decrease in the tablets apparent density was noted for F8 formulation in both container types. Nevertheless, a non-significant (P>0.05) decrease was reported for F9 tablets in both storage conditions except at level C of crushing strength in the open containers where P=0.07. Additionally, tablets apparent density non-significantly (P>0.05) decreased in all the other formulations (F10-F14) after storage at 40°C ± 2°C and 80% ± 5% RH in the closed containers and significantly (P<0.05) after storage in the open ones. An exception was noted for F13 (20% (w/w) sodium carbonate) tablets where the effect was not significant (P>0.05) after storage in the closed containers except at level A of crushing strength (P=0.006) and significant (P<0.05) after storage in the open ones at all the crushing strength levels. This conforms to the increase in the tablet thickness results after 3 months storage as shown in Table 4-4.

The reduction in the apparent density results was higher in the open containers than that in the closed ones for all the formulations except for F13 (20% sodium carbonate) tablets where the effect was reversed. Although F13 tablets had higher tablet thicknesses after storage in the open containers than that in the closed ones, their apparent densities were also higher (Figure 4-34). This may be explained by the decrease in the tablet diameter (Figure 4-60) which may be caused due to the presence of the hygroscopic sodium carbonate under stressful humidity (80%) conditions. Additionally, such decrease in tablets diameters were absent in case of F12 (10% (w/w) sodium carbonate) tablets which suggests a concentration dependent effect of sodium carbonate. Generally, the results of all the formulations except those of F13 (20% sodium carbonate) tablets agrees with the related results of pentoxifylline tablets (F1-F7) (Chapter 3, section 3.2.2) where the tablets stress relaxation during storage and the direct exposure to the stressful humidity level (80% RH) induced these apparent density changes.

The tablet porosity percentages of the formulations F8-F14 are presented in Figure 4-36. Increasing the crushing strength level of all the tablets prepared from the powder mixtures or the granules decreased their porosity results. However, the effect was not significant (P>0.05) for the tablets prepared from the powder mixture (at levels A and B of F8 (10% (w/w)), and at levels B and C of F9 (20% (w/w)), and of the tablets prepared from granules (at levels B and C of F8, and at levels A and B of F9). Moreover, the porosity percentages were decreased non-significantly (P>0.05) for the tablets based on calcium carbonate (F10 (10% (w/w) and F11 (20% (w/w)) and sodium carbonate (F12 (10% (w/w) and F13 (20% (w/w)) prepared from the powder mixture or the granules except between the extreme levels of crushing strength (A and C) of F10, F12, and F13 prepared from the powder mixtures and F13 prepared from the granules where the effect was significant (P<0.05). For cefalexin monohydrate control tablets (F14), the effect was not significant (P>0.05) in the tablets prepared from the powder mixture, but it was significant (P<0.05) in those prepared from the granules (Figure 4-36). This reduction in the porosity data complies with the reduction in the tablet thicknesses presented in Table 4-4, where increasing the tablet crushing strength made the particles to become strongly bonding due to being closer. This also, complies with the related results of pentoxifylline tablets (Chapter 3, section 3.2.2) based on sodium bicarbonate (F1 and F2), calcium carbonate (F3 and F4), sodium carbonate (F5 and F6), and the control ones (F7).

The granulation process increased the porosity levels of the formulations F9, F10, F13, and F14, and decreased the porosity of F8, F11, and F12 tablets (Figure 4-36). Regarding the control tablets of pentoxifylline (F7) and the tablets based on sodium bicarbonate as a gassing agent (F1 and F2) (Chapter 3, section 3.2.2), their porosity percentages decreased following the granulation process because increasing the water binder volume decreases porosity during the wet massing stage (Mukhopadhyay et al., 2008).

Nevertheless, Gokhale et al. (2005) proposed that the drug loading and the amount of excipients could affect the rate and the final degree of densification of the resulted granules. As discussed earlier, the polymeric content was reduced by almost 36% (w/w) in cefalexin monohydrate formulations due to the increase in their drug content (Chapter 2**,** for formulation composition, refer to Table 2-7 and Table 2-8). Therefore, the difference in the effect of the wet granulation process on the porosity levels of the control formulations of pentoxifylline (F7) and cefalexin monohydrate (F14) may be explained. It is clear as presented in Figure 4-36 that adding 10% (w/w) sodium bicarbonate (F8) counter acted the effect of the high drug loading (250 mg cefalexin monohydrate) on the granulation process by decreasing the porosity level. The water solubility of sodium bicarbonate (Chapter 3**,** section 3.2.2) may enhance the formation of a homogenous mixture with the hydrophilic polymers to assist voids filling of F8 matrices, which reduced their final porosity levels. But, the tablet porosity results of F9 (20% (w/w) sodium bicarbonate) formulation increased following the granulation process which agrees with Gokhale et al. (2005) discussion above. The presence of sodium bicarbonate at a higher level (20% (w/w)) compared to that used in F8 formulation (10% (w/w) during the granulation process may dilute the concentration of the (1:1) binary mixture of hydroxyethyl cellulose and sodium alginate and may reduce the efficacy of decreasing porosity levels during the wet massing stage of the granulation.

For the tablets based on calcium carbonate (F10 and F11), the porosity percentages increased after the granulation for F10 (10% (w/w)) (Figure 4-36). This may be related to calcium carbonate water insolubility, as explained also in chapter 3**,** section 3.2.2, that enhanced voids formation between adjacent molecules during the wet massing stage. This complies with the related results of F3 (10% (w/w)) and F4 (20% (w/w)) pentoxifylline tablets based calcium carbonate (Chapter 3**,** section 3.2.2). In contrast, the porosity level decreased after the granulation in F11 (20% (w/w) calcium carbonate) tablets. The good bonding capacity under compression of calcium carbonate and its role as a filler in the pharmaceutical formulations in addition to the granulation process improvement role on tablets mechanical properties (Summers and Aulton, 2007) explain the decrease in the porosity level of F11 formulation.

Porosity results (after granulation) of the tablets based on sodium carbonate as a gassing agent (F12 and F13) were consistent with the results of pentoxifylline tablets (Chapter 3**,** section 3.2.2) based on the relevant gassing agent (F5 and F6). Water solubility of sodium carbonate (Chapter 3**,** section 3.2.2) especially at the lower concentration (F12) assisted a homogeneous mixture formation with the hydrophilic polymers during the wet massing stage of the granulation that reduced the final porosity percentages. However, at 20% (w/w) concentration (F13), the hygroscopicity of sodium carbonate may support more water molecules loss through the granulation drying step which increased their porosity percentages (Figure 4-36).

Raising the concentration of sodium bicarbonate from 10% (w/w) (F8) to 20% (w/w) (F9) in the tablets prepared from granules significantly (P<0.05) increased the porosity levels except at level C of crushing strength which was not significant (P>0.05). Regarding the tablets prepared from the powder mixture, raising sodium bicarbonate concentration significantly (P<0.001) decreased the tablet porosity percentages (Figure 4-36). This fits into the related pentoxifylline tablet results of F1 (10% (w/w)) and F2 (20% (w/w)) formulations (Chapter 3**,** section 3.2.2) where sodium bicarbonate enhanced voids filling between molecules to reduce the percentage of porosity.

Increasing calcium carbonate concentration from 10% (w/w) (F10) to 20% (w/w) (F11) increased significantly (P<0.001) the porosity percentages of the tablets prepared either from the powder mixtures or the granules (Figure 4-36)**.** This also conforms to the related pentoxifylline tablet results based on 10% (w/w) (F3) and 20% (w/w) (F4) calcium carbonate (Chapter 3**,** section 3.2.2) where fragmentation behaviour under compression of calcium carbonate maintained the porosity of such tablets relatively high. In contrast, a significant (P<0.05) decrease in the porosity levels was noted when sodium carbonate concentration raised from 10% (w/w) (F12) to 20% (w/w) (F13) in the tablets prepared from the powder mixtures or the granules. An exception was noted at level A of crushing strength in the tablets prepared from the granules where P=0.378 (Figure 4-36).

The results of F12 and F13 tablets prepared from the powder mixtures were consistent with the related results of pentoxifylline tablets prepared with 10% (w/w) (F5) and 20% (w/w) (F6) sodium carbonate (Chapter 3**,** section 3.2.2) where ability of sodium carbonate to fill voids between molecules after compression clarifies the

reduction in the tablets porosity due to increasing its concentration. For the tablets prepared from the granules, raising sodium carbonate concentration from 10% (F12) to 20% (F13) (w/w) decreased the porosity of cefalexin monohydrate tablets (Figure 4-36), however, it increased the porosity of pentoxifylline tablets (Chapter 3**,** section 3.2.2). The hygroscopic behaviour of sodium carbonate especially at the higher concentration (20% (w/w)) explains the results of pentoxifylline tablets where higher water loss due to granules drying leads to higher porosity levels. Nevertheless, the results of cefalexin monohydrate tablets were different. As shown in (Table 4-2), the percentage of moisture content of F13 (20% (w/w) sodium carbonate) formulation slightly decreased after the granulation from 6.17% to 6.02% which could be related to the mono-hydration nature of cefalexin molecules. This may inverse the hygroscopicity effect of sodium carbonate during the granulation where higher moisture content was kept inside the granules of F13 formulation (after drying till reaching a constant weight). This high moisture content clarifies the decrease in the porosity due to raising sodium carbonate concentration in the granules origin tablets.

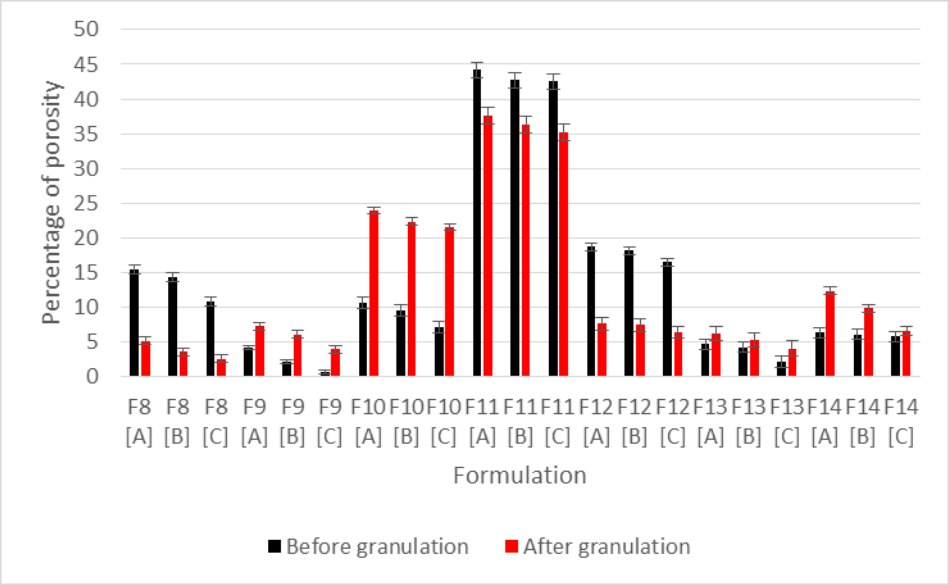


Figure 4-36: Porosity percentage of the formulations F8-F14 before and after granulation.
The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 4-1 or Table 2-8.

4.2.3 Tablet floating capacity

It is vital for floating tablets to avoid premature evacuation from their major absorption area of the stomach and upper intestine, which could be accomplished by achieving the least possible lag time, and longer floating duration. Gassing agents such as sodium bicarbonate, calcium carbonate and sodium carbonate enhanced the floating behaviour of tablets due to the release of carbon dioxide gas, which entrapped in the formed gel layer around the tablets and results in reducing tablet density to facilitate the floating process (Chapter 3, section 3.2.3). Table 4-5 and Table 4-6 represent floating lag time and floating duration results of all prepared tablets respectively. All the formulations (F8-F14) were tested for floating capacity under the same conditions and using the same apparatus for the *in vitro* studies.

A statistical analysis (*P*-value) of changing the crushing strength level on the tablet floating lag time of the formulations F8-F13 prepared from the powder mixture or the granules revealed that changing the crushing strength level in all the prepared tablets caused generally a non-significant ($P>0.05$) increase in the floating lag time. An exception was noted between the extreme level of crushing strength (A and C) of F10 and F11 prepared from the granules where $P<0.05$ (Table 4-5). This agrees with the related results of pentoxifylline tablets (Chapter 3, section 3.2.3) based on sodium bicarbonate (F1 and F2), calcium carbonate (F3 and F4) and sodium carbonate (F5 and F6) where reducing the tablet porosity, as a result of increased compaction force, delayed the penetration of the acidic medium and hence delayed the gas generation process.

The granulation process increased the floating lag time results of all the tablets F8-F13 compared to that of the tablets prepared from the powder mixture before the granulation (Table 4-5). The effect of the granulation process was significant ($P<0.05$) for F8, F10, and F12 tablets and non-significant ($P>0.05$) for F9, F11, and F13 tablets except at level C of crushing strength of F9 and F11 where $P<0.05$.

Table 4-5: Floating lag-time of the formulations F8-F14 at different crushing strength levels before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Floating lag time (min)			
		Origin of prepared tablet			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F8	(A)	0.02 ± 0.01	8.29 ± 3.18	2.67 ± 0.54	No floating
	(B)	0.03 ± 0.01	10.76 ± 2.81	5.18 ± 1.01	No floating
	(C)	0.05 ± 0.02	12.71 ± 3.56	6.46 ± 1.89	No floating
F9	(A)	0.02 ± 0.00	3.05 ± 0.49	2.56 ± 0.27	complete disintegration within 30 min
	(B)	0.03 ± 0.02	4.03 ± 0.85	2.92 ± 0.12	complete disintegration within 30 min
	(C)	0.04 ± 0.01	4.69 ± 0.48	5.27 ± 0.74	complete disintegration within 30 min
F10	(A)	0.12 ± 0.03	1.01 ± 0.06	0.29 ± 0.06	0.16 ± 0.03
	(B)	0.13 ± 0.05	1.58 ± 0.41	0.34 ± 0.06	0.18 ± 0.08
	(C)	0.15 ± 0.08	2.28 ± 0.59	0.38 ± 0.08	0.18 ± 0.01
F11	(A)	0.08 ± 0.03	0.34 ± 0.06	0.20 ± 0.03	0.15 ± 0.03
	(B)	0.12 ± 0.04	0.69 ± 0.09	0.30 ± 0.03	0.16 ± 0.01
	(C)	0.13 ± 0.04	1.17 ± 0.22	0.35 ± 0.09	0.18 ± 0.01

Table 4-5 (continued): Floating lag-time of the formulations F8-F14 at different crushing strength levels before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Floating lag time (min)			
		Origin of prepared tablet			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F12	(A)	1.78 ± 0.25	8.19 ± 3.92	No floating	No floating
	(B)	1.81 ± 0.30	10.28 ± 3.16	No floating	No floating
	(C)	1.87 ± 0.16	10.92 ± 1.80	No floating	No floating
F13	(A)	4.72 ± 0.20	3.63 ± 0.55	No floating	No floating
	(B)	4.79 ± 0.19	5.30 ± 0.92	No floating	No floating
	(C)	4.83 ± 0.14	7.22 ± 1.41	No floating	No floating
F14	(A)	No floating	12.43 ± 3.81	No floating	No floating
	(B)	complete disintegration within 30 min	14.43 ± 3.02	No floating	No floating
	(C)	complete disintegration within 30 min	17.57 ± 1.96	No floating	No floating

Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). For formulation composition, refer to Table 4-1 or Table 2-8.

Table 4-6: Floating duration of the formulations F8-F14 at different crushing strength levels before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Total floating duration (h)			
		Origin of prepared tablet			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F8	(A)	> 8	> 4	> 2	No floating
	(B)	> 8	> 4	> 2	No floating
	(C)	> 8	> 4	> 2	No floating
F9	(A)	> 8	> 10	complete disintegration within 30 min	complete disintegration within 30 min
	(B)	> 8	> 10	complete disintegration within 30 min	complete disintegration within 30 min
	(C)	> 8	> 10	complete disintegration within 30 min	complete disintegration within 30 min

Notes: The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). For formulation composition, refer to Table 4-1 or Table 2-8.

Table 4-6 (continued): Floating duration of the formulations F8-F14 at different crushing strength levels before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Total floating duration (h)			
		Origin of prepared tablet			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F10	(A)	complete disintegration within 30 min	> 8	Partial disintegration	Partial disintegration
	(B)	complete disintegration within 30 min	> 8	Partial disintegration	Partial disintegration
	(C)	complete disintegration within 30 min	> 8	Partial disintegration	Partial disintegration
F11	(A)	complete disintegration within 30 min	> 12	complete disintegration within 30 min	complete disintegration within 30 min
	(B)	complete disintegration within 30 min	> 12	complete disintegration within 30 min	complete disintegration within 30 min
	(C)	complete disintegration within 30 min	> 12	complete disintegration within 30 min	complete disintegration within 30 min

Notes: The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). For formulation composition, refer to Table 4-1 or Table 2-8.

Table 4-6 (continued): Floating duration of the formulations F8-F14 at different crushing strength levels before granulation, after granulation, and after stability (tablets prepared from granules stored at 40°C ± 2°C and 80% ± 5% RH for 3 months in closed or open container).

Formulation	Crushing strength level	Total floating duration (h)			
		Origin of prepared tablet			
		Before granulation	After granulation	After stability (closed container)	After stability (open container)
F12	(A)	> 8	> 10	complete disintegration within 30 min	No floating
	(B)	> 8	> 10	complete disintegration within 30 min	No floating
	(C)	> 8	> 10	complete disintegration within 30 min	No floating
F13	(A)	> 8	> 12	complete disintegration within 30 min	complete disintegration within 30 min
	(B)	> 8	> 12	complete disintegration within 30 min	complete disintegration within 30 min
	(C)	> 8	> 12	complete disintegration within 30 min	complete disintegration within 30 min
F14	(A)	No floating	> 12	complete disintegration within 30 min	complete disintegration within 30 min
	(B)	complete disintegration within 30 min	> 12	complete disintegration within 30 min	complete disintegration within 30 min
	(C)	complete disintegration within 30 min	> 12	complete disintegration within 30 min	complete disintegration within 30 min

Notes: The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). For formulation composition, refer to Table 4-1 or Table 2-8.

The results of F8 (10% (w/w) sodium bicarbonate) tablets may be explained by the decrease in their porosity levels after the granulation process, which also conforms to the results of F1 (10% (w/w) sodium bicarbonate) formulation based on pentoxifylline (Chapter 3, section 3.2.3). The floating lag time of F9 (20% w/w sodium bicarbonate tablets increased after the granulation (Table 4-5) which also complies with the results of F2 (20% (w/w) sodium bicarbonate) tablets. But, unlike F2 tablets, the porosity of F9 tablets increased by the granulation process (Figure 4-36). This may be explained by the higher swelling ability of F9 tablets compared to that of F8 tablets (Section 4.2.4**,** Figure 4-37) which may counteract the increase in F9 tablets porosities by decreasing the acidic media penetration rate inside their matrices and delaying the effervescent reaction and their floating process. Hodsdon et al. (1995) explained the faster release of chlorpheniramine maleate (highly soluble model drug) from alginate matrices in the simulated gastric fluid (SGF) than in the simulated intestinal fluid (SIF) by difference in the formed internal microscopic structure of the alginate hydrated surface layer and by different hydration kinetics of the polymer in these two media. They concluded that the highly hydrated continuous gel layer formed by alginate in SIF in comparison to the particulate and porous hydrated layer formed in SGF was responsible for retarding the drug release. Furthermore, 0.1 M aqueous solution of sodium bicarbonate generates pH=8.3 at 25°C (Cable, 2009), which suggests better ability of the higher concentration of sodium bicarbonate (F9) than that of the lower concentration (F8) to provide an alkaline microenvironment for sodium alginate molecules to initiate a stronger hydrated gel. This clarifies the slower drug release results of F9 tablets compared to that of F8 tablets (Section 4.2.5) and explains the increase in their floating lag time results following the granulation process.

The results of F10 (10% (w/w)) and F11 (20% (w/w)) tablets based on calcium carbonate as a gassing agent were similar to the related results of pentoxifylline tablets (F3 and F4) (Chapter 3, section 3.2.3). The absence of the disintegration behaviour due to strengthening the tablets internal structure after the granulation delayed the entrapment of the acidic medium and increased their lag time results.

Moreover, the increase in the lag time values of the tablets based on sodium carbonate as a gassing agent (F12 (10% (w/w) and F13 (20% (w/w)) complies with the relevant pentoxifylline tablets (F5 and F6) (Chapter 3, section 3.2.3). Although, the decrease in F12 porosity percentages following the granulation (Figure 4-36) hindered the initiation of the effervescent process, the increase in F13 porosity percentages (after the granulation) reduced their matrices ability to retain the liberated gas bubbles and delayed their floating process.

Changing the concentration of sodium bicarbonate from 10% (F8) to 20% (w/w) (F9) and calcium carbonate from 10% (F10) to 20% (w/w) (F11) decreased the lag time results significantly (P<0.05) for the tablets prepared from the granules, nonetheless, the effect was not significant (P>0.05) for the tablets prepared from the powder mixtures (Table 4-5). This complies with the related results of pentoxifylline tablets based on sodium bicarbonate (F1 and F2) and calcium carbonate (F3 and F4) (Chapter 3, section 3.2.3) where increasing the gassing agent content available for the acidic medium enhanced the rate as well as the efficiency of the effervescent reaction, which was represented by the shorter floating lag time values.

Regarding sodium carbonate gassing agent, changing its concentration from 10% (F12) to 20% (w/w) (F13), increased the lag time values non-significantly (P>0.05) in the tablets prepared from the powder mixtures (Table 4-5). This is similar to the related results of F5 (10% (w/w)) and F6 (20% (w/w)) pentoxifylline tablets (Chapter 3, section 3.2.3) where the alkalinity of sodium carbonate enhanced the swelling rate (at 20% w/w) and delayed the effervescent process due to the reduction in the dissolution medium entrapment rate. Additionally, the apparent density of F13 tablets increased due to raising the concentration of sodium carbonate (Figure 4-34) which hindered their floating process. Concerning the tablets prepared from the granules, increasing sodium carbonate concentration from 10% (F12) to 20% (w/w) (F13) decreased the lag time values non-significantly (P>0.05) except at level B of crushing strength where P=0.037 (Table 4-5). This did not agree with the related pentoxifylline tablet results of F5 (10% (w/w)) and F6 (20% (w/w)) where the lag time values increased by changing sodium carbonate concentration.

More time was taken for the floating process due to sodium carbonate alkalinity effect on the dissolution medium entrapment rate and due to the increase in the tablet apparent density at the higher concentration level (20% (w/w)) of sodium carbonate (Chapter 3, section 3.2.3).

As discussed earlier, the polymeric content was reduced by almost 36% (w/w) in cefalexin monohydrate formulations due to the increase in their drug content (Chapter 2**,** for formulation composition, refer to Table 2-7 and Table 2-8). This changed the gassing agent: polymeric mixture ratio from (4.5:10) for pentoxifylline based formulations to (7:10) for cefalexin monohydrate formulations. Consequently, more sodium carbonate molecules became available alongside the hydrophilic polymeric mixture to accelerate the swelling process, and also to generate better effervescent process efficiency for cefalexin formulations. Upon quicker water uptake, chains of the polymeric mixture moved apart from each other resulted in both weight and volume growth which rapidly reduced the density of the swollen matrix and decreased their floating lag time values.

Table 4-6 shows floating duration results of all the formulations F8-F14. Although, F8 (10% (w/w) sodium bicarbonate) tablets prepared from the powder mixture at all crushing strength levels floated for > 8 h, their floating duration after the granulation process was reduced by half. In contrast, the floating duration of F9 (20% (w/w) sodium bicarbonate) formulation increased from > 8 h before the granulation to > 10 h after the granulation at all crushing strength levels. This is also similar to the related results of the formulations F1 and F2 based on pentoxifylline (Chapter 3, section 3.2.3). Obviously, the higher concentration of sodium bicarbonate (20% (w/w)) was more effective than the lowest one (10% (w/w)) to maintain the tablets from the granules origin on the surface of the dissolution medium for a longer duration of time. Increasing sodium bicarbonate level in the tablets prepared from the powder mixture did not cause a difference in the floating duration results where both the formulations (F8 and F9) floated for > 8 h. Although the porosity percentages decreased by increasing the gassing agent reservoir (Figure 4-36), the increase in their apparent density values (Figure 4-32) may inverse the effect of both the porosity reduction and the high gassing agent reservoir, and maintain the floating duration > 8 h.

The tablets based on calcium carbonate as a gassing agent of the formulations F10 and F11 prepared from the powder mixtures showed complete disintegration behaviour within short time (30 min) after the floating process. Following the granulation process, F10 (10% (w/w)) tablets floated for > 8 h and the tablets of F11 (20% (w/w)) floated for > 12 h (Table 4-6). This complies with the related results of F3 (10% (w/w)) and F4 (20% (w/w)) pentoxifylline based tablets (Chapter 3, section 3.2.3) where the higher calcium carbonate reservoir available for the floating process increased the floating duration.

For the tablets based on sodium carbonate as a gassing agent, the granulation process increased the floating duration results for F12 (10% (w/w)) from > 8 to > 10 h and for F13 (20% (w/w)) from > 8 to > 12 h (Table 4-6). Still, pentoxifylline tablets based on sodium carbonate presented better floating duration where F5 (10% (w/w)) tablets floated for > 12 h and F6 (20% (w/w)) tablets floated for > 24 h without a difference between the results before or after the granulation (Chapter 3, section 3.2.3). The reduction (by almost 36% (w/w)) in the polymeric content of cefalexin monohydrate tablets (F12 and F13) reduced their swelling rate (Section 4.2.4) in comparison to that of pentoxifylline tablets (F5 and F6) (Chapter 3, section 3.2.4) which affected the ability of such tablets to hold the generated gas bubbles for longer time. Raising sodium carbonate concentration increased the floating duration from > 10 h (F12) to > 12 h (F13) for the tablets prepared from the granules and kept the floating duration without change (> 8 h) for the tablets prepared from the powder mixtures (Table 4-6). This is similar to the related results of F5 (10% (w/w)) and F6 (20% (w/w)) pentoxifylline tablets based on sodium carbonate where the higher gassing agent concentration (20% (w/w)) was more effective than the lower one (10% (w/w)) to maintain the tablets floated on the surface of the dissolution medium for longer duration of time (Chapter 3, section 3.2.3).

As shown in Table 4-6, the control tablets of cefalexin monohydrate (F14) prepared from the powder mixture did not show any floating behaviour which agrees with the related results of pentoxifylline control tablets (F7) where absence of gassing agents explains this. Moreover, the complete disintegration of F14 tablets was noted within short time (30 min) after immersion in to the dissolution medium except for those compacted at level A of crushing strength which kept sinking through the experiment time.

The reported elastic behaviour of cefalexin under compression with elevated pressure (Kaneniwa et al., 1984) may justify the disintegration behaviour of F14 tablets pressed at levels B and C of crushing strength. Although cefalexin monohydrate control tablets (F14) prepared from the granules had 0% (w/w) content of gassing agents, those tablets compacted at the levels A, B, and C of crushing strength floated at 12.43, 14.43, and 17.57 min. respectively (Table 4-5) and all of them kept floating for > 12 h on the surface of the dissolution medium (Table 4-6). This did not agree with the related results of F7 control tablets of pentoxifylline prepared from the granules. The granulation process improved F14 tablets internal structure, decreased their apparent density results (Figure 4-35) and increased their porosity percentages (Figure 4-36). This may entrap more dissolution medium and consequently enhanced rapid swelling rate behaviour (Section 4.2.4) which further reduced their tablets density to initiate and to maintain the floating process. In contrast, the granulation process decreased the porosity level of F7 control tablets (Chapter 3, Figure 3-40). Moreover, although the granulation process decreased F7 tablets apparent density results (Chapter 3, Figure 3-39); their values were higher than the apparent density results of F14 tablets (Figure 4-35). This clarifies the better floating ability of F14 tablets in comparison with F7 tablets.

Regarding stability studies, the effect of storage at 40°C ± 2°C and 80% ± 5% RH for 3 months on the tablets floating lag time and the floating duration was evaluated and presented in Table 4-5 and Table 4-6 respectively. For the tablets based on sodium bicarbonate as a gassing agent, storage in closed containers significantly decreased (P<0.05) the floating lag time of F8 (10% (w/w)) tablets and non-significantly (P>0.05) decreased the floating lag time of F9 (20% (w/w)) tablets (Table 4-5). Tablets of F8 formulation floated for only > 2 h, but F9 tablets completely disintegrated after short time (within 30 min) of the floating process (Table 4-6). The increase in the tablet thicknesses after the storage (Table 4-4) may cause a rapid contact between the gassing agent (sodium bicarbonate) and the acidic medium to start rapidly the effervescent and the floating processes which was consistent with the floating lag time results of the related pentoxifylline tablets (F1 and F2) (Chapter 3, section 3.2.3). Nevertheless the floating duration results of F8 and F9 tablets were different from those of F1 and F2 tablets. The reduction by almost 36% (w/w) in the polymeric content of cefalexin monohydrate formulations (F8 and F9) in addition to the tablet relaxation behaviour due the aging process decreased the matrices ability to hold the liberated gas baubles for longer time. Moreover, the higher content of sodium bicarbonate for F9 tablets (20% (w/w)) assisted rupturing of the relaxed tablets which clarifies the floating duration results of F8 and F9 formulations after storage at 40°C ± 2°C and 80% ± 5% RH for 3 months in the closed containers.

In the open containers, the tablets of F8 (10% (w/w)) formulation lost their ability to float, however, the tablets of F9 (20% (w/w)) disintegrated after a short period of time (within 30 min) of immersion inside the dissolution medium (Table 4-5) and (Table 4-6). These results were different from the related results of F1 and F2 pentoxifylline based formulations (Chapter 3, section 3.2.3). The loss in the floating ability of F8 tablets complies with its open container DSC stability thermogram (Figure 4-11) where the complete loss of sodium bicarbonate crystallinity affected its role in the effervescent reaction. Moreover, the open container DSC stability results of F9 formulation (Figure 4-12) showed partial presence of sodium bicarbonate in the crystalline form which was responsible for the complete disintegration behaviour of the relaxed aged tablets.

Concerning the tablets based on calcium carbonate as a gassing agent (F10 and F11), storage in closed or open containers decreased their floating lag time results significantly (P<0.05) for F10 (10% (w/w)) at all crushing strength levels in comparison with the freshly prepared tablets. Conversely, the effect was not significant (P>0.05) for F11 (20% (w/w)) except at level C of crushing strength where P<0.05 (Table 4-5). Moreover, both F10 and F11 tablets could not maintain the floating on the surface of the dissolution medium as both formulations showed partial and complete disintegration behaviour respectively after short time (30 min) of their floating process (Table 4-6). This decrease in the stability floating lag time results is similar to the related stability results of F3 and F4 tablets based on pentoxifylline (Chapter 3, section 3.2.3) where the increase in the tablet thicknesses after the storage (Table 4-4) caused a rapid contact between the gassing agent and the acidic medium to start the effervescent and the floating processes rapidly. The absence of the significance effect for F11 (20% (w/w) calcium carbonate) tablets could be the related to their higher gassing agent reservoir. The floating duration results of F10 and F11 tablets (Table 4-6) were different from those of F3 and F4 tablets (Chapter 3, section 3.2.3). This because of the reduction in the polymeric content of cefalexin monohydrate formulations (F10 and F11) in addition to the high effervescent activity of calcium carbonate caused the partial or complete rupture of the aged relaxed tablets according to calcium carbonate concentration. However, calcium carbonate is still the most effective gassing agent to keep floating integrity compared to other gassing agents (sodium bicarbonate and sodium carbonate).

