MODIFIED DRUG RELEASE ORAL SOLID FORMULATIONS OF FLOATING PELLETS, USING EXTRUSION AND SPHERONISATION METHOD

MOHAMMED TARIQ REBHI DAHMASH

The thesis is submitted in partial fulfillment of the requirements of the University of Sunderland for the Degree of Doctor of Philosophy

January 2020

Abstract

Gastro-retentive drug delivery systems (GRDDS) can improve the erratic drug absorption of certain drugs, for example, theophylline. The formulation design of floating pellets is of a particular interest, due to the minimised risk of complete emptying into the intestine and the minimised gastro-intestinal tract (GIT) irritation. Core pellets are usually prepared by extrusion and spheronisation (E/S) processes, and are usually coated with more than one film before capsule filling or tableting processes. This research increased the understanding in the pharmaceutical floating pellets systems. The main aim of this research study was to develop novel gastro-retentive floating pellets, using the E/S processes with a new spheronisation aid not used before (Avicel HFE 102; co-processed microcrystalline cellulose with ~10% mannitol) and the use of 10% ethanol as a liquid binder for obtaining high sphericity (target: Aspect ratio; AR <1.2). Avicel HFE 102 was also used as a cushioning aid in the form of powder or pellets, to allow the compression of coated pellets into tablets whilst maintaining sufficiently sustained drug release and floating properties. In addition, the use of a single and thin film coat (made by Eudragit NE15 diluted by 25% ethanol) was studied to produce pellets with properties of sustained drug release (preferable target: 12-24 hours) and floating (preferable target: 6-12 hours, >90% floated, <15 minutes lag time). Mainly, the size and shape analysis of the core pellets was determined. The drug release and floating properties of the coated pellets were determined. The core pellets studies prior the enhancement of the single-coating (where the 10% ethanol was used as a liquid binder) showed that they exhibited spherical shape AR<1.2. In either 0.1N HCl medium or distilled water medium, the enhanced and novel single-coated floating pellets (where the film made by the Eudragit NE15 dispersion -diluted with 100% ethanol, to obtain 25 w/w% ethanol containing dispersion-) showed that they exhibited drug release for 24 hours or more. And, >98% of the latter pellets floated on surface, for at least 12 hours, with a lag time of 10-15 minutes. After which, the enhanced single-coated pellets were

compressed along with the cushioning powder. Upon tablets disintegration in 0.1N HCl medium, the single-coated floating pellets showed sustained drug release for up to 8 hours or more, and the floating was at least for 24 hours. That is, the compression of the enhanced single-coated pellets into tablets still produced useful pellets. To sum the main points, core pellets were successfully made regarding shape properties, using the new spheronisation aid (Avicel HFE102). And, the single-coated floating pellets were successfully made and intensively investigated for properties, like shape, drug release, and floating properties. The success of the latter pellets is mainly attributed to the use of ethanol in the liquid binder and the coating dispersion, respective to the enhanced core pellets and the enhanced single-coated pellets. The spherical core pellets and the single thin layer of only ~6.5% weight gain were obtained. The latter coating layer had the enhanced floating and sustained drug release properties.

Table of Content

[1] To ease readability, the third sub-sections are not stated here, because some of the testing techniques used in more than one formulation stage throughout the results chapters. See the illustrative Figure 2.4, to know where these tests were used.

Abbreviations

AUP: Area under the Peak. An area in the DSC thermogram.

AR: Aspect Ratio. A shape factor. It is the ratio of the maximum Feret diameter (FD_{max}) to the minimum Feret diameter (FD_{min}). The AR maybe used outside the pharmaceutical pellets field as FD_{min}/FD_{max}.

A (mm^2): Area. It is the number of square units inside a two dimensional shape, like a circle, where $A=pi*r^2$. The Greek letter of Pi is the circumference: diameter ratio. While, the surface area is the area or the number of square units inside a three dimensional shape, like a sphere, where $A=4*pi*r^2$.

CPPs: Critical Process Parameters, or can be used for the Critical Product Parameters

CQAs: Critical Quality Attributes, which is also called Critical Product Attributes (CPAs). However, CPAs may also be used for the process parameters. Therefore, the critical process parameters and the critical product parameters will be abbreviated here as CProcPs and CProdPs, respectively

Cros-PVP: Cros-Povidone. It is a cross-linked vinyl polymer, and a hydrophobic one. The cros-PVP is a semi-crystalline polymer, due to the increased order induced by cros-linking.

DoE (Statistical): Statistical Design of Experiment. A tool in the 'risk evaluation' stage of the risk assessment category per QbD.

DSC: Differential Scanning Calorimetry. A calorimetric technique that is commonly used for thermal testing. It provides thermochemical information, like the melting point, and the change in enthalpy (ΔH) (joule/kg). The latter is a component in the Gibbs free energy (G) equation; $\Delta G= \Delta H- T \Delta S$, where T is the Kelvin temperature, and ΔS is the change in entropy.

F-Circle (mm): Circularity. A shape factor. It is the largest circle diameter inside the circle or inside the imperfect circle. Hence, it is either the same of the circle diameter or smaller. It equals to $\sqrt{(4 * \mathrm{pi} * \mathrm{A})/\mathrm{P\^{}2}}$,

where A is the area and P is the perimeter of the sphere. Pi equals to 3.14. This can be directly measured by an imaging software.

FD: Feret's Diameter. A shape factor. It is defined by (Taylor, 2018) as “the mean value of the distance between pairs of parallel tangents to the projected outline of the particle. This can be considered as the boundary separating equal particle areas”. This diameter can be calculated be an imaging software.

FMEA: Failure Mode Effect Analysis. A tool in the ‘risk analysis’ of the risk assessment category per QbD.

FR: Feret’s Ratio. A shape factor. Like circularity, it ranges from 0 to 1, the closer to one the higher is the sphericity of the core pellets.

GIT: Gastro Intestinal Tract. A physiological organ.

GRDDS: Gastro-Retentive Drug Delivery Systems. One of the sustained drug release system (SDRS). Hence, it is a Modified Release (MR) Drug Delivery System.

HBS: Hydro-Dynamically Balanced System, it implies the Floating Systems

HPMC: Hydroxy Propyl Methyl Cellulose. A cellulosic polymer.

ICH: International Conference of Harmonisation. A quality guidelines authority in pharmaceuticals.

IQR: Inter-Quartile Range. A parameter for assessing the particle size distribution variability, based on two quartiles. It equals to Q3-Q1, where Q3 is the diameter (mm) at 75% cumulative undersize percentage, and Q1 is at 25%.

KgF: Kilogram-Force or Kilopond (kp) is a gravitational metric unit of force applied by a one kilogram of mass. 1KgF=9.80665 Kg-m/s² or Newton. The unit can be used for quantifying the applied force on the sample.

MCC: Micro-Crystalline-Cellulose. A Cellulosic Polymer.

MMC: Myo-Electric Complex, happens during the gastric emptying in the fasted state

MP: Melting Point in Celsius temperature. An endothermic peak for a crystal in the DSC thermogram.

MPa: Mega Pascal. 1 MPa= 1 million N/m^2. A unit of Force, which can be used for the surface tensile strength of tablets.

MSI: Mechanical Strength Index. A percentage used in the friability study, to measure the strength of tablets, especially the exterior strength of tablets.

mupFDDS: Multiple Units of Pellets Floating Drug Delivery Systems (Floating Pellets). A specific oral solid and a specific GRDDS design.

N: Newton. A unit of Force. kN is particularly easier to use when quantifying the force applied on a sample during tabletting for instance.

PAT: Process Analytical Technology. Various analytical tools used in-process during the drug product manufacturing. It is one area in the risk control category of QbD

Perimeter (mm): Circumference. A shape factor. It equals to C=2*pi*r.

PMAs: Poly-Meth-Acrylates. They are acrylic co-polymers. These are semi-crystalline co-polymers, or sometimes referred to as amorphous co-polymers, owing to their high amorphousity. These copolymers can be anionic, cationic, or neutral. The common derivatives of PMAs are the amino-alkyl (immediate release), carboxylic acid (delayed release), ester or ammonio-alkyl (time-controlled release). Eudragit RL, RS, NE, and NM are time-controlled release PMAs, which are all insoluble and have pH-independent swelling. However, only RS grade is of high permeability, and only NE and NM grades are highly flexible, that do not require plasticiser. Though all of the copolymers are insoluble, they have varied permeability. RL and RS grade are quaternary ammonium derivatives of PMAs, while NE and NM are ester derivatives of PMAs (Evonik, 2017) and (Thakral, et al., 2013).