A complete loss of the floating ability was noted in sodium carbonate based formulations (F12 and F13) after storage at 40°C ± 2°C and 80% ± 5% RH for 3 months in either closed or open containers (Table 4-5). This was accompanied with a complete disintegration behaviour in all the tablets except those of F12 (10% (w/w)) formulation stored in the open containers (Table 4-6) which sank till the end of the experiment. This did not agree with the related results of pentoxifylline tablets (F5 and F6) based on sodium carbonate which kept their floating properties after storage under the same conditions (Chapter 3, section 3.2.3). Storage under the stressful humidity conditions may decrease the available sodium carbonate molecules (due to hygroscopicity) for the effervescent process and consequently delayed the floating process.

This also clarifies the absence of the floating behaviour in the closed container stability samples of F12 (10% (w/w) sodium carbonate) and F13 (20% (w/w) sodium carbonate) tablets which could not float, and their relaxed aged structure completely ruptured within a short time (30 min) of immersion in the dissolution medium. Moreover, the aged matrices of the formulations F12 and F13 were weaker (due to their polymeric content) than those of F5 (10% (w/w) sodium carbonate) and F6 (20% (w/w) sodium carbonate) pentoxifylline tablets. The loss in the floating ability of F12 tablets complies with its open container DSC stability thermogram (Figure 4-15) which indicates absence of sodium carbonate crystals and its role in the effervescent reaction. Although the open container DSC stability thermogram of F13 formulation (Figure 4-16) also indicates absence of the crystallinity of sodium carbonate, F13 tablets completely disintegrated while F12 tablets did not. This may be explained by the morphological changes in F13 tablets after storage under the stressful conditions which suggests a concentration dependent interaction of sodium carbonate.

Results of the control tablets (F14) stored either in closed or open containers presented complete disintegration behaviour within a short period of time (30 min) of starting the test. This is not similar to the related results of pentoxifylline control tablets (F7) which conform the effect of their polymeric content on their ability to control the drug release rate (Section 4.2.5).

4.2.4 Swelling and erosion studies

Swelling and erosion studies were carried out to make a correlation with the drug release rate and the release mechanisms. The percentage of dissolution medium uptake and the percentage of mass loss of all the tablets prepared from the granules (F8-F14) in 0.1 M HCl medium are presented in Figure 4-37 to Figure 4-40 and in Figure 4-41 to Figure 4-44 respectively. Increasing the tablet crushing strength in all the formulations did not cause a significant (P>0.05) effect neither in the swelling rate results nor in the mass loss ones at majority of the time points. This is similar to the related results of pentoxifylline tablets based on sodium bicarbonate (F1 and F2), calcium carbonate (F3 and F4), sodium carbonate (F5 and F6), and the control tablets (F7) where the tablet strength had only a small effect on the swelling rate and the mass loss percentage of the hydrophilic tablets (Chapter 3, section 3.2.4).

Raising the level of calcium carbonate from 10% (w/w) (F10) to 20% (w/w) (F11) caused a significant (P<0.05) decrease in the tablet swelling rate at most of the time points (Figure 4-38) and a significant (P<0.05) increase in the mass loss percentages at bulk of the time points (Figure 4-42). This complies with the related pentoxifylline tablets results (F3 and F4) (Chapter 3, section 3.2.4) where the swelling rate was inversely proportional with the floating duration of F10 and F11 tablets (Table 4-6). Moreover, the high effervescent activity of calcium carbonate explains the higher erosional behaviour in 20% (w/w) tablets in comparison with that in 10% (w/w) concentration.

In contrast, changing the concentration of the gassing agent from 10% (w/w) to 20% (w/w) in the formulations based on sodium bicarbonate (F8 and F9) and the formulations based on sodium carbonate (F12 and F13) significantly (P<0.05) increased the DMU results at majority of the time points (Figure 4-37 and Figure 4-39 respectively). A non-significant (P>0.05) decrease in the percentage of the mass loss was noted for the formulations based on sodium bicarbonate at larger part of the time points (Figure 4-41), nevertheless, a non-significant (P>0.05) increase except at the level C of crushing strength where P<0.05 was noted for the formulations based on sodium carbonate at bulk of the time points (Figure 4-43).

These results are not similar to those of the related pentoxifylline tablets based on sodium bicarbonate (F1 and F2), where the DMU decreased and the mass loss percentage increased as the concentration of the gassing agent increased. Regarding the tablets based sodium carbonate gassing agent, the results were statistically different from those of the related pentoxifylline tablets (F5 and F6), yet, the effect was similar (Chapter 3, section 3.2.4). Alginates have better ability to swell in a higher pH environment, hence, the higher sodium bicarbonate or sodium carbonate concentration may influence the swelling rate behaviour. Besides, the strength of the hydrated microstructure of the swollen matrix tablets may be altered by the concentration of the gassing agent available in the gassing agent: polymeric mixture ratio (Section 4.2.3). Therefore, the coherent gel layer formed around F9 (20% (w/w) sodium bicarbonate) and F13 (20% (w/w) sodium carbonate) matrices may assist a higher swelling rate (Figure 4-37 and Figure 4-39 respectively) and a better resistance to the erosional behaviour due to the effervescent reaction (Figure 4-41 and Figure 4-43 respectively) in comparison with 10% (w/w) gassing agent based formulations.

Regarding cefalexin monohydrate control tablets (F14), their swelling rate at majority of the time points (Figure 4-40) was significantly (P<0.05) the highest at bulk of the time points in comparison with all the other formulations except with F13 (20% (w/w) sodium carbonate) tablets where P>0.05 at most of the time points. Additionally, their mass loss percentages were almost the lowest (Figure 4-44), but the difference was not significant (P>0.05) at larger part of the time points in comparison with all the other tablets except with F11 (20% (w/w) calcium carbonate) tablets where P<0.05 at most of the time points. Although, cefalexin monohydrate control tablets (F14) floated on the surface of the dissolution medium for all the experiment time, they had the highest swelling rate (Figure 4-40). The absence of the gassing agents in such tablets may explain their highest swelling rate and lowest mass loss results as it excluded additional accelerated erosional process by the gas bubbles (liberated through the effervescent reaction) and enhanced normal polymeric swelling process.

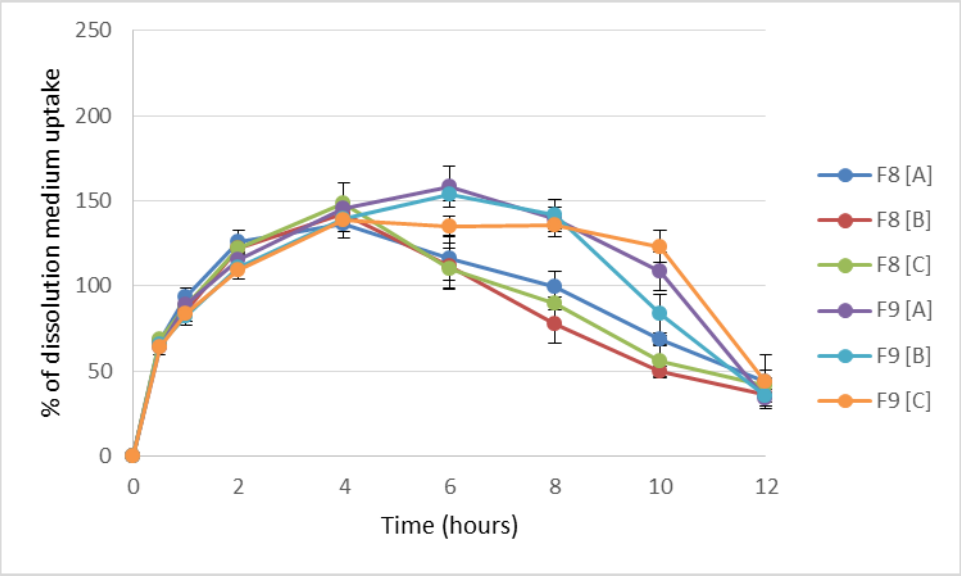


Figure 4-37: Percentage of medium uptake for the formulations F8 and F9 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).

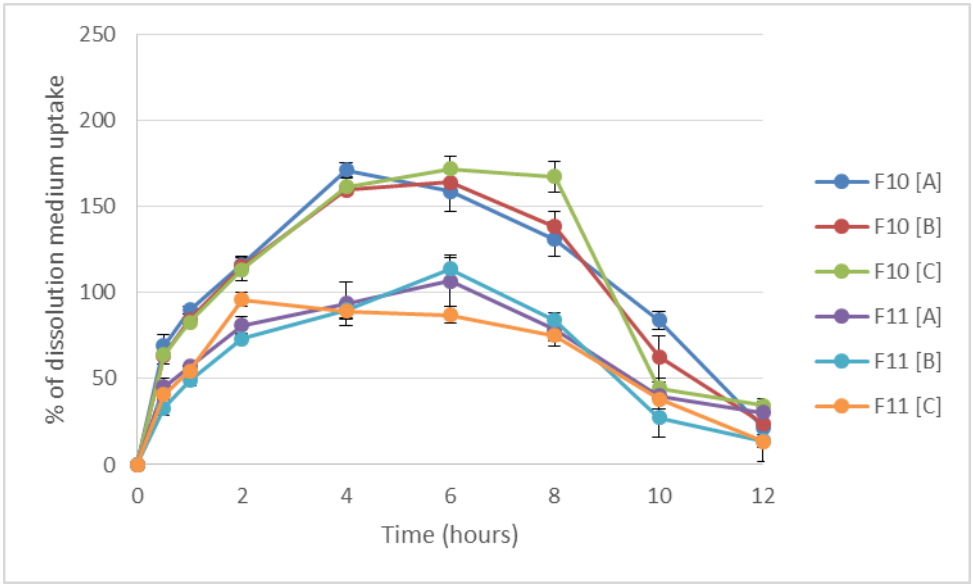


Figure 4-38: Percentage of medium uptake for the formulations F10 and F11 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 4-1 or Table 2-8.

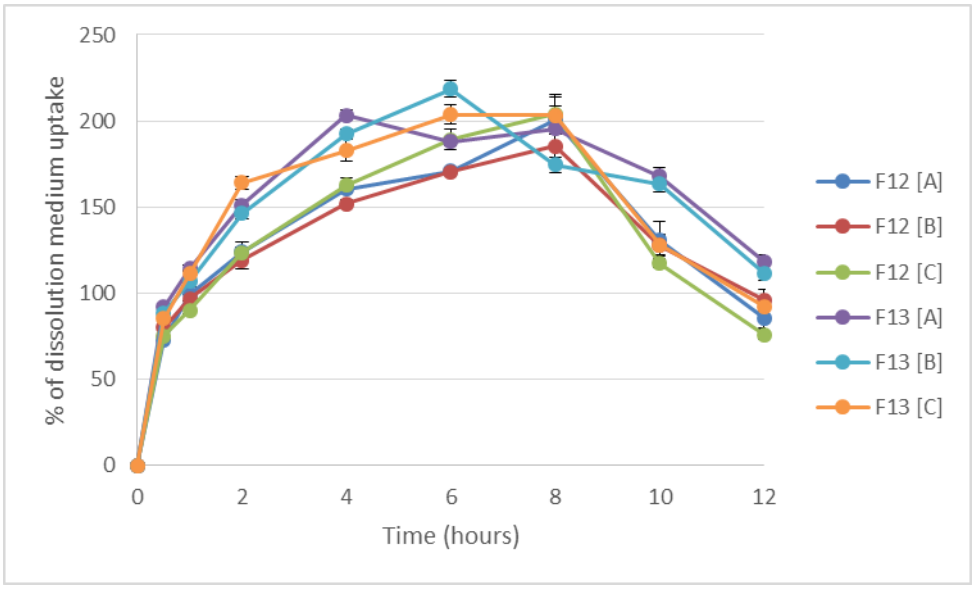


Figure 4-39: Percentage of medium uptake for the formulations F12 and F13 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).

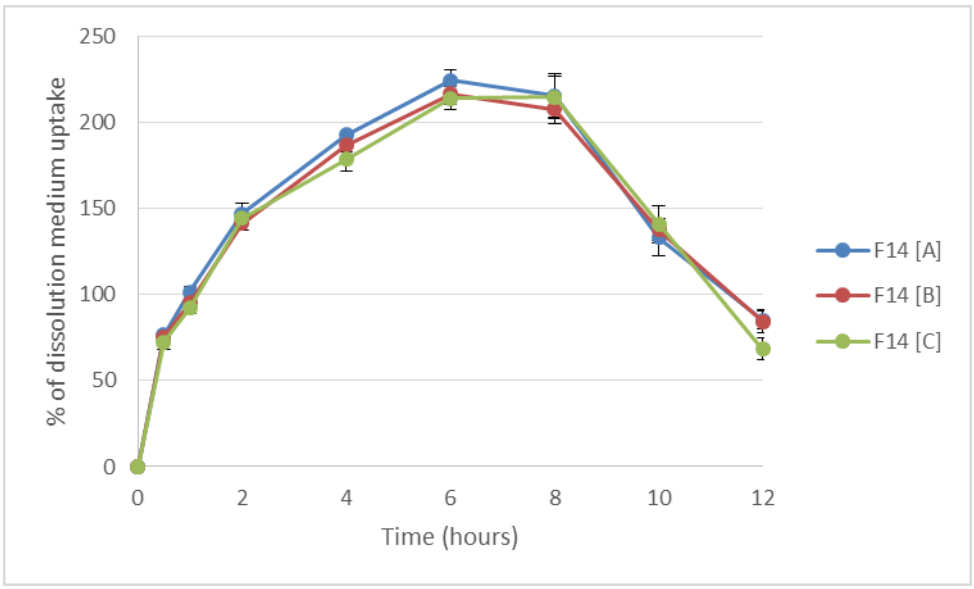


Figure 4-40: Percentage of medium uptake for the formulation F14 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 4-1 or Table 2-8.

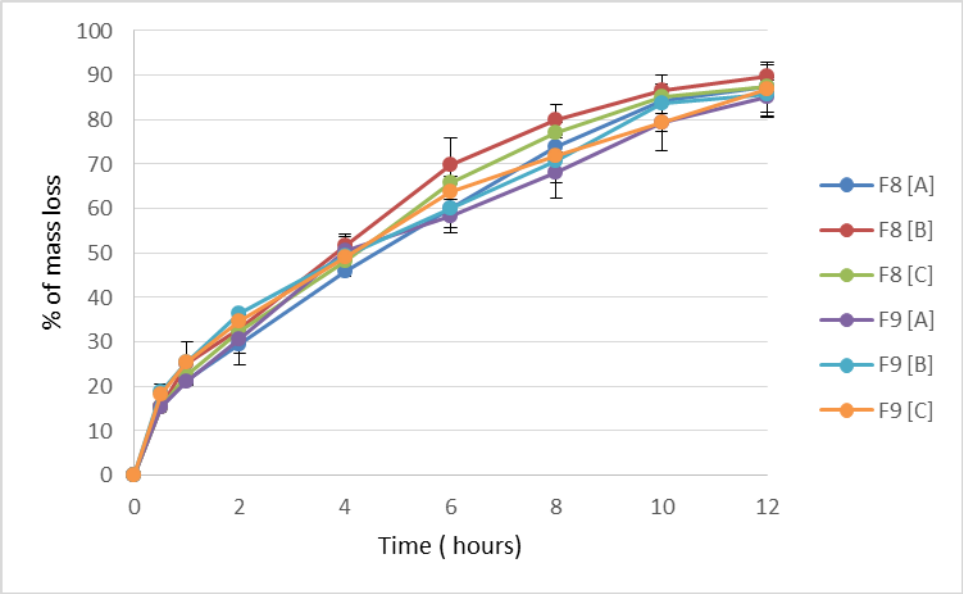


Figure 4-41: Percentage of mass loss for the formulations F8, and F9 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).

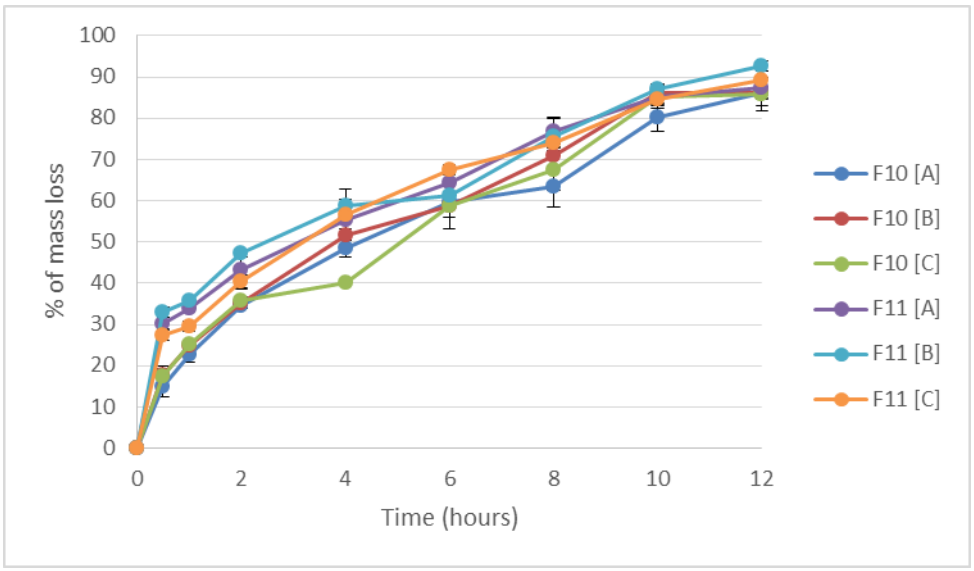


Figure 4-42: Percentage of mass loss for the formulations F10, and F11 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 4-1 or Table 2-8**.**

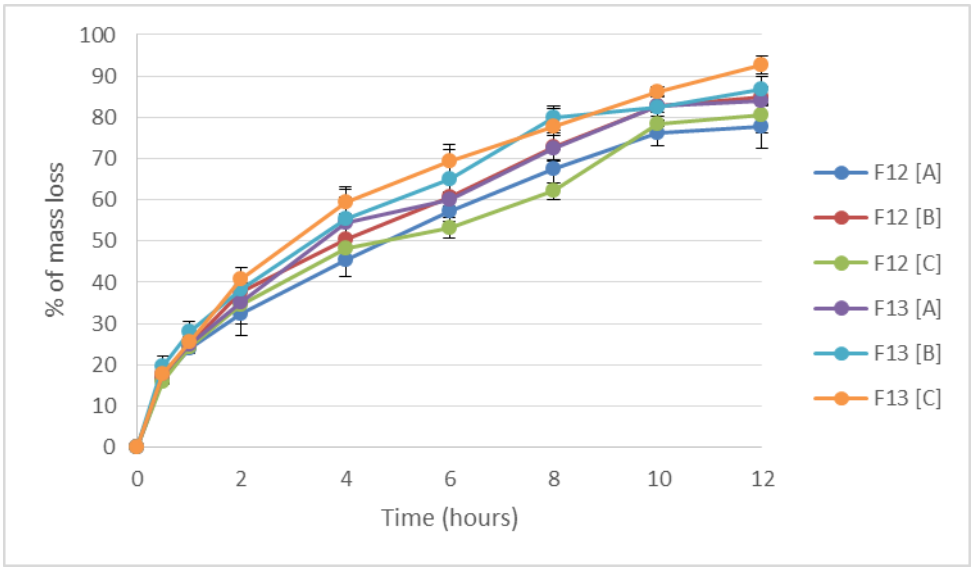


Figure 4-43: Percentage of mass loss for the formulations F12, and F13 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).

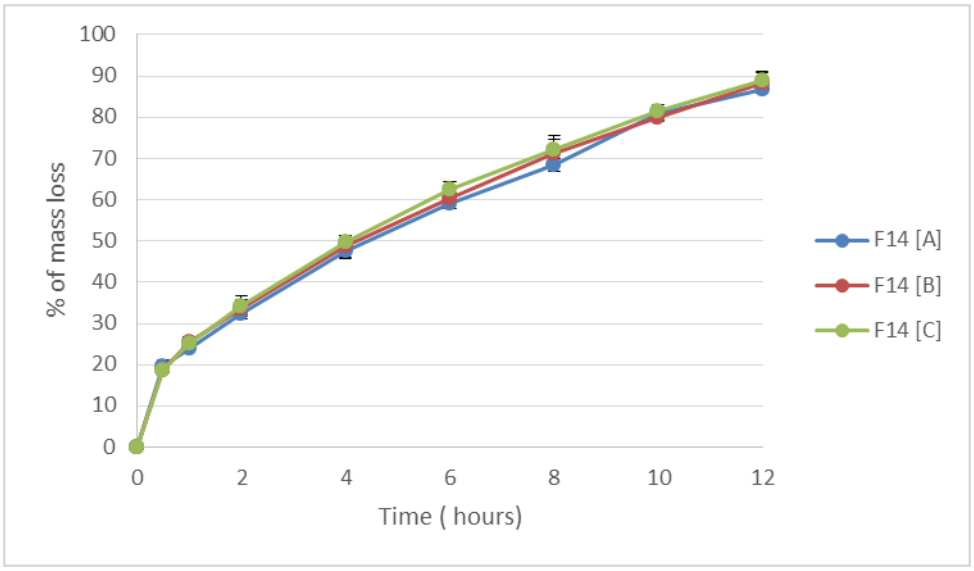


Figure 4-44: Percentage of mass loss for the formulation F14 (prepared from granules) in 0.1 M HCl medium.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N).
For formulation composition, refer to Table 4-1 or Table 2-8**.**

4.2.5 *In vitro* drug release studies

The dissolution profiles of all the tablets (F8-F14) prepared from the powder mixtures are presented in Figure 4-45 to Figure 4-48 respectively. Generally, increasing the tablet crushing strength level increased the drug release rate of F8 (10% w/w) and F9 (20% w/w) tablets based on sodium bicarbonate (Figure 4-45). Statistically, a significant (P<0.05) effect at majority of the time points was noted except between the tablets prepared at the levels A and B of F8, and at the levels B and C of F9 where the effect was not significant (P>0.05) at most of the time points. This does not agree with the related results of pentoxifylline tablets (F1 and F2) as a significant (P<0.05) decrease in their drug release rate when their crushing strength level increased from level (A) to level (B) was noted at bulk of the time points (Chapter 3, section 3.2.5). Increasing the tablet crushing strength decreased the porosity percentage of both F8 and F9 tablets prepared from the powder mixture (Figure 4-36) which should reduce the penetration of the dissolution medium inside their matrices and decrease their drug release rate. But their dissolution profiles were not clear enough to match them with the porosity results.

Kaneniwa et al. (1984) reported that cefalexin showed elastic behaviour on high compression pressure which may clarify inability of the relaxed dry matrices to reduce the drug release rate at the higher crushing strength levels. Increasing the tablet crushing strength level did not show any significant (P>0.05) effect on both the formulations F10 (10%) and F11 (20%) at larger part of the time points because the high effervescent activity of the gassing agent (calcium carbonate) facilitated the disintegration process of these tablets (Figure 4-46), which complies with the related results of F3 and F4 pentoxifylline tablets (Chapter 3, section 3.2.5). Regarding the formulations based on sodium carbonate as a gassing agent (F12 and F13), neither disintegration behaviour nor significant difference (P>0.05) between their drug release rate was noted (Figure 4-47). This also agrees with the related results of pentoxifylline tablets (F5 and F6) (Chapter 3, section 3.2.5) where the ability of sodium carbonate to generate an alkaline microenvironment in the swelled matrices protected their tablets from the disintegration process due to the rapid gel formation.

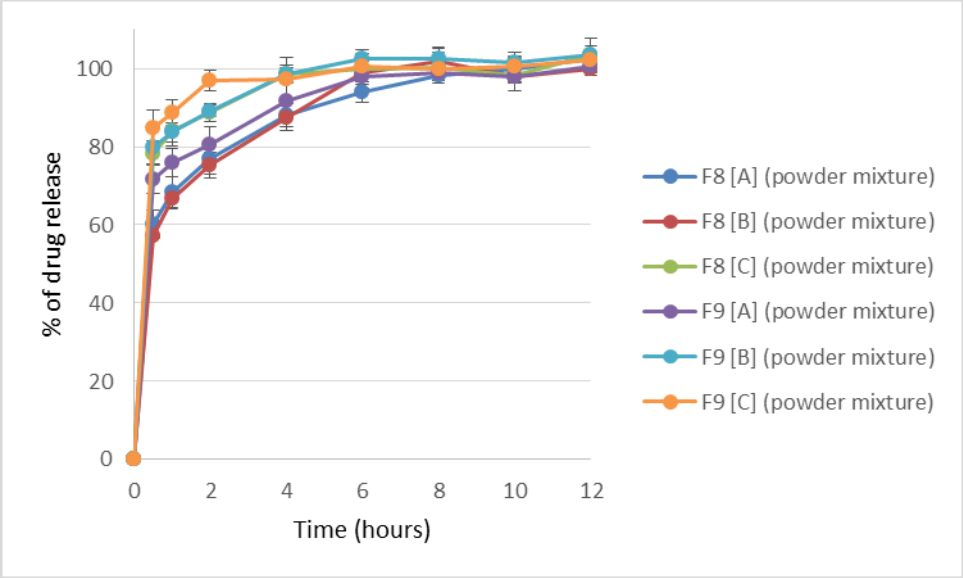


Figure 4-45: Percentage of drug release of F8, and F9 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium before granulation.

Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

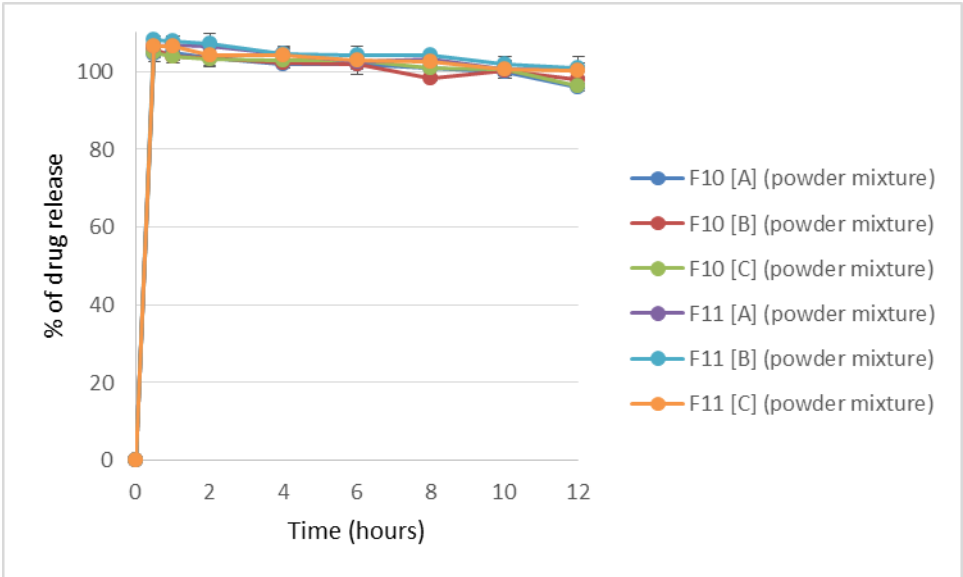


Figure 4-46: Percentage of drug release of F10, and F11 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium before granulation.

Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

For formulation composition, refer to Table 4-1 or Table 2-8.

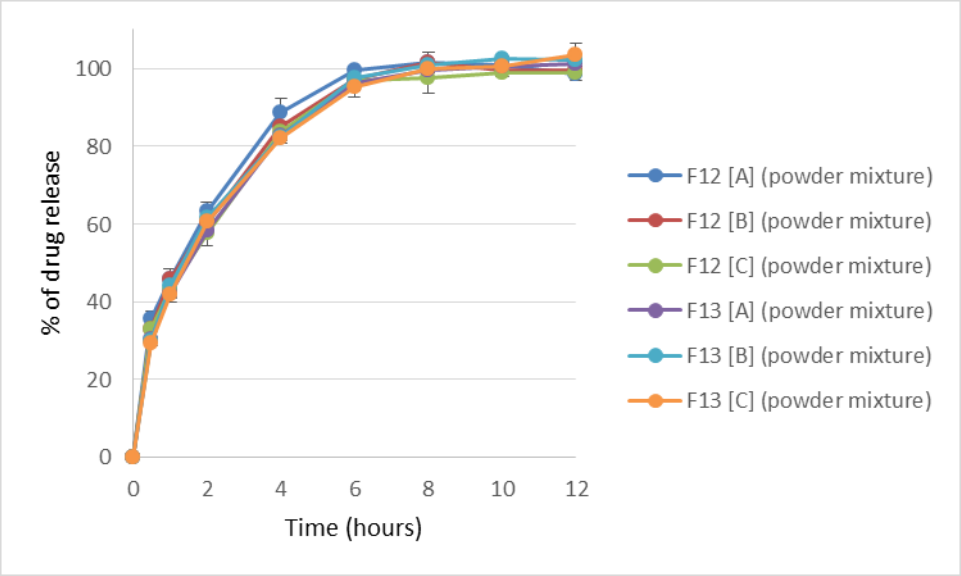


Figure 4-47: Percentage of drug release of F12, and F13 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium before granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

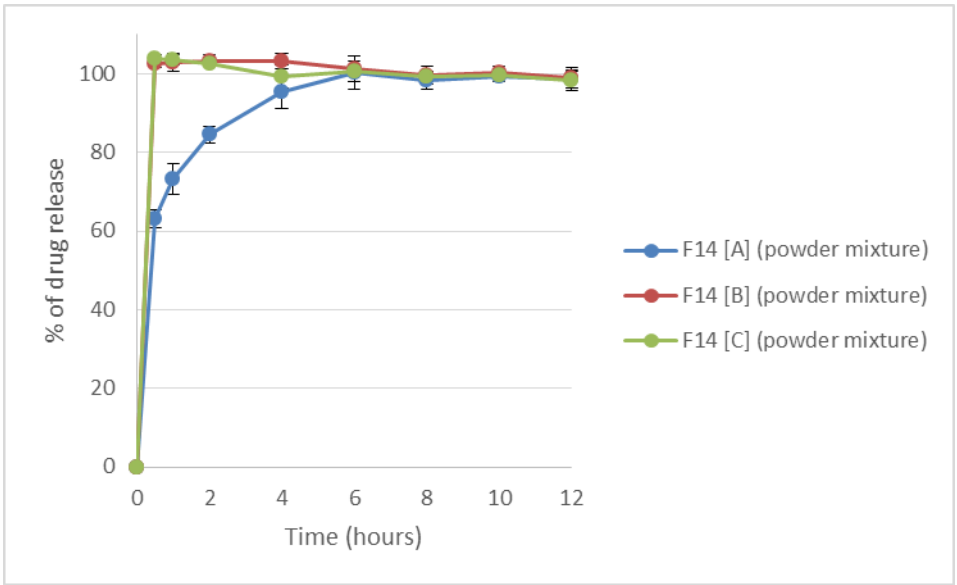


Figure 4-48: Percentage of drug release of F14 control tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium before granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 4-1 or Table 2-8.