PVP: Poly-Vinyl-Pyrrolidone (Povidone). It is a vinyl polymer, and a hydrophilic one. The PVP is an amorphous polymer.

QbD: Quality by Design. It is a quality management methodology in the pharmaceutical industry.

QTPP: Quality Target Product Profile. It is one of the initial work required in the risk assessment of QbD.

R: Coefficient of Determination. It is a parameter that measure the goodness of data fit in the 'regression' line. It is used to measure the linearity of data fitted between specific x-axis and y-axis components.

RPN: Risk Priority Number. It is a number calculated semi-quantitatively from the multiplication of the severity, impact, and detectability values of each risk factors. This number is a threshold risk score, above which, risk factors are considered to be high risk factors.

RSD: Relative Standard Deviation. It is a parameter to measure variation in data, in particular, it measures precision. It equal to SD of values divided by the average of values. The RSD times 100 gives the RSD%, which is more numerically representative than RSD.

SA:V ratio: Surface area to volume ratio, where both of the latter calculated from the diameter values, which was calculated from the perimeter values. Surface Area of sphere (SA)= $4*pi*r^2$, Volume of sphere= $(4/3)*pi*r^3$. Hence, SA/V=3/r.

SD: Standard Deviation. It is a parameter to measure variation (dispersion) of the sample values from the mean value.

SEM: Scanning Electron Microscopy. It is an advanced imaging technique.

STS: Surface Tensile Strength.

Tg: Glass Transition Temperature. It is the softening temperature of the amorphous form material.

Chapter One:

Introduction

1.1. Introduction

Pharmaceutics is a voyage of multi-disciplinary collections of theories and technologies that mainly focus on the physical chemistry and design of dosage forms of drug products, and accompanying methods of preparation and testing. In this project, the dosage form of interest is the one that contains pellets. The specific designs of interest are the double-coated floating pellets design and the single-coated floating pellets design, such pellets can be compressed into tablets.

Pellets can be defined as oral solid intermediate formulations, spherical in shape, relatively small in size, and made by a pelletisation technique, usually by extrusion and spheronisation techniques with a spheronisation aid, the latter method is to obtain dense agglomerates of pellets. Floating pellets achieve floating as they contain floating agents and retard polymeric agents, usually through the application of coating layer/s.

The pellets can be made to act as a gastro-retentive drug delivery system (GRDDS), the floating pellets system as an example. The gastro-retentive term, is derived from its ability to achieve retention of the dosage form in the stomach. Unlike the other GRDDS, floating systems are currently available on the market, like the floating liquid of alginates (Gaviscon®), and these systems avoid irritation to the epithelium of the gastro-intestinal tract (GIT). The latter is especially advantageous when the floating system utilise pellets, owing to the high distribution of the dose in the pellets, which further reduces dose localisation. Unlike the floating tablet, the floating MUPS tablet/capsule lack the *"all or none"* risk of emptying into the small intestine. This is because that the dose is distributed usually in few hundreds of units instead of being placed in one unit only. That is, unlike the single-unit system, if only one pellet sink, a negligible dose will escape the gastro-retention. Therefore, the floating pellets system is said to be one of the most preferred approaches in the GRDDS (Singh & Kim, 2000) and (Solanki, et al., 2017).

The floating pellets system is of a particular interest for drugs with narrow absorption windows or of erratic absorption, such as theophylline. The erratic absorption means non-uniformity drug absorption in the GIT, resulting in a variable drug bioavailability (Kang and Lee, 2009).

The factors that affect the drug absorption are numerous including the drug product and the physiological factors, which subsequently affect drug bioavailability. All of these factors may cause variable absorption in the gastro-intestinal tract (GIT) for drugs, like theophylline; and this can result in unfavourable fluctuated plasma drug levels. However, the risk of attaining a toxic dose or not attaining the efficacious dose becomes more pronounced when such drugs also have a narrow therapeutic window. Hence, the floating pellets system is expected to ensure the consistency of the bioavailability of the drug, by the gastro-retention and the sustained drug release properties.

1.2. Pharmaceutical Oral Solids

1.2.1. Oral Solid Dosage forms

Designing a dosage form for the oral route is a very common path for formulating drugs into medicine. This topic is introduced in several sources, including one of the most popular, concise, comprehensive, and sufficiently detailed book; the Aulton's pharmaceutics, where a clear introduction to the oral route is briefly articulated by (York, 2013).

Unlike other routes of drug delivery, the oral route is considered one of the most important in drug delivery, owing to its superiority for reasons, like being a non-invasive and the safest in drug delivery, comparing to the invasiveness and increased toxicity of the parenteral route of drug delivery. Moreover, the oral route is the most common and convenient in drug delivery. All of latter advantages resulted in an improved patient compliance. For the manufacturing point of view, the oral products are easier, more agile and versatile to manufacturers, resulting in a superior cost to benefit value. Common disadvantages for some oral dosage

forms of the various formulation designs can be related to drug stability in GIT, erratic absorption, and subsequent poor bioavailability profiles (York, 2013). Oral dosage forms can have various forms, such as the oral solids, the most common example is tablets, also, hard and soft capsules, pellets, and less commonly oral films. The second common form of oral products is the oral liquids, for example, solutions, suspensions, and emulsions. The oral gas products, such as nebuliser, are also fairly common in the market.

In particular, the oral solid dosage forms are the most common amongst all other oral dosage forms, owing to their additional superiority when compared to other forms of oral and non-oral delivery. Oral solid products advantages include the convenience for the patient self-monitoring and administration; with the possibility of handling the pills in a pillbox. Then, that can result in an increased patient compliance. Also, the chemical stability, the physical stability, and the microbiological stability of the oral solids are higher when compared to the oral liquids, resulting in a higher and less variable shelf life. For the manufacturing point of view, oral solids are particularly convenient to handle during production, with high versatility and flexibility in fabricating the dosage form design for their intended use and delivery. Moreover, oral solids, especially the conventional tablets, have a well-developed know-how by manufacturers, with relatively cheap and controlled mass. Hence, this was owing to the robust preparation procedures that provide accurate drug dosing, as stated by (Alderborn, 2013). This high manufacturability of the oral solids results in a superior advantage for the scale up planning and troubleshooting. Hence, it will result in a higher possibility to deploy innovative products that offer long-term cost-effectiveness.

Most oral solids can be classified into two broad categories based on their mean diameter size, the single unit systems (SUS), such as tablets of 6-12 mm. Secondly, the multiple units of particulates systems (MUPS), such as mini-tablets of 1-6 mm, pellets of 0.5-2 mm (typically 0.71-1.4 mm), and the micro-pellets of 0.1-0.5 mm. The micro-pellets

dosage forms are easier to coat when compared to other MUPS and to other larger tablets (Porter, 2013).

Additionally, mini-tablets have the least variable size, shape, and surface roughness when compared to other MUPS forms. MUPS can also be obtained from drug crystals (except elongated and acicular crystals), and also from irregular granules, which have the disadvantage of angular nature, resulting in batch-to-batch variation, owing to thier poor coating uniformity (Porter, 2013).

1.2.2. Multiple-units of particulates systems (MUPS)

This section will focus on the pellets as a type of MUPS. Based on Ghebre-Sellassie (1989) definition, the word pellet is described as "a variety of systematically produced, geometrically defined agglomerates obtained from diverse starting materials utilising different processing conditions." The pellets products can include fertilisers, animal feeds, iron ores, confectioneries, or pharmaceutical dosage forms. Pellets are known for their inherently high flowability and compatibility (Ghebre-Sellassie, 1989). As stated by Nokhodchi, et al (2010), other oral solid formulations can also have high flowability and compatibility, such as the liqui-solid formulations.