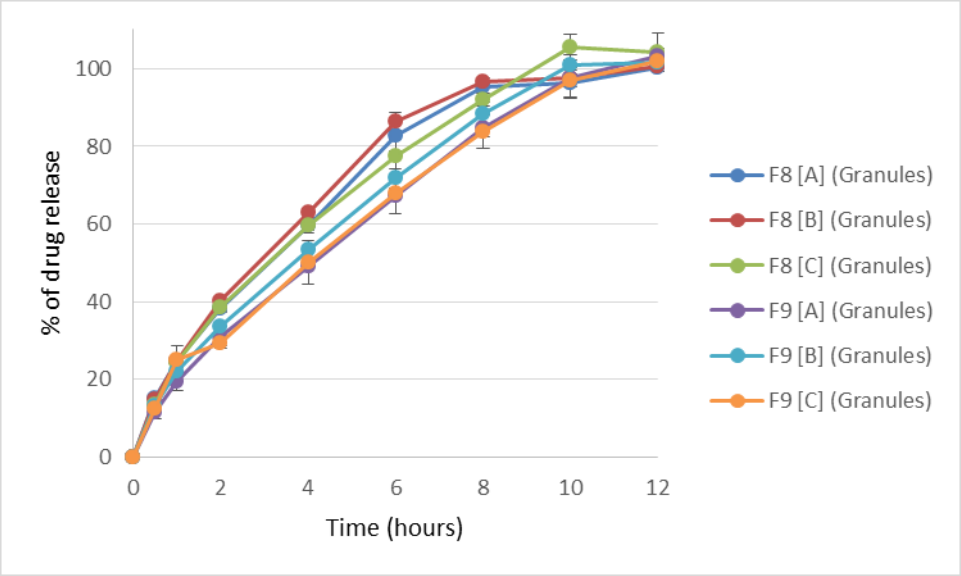


Figure 4-49: Percentage of drug release of F8, and F9 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

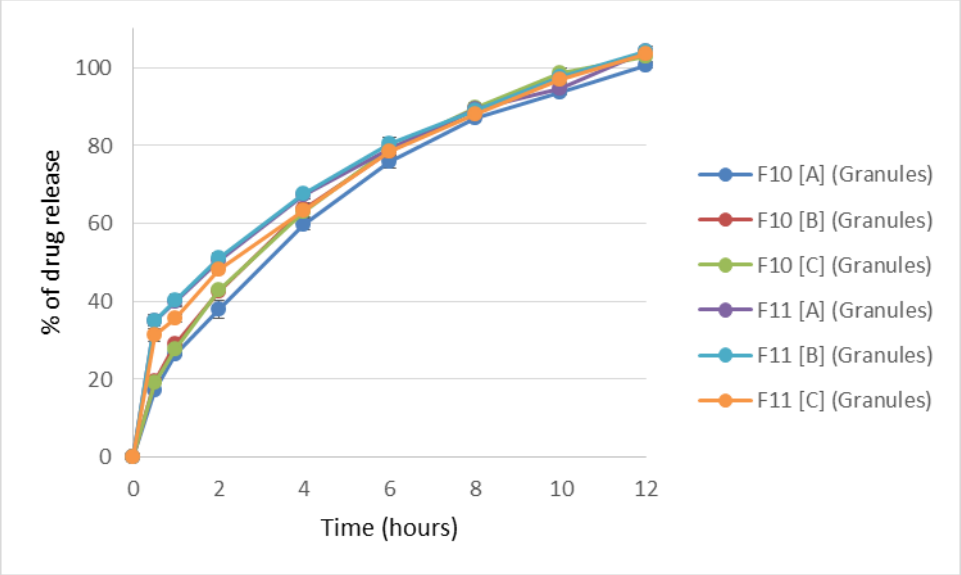


Figure 4-50: Percentage of drug release of F10, and F11 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 4-1 or Table 2-8.

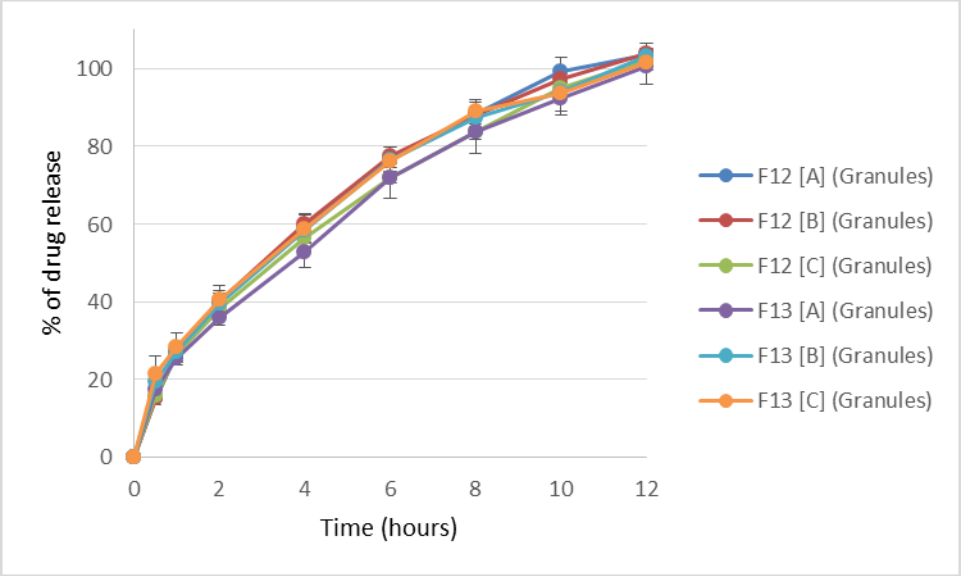


Figure 4-51: Percentage of drug release of F12, and F13 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

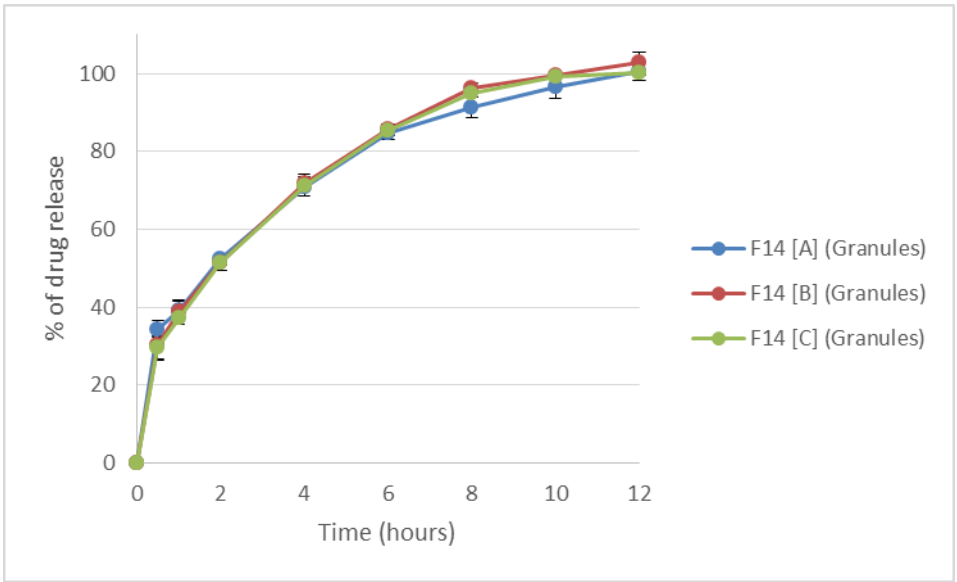


Figure 4-52: Percentage of drug release of F14 control tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after granulation.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 4-1 or Table 2-8.

Cefalexin monohydrate control tablets (F14), showed a significant (P<0.05) difference between the release profiles of the tablets pressed at the levels A and B and the levels A and C of crushing strength at majority of the time points (Figure 4-48). This may be explained by the complete disintegration behaviour of F14 tablets compacted at the levels B and C of crushing strength. However, for pentoxifylline control tablets (F7), only those tablets compacted at the level A of crushing strength showed a disintegration behaviour while those compacted at the levels B and C did not (Chapter 3, section 3.2.5). The elastic behaviour of cefalexin powder (Kaneniwa et al., 1984) may explain the disintegration behaviour of those tablets pressed at the higher compression force.

For the tablets prepared from the granules, the dissolution profiles of all the tablets (F8-F14) are presented in Figure 4-49 to Figure 4-52 respectively. Generally, increasing the tablets crushing strength level in all the formulations (F8-F14) caused a non-significant (P>0.05) difference in their drug release rate at bulk of the time points. This fits into the DMU results (Section 4.2.4) as well as the related pentoxifylline tablet results based on sodium bicarbonate (F1 and F2), calcium carbonate (F3 and F4), sodium carbonate (F5 and F6), and the control tablets (F7) (Chapter 3, section 3.2.5) where the tablet strength had only a small effect on the *in vitro* drug release rate. This negligible influence of increasing the compression force on the drug release rate following the granulation gives an advantage to control the high tablet friability percentages (Section 4.2.1) without disturbing the drug release rate.

The effect of the granulation process on drug release rate from the tablets (F8-F14) revealed that the granulation extended the drug release rate of all the prepared tablets significantly (P<0.05) at most of the time points (Figure 4-49 to Figure 4-52 respectively). Results of F8 (10% (w/w) sodium bicarbonate) tablets were consistent with the reduction in their porosity percentages following the granulation (Figure 4-36). Additionally, this agrees with the related results of F1 (10% (w/w)) formulation based on pentoxifylline (Chapter 3, section 3.2.5). The decrease in their porosity levels occurred during the wet massing stage of the granulation process could delay the dissolution medium entrapment through the matrix at an early stage of the dissolution test and decreased the drug release process.

Although the porosity levels of F9 (20% (w/w) sodium bicarbonate) tablets increased after the granulation (Figure 4-36), their dissolution profiles decreased. The better gel hydration ability of F9 tablets because of their higher sodium bicarbonate content (Section 4.2.3) may inverse the increase in their porosity percentages and decrease their drug release rate. The granulation process made the formulations F10 (10% (w/w)) and F11 (10% (w/w)) more resistant to rupture due to calcium carbonate effervescent behaviour and gave sufficient time for swelling and gel layer formation to control the drug release process (Figure 4-50) which is similar to the related results of F3 and F4 pentoxifylline tablets (Chapter 3, section 3.2.5). For the tablets based on sodium carbonate (F12 and F13), the decrease in their drug release rate following the granulation complies with the reduction in their porosity percentages after the granulation (Figure 4-36) where penetration rate of the dissolution medium inside these tablets decreased as well as drug release rate (Figure 4-51).

In comparison with the related results of pentoxifylline tablets, although the granulation process decreased the porosity levels of F5 (10% (w/w) sodium carbonate) tablets and increased the porosity of F6 (20% (w/w) sodium carbonate) tablets based on pentoxifylline, the difference in their drug release rate before and after the granulation was not significant (P>0.05) at majority of the time points (Chapter 3, section 3.2.5). For F14 tablets, after the granulation, their porosity level increased (Figure 4-36) and their internal structure became stronger. This rapidly initiated a gel layer (due to more dissolution medium entrapment rate) that prevented the tablet rupture by the disintegration and reduced the drug release rate (Figure 4-52) in comparison with the tablets prepared from the powder mixture. The drug release rate of pentoxifylline control tablets (F7) also decreased following the granulation (Chapter 3, section 3.2.5); however, this effect was explained by the reduction in their porosity levels in comparison with the tablets prepared from the powder mixture (Chapter 3, Figure 3-40). The (1:1) binary mixture of hydroxyethyl cellulose and sodium alginate content was reduced by almost 36% (w/w) in cefalexin monohydrate tablets (F8-F14) compared to pentoxifylline tablets (F1-F7) due to the change in their drug content (Chapter 2, Table 2-7 and Table 2-8) which made the lower polymeric content tablets (F8-F14) more sensitive to the effect of granulation process and explain these differences.

Increasing the concentration of sodium bicarbonate from 10% (w/w) (F8) to 20% (w/w) (F9) increased the drug release rates of the tablets prepared from the powder mixture (Figure 4-45). At majority of the time points, the effect was not significant (P>0.05) except at the level B of crushing strength where P<0.05. This is similar to the related results of F1 (10% (w/w)) and F2 (20% (w/w)) tablets (Chapter 3, section 3.2.5) where increasing the gassing agent level increased the pore formation in the wet matrix tablets due to liberation of more carbon dioxide bubbles, which caused higher drug release rate. In contrast, for tablets prepared from the granules, increasing the concentration of sodium bicarbonate significantly (P<0.05) decreased their dissolution behavior at bulk of the time points (Figure 4-49). This conforms to the related results of F1 and F2 tablets based on pentoxifylline. F1 tablets (10% (w/w)) demonstrated a higher swelling rate in comparison with F2 (20% (w/w)) tablets (Chapter 3, section 3.2.4) which indicates more entrapment of the dissolution medium in their matrices that dissolves and releases more drug molecules. In contrast, the swelling rate of F9 (20% (w/w) sodium bicarbonate) formulation was higher than that of F8 (10% (w/w) sodium bicarbonate) (Section 4.2.4). As discussed earlier (Section 4.2.3), a coherent microstructure of the swollen gel layer may be formed due to the higher gassing agent level which explains the lower drug release rate of F9 tablets prepared from the granules.

As shown in Figure 4-46, increasing the concentration of calcium carbonate from 10% (w/w) (F10) to 20% (w/w) (F11) in the tablets prepared from the powder mixture did not affect significantly (P>0.05) on their drug release rate at most of the time points because of the complete disintegration behavior. This is similar to the related pentoxifylline tablet results of the formulations F3 (10% (w/w)) and F4 (20% (w/w)) (Chapter 3, section 3.2.5). Yet, at larger part of the time points for the tablets prepared from the granules, increasing calcium carbonate concentration caused a significant (P<0.05) increase in the drug release except at level C of crushing strength where P>0.05 (Figure 4-50). This also conforms with the related results of pentoxifylline tablets (Chapter 3, section 3.2.5) where increasing the concentration of calcium carbonate from 10% (F3) to 20% (w/w) (F4) increased pore formation in the formed gel layer due to the entrapped gas bubbles, and this resulted in the higher drug release rate.

Increasing sodium carbonate concentration from 10% (F12) to 20% (w/w) (F13) caused a non-significant (P>0.05) decrease in the drug release rate from the tablets prepared from the powder mixtures at majority of the time points (Figure 4-47) and a non-significant (P>0.05) increase from the tablets prepared from the granules at larger part of the time points (Figure 4-51). This agrees with the related results of the formulations F5 (10% (w/w) sodium carbonate) and F6 (20% (w/w) sodium carbonate) based on pentoxifylline (Chapter 3, section 3.2.5) where the ability of sodium carbonate to generate an alkaline microenvironment enhanced pentoxifylline tablets (F5 and F6) to swell and to release the drug in almost similar rate. Nevertheless, as discussed earlier (Section 4.2.4), a higher swelling rate was noted with cefalexin monohydrate tablets based on 20% (w/w) sodium carbonate (F13) compared to 10% (w/w) (F12). This agrees with the increase in the number of parts of sodium carbonate available for the hydrophilic polymeric mixture in these formulations (Section 4.2.4) which enhanced their swelling rate behaviour. This difference in the swelling rate did not cause a difference in the drug release rate of F12 and F13 tablets suggesting that the coherent hydrated gel microstructure that was formed at 10% (w/w) sodium carbonate (F12) reached a point of strength after which no further decrease in the drug release rate can be noted.

The effect of adding a gassing agent on the drug release rate of the tablets prepared from the powder mixture or the granules was evaluated by comparing the control formulation (F14) results with all the other formulations (F8-F13). A significant (P<0.05) higher release rate at bulk of the time points of cefalexin monohydrate from F14 control tablets prepared from the powder mixture (Figure 4-48) or the granules (Figure 4-52) compared to both the formulations F8 (10% (w/w)) and F9 (20% (w/w) was noted. This conforms to the related results of pentoxifylline tablets based on sodium bicarbonate (F1 and F2) and the control ones (F7) where the swelling rate of the control tablets (F14) showed a higher swelling rate compared to the tablets of F8 and F9 formulations.

Conversely, increasing the number of parts of sodium bicarbonate available for the hydrophilic polymeric mixture in the formulations based on cefalexin monohydrate (Section 4.2.4) could alter the strength of the hydrated microstructure of the swollen matrix tablets due to the prospected difference in the microenvironment alkalinity level generated during the dissolution process. Accordingly, absence of the gassing agent (sodium bicarbonate) from F14 tablets generated thicker but weaker gel structure that could not retard the drug molecules as those of the formulations F8 and F9.

Regarding the addition of calcium carbonate, a significant (P<0.05) lower dissolution rate of cefalexin monohydrate from F14 control tablets prepared from the powder mixture at most of the time points was noted (Figure 4-48) compared to both the formulations F10 (10% (w/w)) and F11 (20% only at the level A of crushing strength as F14 tablets did not disintegrate). But, at the levels B and C of crushing strength the effect was not significant (P>0.05) at majority of the time points due to the complete disintegration behaviour of the tablets F10, F11, and F14. Nonetheless, for the tablets prepared from the granules, the drug release rate significantly (P<0.05) decreased at larger part of the time points on the addition of 10% (w/w) calcium carbonate and non-significantly (P>0.05) decreased on the addition of 20% (w/w) of it.

This was not similar to the related results of pentoxifylline tablets prepared from the granules where adding calcium carbonate at 10% (w/w) (F3) or at 20% (w/w) (F4) increased the drug release rate due to the liberation of the gas bubbles that enhanced more pore formation (Chapter 3, section 3.2.5). Changing the (gassing agent: polymeric mixture) ratio in cefalexin monohydrate tablets facilitated the formation of a more cohesive hydrated gel microstructure. This explains the significant decrease in the drug release rate upon addition of 10% (w/w) calcium carbonate. Still, the absence of the significance effect at the higher level (20 % w/w) suggests that the effervescent activity of calcium carbonate increased the pore formation in the hydrated gel layer which may inverse the effect of the (gassing agent: polymeric mixture) ratio.

Adding sodium carbonate as a gassing agent at 10% (w/w) (F12) or at 20% (w/w) (F13) decreased significantly (P<0.05), at majority of the time points, the drug release rate from the tablets either prepared from the powder mixture or the granules, which is similar to the related results of pentoxifylline tablets but the effect was generally not significant (Chapter 3, section 3.2.5). Although (sodium carbonate: polymeric mixture) ratio was higher in cefalexin monohydrate formulations than that used in pentoxifylline formulations, the drug release rate decreased on addition of sodium carbonate in both formulations. This complies with the earlier suggestion that sodium carbonate may form a coherent gel microstructure regardless of the used concentration. Generally, it is worth in the future to do further evaluation regarding the swollen gel microenvironment pH, strength, and morphology which will support the previously mentioned explanations.

Cefalexin monohydrate tablets (F8-F14) generally showed faster drug release rate in comparison with pentoxifylline tablets (F1-F7). Changing the drug content from 60 mg (pentoxifylline) to 250 mg (cefalexin monohydrate) changed the (polymeric mixture: tablet weight) ratio. For example, it was changed from (5.0:10) for F1 and (4.5:10) for F2 to (3.2:10) for F8 and (2.8:10) for F9. This reduction (by almost 36% (w/w)) in the polymeric content reduced ability of the later tablet matrices to sustain the drug release process. Still, further investigations on cefalexin monohydrate floating tablets based on higher polymeric mixture content could be tried in the future to enhance their dissolution profiles.

Concerning the stability studies of the formulations F8-F14, effect of the storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers is shown in Figure 4-53 to Figure 4-59 respectively. A significant (P<0.05) increase in the drug release rate of the tablets F8 (10% (w/w) sodium bicarbonate) and F9 (20% (w/w) sodium bicarbonate) at bulk of the time points in comparison to the freshly prepared ones was noted after storage in the closed containers (Figure 4-53 and Figure 4-54 respectively). This rapid drug release rate of F8 and F9 tablets complies with reduction in their floating lag time results after storage. The dissolution medium easily penetrated the relaxed tablet matrices to dissolve the drug and release it in a higher rate than that of the freshly prepared tablets. In contrast, the stability results of F8 formulation in the open containers showed a significant (P<0.05) reduction in their dissolution profiles at majority of the time points (Figure 4-53) in comparison with their freshly prepared samples. Almost 80% of the drug was released after 12 h; however, after 24 h a complete drug release was reported. Moreover, these tablets (F8) lost their ability to float and kept sinking during the experiment time. As discussed earlier (Section 4.1.3), the stressful humidity level (80%) may generate a concentration dependent alkaline microenvironment, which may facilitate a rapid generation of a coherent gel microstructure around the tablets once they contacted the dissolution medium to retard the drug release rate. Also, the loss of the effervescent activity of sodium bicarbonate, after the storage, decreased the erosional behaviour of these tablets which may explain the sharp decrease in the drug release process.

For F9 tablets, storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in the open containers (Figure 4-54) indicates cefalexin monohydrate degradation as presented in the related DSC thermogram (Figure 4-12) and the IR spectra (Figure 4-26). Accordingly, the release profiles of F9 tablets after storage in the open containers may be related to degradation product(s). Also, sodium carbonate based formulations (F12 (10% (w/w) and F13 (20% (w/w)), as shown respectively in their DSC thermograms (Figure 4-15 and Figure 4-16) and their IR spectra (Figure 4-29 and Figure 4-30), storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in the open containers indicates degradation of cefalexin monohydrate. Accordingly, the related release profiles (Figure 4-57 and Figure 4-58) could represent degradation product(s).

Conversely, the stability studies of the tablets based on calcium carbonate as a gassing agent (F10 and F11) and the control tablets (F14) stored either in the closed or the open containers showed a significant (P<0.05) increase in their drug release rate at majority of the time points. This complies with earlier discussion about the relaxation behaviour of the tablets during the storage time where a complete disintegration was reported. An exception was noted for F10 tablets (10% calcium carbonate) which presented a partial control of the drug release (Figure 4-55). This conforms to the *in situ* ability of the anionic alginate molecules to form a gel in the presence of multivalent cations such as calcium ions in aqueous medium. During the storage process, especially under a relatively high moisture level (80%), this may generate an insoluble gel that could decrease the drug release rate. But, the lower polymeric content in cefalexin monohydrate based tablets and the higher calcium carbonate level for F11 (20% (w/w)) tablets counteracted the *in situ* cross linking effect and resulted in a complete disintegration behaviour (Figure 4-56).

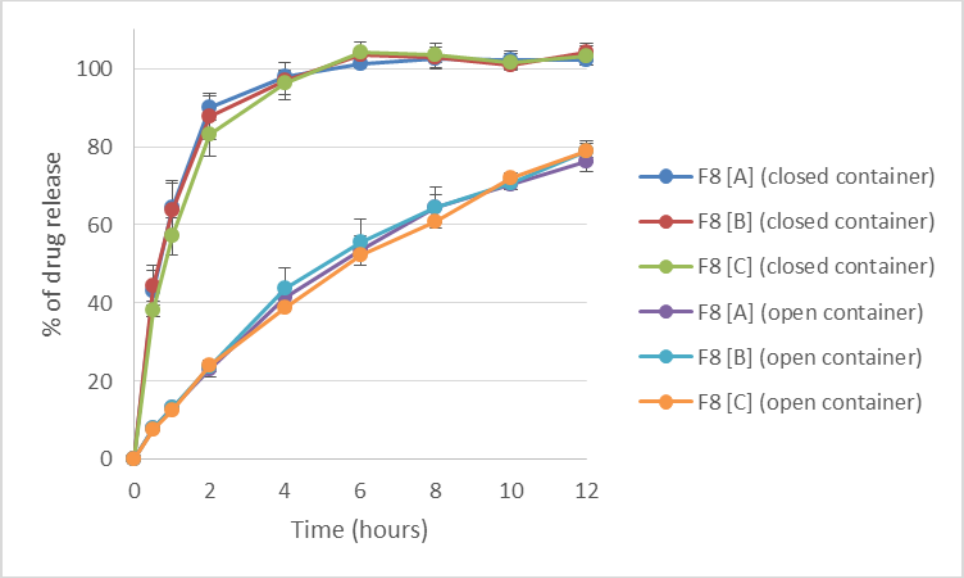


Figure 4-53: Percentage of drug release of F8 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 4-1 or Table 2-8.

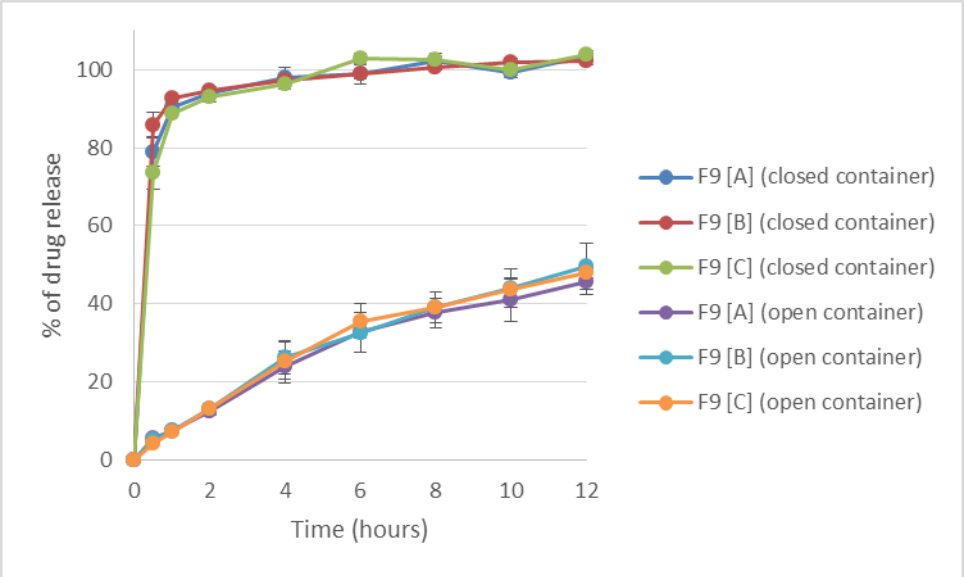


Figure 4-54: Percentage of drug release of F9 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

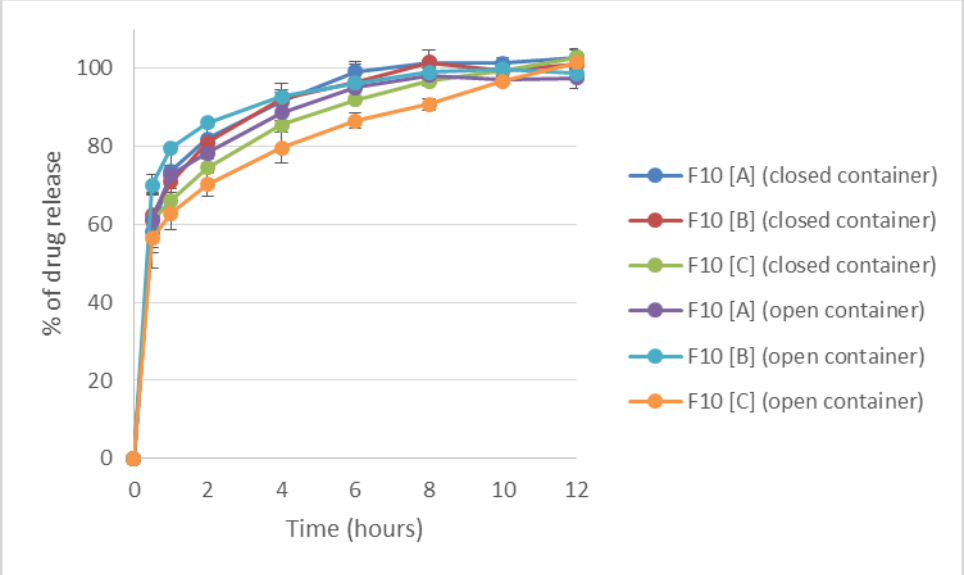


Figure 4-55: Percentage of drug release of F10 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 4-1 or Table 2-8.
This makes this formulation with calcium carbonate successful and confirms the feasibility of using calcium carbonate as an stability indicating gassing agent within floating drug delivery systems.

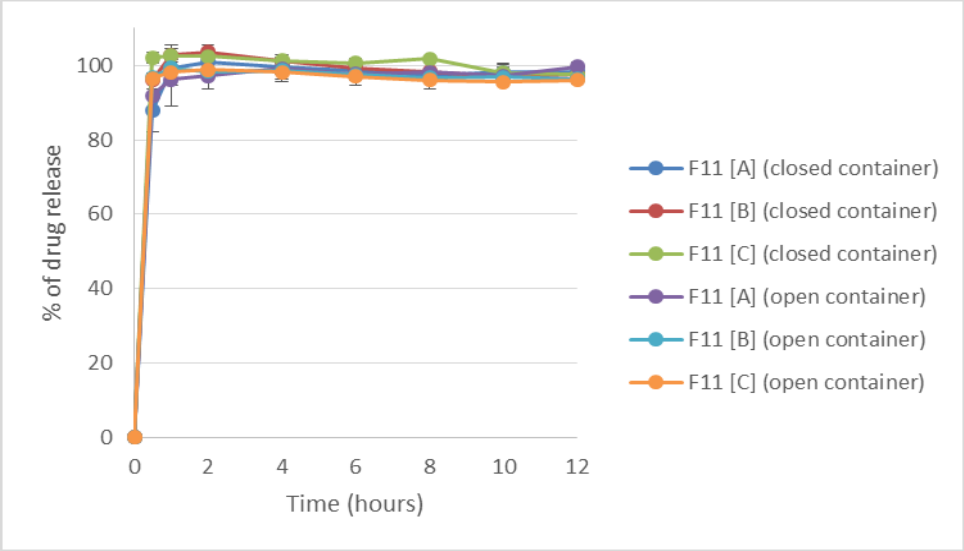


Figure 4-56: Percentage of drug release of F11 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

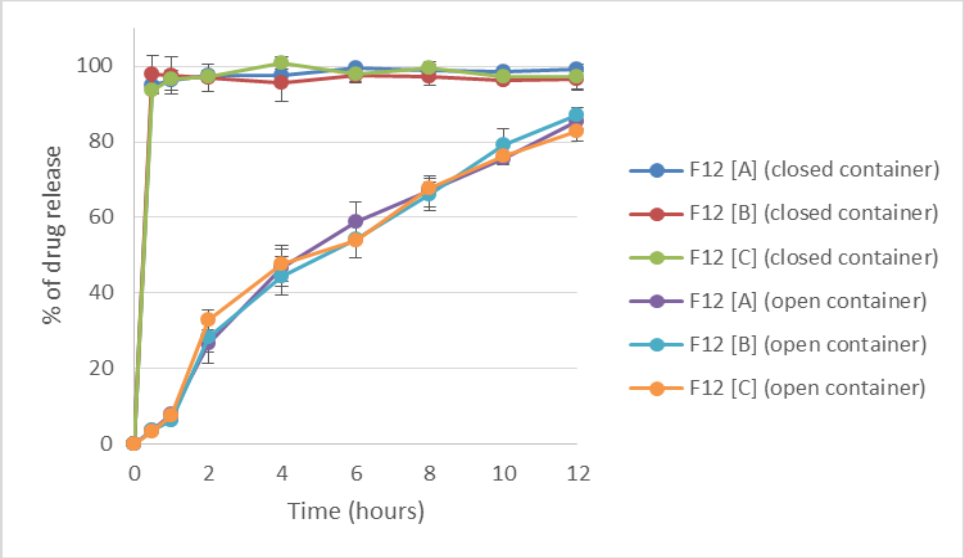


Figure 4-57: Percentage of drug release of F12 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 4-1 or Table 2-8.

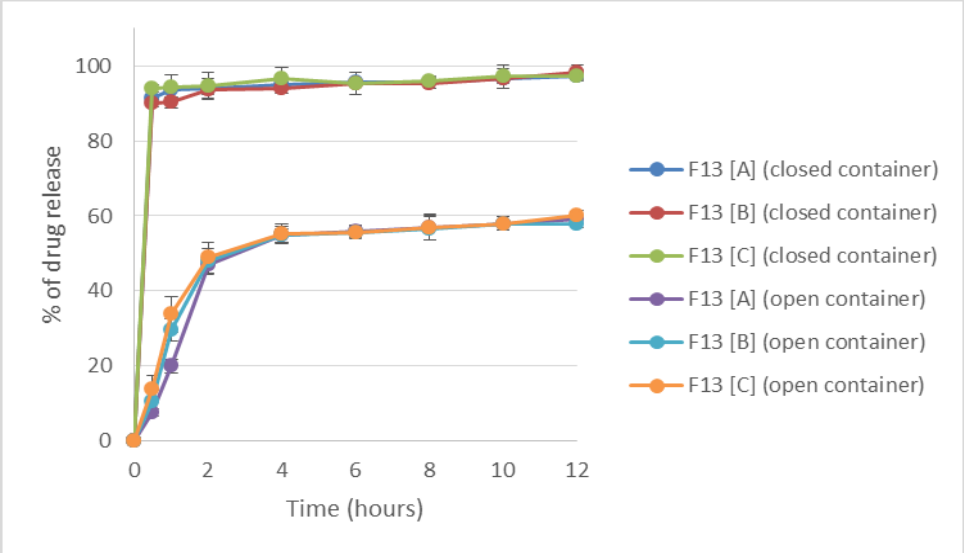


Figure 4-58: Percentage of drug release of F13 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.