The dosage form containing pellets is particularly attractive when compared to mini-tablets and larger non-disintegrating tablets, because pellets are smaller in size (< 2 mm). The latter size will have a similar gastric emptying to the liquid, resulting in more uniform distribution in the GIT as it has more consistent emptying into the typical absorption site of the small intestine (Davis, 2005) and (Kallakunta, et al., 2017). Pellets are less commonly called beads or spheroids dosage form. The uncoated form also known as core pellets, matrix pellets, or naked pellets. Inert sugar/starch spheres are also called nonpareil beads, or starter pellets/cores. The MUPSs are superior when compared to the single unit systems, owing to the small size and rounded shape of MUPS (Prasad, et al., 2013) and (Porter, 2013).

During MUPS manufacturing, additional flexibility in fabrication can be obtained for a broader range of drug formulation designs. These features will ease the coating and better control the liquid diffusion through the coating layer, and subsequently improve drug bioavailability. This flexibility allows for the co-delivery of the incompatible drugs (fixed-dose combination), or for the delivery of the same drug but co-delivered in two different release profiles units (pulsatile release). This co-delivery is possible as the two different combinations can be made in separate batches of pellets and can be coated separately, and then mixed in one dosage form (Caleva, 2015). The MUPS can be more uniformly coated, owing to their size and shape. In a smaller scale, the single unit system may have a superior coating uniformity over MUPS. Moreover, coating uniformity depends on other process and formulation factors as well. The MUPS can be uniformly packed, owing to their spherical shape units, results in an inevitable excellent flowability. The MUPS have an increased resistance toward the external environmental effects of moisture, air, and light, especially when a hydrophobic coating is applied (Kallakunta, et al., 2017) and (Reddy, et al., 2011). This protection is particularly important if those coated units were intended for capsule filling, which will more likely reserve the water content in the hard gelatine capsule, ensuring higher product stability. Here, the protective coating of conventional tablets can be equally advantageous.

Gastrointestinal tract (GIT) irritation can be reduced using these dosage forms, due to the higher surface area of the dosage units that results in an even dose distribution in the GIT. The dose is being in multiple units that are readily dispersible in the GIT, this results in a decreased unfavourable drug localisation, and this then impact on GIT irritation. The MUPS have reduced the amount and impact of dose dumping, owing to the fact that the dose is distributed in many sub-units, usually a few hundred of pellets contribute to a single dose. Thus any coating defect in one pellet will cause a sudden drug release in a very small fraction of the dose (~0.5 to 2% of the overall dose). As a result, the risk reduction in dose dumping is minimised. The MUPS ensure a uniform

drug release profiles, owing to their high surface area and the more uniform coating that results in less variability in the water permeation mechanisms into the drug formulation. And, this will also result in decreased impact if poor coating uniformity obtained, reduces the impact of batch-to-batch variation. Moreover, the coating processes of pellets are renowned for their better spreading and uniformity of coating. Each pellet controls its drug release rate, which is if assumed that no clumping of pellets occurred during coating, storing, and/or during immersion in the gastric fluids. The latter results in an absorption with lowered inter-subject variation and intra-subject variation. This reduced variation is especially important for the narrow therapeutic drugs, such as theophylline. That will minimise the variable drug plasma concentration, which may result in a reduced occurrence of adverse effects in the central nervous system (CNS), and for maintaining an effective concentration for the therapeutics site. Hence, the reduced variability can result in a higher reproducibility of the drug plasma levels, owing to the more consistent absorption (Abdul, et al., 2010). Based on the European Medicines Evaluation Agency (EMEA), the pellets have more predictable residence time and in general longer residence time than the non-disintegrating tablet (Caleva, 2015). The latter will provide more time to allow for a complete drug release before the dosage form escape the site/s of drug absorption.

The physiological advantages of MUPS tablet/capsule will make the option for the modified drug release to be more favourable, when compared to the conventional tablet, for instance (Caleva, 2015). More discussion regarding the MUPS tablets and MUPS capsules is in the following section.

1.2.3. Tablet of the multiple-units of pellets system (MUPS tablet)

The capsule filling of pellets is more common than the compaction of pellets, owing to the complexity added by the compaction/compression of pellets, making the formulation of MUPS tablet a challenging option.