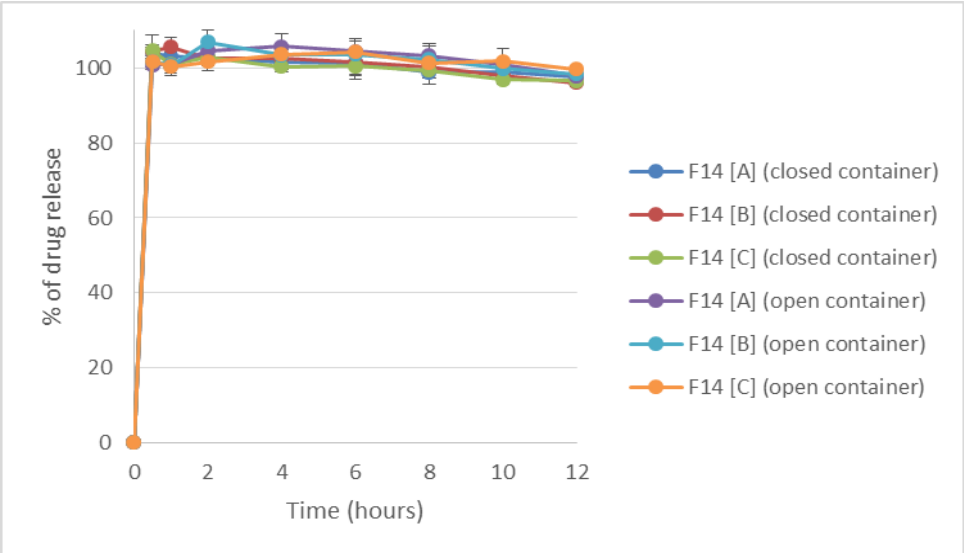


Figure 4-59: Percentage of drug release of F14 floating tablets pressed at levels (A), (B), and (C) of crushing strength in 0.1 M HCl medium after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
Notes: The data represents the mean ± SD of three determinations. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time.
For formulation composition, refer to Table 4-1 or Table 2-8.

In order to investigate morphological changes of all the tablets (F8-F14) before and after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers, pictures were evaluated (Figure 4-60). Concerning the tablets based on sodium bicarbonate as a gassing agent, a change in the colour from white to yellow (F8) or dark brown (F9) was observed in the open container tablets. However a very slight change in the colour was noted in the tablets stored in the closed ones. The formulations which were loaded with sodium carbonate showed a change in the colour from white to yellow (F12) or dark brown (F13) in the open container tablets, and a very slight change in colour was seen in tablets stored in closed ones. The intensity of the colour was proportional to both sodium bicarbonate and sodium carbonate concentrations in the related formulations. This agrees with the results of DSC (Section 4.1.2) and FTIR (Section 4.1.3) that an interaction occurred between these gassing agents and cefalexin monohydrate after storage in the open containers. Since sodium bicarbonate and sodium carbonate are water soluble, direct exposure to a stressful humidity level (80%) for 3 months could increase the pH of the matrix microenvironment in a concentration dependent rhythm causing degradation for cefalexin monohydrate as it is unstable in such conditions (Marrelli, 1975; Yin et al., 2013). F10 and F11 calcium carbonate based formulations and F14 control formulation did not show change in colour which approves that calcium carbonate is a promising gassing agent. According to the ICH guidelines, a specific stability-indicating assay method such as HPLC to determine the drug content and any possible degradation products in the formulations will be required in the future to do more investigations (ICH, 1999). Consequently, it is suggested that all cefalexin monohydrate floating systems based on such gas forming agents should be packaged by the pharmaceutical companies in tightly closed containers with an eye-catching label to direct patients for good practice.

Formulation	Freshly prepared tablets	Tablets after storage at 40°C ± 2°C and 80% ± 5% RH	
		Closed container	Open container
F8			
F9			
F10			
F11			
F12			
F13			
F14			

Figure 4-60: Pictures of F8-F14 tablets freshly prepared and after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in closed or open containers.
For formulation composition, refer to Table 4-1 or Table 2-8.

4.2.6 Release data modeling and analysis

Table 4-7 shows the release rate constants (*k*), and the correlation coefficients (R^2) calculated after fitting the dissolution profiles of the formulations F8-F14 into zero order, first order, Hixson-Crowell, and Higuchi drug release mathematical models. Because of the rapid dissolution profiles of F8, F9 (Figure 4-45) F10, F11 (Figure 4-46), and F14 (Figure 4-48) tablets, prepared from the powder mixtures, only their drug release rate of the tablets prepared from the granules were considered beside those of F12, and F13 tablets prepared from either the powder mixtures or the granules for Table 4-7 evaluation.

The *in vitro* drug release rate of the formulations F8-F14 were best explained by Higuchi's and Hixson-Crowell equations, as the highest linearity (R^2) values were obtained. This indicates that the release of cefalexin monohydrate from the evaluated floating matrices (F8-F14) as a square root of time was dependent process based on Fickian diffusion alongside with a change in diameter and surface area of the matrices with the progressive dissolution process as a function of time. Korsmeyer–Peppas equation (Equation 11, chapter 2, section 2.2.6.6) was used, as it describes the drug release from polymeric systems, to evaluate the effect of tablet crushing strength, the granulation process, and the gassing agent concentration on the drug release mechanism of the prepared tablet formulations (F8-F14).

Table 4-7: Release rate constants (*k*), and correlation coefficients (R^2) calculated after fitting the release profiles of F8-F14 into of zero order, first order, Hixson-Crowell, and Higuchi drug release mathematical models.

Formulation	Origin of prepared tablets	Crushing strength level	Drug release mathematical model							
			Zero order		First order		Hixson-Crowell		Higuchi	
			R^2	K_0 ($mg*h^{-1}$)	R^2	K_1 (h^{-1})	R^2	K_{HC} ($mg^{1/3}*h^{-1}$)	R^2	K_H ($mg^{1/2}*h^{-1}$)
F8	Powder	(A)	0.8863	3.9990	0.9465	0.5048	0.9977	0.2882	0.9686	16.307
		(B)	0.8343	4.4056	0.8208	0.4115	0.6709	0.3711	0.9308	18.152
		(C)	0.7018	2.0625	0.3286	0.4021	0.6056	0.2742	0.8360	8.781
	Granules	(A)	0.9449	8.9962	0.9681	0.3554	0.9819	0.3240	0.9856	35.839
		(B)	0.9301	9.1435	0.9687	0.3986	0.9804	0.3461	0.9818	36.642
		(C)	0.9797	9.4911	0.8994	0.4178	0.8179	0.5362	0.9994	37.392
F9	Powder	(A)	0.8460	2.9198	0.8595	0.3547	0.8800	0.2226	0.9354	11.976
		(B)	0.7878	2.3566	0.9581	0.8012	0.8746	0.4919	0.9003	9.826
		(C)	0.6743	1.4251	0.8802	0.4599	0.7616	0.3289	0.8041	6.070
	Granules	(A)	0.9934	9.0537	0.8716	0.3314	0.9601	0.3052	0.9913	35.279
		(B)	0.9896	9.1997	0.8466	0.4016	0.8228	0.4717	0.9950	35.982
		(C)	0.9905	8.6846	0.8860	0.3051	0.9632	0.2887	0.9861	33.801

The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). For formulation composition, refer to Table 4-1 or Table 2-8.

Table 4-7 (continued): Release rate constants (k), and correlation coefficients (R^2) calculated after fitting the release profiles of F8-F14 into of zero order, first order, Hixson-Crowell, and Higuchi drug release mathematical models.

Formulation	Origin of prepared tablets	Crushing strength level	Drug release mathematical model							
			Zero order		First order		Hixson-Crowell		Higuchi	
			R^2	K_0 ($mg*h^{-1}$)	R^2	K_1 (h^{-1})	R^2	K_{HC} ($mg^{1/3}*h^{-1}$)	R^2	K_H ($mg^{1/2}*h^{-1}$)
F10	Powder	(A)	0.9551	-0.5019	0.4439	0.1573	0.7697	-0.1805	0.4109	0.566
		(B)	0.7933	-0.6129	0.1798	-0.0242	0.5346	-0.2081	0.8333	-2.451
		(C)	0.8903	-0.4031	N.A	N.A	0.8770	-0.0856	0.8780	-1.561
	Granules	(A)	0.9610	8.1567	0.9872	0.2642	0.9998	0.2640	0.9965	32.400
		(B)	0.9588	8.1645	0.9438	0.3332	0.9940	0.2986	0.9979	32.490
		(C)	0.9605	8.3348	0.9030	0.3763	0.9850	0.3179	0.9981	33.142
F11	Powder	(A)	0.9315	-0.6329	N.A	N.A	0.8798	-0.0952	0.8998	-2.426
		(B)	0.9121	-0.6109	N.A	N.A	0.9137	-0.0715	0.9392	-2.418
		(C)	0.9171	-0.5527	N.A	N.A	0.8955	-0.0874	0.9291	-2.170
	Granules	(A)	0.9672	6.4713	0.9838	0.2589	0.9994	0.2415	0.9967	25.624
		(B)	0.9734	6.6079	0.9315	0.3079	0.9881	0.2661	0.9984	26.105
		(C)	0.9781	7.0334	0.9311	0.3022	0.9869	0.2691	0.9972	27.702

The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). For formulation composition, refer to Table 4-1 or Table 2-8.

Table 4-7 (continued): Release rate constants (k), and correlation coefficients (R^2) calculated after fitting the release profiles of F8-F14 into of zero order, first order, Hixson-Crowell, and Higuchi drug release mathematical models.

Formulation	Origin of prepared tablets	Crushing strength level	Drug release mathematical model							
			Zero order		First order		Hixson-Crowell		Higuchi	
			R^2	K_0 ($mg*h^{-1}$)	R^2	K_1 (h^{-1})	R^2	K_{HC} ($mg^{1/3}*h^{-1}$)	R^2	K_H ($mg^{1/2}*h^{-1}$)
F12	Powder	(A)	0.8232	6.9840	0.9120	0.8749	0.9628	0.5901	0.9265	28.902
		(B)	0.8433	7.0862	0.9900	0.5576	0.8010	0.4668	0.9397	29.178
		(C)	0.8477	7.0778	0.9777	0.4670	0.9500	0.3441	0.9406	29.082
	Granules	(A)	0.9709	8.6529	0.8518	0.4058	0.9680	0.3306	0.9994	34.245
		(B)	0.9606	8.4918	0.9389	0.3284	0.9919	0.2999	0.9981	33.764
		(C)	0.9809	8.0994	0.9436	0.2692	0.9884	0.2646	0.9995	31.972
F13	Powder	(A)	0.8593	7.3927	0.9665	0.6243	0.9893	0.4883	0.9504	30.327
		(B)	0.8618	7.4746	0.9808	0.5852	0.9698	0.6097	0.9535	30.668
		(C)	0.8560	7.4062	0.9204	0.6941	0.9916	0.4969	0.9501	30.436
	Granules	(A)	0.9799	7.9649	0.9769	0.2388	0.9968	0.2467	0.9954	31.313
		(B)	0.9658	8.0112	0.9847	0.2658	0.9991	0.2635	0.9962	31.736
		(C)	0.9674	7.8763	0.9840	0.2671	0.9965	0.2632	0.9945	31.151
F14	Powder	(A)	0.7257	3.4234	0.9045	0.4210	0.5643	0.2860	0.8580	14.520
		(B)	0.7384	-0.3480	0.1798	0.0520	0.4553	-0.1451	0.6525	-1.274
		(C)	0.7387	-0.4828	0.5993	0.0811	0.6453	-0.2584	0.8332	-2.000
	Granules	(A)	0.9428	6.8051	0.9859	0.3047	0.9987	0.2689	0.9900	27.002
		(B)	0.9427	7.4179	0.9137	0.4928	0.9937	0.3490	0.9915	29.680
		(C)	0.9419	7.4527	0.9236	0.4459	0.9957	0.3343	0.9919	29.832

The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). For formulation composition, refer to Table 4-1 or Table 2-8.

As shown in Table 4-8, the drug release results of F8-F14 tablets fitted into Korsmeyer–Peppas equation as the correlation coefficients (R^2) greater than 0.98 were obtained in all the tablets except for the tablets prepared from the granules of the formulations F9 (20% (w/w) sodium bicarbonate) at the crushing strength level C, F11 (20% (w/w) calcium carbonate) at all the crushing strength levels, and F14 (the control tablets) at the crushing strength level A. But, there were insufficient data points on the release profile ≤ 60% drug release in order to provide accurate values for the tablets prepared from the powder mixture of the formulations F8, F9 (Figure 4-45), F10, F11 (Figure 4-46), and F14 (Figure 4-48). The values of the release rate constant (K_P) were consistent with the *in vitro* drug release results (Section 4.2.5). Generally, increasing the tablet crushing strength, slightly changed K_P values of the tablets prepared from the powder mixtures or the granules. The granulation process decreased the release rate constant (K_P) of the tablets F12 and F13 based on sodium carbonate as a gassing agent, however the effect was not clear for the other formulations due to the insufficient data points.

For the tablets prepared form the powder mixtures, the effect of increasing the gassing agent concentration from 0% to 20 % (w/w) on the release kinetics was not clear due to the rapid drug release rate; but, increasing sodium carbonate concentration from 10% to 20% (w/w) decreased their K_P values (Table 4-8). Regarding the tablets prepared from the granules the effect was much clearer. Raising sodium bicarbonate concentration decreased the release rate constant (K_p). For calcium carbonate, increasing its level decreased the release rate constant (K_P) at 10% (w/w) concentration (F10), but, at 20% (w/w) concentration (F11), it increased K_P values up to almost similar level of the control tablets (F14, 0% (w/w)). Additionally, raising sodium carbonate content decreased the drug release rate constant (K_P) at 10% (w/w) level (F12) and slightly increased it at the higher level (F13).

The effect of these factors on the drug release mechanism was also evaluated through the release exponent (n) values. As shown in Table 4-8 changing the crushing strength level slightly changed (n) values but without changing the release mechanism of all the prepared tablets (with sufficient data points).

The granulation process changed the drug release mechanism for the formulation F12 (10% (w/w) sodium carbonate) from release by diffusion (Fickian) to release by diffusion and polymer relaxation (non-Fickian) and retained it by non-Fickian release for the formulation F13 (20% (w/w) sodium carbonate). This is almost similar to the related results of pentoxifylline tablets (F5 and F6) where more involvement of polymer relaxation in addition to drug diffusion was predominant in the release process from such matrices (Chapter 3, section 3.2.6).

The effect of raising the gassing agent concentration (sodium bicarbonate, calcium carbonate or sodium carbonate) from 10% to 20% (w/w) was also evaluated in all the tablets with sufficient data points (Table 4-8). Regarding sodium bicarbonate, no change in the release mechanism was reported by raising its concentration which agrees with the related results of F1 and F2 tablets based on pentoxifylline where release by diffusion and polymer relaxation (non-Fickian) was reported (Chapter 3, section 3.2.6). Increasing calcium carbonate concentration in the tablets of the granules origin changed the release mechanism from non-Fickian at 10% (w/w) (F10) to Fickian release at 20% (w/w) (F11). This conforms to the related results of F3 (10% (w/w)) and F4 (20% (w/w)) tablets of pentoxifylline based on calcium carbonate (Chapter 3, section 3.2.6). Although the (calcium carbonate: polymeric mixture) ratio was different between these formulations, where it was (2:10) for F3, (4.5:10) for F4, (3.1:10) for F10, and (7:10) for F11 (Chapter 2, Table 2-7 and Table 2-8), the release mechanism results of pentoxifylline tablets (F3 and F4) were similar to the related ones of cefalexin monohydrate tablets (F10 and F11). This suggests that calcium ion concentration available in the formulations F3 and F11 (10% (w/w)) was insufficient to properly cross-link with the anionic alginate molecules of the polymeric mixture. Still, the concentration was enough in the formulations F4 and F12 (20% (w/w)) as only diffusion mechanism became the controller of the drug release.

For the tablets based on sodium carbonate as a gassing agent (F12 and F13), a change in the drug release mechanism from Fickian to non-Fickian release was noted by increasing its concentration from 10% to 20% (w/w) in the tablets prepared from the powder mixtures. In contrast, the release mechanism changed in the related results of pentoxifylline tablets from non-Fickian at 10% (w/w) (F5) to Fickian release at 20% (w/w) (F6) (Chapter 3, section 3.2.6).

Concerning the tablets prepared from the granules, no change in the release mechanism was reported by raising sodium carbonate concentration which agrees with the related results of F5 and F6 tablets based on pentoxifylline where release was by diffusion and polymer relaxation (non-Fickian) (Chapter 3, section 3.2.6). Accordingly the change in the (gassing agent: polymeric mixture) ratio suggests that the role of sodium carbonate in the tablets of the powder mixture origin was concentration dependent. As sodium carbonate concentration increased the coherency of the hydrated gel microstructure increased to an optimum level (release by diffusion) after which polymer relaxation started to involve in the release mechanism due to more gas bubbles liberation. However, following the granulation, the matrices became less sensitive to the change in sodium carbonate concentration and more contribution of polymeric relaxation in the release mechanism was noted.

Fickian release mechanism (release by diffusion) was reported in the control tablets (F14) prepared from the granules. Nonetheless, non-Fickian release mechanism (release by diffusion and polymer relaxation) was noted in pentoxifylline control tablets (F7) (Chapter 3, section 3.2.6). Adding the gassing agents (sodium bicarbonate, calcium carbonate, or sodium carbonate) changed the release mechanism from release by diffusion (F14) to release by diffusion and polymer relaxation in the tablets prepared from the granules (F8-F13 respectively). This could be related to the movement of the generated carbon dioxide bubbles from the internal to the peripheral sides of the floating tablets, which increased the mass loss or the polymeric erosional behaviour (Section 4.2.4). This does not agree with the related results of pentoxifylline tablets (F1-F7) where the release mechanism was kept by diffusion and polymer relaxation, but, adding calcium carbonate at 20% (w/w) level changed the release mechanism to diffusion mechanism (Chapter 3, section 3.2.6). The reduction by almost 36% (w/w) in the polymeric content of cefalexin monohydrate control tablets (F14) compared to pentoxifylline control tablets (F7) explains this difference in their drug release mechanisms.

Table 4-8: Korsmeyer-Peppas kinetic parameters of F8-F14 cefalexin monohydrate tablet formulations.

Formulation	Origin of prepared tablets	Crushing strength level	Korsmeyer-Pepas		
			R^2	n	K_p (h^{-n})
F8	Powder	(A)	N.A	N.A	N.A
		(B)	N.A	N.A	N.A
		(C)	N.A	N.A	N.A
	Granules	(A)	0.9995	0.655	0.2424
		(B)	0.9997	0.7257	0.2444
		(C)	0.9949	0.7136	0.2294
F9	Powder	(A)	N.A	N.A	N.A
		(B)	N.A	N.A	N.A
		(C)	N.A	N.A	N.A
	Granules	(A)	0.999	0.6986	0.1884
		(B)	0.9985	0.6674	0.2138
		(C)	0.9528	0.6199	0.2104
F10	Powder	(A)	N.A	N.A	N.A
		(B)	N.A	N.A	N.A
		(C)	N.A	N.A	N.A
	Granules	(A)	0.9986	0.5937	0.2582
		(B)	0.9999	0.5637	0.2888
		(C)	0.9978	0.5837	0.2831
F11	Powder	(A)	N.A	N.A	N.A
		(B)	N.A	N.A	N.A
		(C)	N.A	N.A	N.A
	Granules	(A)	0.9718	0.2637	0.4115
		(B)	0.9772	0.2709	0.4166
		(C)	0.9492	0.3107	0.376
F12	Powder	(A)	0.9947	0.4172	0.4683
		(B)	0.9971	0.4315	0.4506
		(C)	0.9995	0.4052	0.4341
	Granules	(A)	0.9934	0.6457	0.2486
		(B)	0.9905	0.6587	0.2501
		(C)	0.9945	0.6009	0.2505
F13	Powder	(A)	1	0.4673	0.4221
		(B)	0.9984	0.5214	0.4327
		(C)	0.9999	0.5267	0.4198
	Granules	(A)	0.9997	0.5301	0.2514
		(B)	0.9985	0.5324	0.2807
		(C)	0.9961	0.4877	0.2924
F14	Powder	(A)	N.A	N.A	N.A
		(B)	N.A	N.A	N.A
		(C)	N.A	N.A	N.A
	Granules	(A)	0.952	0.3015	0.4138
		(B)	0.999	0.3793	0.3948
		(C)	0.991	0.3985	0.3856

Notes: N.A: There are insufficient data points on the release profiles ≤ 60% drug release in order to provide accurate values. The compression force of the prepared tablets was adjusted to give three crushing strength levels: A (49-54 N), B (54-59 N), and C (59-64 N). For formulation composition, refer to Table 4-1 or Table 2-8.

4.3 Conclusions

In this chapter, effervescent floating tablets of cefalexin monohydrate were successfully compacted using sodium bicarbonate, calcium carbonate, or sodium carbonate as a gas forming agent and a (1:1) binary mixture of hydroxyethyl cellulose and sodium alginate as a drug retarding polymeric matrix. All the prepared tablets through the granulation showed acceptable physical properties regarding weight and drug content uniformity tests. Friability results of sodium bicarbonate based formulations F8 (10% (w/w)) and F9 (20% (w/w)), calcium carbonate based formulations F10 (10% (w/w)) and F11 (20% (w/w)), and cefalexin monohydrate control tablets F14 exceeded the BP limit of friability (< 1%), however, as the tablet crushing strength level increased as the mass loss percentage decreased in all the formulations.

Increasing the compression force showed minor influence on the drug release rate of the tablets prepared after the granulation. Raising the gassing agent (sodium bicarbonate, calcium carbonate, or sodium carbonate) concentration, in the tablets prepared from the granules, decreased their floating lag time results and increased their floating duration time. Cefalexin monohydrate control tablets prepared following the granulation showed acceptable floating capacity behaviour due to the rapid swelling rate profiles which reduced their tablets density to initiate and to maintain the floating process. The drug release rate indicates a release by non-Fickian mechanism except for F11 tablets based on 20% (w/w) calcium carbonate as a gassing agent and the control tablets of cefalexin monohydrate (F14) which fitted to Fickian release mechanism. The addition of the gassing agents enhanced the movement of the generated carbon dioxide bubbles from the internal to the peripheral sides of the floating tablets which influenced the polymer erosional behaviour and changed cefalexin monohydrate release mechanism from release by diffusion (Fickian) to release by diffusion and polymer relaxation (non-Fickian). However 20% (w/w) concentration of calcium carbonate was enough to influence the *in situ* ability of the anionic alginate molecules to be cross linked and changed the drug release mechanism to release by diffusion (Fickian). The tablets could float on the surface of the dissolution medium and the drug release was sustained over 10 h.

DSC and FTIR indicates instability of the formulation based on sodium bicarbonate (F8 and F9) or sodium carbonate (F12 and F13) after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in the open containers. Still, the closed containers showed better physical stability of cefalexin monohydrate loaded in such formulations. A specific stability-indicating assay method such as HPLC to determine the drug content and any possible degradation products in the formulations will be required in the future to do more investigations. The tablets prepared with 10% (w/w) calcium carbonate (F10) at 59-64 N crushing strength were promising with respect to their floating lag time, floating duration, swelling ability, sustained drug release rate, and physical stability results. Accordingly, calcium carbonate revealed promising results not only with cefalexin monohydrate but also with pentoxifylline and this makes the chosen ingredients (for this research)and their quantities feasible to be applied with other drugs intend for gastroretentive delivery systems.

Chapter Five: preliminary *in vivo* study in rats

5.1 Preliminary *in vivo* pharmacokinetic study

Tablets manufactured from the granules with 20% (w/w) calcium carbonate (F4) were promising with respect to their floating lag time (~ 7 min), floating duration (> 24 h), swelling ability, sustained drug release rate and physical stability (Chapter 3). As *in vitro* studies remain largely inadequate to evaluate the complexities of human gastrointestinal tract (GIT) physiology, *in vivo* evaluation is required. But, it is not easy to run *in vivo* in human for this research as ethical approval will not be approved, so animal model was used. Small rodents such as mouse, rat, guinea pig, and rabbit; and larger mammals like dog, pig, and monkey are commonly used in clinical studies. Primarily, it was required to test the *in vivo* ability of the designed F4 tablets to sustain the drug release. Rats were chosen for the preliminary *in vivo* evaluation as rodents are more popular choice in biomedical research (Hatton et al., 2015). Nevertheless, using small rodents is not suitable to evaluate the gastric retention capability of the promising F4 tablets. Therefore, *in vivo* studies in appropriate larger mammals are essential in the future. Rats' duodenum diameter is 2.5 - 3 mm (Kararli, 1995), their stomach fluid volume is 2.29 ± 1.59 g (Hatton et al., 2015), and their gastric pH (3.9 and 3.2 in fasted and fed state respectively (McConnell et al., 2008)). It is obvious that rats' gastric anatomy and physiology is not similar to that of human (Chapter 1, section 1.2), yet, the taken F4 tablet (4 mm) will be retained in the rats' stomach not because of the floating process which may be exist but because of the duodenum diameter. Additionally, rats' gastric pH is enough to initiate the acid base reaction with the loaded calcium carbonate (gassing agent) in F4 tablets. This can further challenge the drug release rate of the tested tablets, thus, it was worth to evaluate the *in vivo* behaviour of the selected formulation (F4) preliminary in rats.

It was a challenge to use pentoxifylline, highly soluble model drug (191 mg/ml at 37°C), to investigating the ability of the formulation for improvements to pentoxifylline pharmacokinetic parameters as a controlled release dosage form. Pentoxifylline is completely absorbed from the gastrointestinal tract (GIT) when given either in the form of sustained release tablets or immediate release capsules; however, its bioavailability averages only 20% to 30% due to extensive first pass metabolism (Beermann et al., 1985).

No advantage was expected from a comparative *in vivo* evaluation between non-floating sustained release tablets (F7) and the selected floating tablets (F4), therefore pentoxifylline solution, as a reference, was selected for the study.

In this study F4 floating tablets and a reference solution of pentoxifylline were investigated following oral administration of 5.75 ± 0.15 mg in rats. Drug plasma levels were determined by HPLC-MS/MS, and the regression equation was y = 0.0251x - 0.000893 (r=0.9993) for pentoxifylline with a linear concentration of 4 - 400 ng/ml. The retention time was 0.45 and 0.29 min for pentoxifylline and the internal standard (Emitrecitabine), respectively.

The individual pentoxifylline plasma concentration-time curves following oral administration of F4 floating tablets (G1) and reference solution (G2) in rats are shown in Figure 5-1 to Figure 5-12. Unusual (outlier) data points were shown following oral administration of F4 floating tablets in rat 1, G1, thus it was excluded from the statistical evaluation.The average plasma concentration-time profiles for the two formulations are shown in Figure 5-13, and the pharmacokinetic parameters are shown in Table 5-1. The maximum plasma concentrations (C_{max}) of F4 tablets and the reference solution were 982.24 ± 484.71 and 2552.30 ± 110.85 ng/ml, respectively, and these were achieved at 1.80 ± 0.45 and 0.50 ± 0.00 h (T_{max}), respectively. Compared to the reference solution, the C_{max} of the tablets decreased significantly (P<0.05), and the T_{max} was prolonged significantly (P<0.05). The half-life ($t_{1/2}$) value significantly increased (P<0.05) from 0.29 ± 0.03 to 0.65 ± 0.24 h in F4 tablets in comparison with the reference solution; thus indicating relatively sustained-release behaviour of F4 tablets.

The relative bioavailability (F_{rel}) of the tablets compared to the reference solution was 80.86%. This can be explained by the significant (P<0.05) reduction in the $AUC_{0-\infty}$ value of F4 tablets in comparison with the reference solution which were 2371.25 ± 797.54 and 2932.53 ± 351.23 ng h/ml respectively. Although pentoxifylline is completely absorbed from the gastrointestinal tract, drug absorption is highly variable in the individuals (Davis, 2005) and it depends on the administered dosage form. Beermann et al. (1985) evaluated the kinetics of intravenous and oral pentoxifylline capsules and tablets in healthy subjects.

Results revealed a significant difference between C_{max} levels of pentoxifylline after 400 mg oral dosing of capsules and tablets where mean values of 1218 and 248 ng/ml was noted respectively. Moreover, absolute bioavailability of the capsules was 30.7 ± 19.1% and of the tablets was 19.4% ± 12.7% due to higher *AUC* value of the capsules in comparison to that of the tablets.

It is difficult to evaluate the gastric retention along with bioavailability for a regular size tablet dosage form by using small animals like mice, rats, guinea pigs or rabbits (Turner et al., 2011). Still, a well-designed *in vivo* studies in appropriate animal model such as dogs or healthy human volunteers are essential in the future to verify the *in vivo* efficacy of the promising floating tablets.

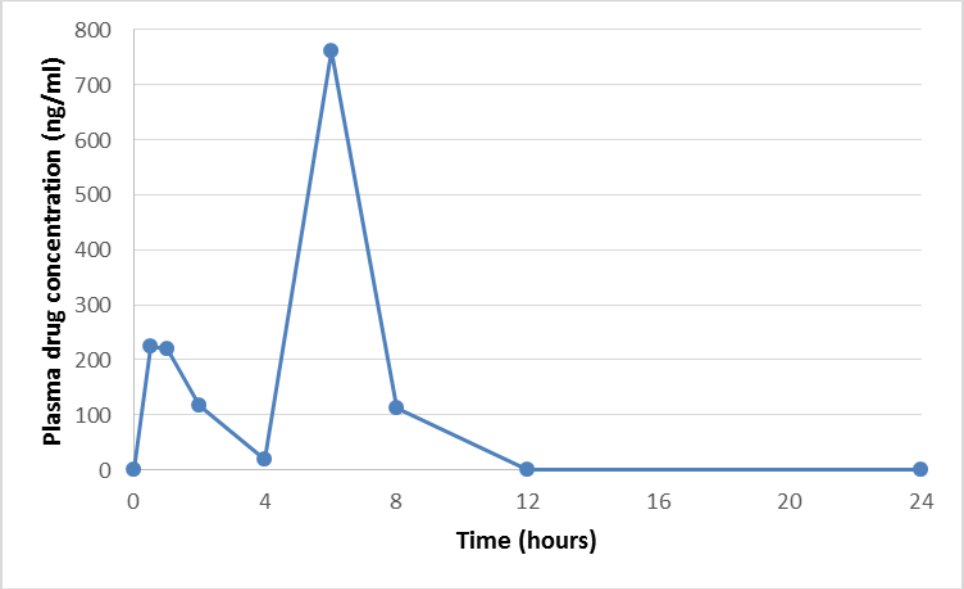


Figure 5-1: Pentoxifylline plasma concentration-time curve following oral administration of F4 floating tablets in rat 1, G1.
Note: HPLC chromatograms are shown in Figure A 1 and Figure A 2.

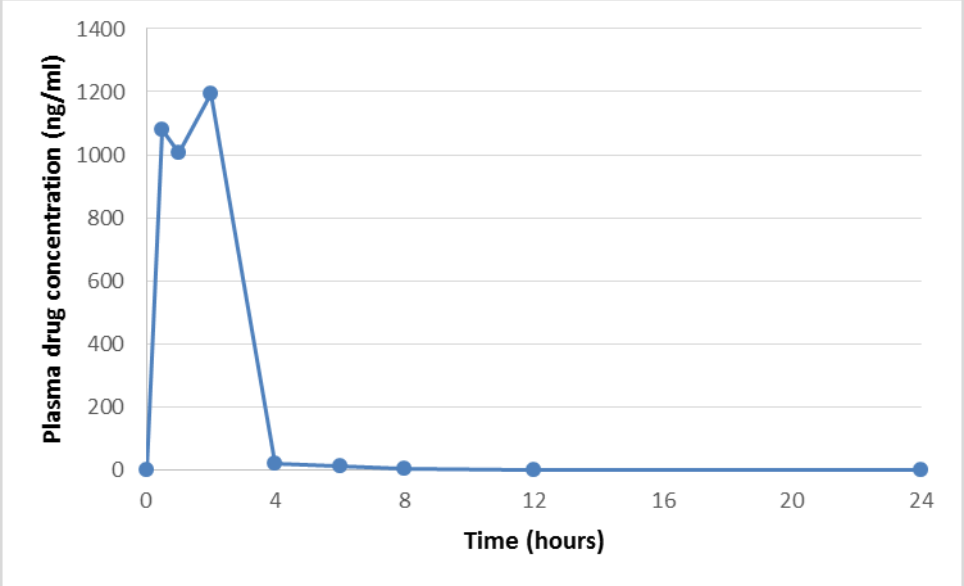


Figure 5-2: Pentoxifylline plasma concentration-time curve following oral administration of F4 floating tablets in rat 2, G1.
Note: HPLC chromatograms are shown in Figure A 3 and Figure A 4.

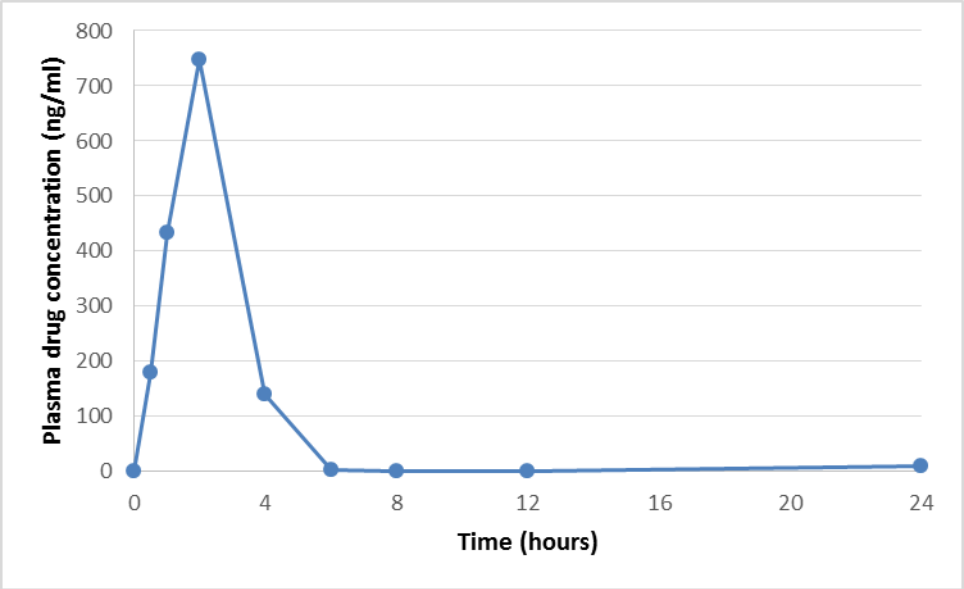


Figure 5-3: Pentoxifylline plasma concentration-time curve following oral administration of F4 floating tablets in rat 3, G1.
Note: HPLC chromatograms are shown in Figure A 5 and Figure A 6.

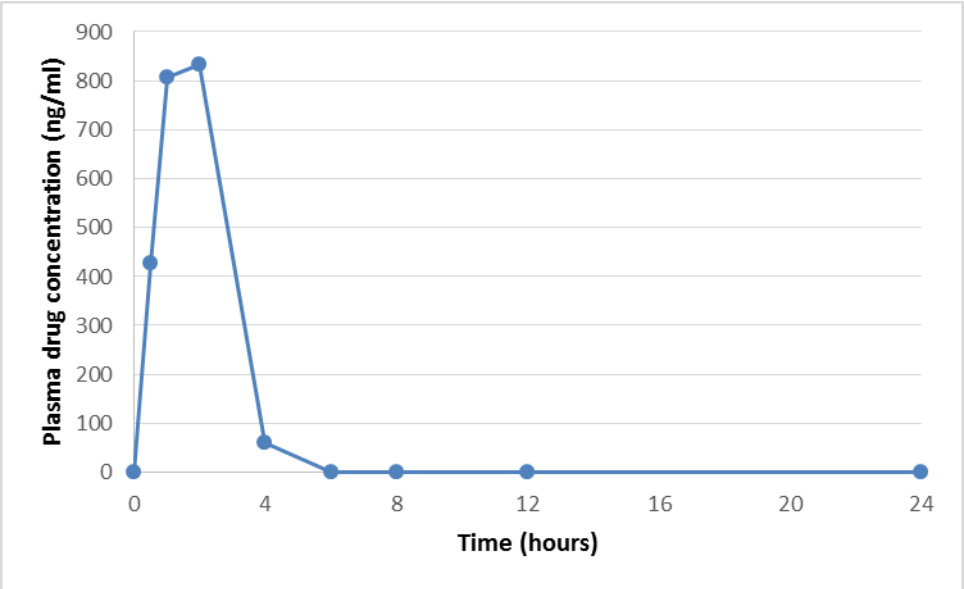


Figure 5-4: Pentoxifylline plasma concentration-time curve following oral administration of F4 floating tablets in rat 4, G1.
Note: HPLC chromatograms are shown in Figure A 7and Figure A 8.

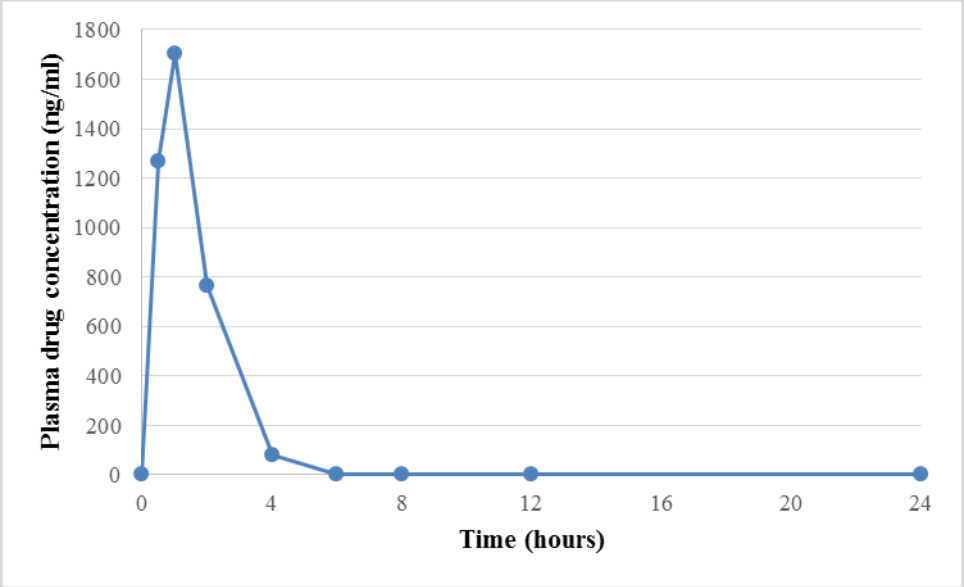


Figure 5-5: Pentoxifylline plasma concentration-time curve following oral administration of F4 floating tablets in rat 5, G1.
Note: HPLC chromatograms are shown in Figure A 9 and Figure A 10.

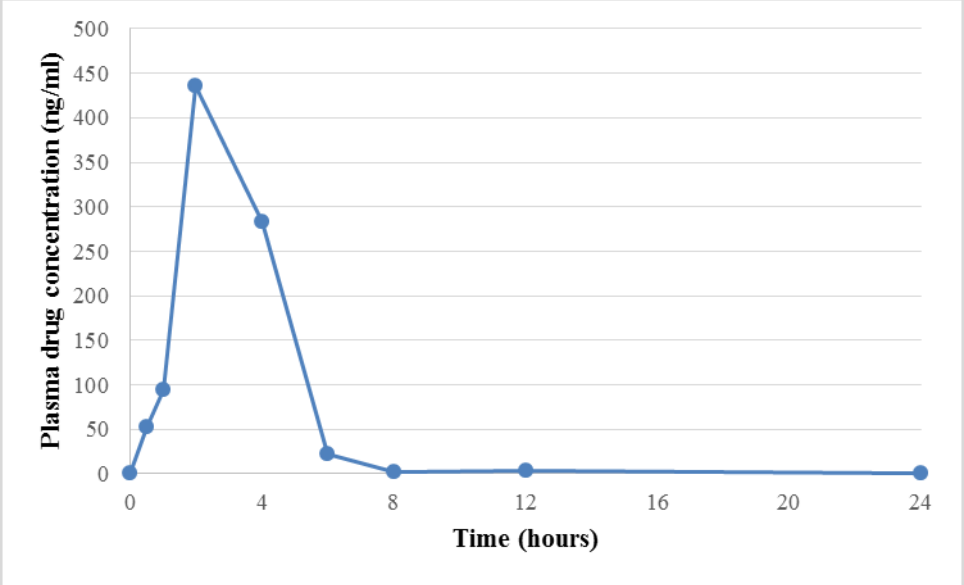


Figure 5-6: Pentoxifylline plasma concentration-time curve following oral administration of F4 floating tablets in rat 6, G1.
Note: HPLC chromatograms are shown in Figure A 11 and Figure A 12.

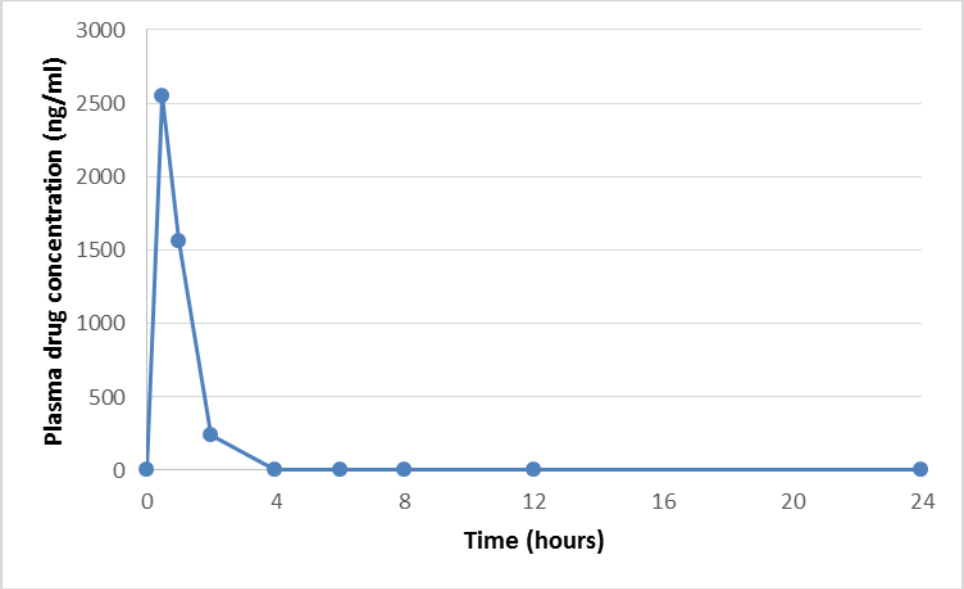


Figure 5-7: Pentoxifylline plasma concentration-time curve following oral administration of reference solution in rat 1, G2.
Note: HPLC chromatograms are shown in Figure A 13 and Figure A 14.

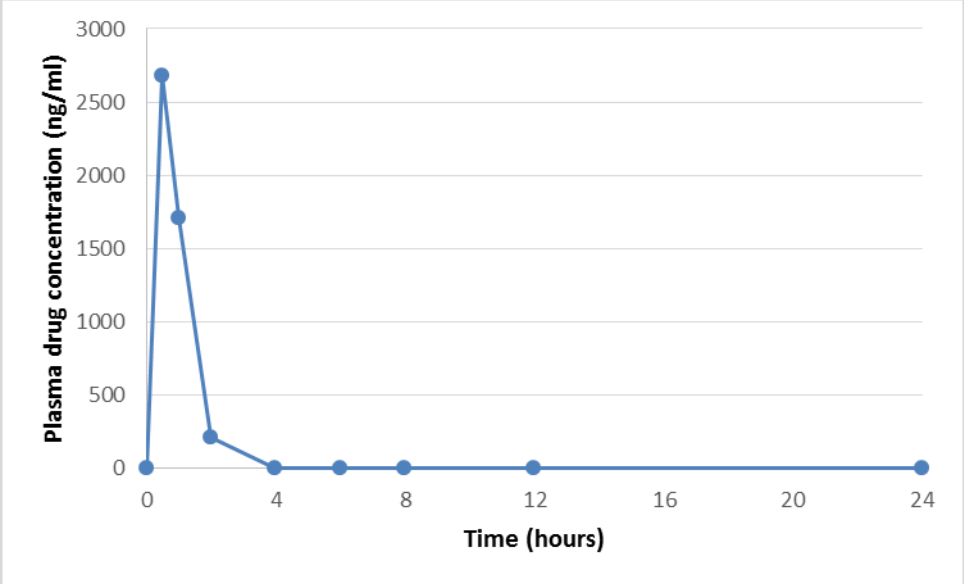


Figure 5-8: Pentoxifylline plasma concentration-time curve following oral administration of reference solution in rat 2, G2.
Note: HPLC chromatograms are shown in Figure A 15 and Figure A 16.

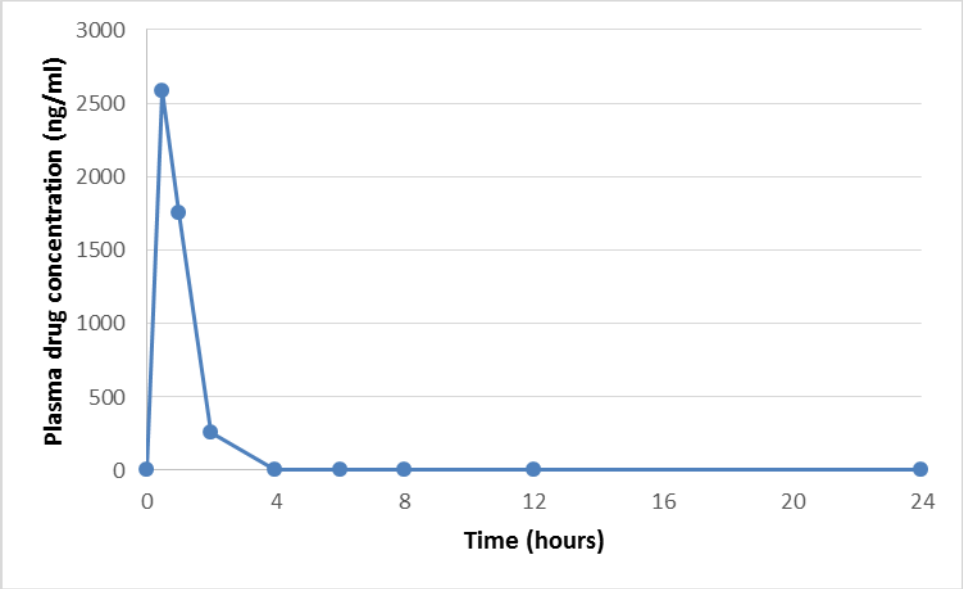


Figure 5-9: Pentoxifylline plasma concentration-time curve following oral administration of reference solution in rat 3, G2.
Note: HPLC chromatograms are shown in Figure A 17 and Figure A 18.

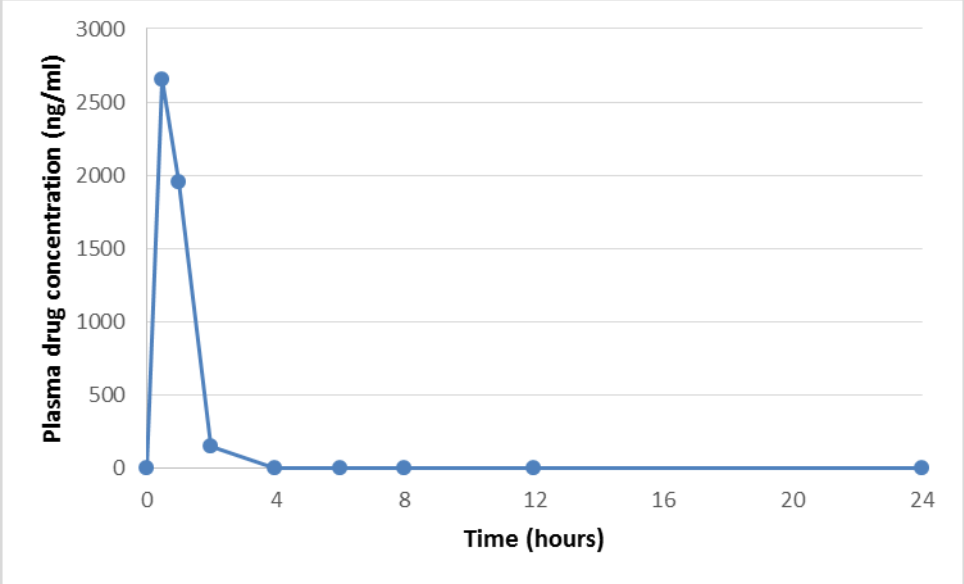


Figure 5-10: Pentoxifylline plasma concentration-time curve following oral administration of reference solution in rat 4, G2.
Note: HPLC chromatograms are shown in Figure A 19 and Figure A 20.

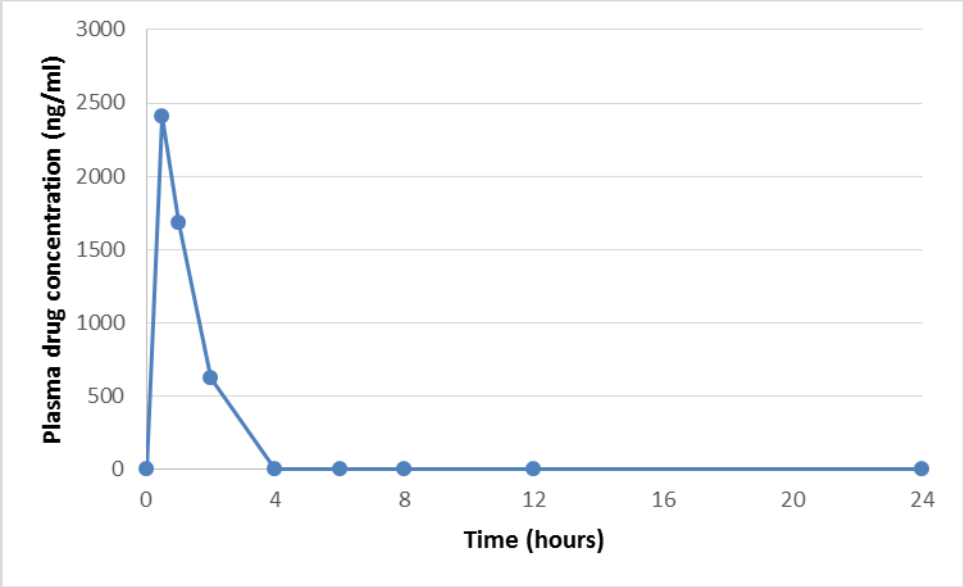


Figure 5-11: Pentoxifylline plasma concentration-time curve following oral administration of reference solution in rat 5, G2.
Note: HPLC chromatograms are shown in Figure A 21 and Figure A 22.

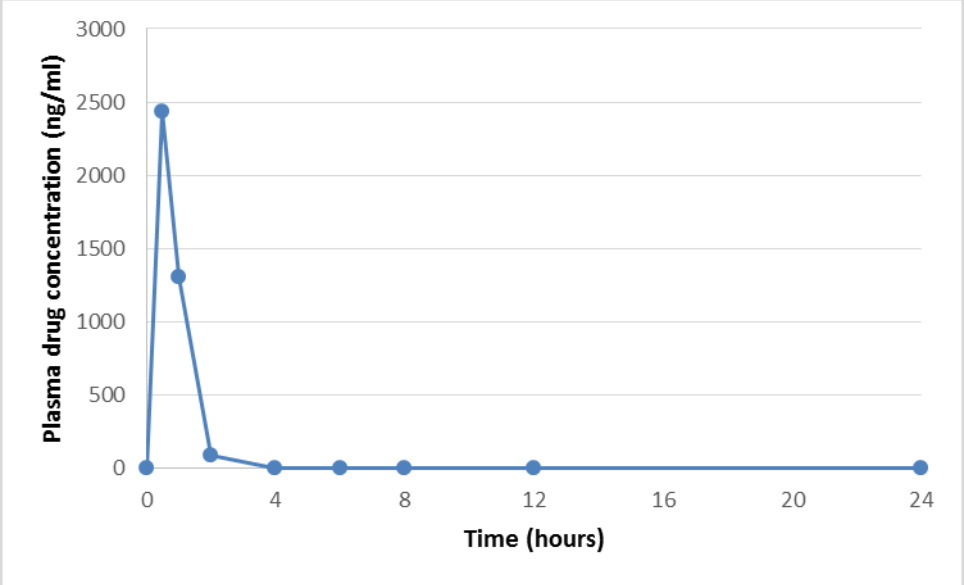


Figure 5-12: Pentoxifylline plasma concentration-time curve following oral administration of reference solution in rat 6, G2.
Note: HPLC chromatograms are shown in Figure A 23 and Figure A 24.

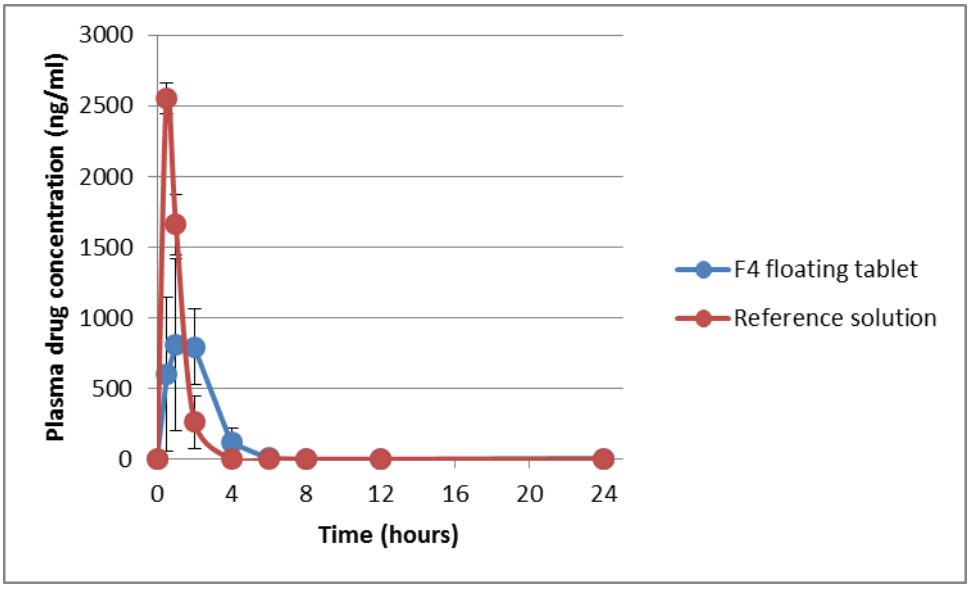


Figure 5-13: Average pentoxifylline plasma concentration-time curves following oral administration of F4 floating tablets and reference solution in rats.
The data represents the mean ± SD of six determinations.
Note: The plasma drug profile of rat 1, G1 was excluded due to the outlier data points.

Table 5-1: Pharmacokinetic parameters of pentoxifylline F4 tablets and a reference solution.

Formulation	K_e (h^{-1})	$t_{1/2}$ (h)	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0-\infty}$ (ng h/ml)
F4 floating tablets	1.21 ± 0.52	0.65 ± 0.24	982.24 ± 484.71	1.80 ± 0.45	2371.25 ± 797.54
Reference solution	2.42 ± 0.21	0.29 ± 0.03	2552.30 ± 110.85	0.50 ± 0.00	2932.53 ± 351.23

The data represents the mean ± SD of six determinations.
Note: The plasma drug profile of rat 1, G1 was excluded due to the outlier data points.F4 floating tablets composed of pentoxifylline, hydroxyethyl cellulose, sodium alginate, Prosolv® 90, calcium carbonate, and magnesium stearate. Reference solution composed of pentoxifylline and water.
For formulation composition, refer to Table 3-1or Table 2-7

5.2 Conclusions

F4 tablets prepared with 20% (w/w) calcium carbonate were promising with respect to their quality control tests, floating lag time, floating duration, swelling ability, sustained drug release rate, and physical stability results. A preliminary *in vivo* study of tablets of F4 formulation and a reference solution of pentoxifylline were tested following oral administration of 5.75 ± 0.15 mg in rats. The C_{max} of F4 tablets and the reference solution were 982.24 ± 484.71 and 2552.30 ± 110.85 ng/ml, respectively, and these were achieved at T_{max} 1.80 ± 0.45 and 0.50 ± 0.00 h, respectively. The $t_{1/2}$ value significantly increased (P<0.05) from 0.29 ± 0.03 to 0.65 ± 0.24 h in F4 tablets in comparison with the reference solution; thus indicating relatively sustained-release behaviour of the tablets. Although pentoxifylline is completely absorbed from the gastrointestinal tract, the relative bioavailability (F_{rel}) of the tablets compared to the reference solution was 80.86% because drug absorption is highly variable in the individuals.

The preliminary data presented are valuable as they provide insight to the sustained effect of the novel formulations prepared. Although there are sustained formulations in the market but the prepared may offer less side effects to patients and save money to industry. Research is not stopping if the drug is available as sustained release medicine in the market hence many drugs are available in more than one sustained release brand in the market so that is why this research.

Chapter Six: Conclusions and future work

6.1 Conclusions

In this study, floating tablets of pentoxifylline or cefalexin monohydrate were prepared using a (1:1) ratio of hydroxyethyl cellulose and sodium alginate polymeric mixture based on sodium bicarbonate, calcium carbonate or sodium carbonate gas forming agent. The variables affecting the drug release and the floating properties, such as tablet crushing strength, wet granulation, type and ratio of the gas forming agent, were examined.

Tablets prepared through the wet granulation process showed acceptable physical properties via complying with the BP requirements of friability, weight and drug content uniformity. Some of the formulations exceeded the BP limit of friability (< 1%), nonetheless, as the tablet crushing strength level increased as the mass loss percentage decreased in all the formulations. Increasing the compression force showed minor influence on the drug release rate of the tablets prepared after the granulation. This gives an advantage to control the other formulation parameters, such as high friability percentages, by raising the compression force without disturbing the drug release rate.

Effect of the granulation process on the drug release rate from all the formulations at different crushing strength levels revealed that the granulation process reduced the drug release rate. The decrease in the porosity levels due to the wet massing stage of the granulation process delayed the dissolution medium entrapment through the matrix at an early stage of the dissolution test and decreased the drug release process. However, the better gel hydration ability of cefalexin monohydrate tablets because of their higher sodium bicarbonate content probably inversed the increase in their porosity percentages after the granulation and decreased their drug release rate. Also, calcium carbonate formulations became more resistant to rupture due to strengthening of the tablets internal structure following the granulation which gave sufficient time for swelling and gel layer formation to control the drug release process.

Regarding the tablets prepared from the granules, increasing the gassing agent concentration from 10% to 20% (w/w) influenced the drug release rate. Raising sodium bicarbonate level decreased the drug release rate depending on the microstructure of the swollen gel layer formed around the tablets. In contrast, increasing calcium carbonate concentration increased the drug release rate because of pore formation in the swollen gel layer resulted from the entrapped gas bubbles. A slight increase in the drug release rate was noted because of increasing sodium carbonate concentration. The ability of sodium carbonate, regardless the concentration, to generate an alkaline microenvironment enhanced the tablets to swell and to release the drug in almost similar rate. Noticeably, the higher gassing agent concentration was more effective than the lower one to maintain the tablets, from the granules origin, on the surface of the dissolution medium for a longer duration of time. Most tablets floated on the surface of the dissolution medium and showed an adequate floating lag time (< 30 min) and floated for more than 8 h. Cefalexin monohydrate control tablets (0% (w/w) gassing agent) prepared following the granulation showed acceptable floating capacity behaviour because of their rapid swelling rate which reduced their apparent densities to initiate and to maintain the floating process.

The granulation process increased the floating lag time results of all the floating tablets compared to that of the tablets prepared from the powder mixture before the granulation. Similarly, increasing the tablet crushing strength increased the lag time of all the tablets designed to float. However, increasing the concentration of the gassing agent decreased the floating lag time results of the tablets based on sodium bicarbonate or calcium carbonate due to the higher effervescent efficiency. In contrast, the lag time results increased in the tablets based on sodium carbonate due to increasing their apparent densities.

The drug release rate of all the prepared tablets fitted into non-Fickian release mechanism. An exception was seen in the tablets containing 20% (w/w) calcium carbonate gassing agent. They fitted into Fickian release mechanism due to the *in situ* ability of the anionic alginate molecules to be cross-linked in the presence of enough concentration of calcium ions. Generally, addition of the gassing agents enhanced movement of the generated carbon dioxide bubbles from the internal to the peripheral sides of the floating tablets which influenced more of the polymer erosional behaviour.

Tablets loaded with pentoxifylline showed better stability results in comparison to those of cefalexin monohydrate in either closed or open containers. DSC and FTIR indicated instability of the formulation based on sodium bicarbonate or sodium carbonate after storage for 3 months at 40°C ± 2°C and 80% ± 5% RH in the open containers. Still, the closed containers showed better physical stability of cefalexin monohydrate formulations.

Pentoxifylline tablets manufactured with 20% w/w calcium carbonate were promising with respect to their floating lag time, floating duration, swelling ability, sustained drug release rate, and stability results. A preliminary *in vivo* investigation of these promising tablets against a reference solution of pentoxifylline was performed by oral administration of 5.75 ± 0.15 mg to rats. Compared with the reference solution, the maximum plasma concentration (C_{max}) of the tablets decreased, while the time to reach this concentration (T_{max}) and the $t_{1/2}$ were prolonged.

This study shows that a binary mixture of hydroxyethyl cellulose and sodium alginate, together with different gassing agents at variable levels, offers a promising opportunity to develop sustained release preparations.

6.2 Suggestions for future work

Formulations based on calcium carbonate as a gas generating agent, are suggested to be promising through this study. However, further formulation development studies are worth to be accomplished in the future to achieve a suitable floating tablet dosage form to benefit the pharmaceutical industry. For example, friability results of these formulations exceeded the accepted BP limit (< 1%), and tablets showed relaxation through the stability studies. Yet, increasing the compression force presented negligible influence on the drug release rate after the granulation. This gives an advantage to reduce the high friability percentages and tablet relaxation during storage without affecting the drug release rate.

Furthermore, it would be useful to increase pentoxifylline content of the designed floating tablets from 60 mg up to the therapeutic dose (400 mg). Primarily, increasing the tablet weight will increase its drug content, but almost 2 g tablet weight will be required to contain 400 mg pentoxifylline. This may be not convenient for patients' oral administration, thus, reducing the polymeric mixture level of hydroxyethyl cellulose and sodium alginate to increase the drug content may be helpful. Moreover, the *in vitro* drug release rate of cefalexin monohydrate floating tablets based on calcium carbonate was successfully controlled over 12 h, however, due to the tablet relaxation through the stability studies, the *in vitro* drug release was sharply increased. It would be useful to increase the polymeric mixture content of such formulations to control the drug release rates of fresh and stability samples. Generally, applying factorial design would be valuable to extend the study to cover more suitable model drugs for gastroretentive dosage forms; more ratios of hydroxyethyl cellulose: sodium alginate mixture such as (0:1), (0.25:0.75), (0.75:0.25), and (1:0); and more concentrations of gassing agents such as 5, 15, and 25% to achieve the best possible combination. This also could benefit exploring different mechanisms governing the release kinetics.

It has been reported that carbonates could generate an alkaline microenvironment for pH sensitive polymers to initiate gel formation, but, no significant change in the dissolution medium (macroenvironment) pH was recorded through the experiment time. Therefore, it is worth doing further investigations regarding the effect of the gassing agents (sodium bicarbonate, calcium carbonate, and sodium carbonate) on the swollen gel microenvironment pH and morphology. The microenvironment pH can be tested by adding a pH indicator, such as methyl red, to the matrix and visually monitor the pH within the tablets during drug release process as the indicator is red at acidic pH and converts into yellow at pH values > 5.8 (Streubel et al., 2000). Morphology of the gel structure can be evaluated using the scanning electron microscopy (SEM) technique.

Regarding the stability results, a specific stability-indicating assay method such as HPLC is critically required to do more evaluation. The study suggested that sodium bicarbonate and sodium carbonate, the gas forming agents loaded in the floating tablets, under stressful humidity conditions may affect the formulation stability. Consequently, it is important to apply such stability-indicating methods to determine the drug content and any possible degradation products in the formulations.

According to literature, a critical challenge for floating gastroretentive systems is their requirement for an adequate level of fluids in the stomach to float effectively. Combinations of different gastroretentive concepts, such as low-density floating and mucoadhesion can be expected to be particularly promising to have a significant influence on improving the therapeutic effect of drugs involved. Ability of sodium alginate to adhere to epithelial surface of the stomach could benefit the designed floating tablets. Tablet adhesion retention period could be investigated by using suitable methods such as modified balance tensiometer to quantify the mucoadhesive properties of the prepared tablets (Kast and Bernkop-Schnürch, 2011).

Furthermore, *in vitro* drug release tests in simulated gastric fluids with enzymes would be more representative to the gastric medium conditions at fed and fasted state in order to simulate the influence of meal digestion on the solubility of drugs (Freire and Basit, 2013). In this study, the prepared tablets were able to float on the surface of the dissolution medium due to the ability of the swelled matrices to retain the liberated gas bubbles. The tablets might become weaker due to swelling and floating processes. Hence, it is worth linking this to the mechanical destructive force in the human stomach by evaluating the tablets' mechanical strength.

A computer-controlled dynamic gastric model, which simulate the mechanical grinding forces (by gentle contractions) and gastric secretions (acid and enzymes) occurring in the fundus, body and antrum parts of the stomach and lead to food digestion, could be used for this purpose (Vardakou et al, 2011). But, this system is unlikely to give a widespread estimation of the tablet performance in the gastrointestinal tract. Thus, using the most complete simulator of the gastrointestinal tract (TIM-1) could benefit the development of the best selected formulations before the *in vivo* studies. This system is composed of interconnected segments representing the stomach, duodenum, jejunum and ileum with simulation to most physiological gastrointestinal tract parameters (Blanquet et al, 2004). Although it simulates passive absorption of water and small molecules via dialysis membranes, which can be considered a unique advantage for oral pharmaceutical dosage forms development, active transport, efflux and intestinal wall metabolism are also existing (Freire and Basit, 2013). Therefore, a well-designed *in vivo* study in healthy human volunteers is essential in the future to verify the *in vivo* efficacy of the most promising floating tablets.

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Appendices

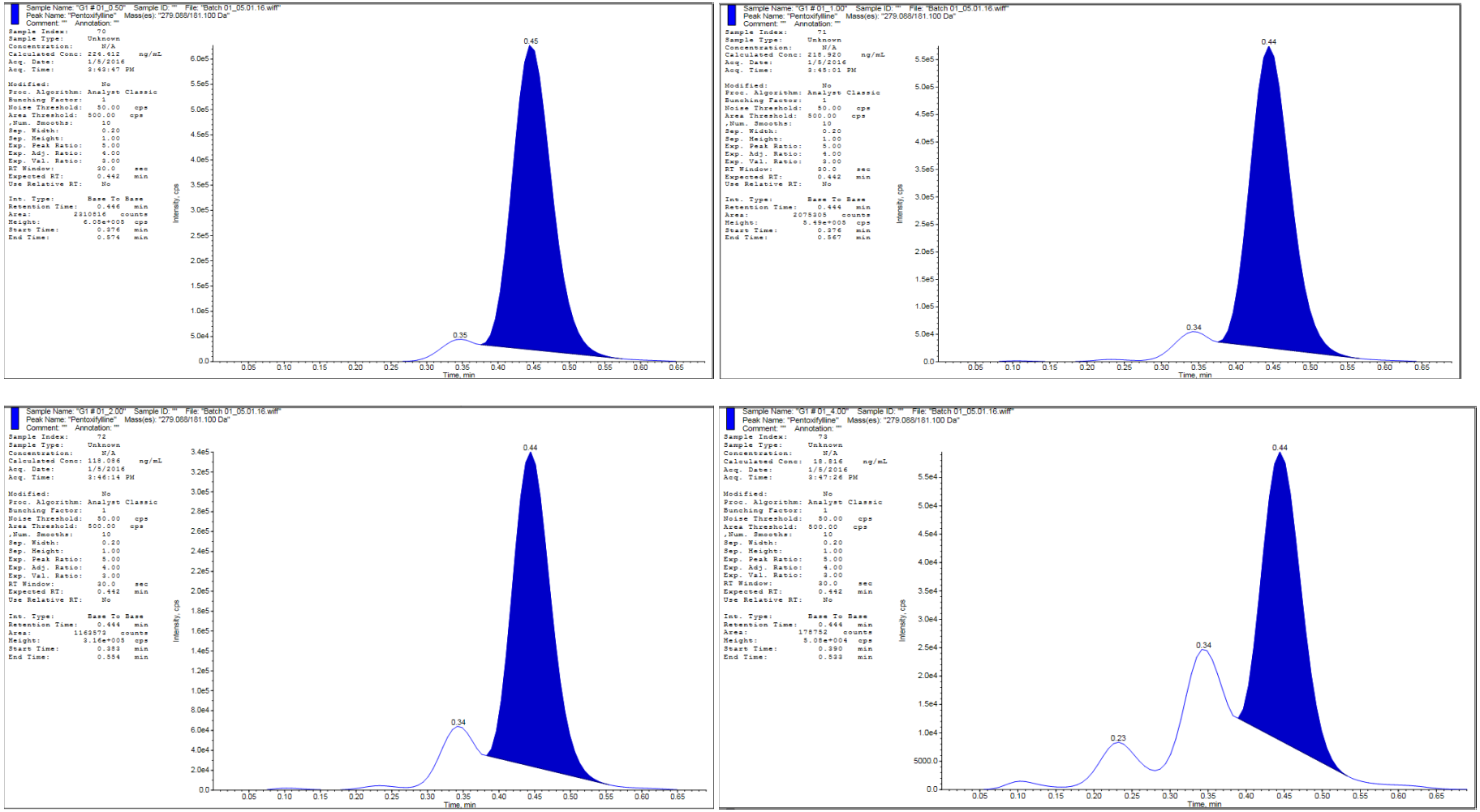


Figure A 1: HPLC chromatograms of rat 1, G1 plasma sample at 0.5, 1, 2, and 4 h.

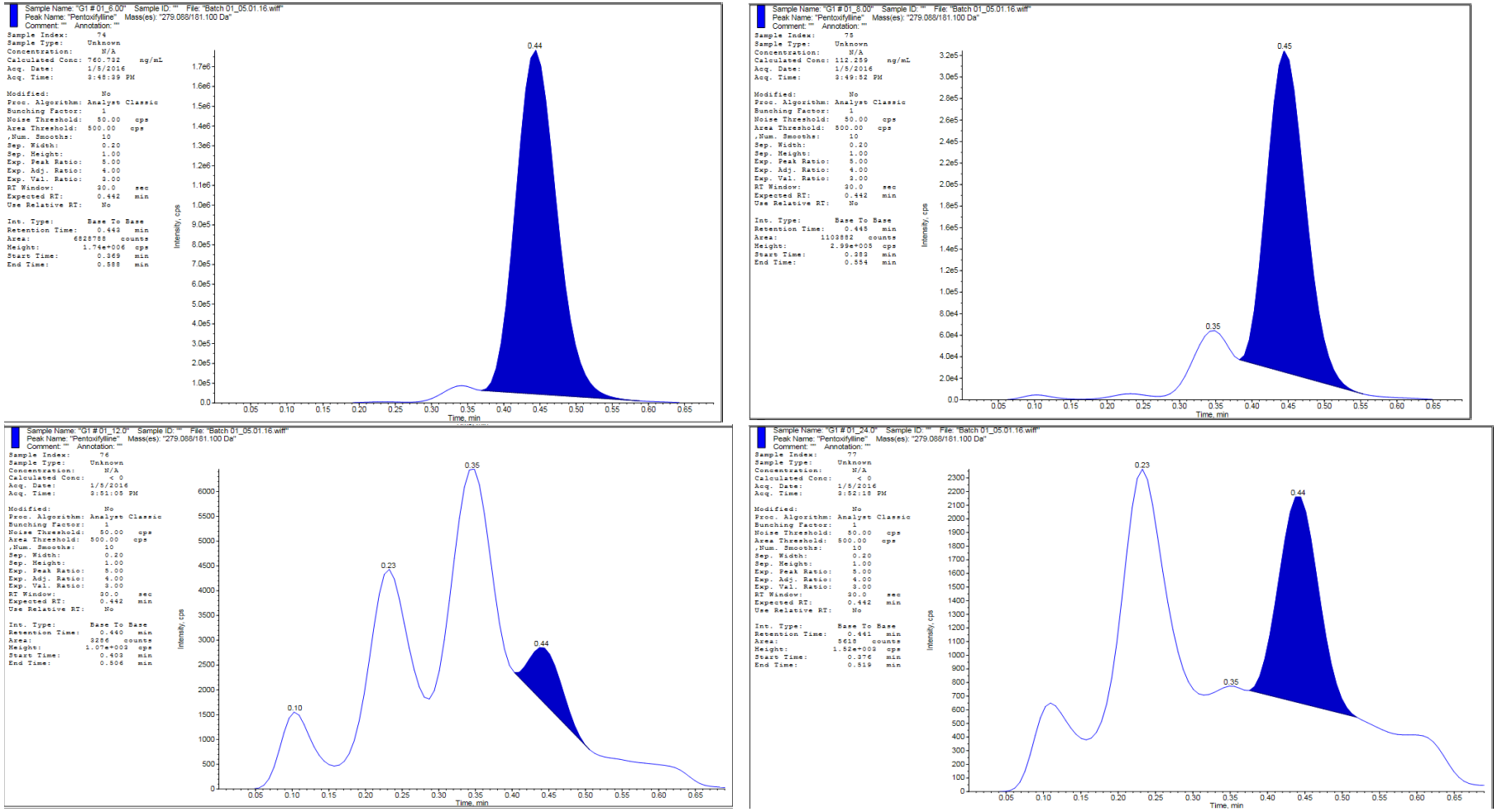
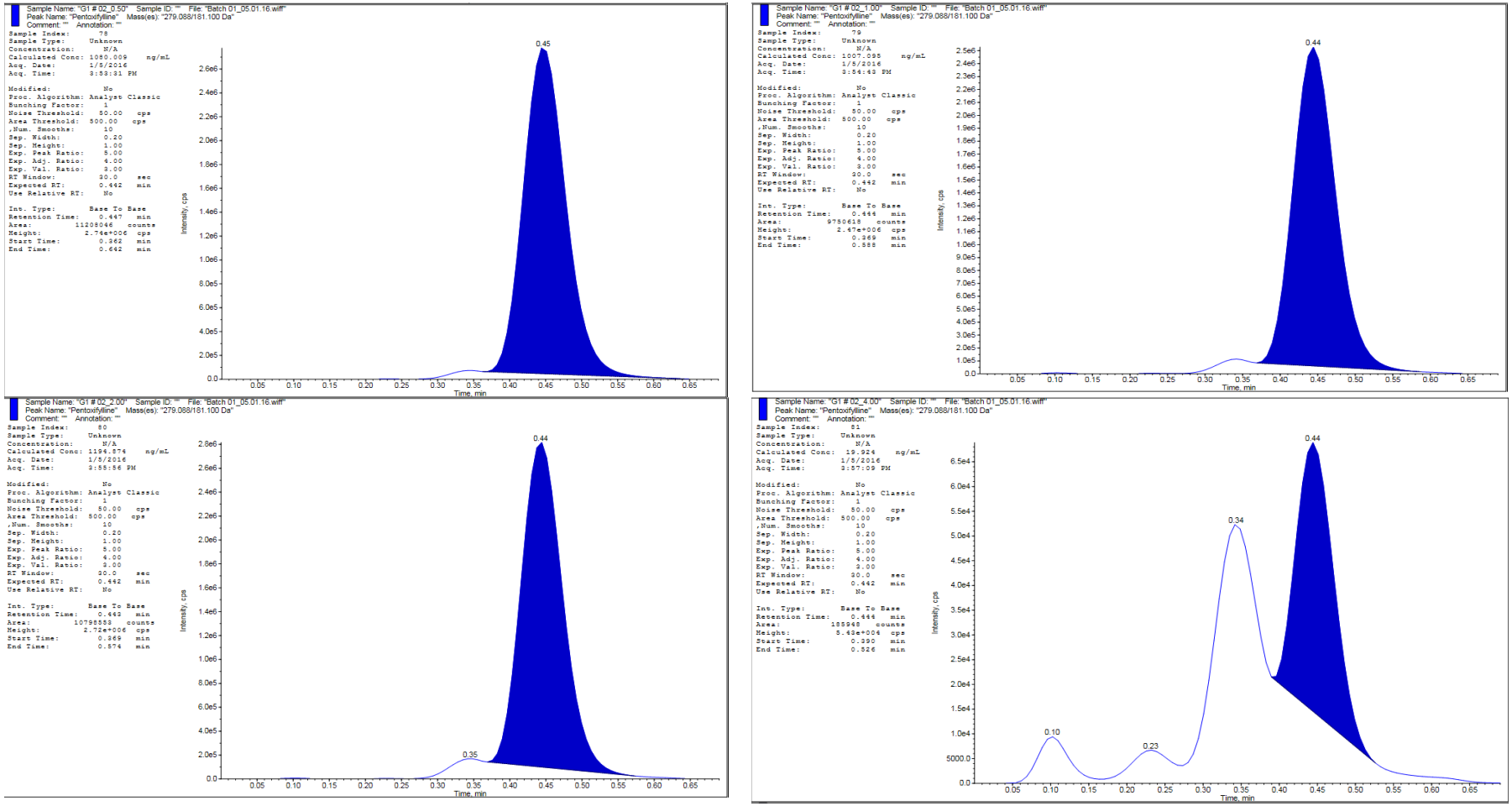


Figure A 2: HPLC chromatograms of rat 1, G1 plasma sample at 6, 8, 12, and 24 h.



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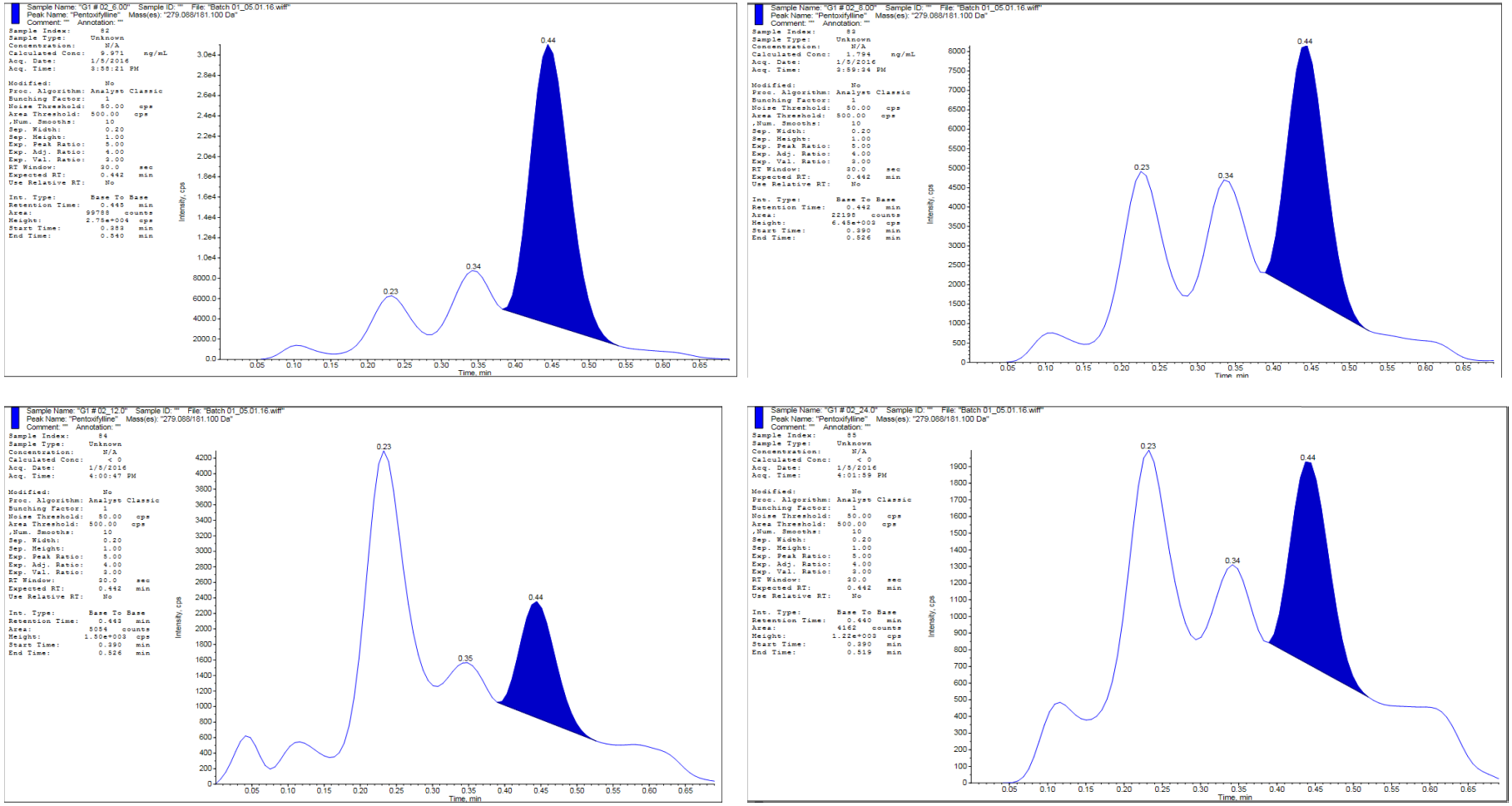

Figure A 4: HPLC chromatograms of rat 2, G1 plasma sample at 6, 8, 12, and 24 h.

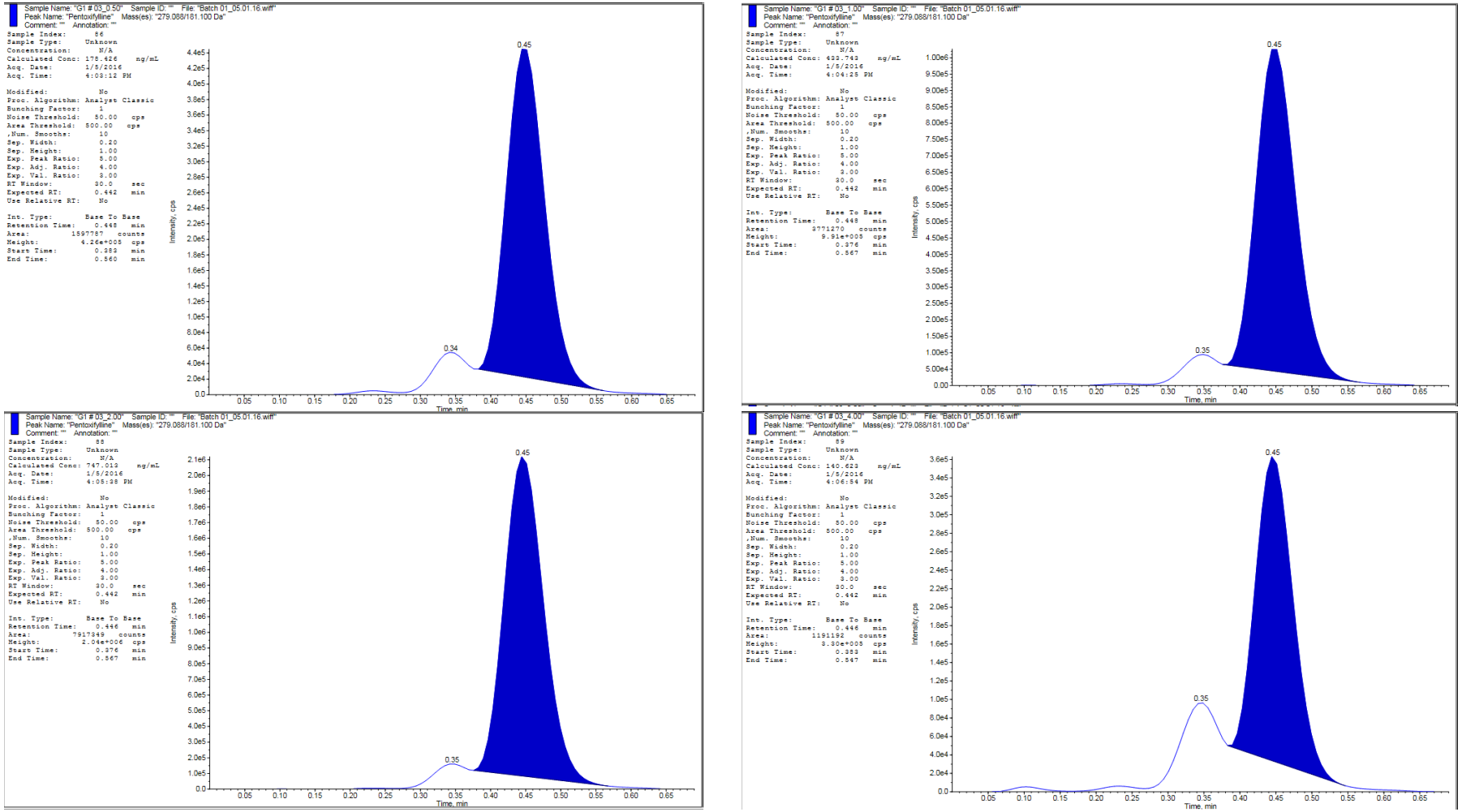

Figure A 5: HPLC chromatograms of rat 3, G1 plasma sample at 0.5, 1, 2, and 4 h.

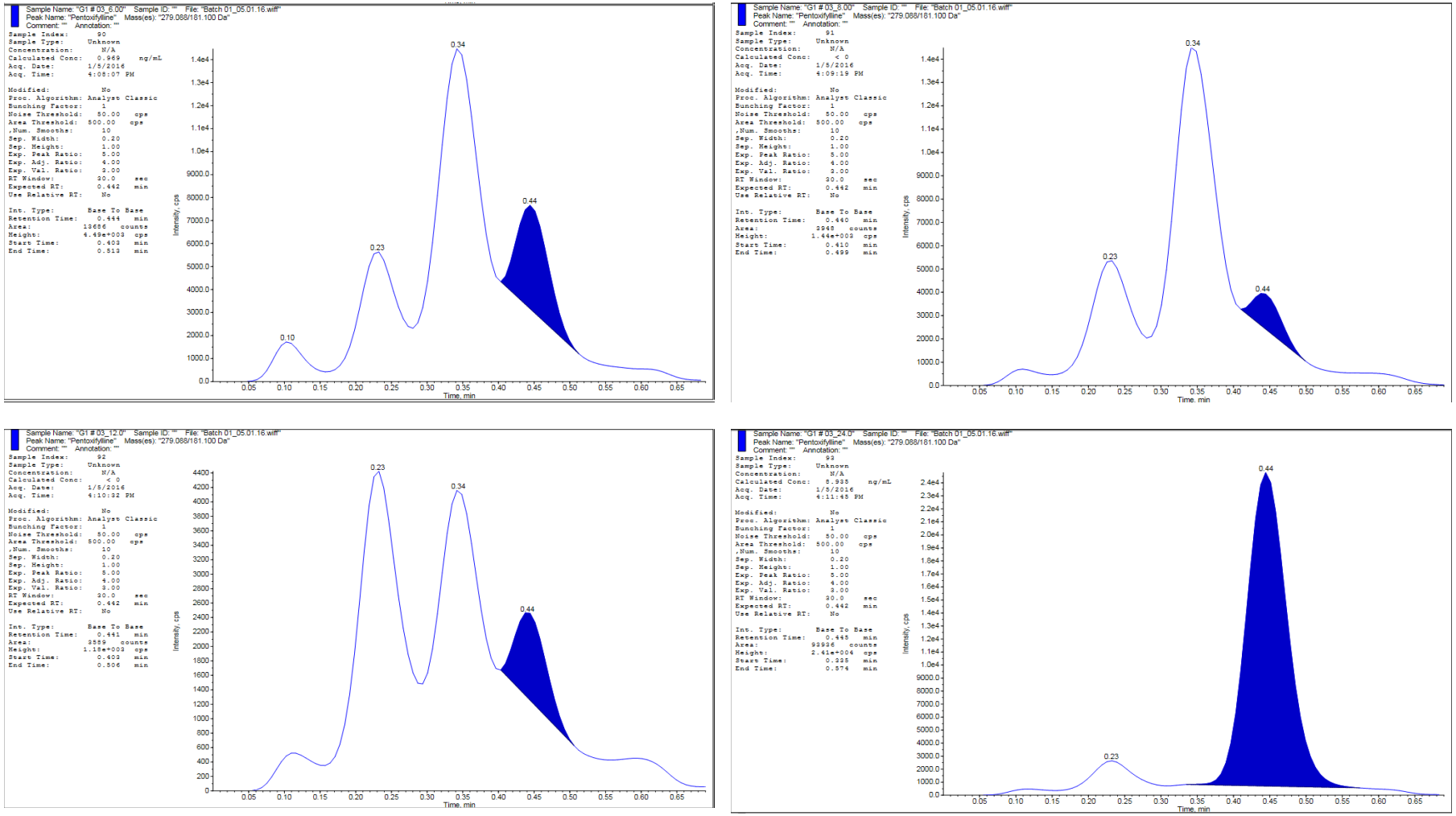

Figure A 6: HPLC chromatograms of rat 3, G1 plasma sample at 6, 8, 12, and 24 h.

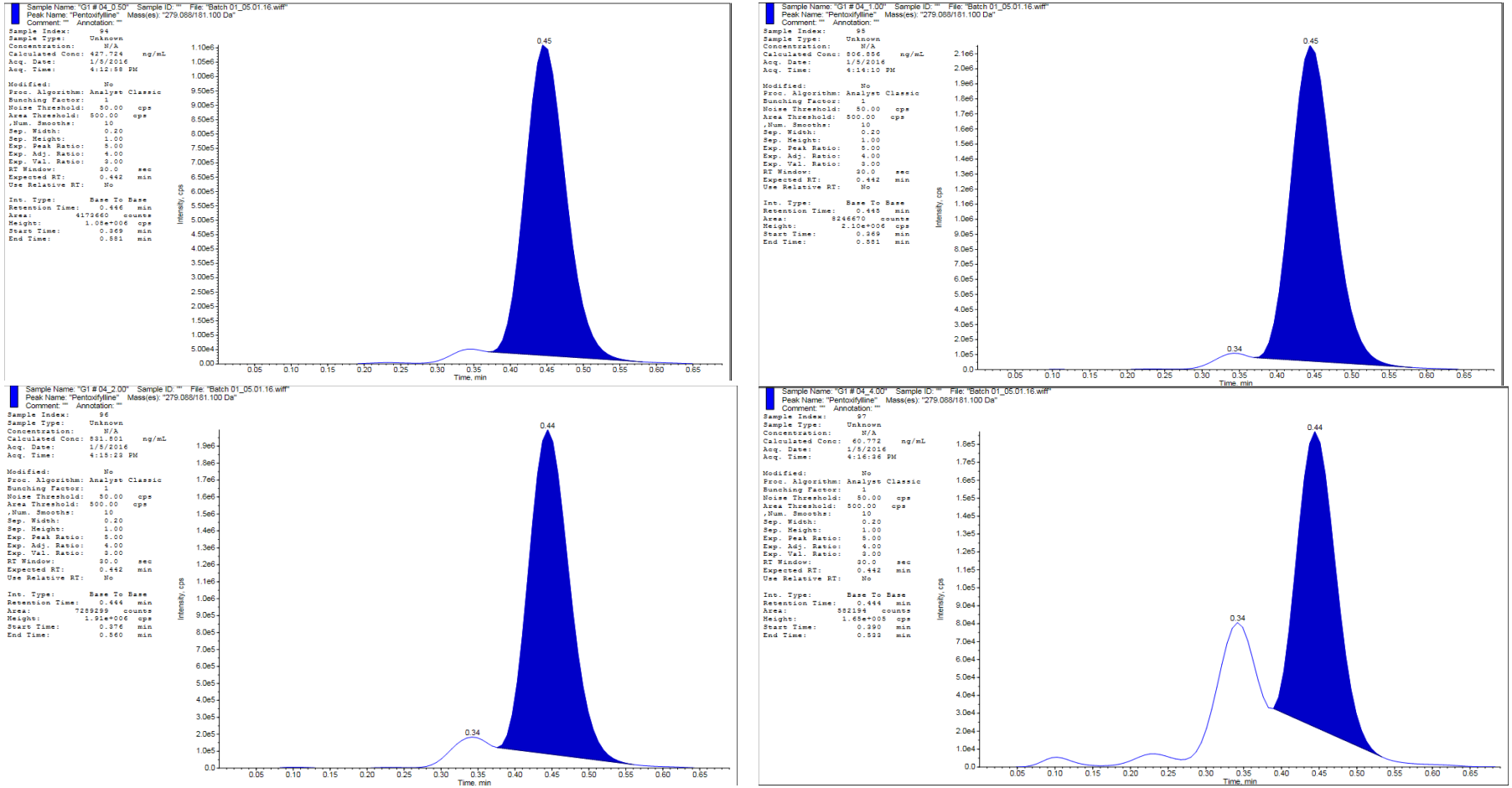

Figure A 7: HPLC chromatograms of rat 4, G1 plasma sample at 0.5, 1, 2, and 4 h.

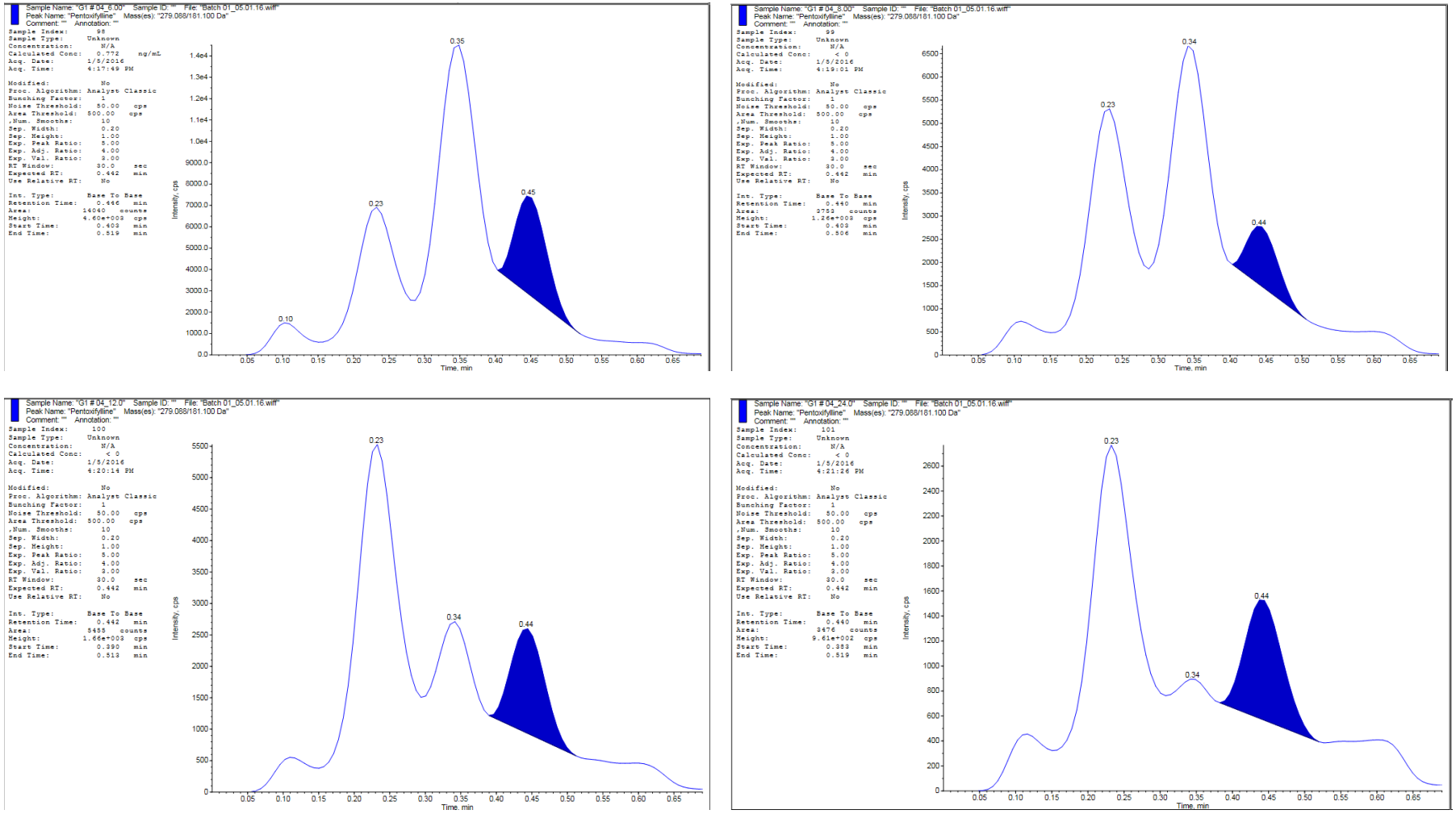

Figure A 8: HPLC chromatograms of rat 4, G1 plasma sample at 6, 8, 12, and 24 h.

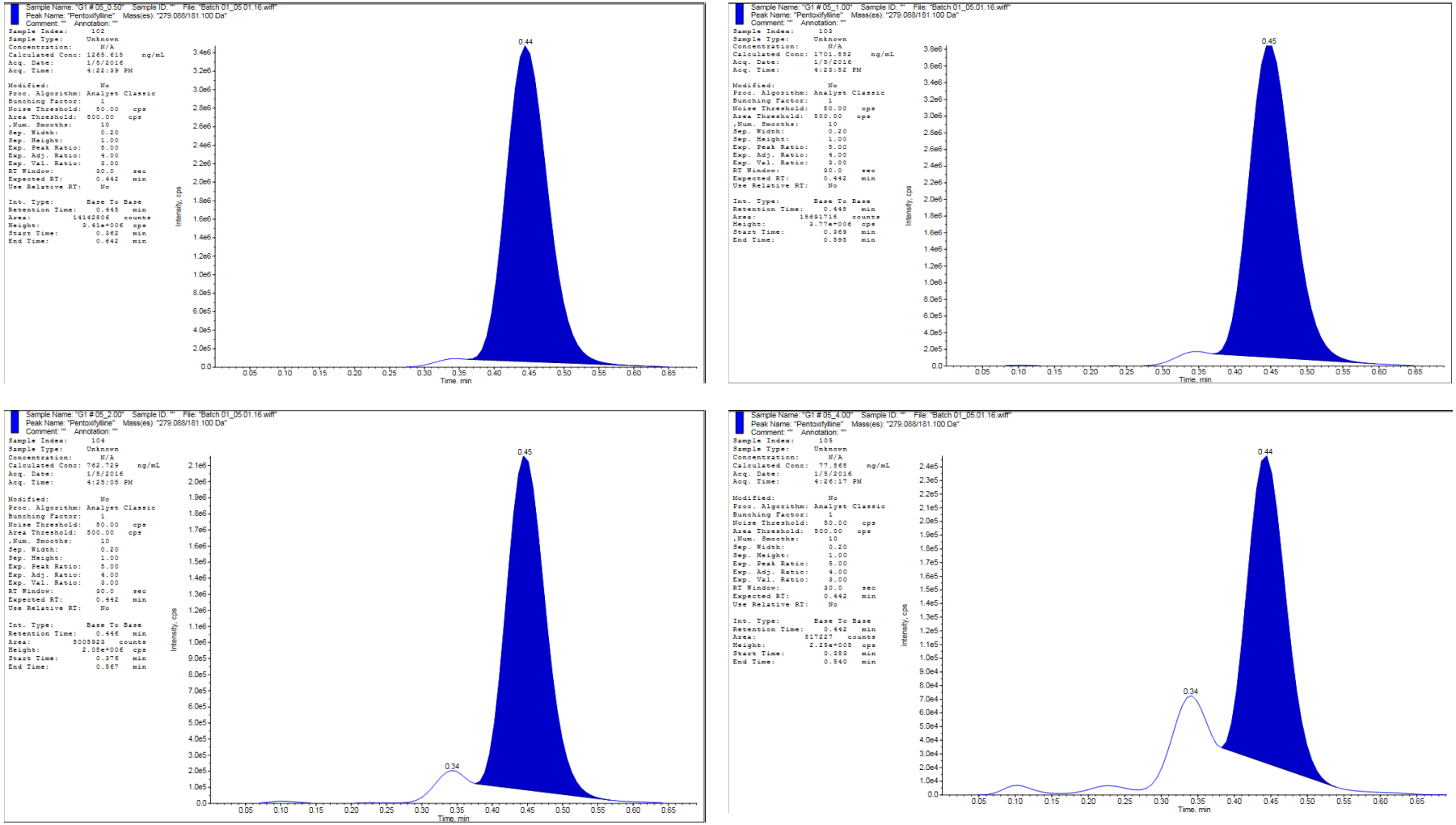

Figure A 9: HPLC chromatograms of rat 5, G1 plasma sample at 0.5, 1, 2, and 4 h.

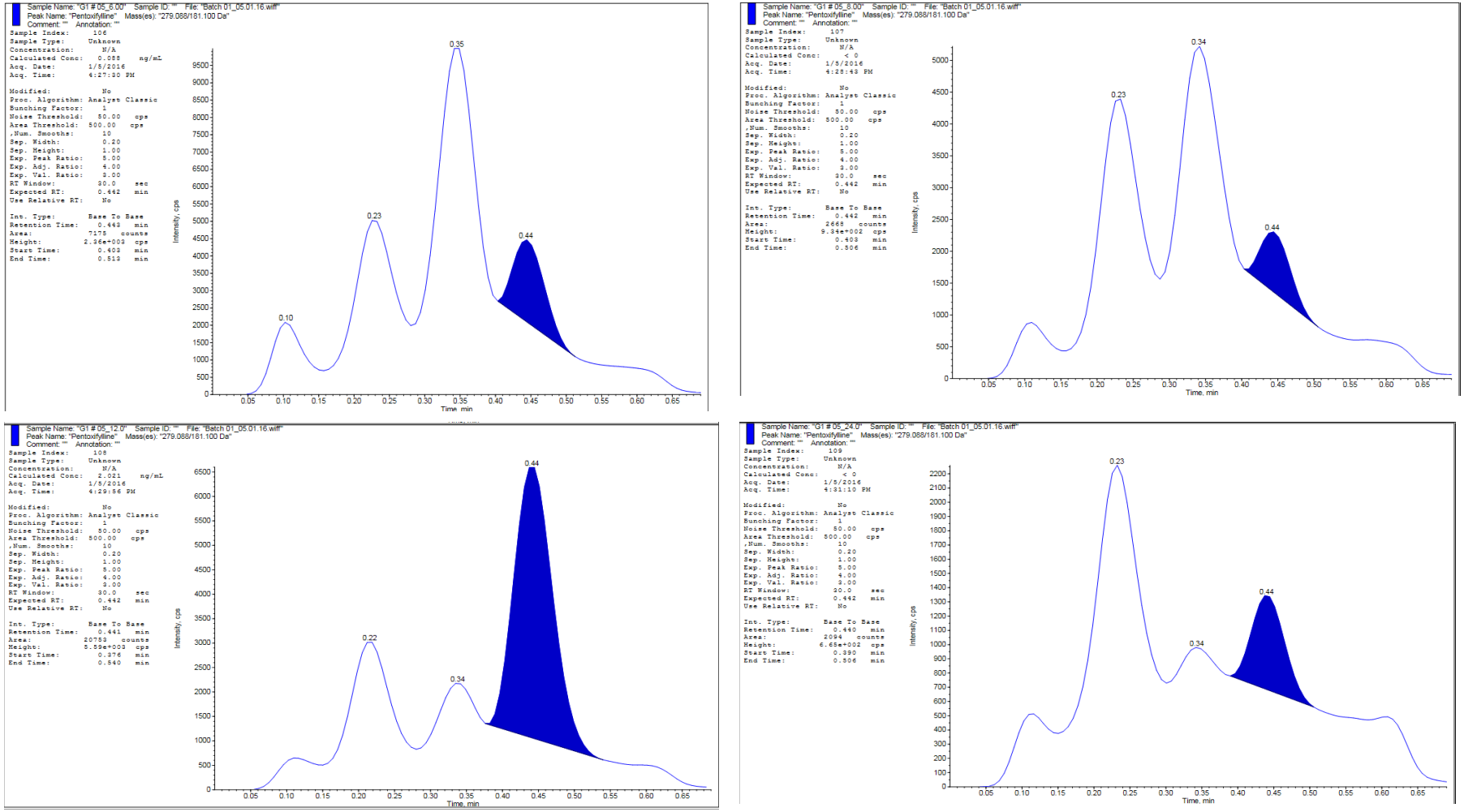

Figure A 10: HPLC chromatograms of rat 5, G1 plasma sample at 6, 8, 12, and 24 h.

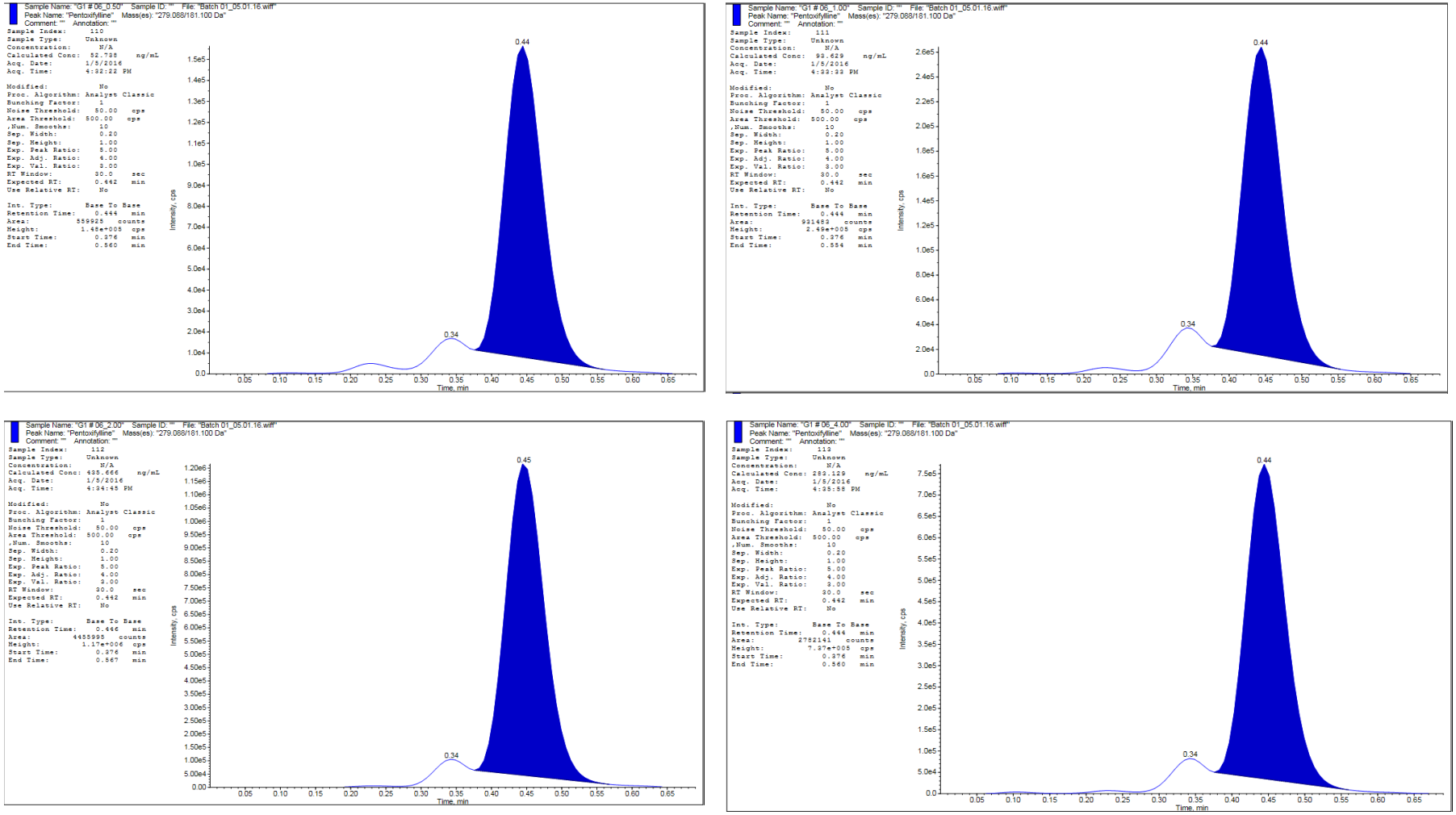

Figure A 11: HPLC chromatograms of rat 6, G1 plasma sample at 0.5, 1, 2, and 4 h.

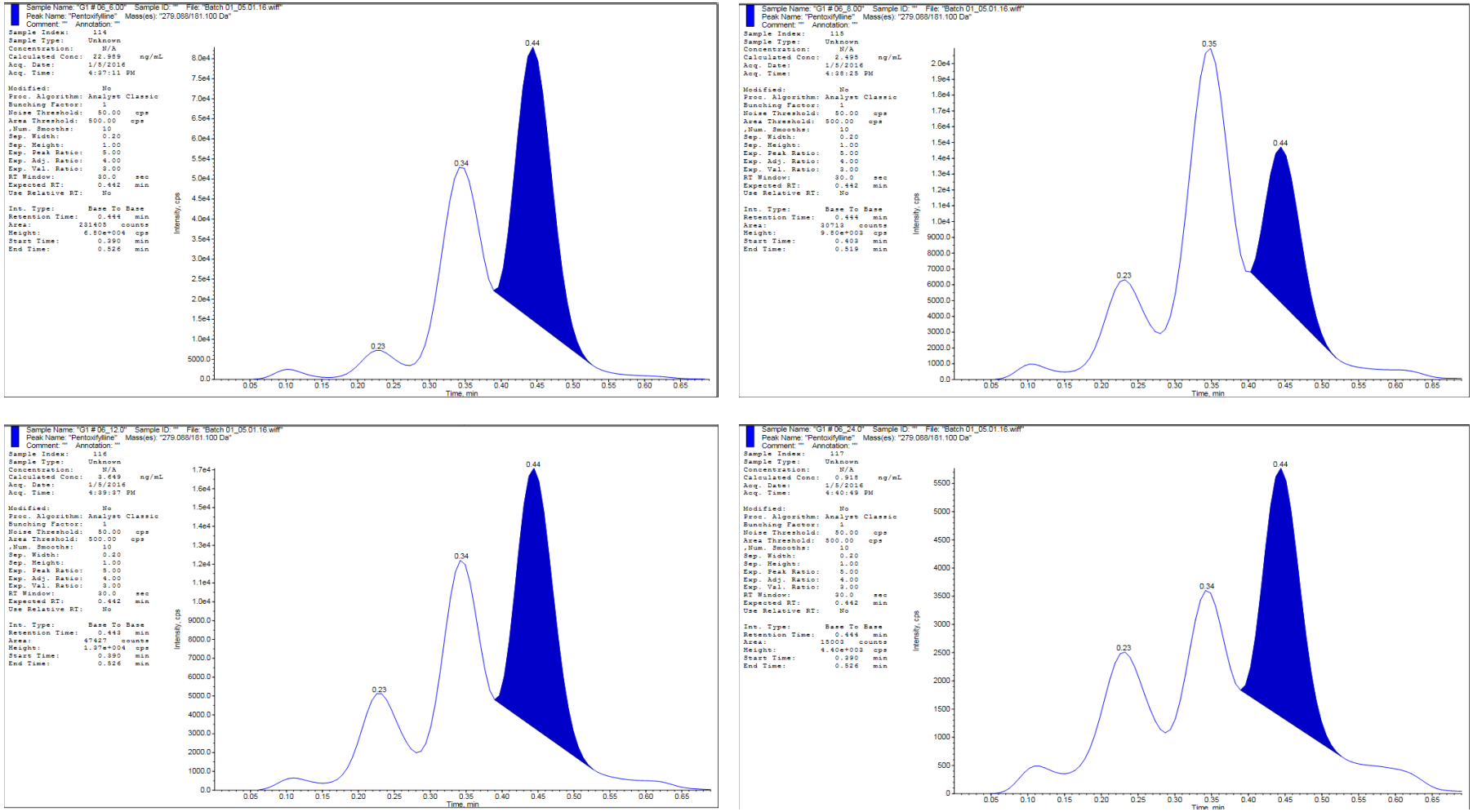

Figure A 12: HPLC chromatograms of rat 6, G1 plasma sample at 6, 8, 12, and 24 h.

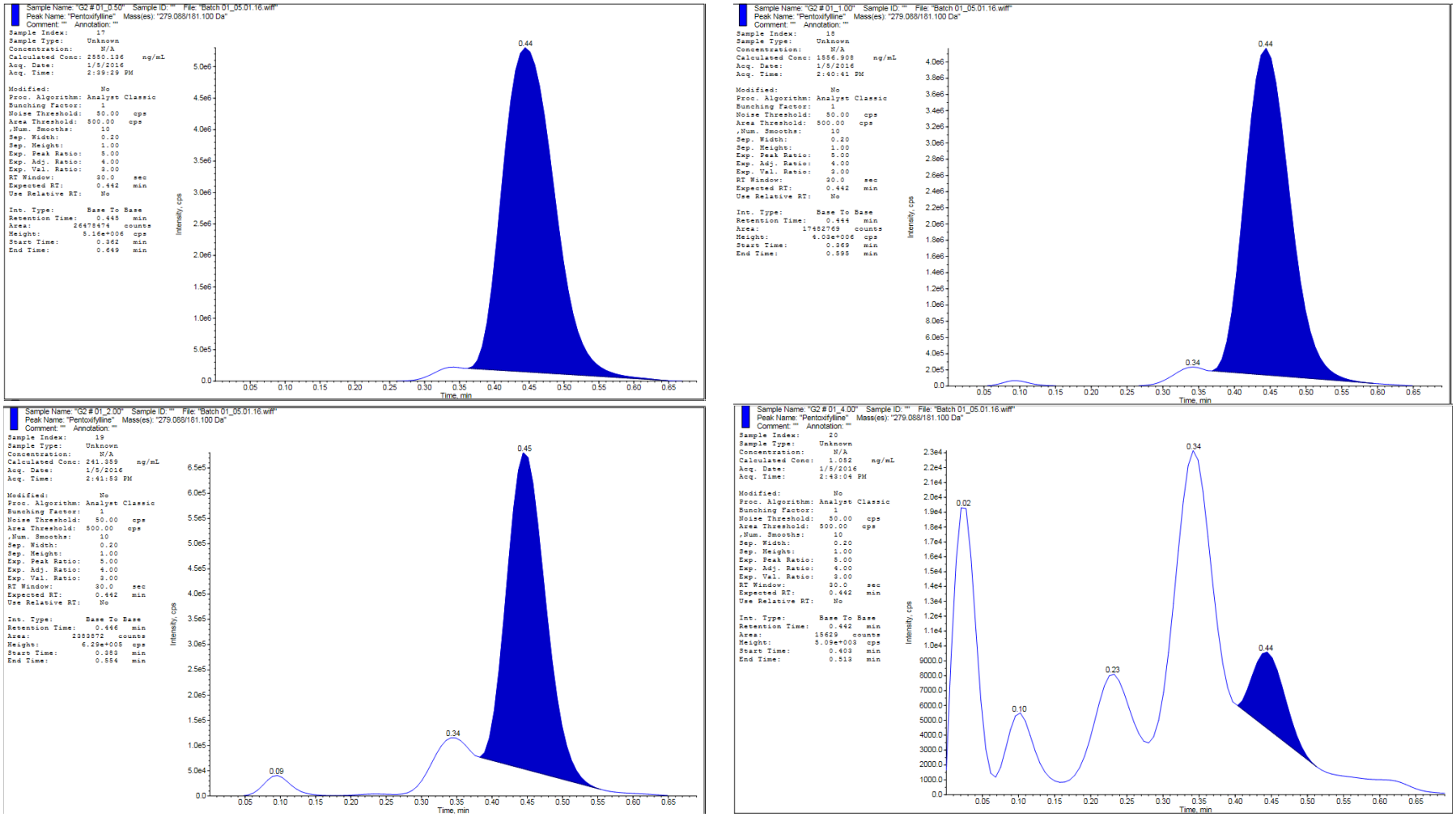

Figure A 13: HPLC chromatograms of rat 1, G2 plasma sample at 0.5, 1, 2, and 4 h.

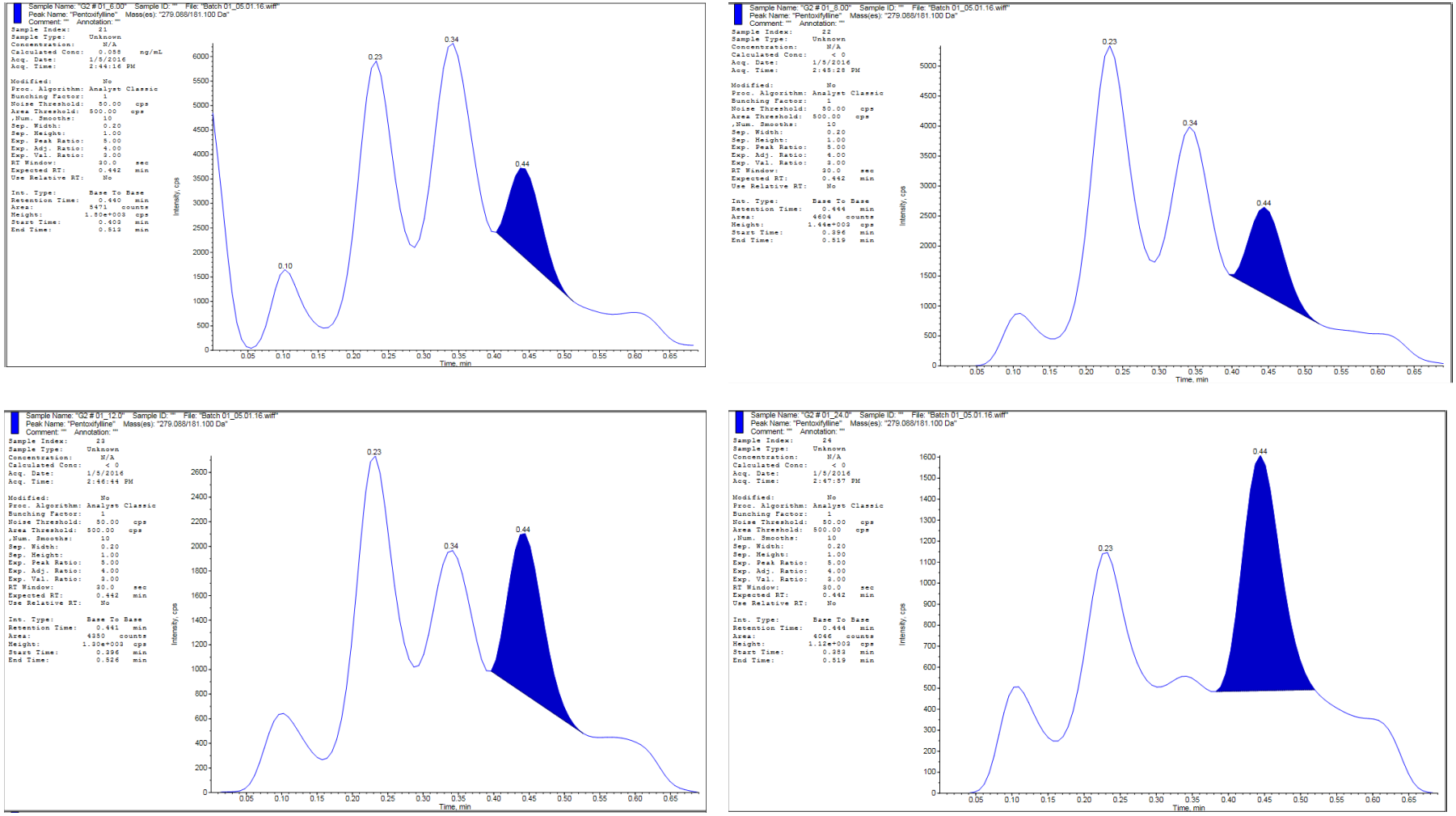

Figure A 14: HPLC chromatograms of rat 1, G2 plasma sample at 6, 8, 12, and 24 h.

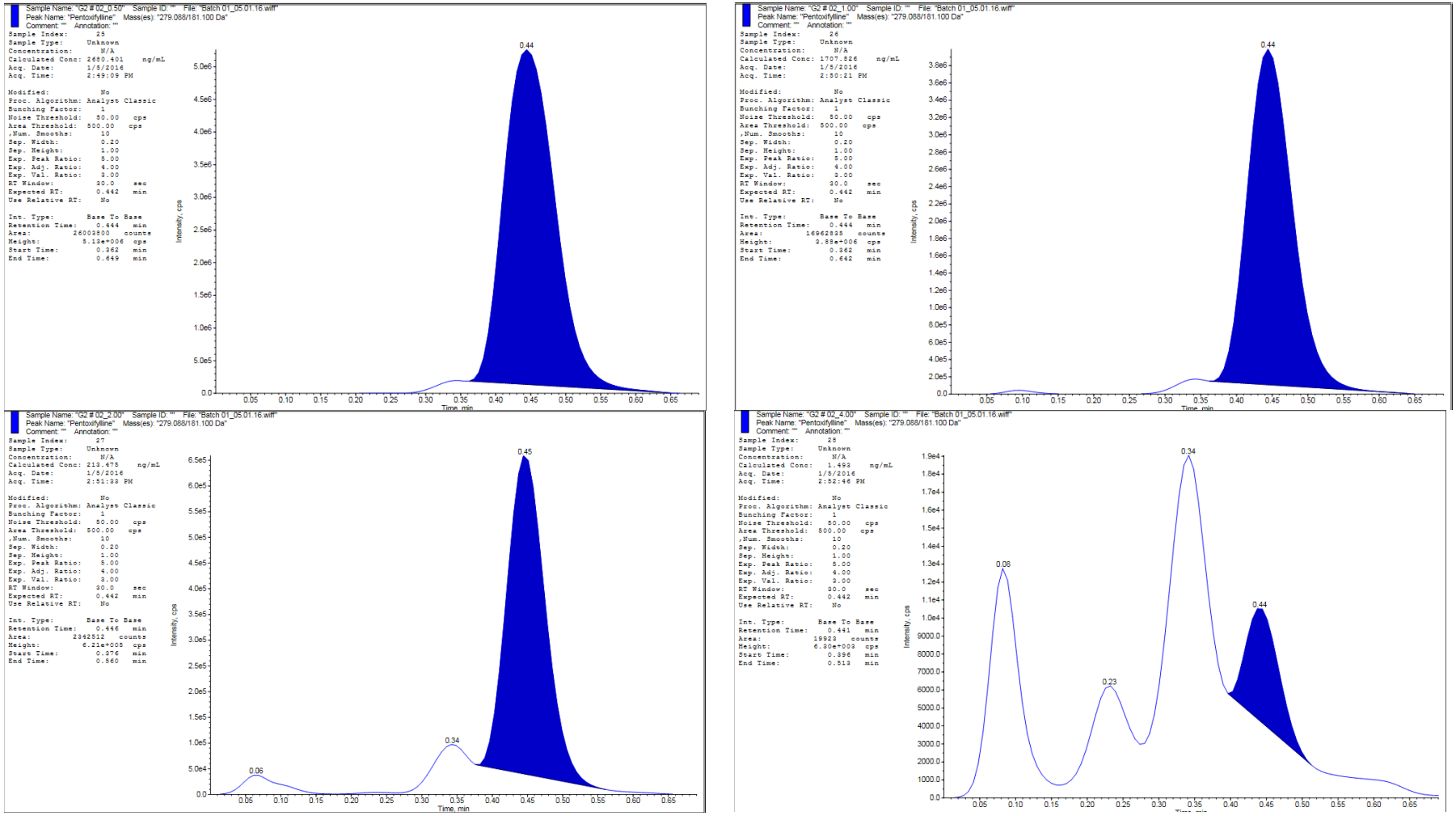

Figure A 15: HPLC chromatograms of rat 2, G2 plasma sample at 0.5, 1, 2, and 4 h.

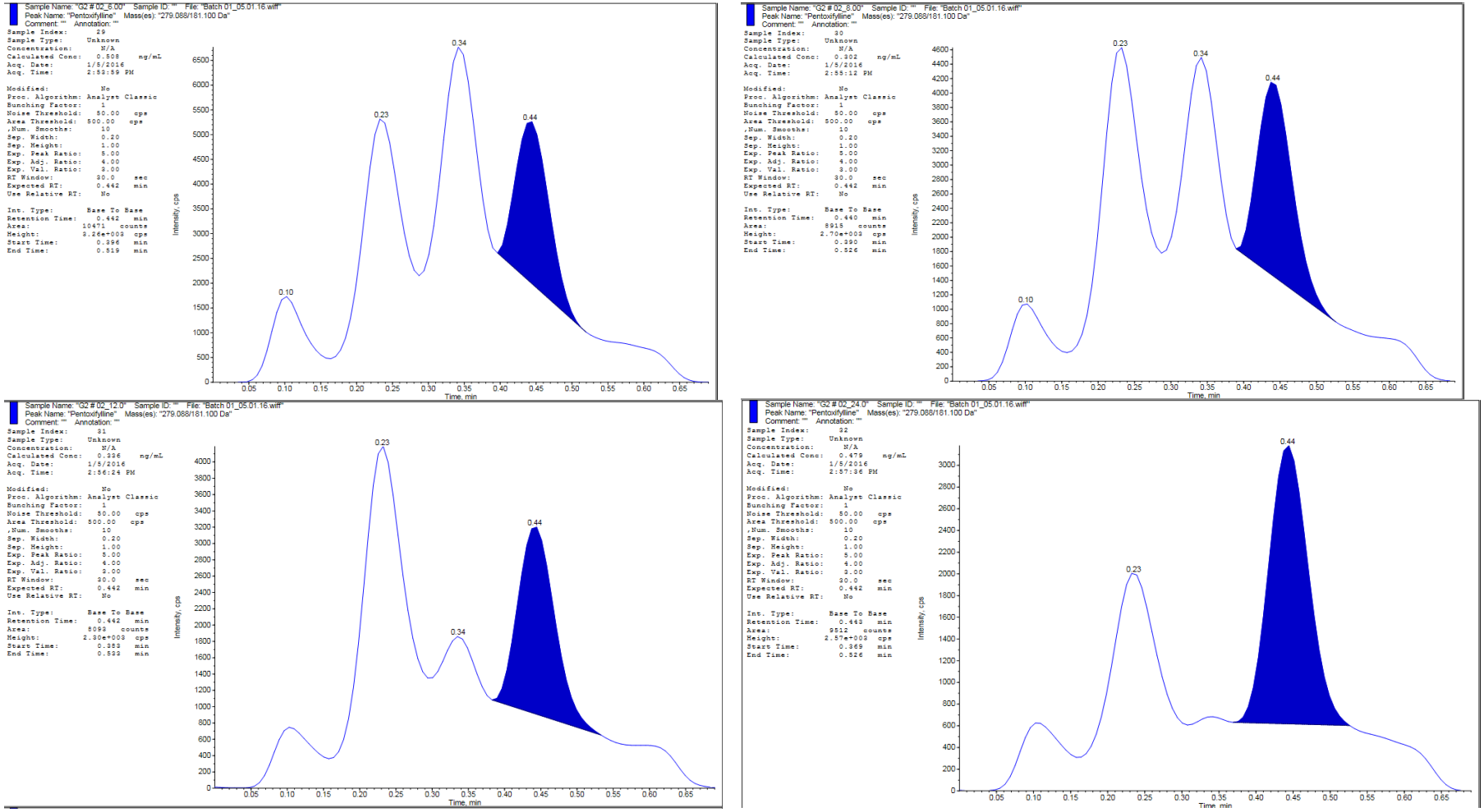

Figure A 16: HPLC chromatograms of rat 2, G2 plasma sample at 6, 8, 12, and 24 h.

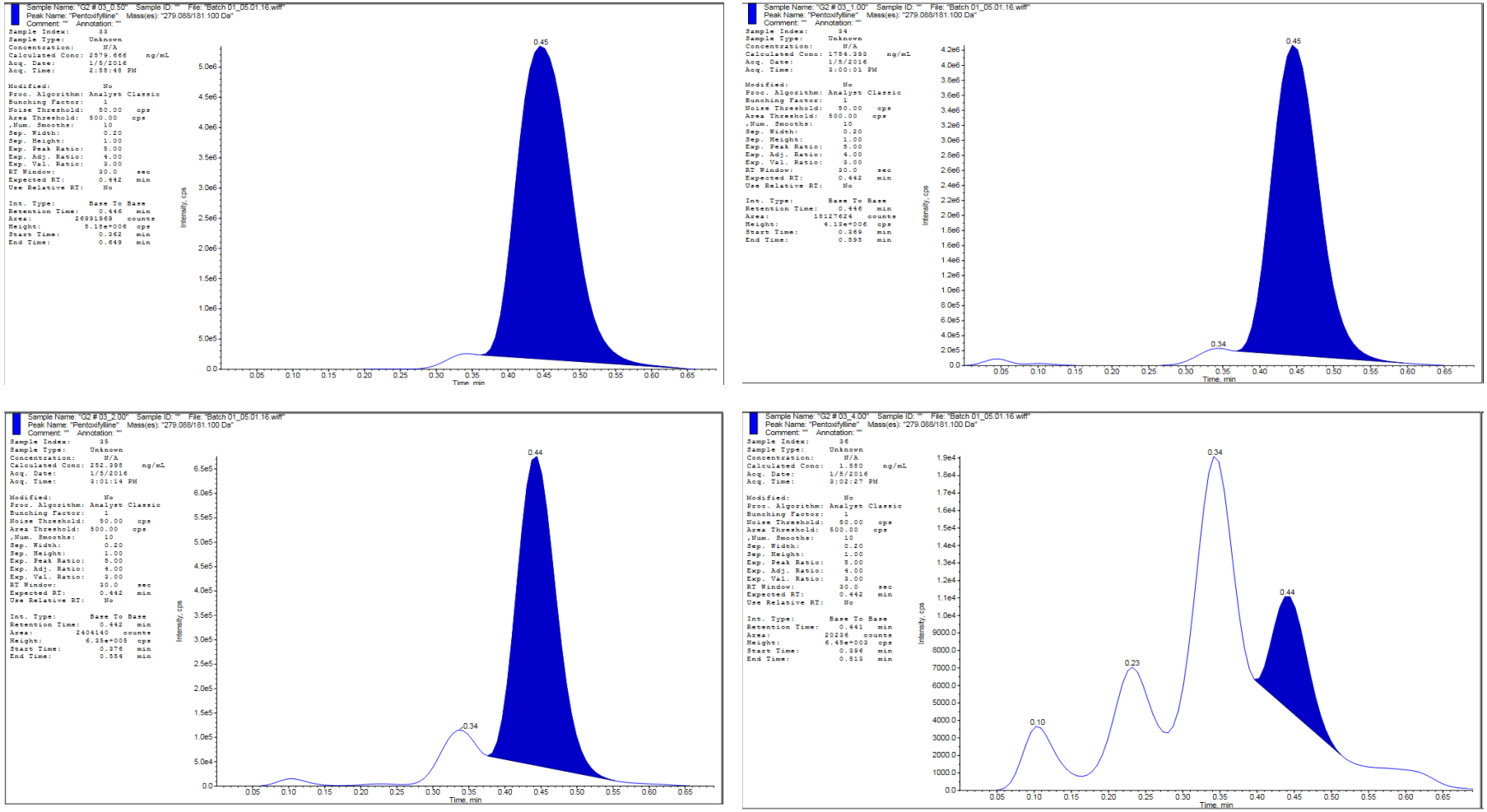

Figure A 17: HPLC chromatograms of rat 3, G2 plasma sample at 0.5, 1, 2, and 4 h.

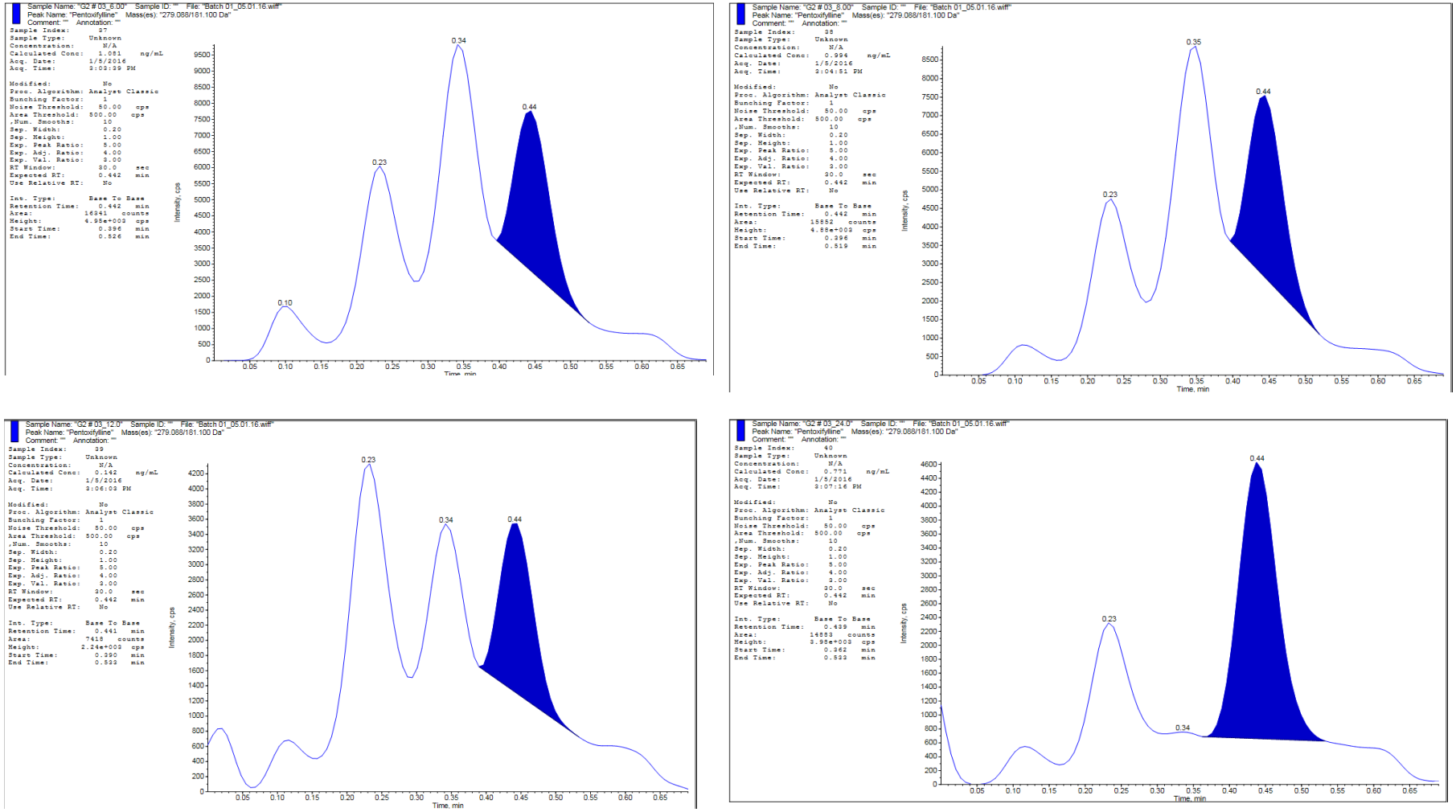

Figure A 18: HPLC chromatograms of rat 3, G2 plasma sample at 6, 8, 12, and 24 h.

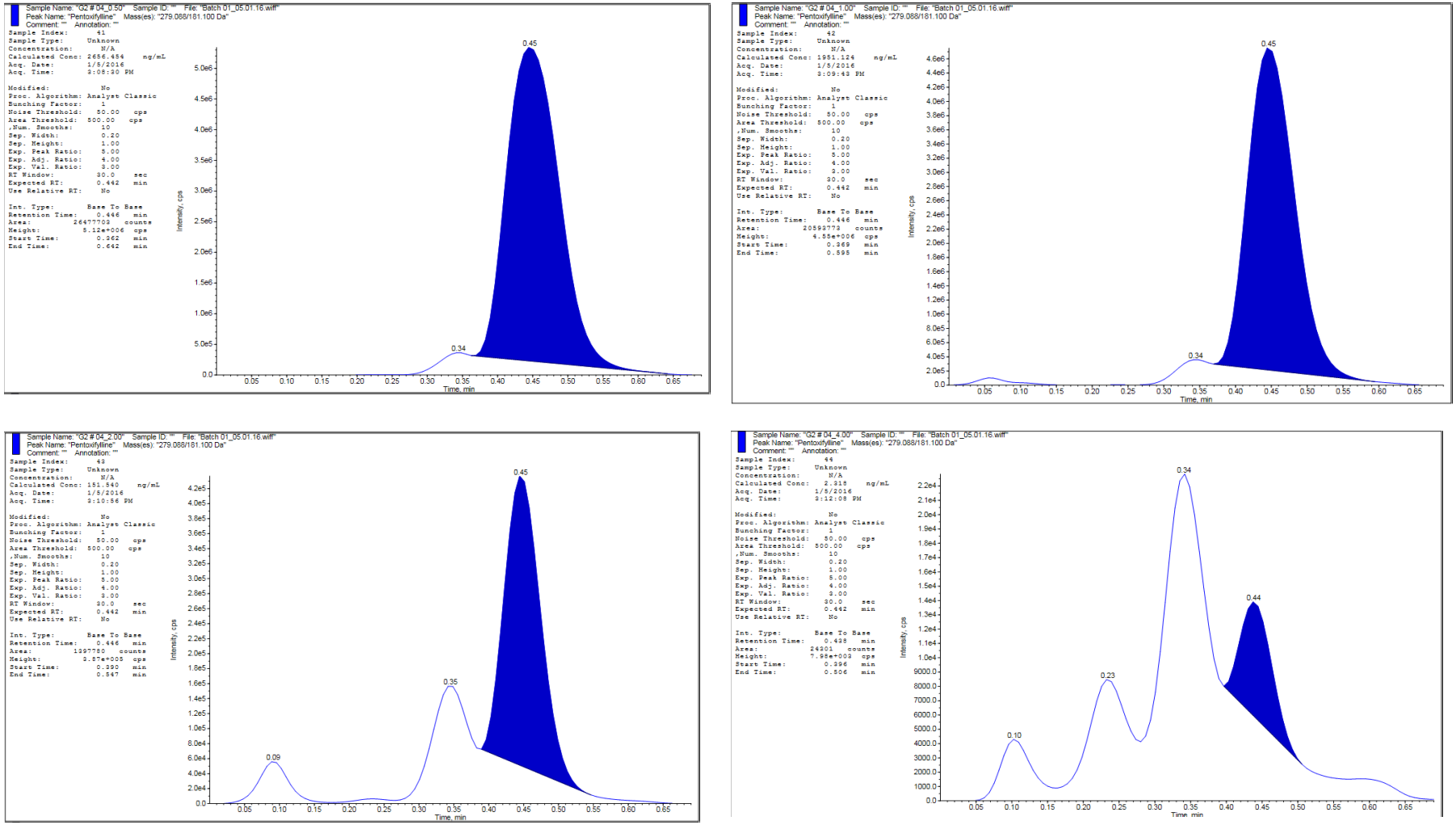

Figure A 19: HPLC chromatograms of rat 4, G2 plasma sample at 0.5, 1, 2, and 4 h.

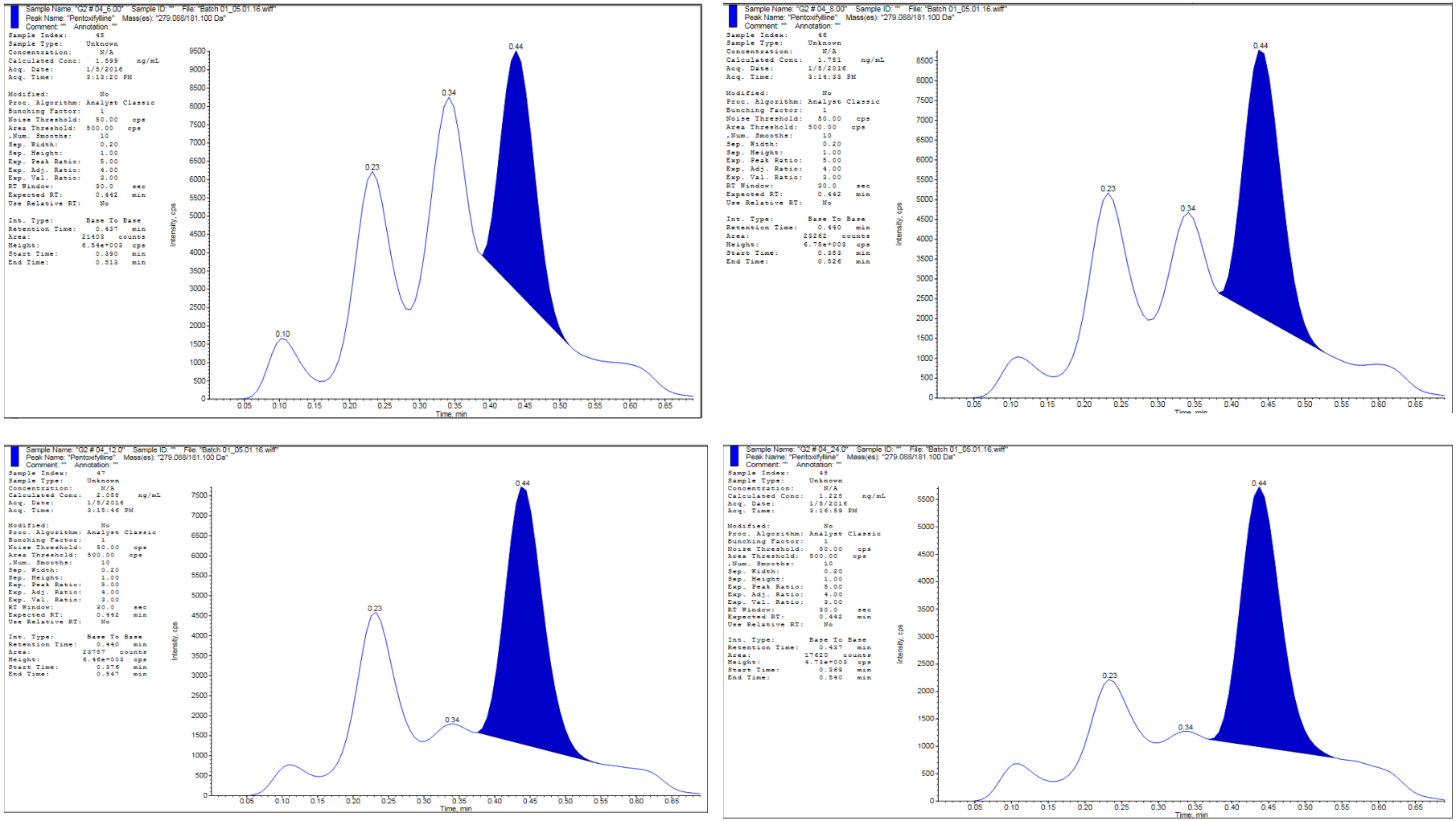

Figure A 20: HPLC chromatograms of rat 4, G2 plasma sample at 6, 8, 12, and 24 h.

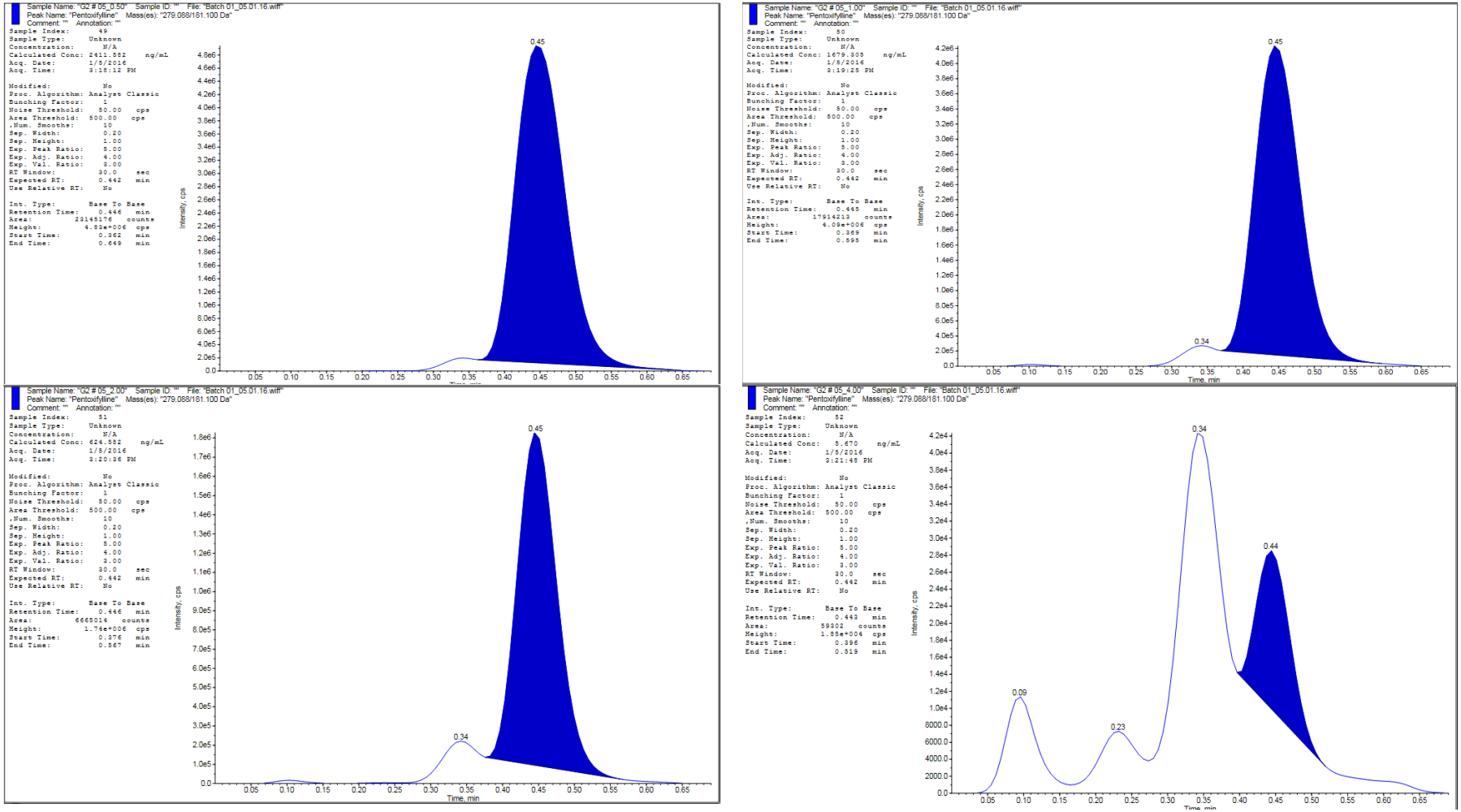

Figure A 21: HPLC chromatograms of rat 5, G2 plasma sample at 0.5, 1, 2, and 4 h.

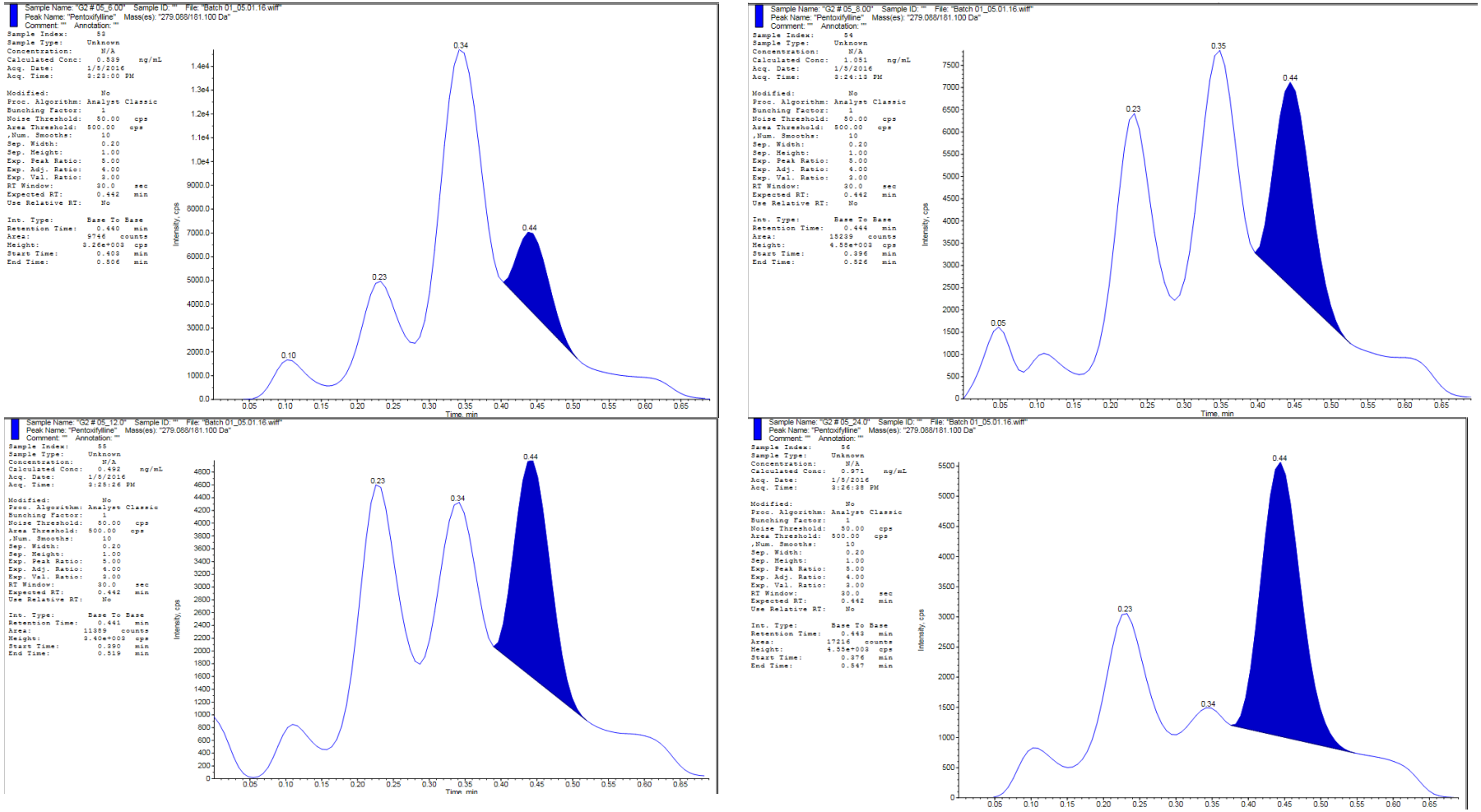

Figure A 22: HPLC chromatograms of rat 5, G2 plasma sample at 6, 8, 12, and 24 h.

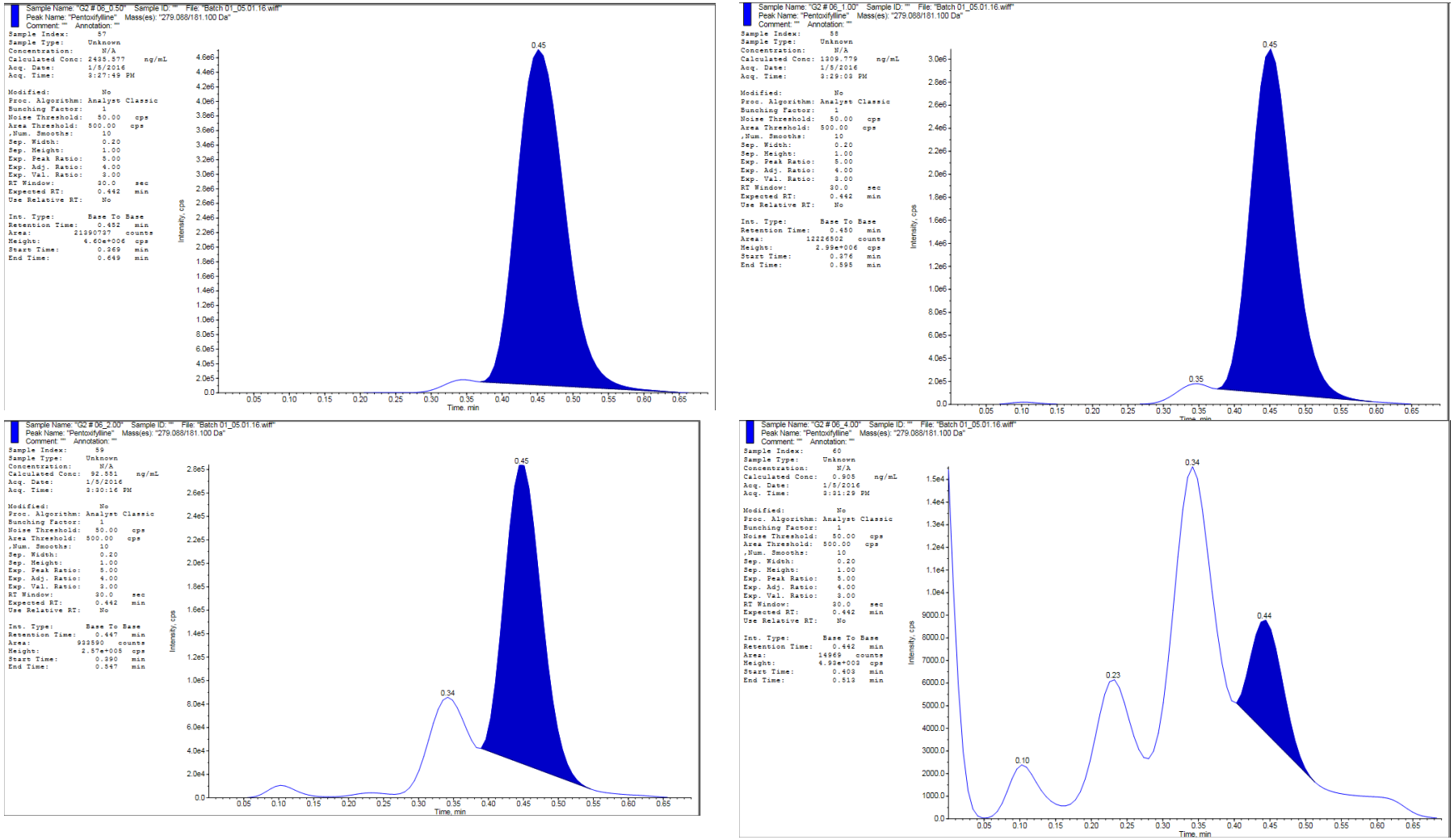

Figure A 23: HPLC chromatograms of rat 6, G2 plasma sample at 0.5, 1, 2, and 4 h.

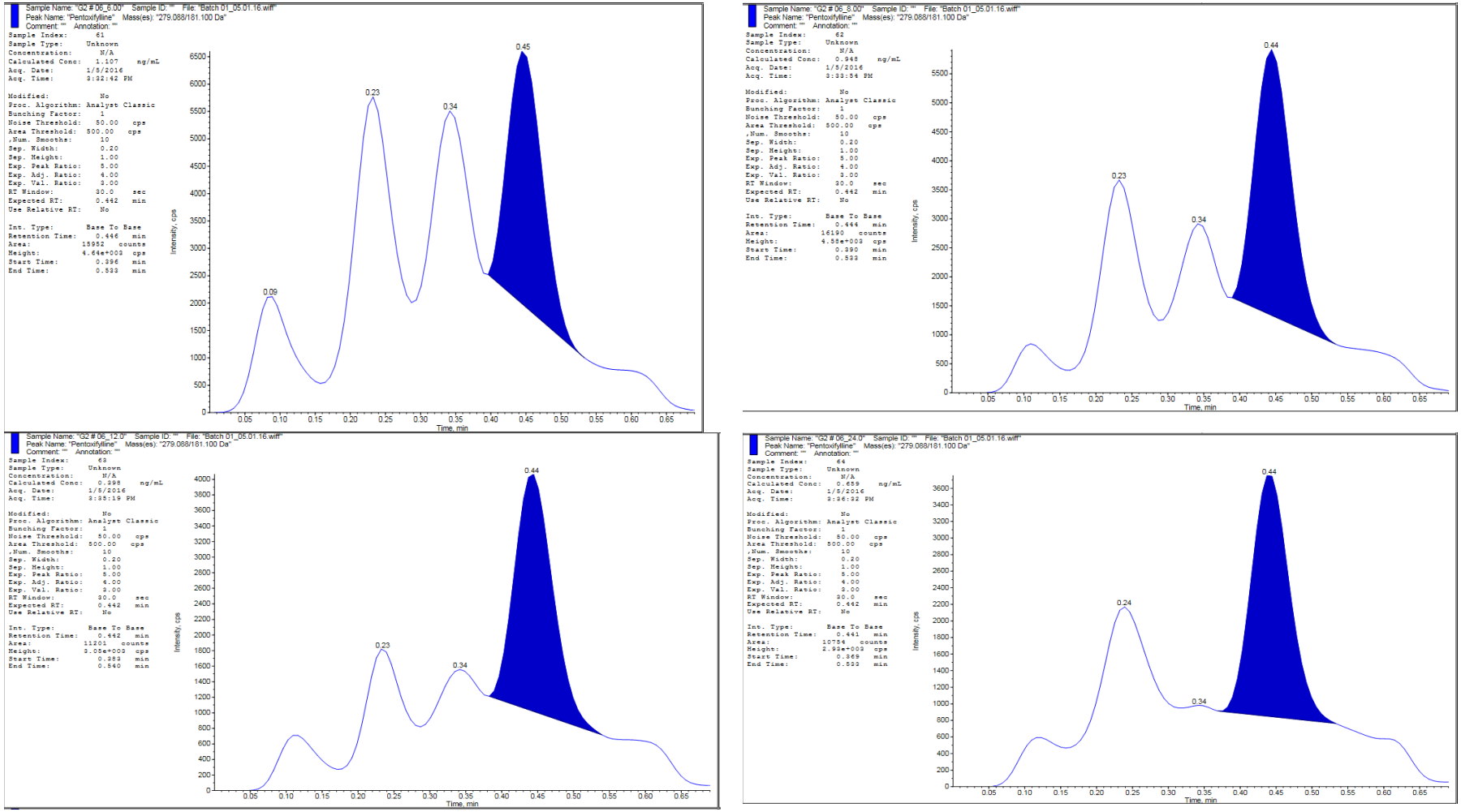

Figure A 24: HPLC chromatograms of rat 6, G2 plasma sample at 6, 8, 12, and 24 h.