Nevertheless, the MUPS tablets have many superior advantages over MUPS capsules (Abdul, et al., 2010).

During the MUPS tablet manufacturing, faster and lower cost of production costs are obtained, owing to three reasons, the capsule-filling is slower, the capsules' shells themselves add more cost, and the control of capsule integrity after filling is considered expensive as well. In addition, tabletting does not require a complicated process control when compared with the capsule-filling for pellets. Hence, the MUPS tablets will have simpler, cheaper, and more efficient method of preparation. However, the drug formulation optimisation of MUPS tablet is considered more challenging due to the particular impact of compression force in the quality of the coated pellets. The MUPS tablet can have a higher dose loaded in the tablet, but that depend on the amount of the other excipients added to cushion the coated pellets. The MUPS tablet tolerates scoring without losing the modified release properties, resulting in flexibility for identifying the modified release tablets. The MUPS tablet provides the chance for understanding the complication of the compaction process of pellets.

In addition, MUPS tablets will have a decreased tampering/counterfeit risk, owing to the difficulty of mimicking the internal components (the coated pellets) of the tablet; this requires equipment to make the pellets, coating of pellets, and compression of pellets, which are challenges for the counterfeit production (Wagner, 2015). Upon the MUPS capsule patent expiry, a change to MUPS tablet will bring new patency to the coated pellets. The design complexity and flexibility to change can also result in an extension of the patent lifecycle that maintains the competitive advantage of the product. However, a change from MUPS capsule to MUPS tablet need to be risk mitigated by ensuring that the bioequivalence study was sufficiently comparable (Wagner, 2015). After the patent expiry of the MUPS tablet, the tablet will be harder to match by a generic competitor when compared to a MUPS capsule. An example of that is the Beloc ZOC (innovator), after a time of its patent

expiry, it finally had one generic competitor LEK, from Novartis in 2005/6 (Wagner, 2015). The MUPS tablets ensures a lower risk of copying the technology process by a competing manufacturer. Hence, this is owing to the innovative complexity of MUPS tablet when compared to the MUPS capsules and conventional tablets.

For the patient use, the MUPS tablet is also more favourable than the MUPS capsule. It has better patient compliance owing to the better swallowing, due to two reasons as follows (FDA-CDER, 2015). Upon swallowing, the tablet has less tendency to adhere to the oesophagus wall when compared to the hard-gelatine capsule of the same dose. Also, compacted tablet will be smaller than the capsule-size of the same dose. The latter reason is particularly important when a high dose is required for low potency drugs. The size of the dosage form is also dependent on the amount of the binder and the cushioning excipients. The MUPS divisibility is another advantage, because the capsule cannot be divided into two halves, while the tablet can be divided. For the modified drug release system, dividing MUPS tablet is safer than dividing conventional tablet. The latter is regardless of the conventional tablet being of a matrix or a reservoir type. Because, the coated pellets are numerous individual units, and a coating damage in some pellets will not impact the other coated pellets performance (FDA-CDER, 2015).

Therefore, the compression of pellets into tablets is considered more technologically modern and more ideal than the hard-gelatine capsule filling process. Though that should be considered based on the desires of maintaining patency of the drug formulation and the dosage form. Moreover, unlike the tabletting of powder, the process to make the MUPS tablet reduces the dust formation. However, this is also dependent on the binder form and cushioning form used. In conclusion, when compared to the tablets and capsules, the pellets and especially the tableted pellets can be claimed to have ideal characteristics to be selected as a superior dosage form in the pharmaceutical oral solids. The pellets can be prepared by various methods and can be

functionalised with one or more coating layers, or less commonly functionalised without coating.

The coated pellets either finalised by filling into a hard gelatine capsule or compressed into a tablet, the compressed pellets are usually called MUPS tablet, ensemble pellets, or tableted pellets. The resulted capsule or tablet is ready for the patient administration for a specific therapeutic indication. See the final dosage form illustration of pellets in Figure 1.1, where the naming of the floating property is indicated. For details about the pellets made by extrusion and spheronisation method and other preparation processes, see sections 1.8.2 and 1.8.3. The following section will address the modified drug release systems, where the sustained drug release systems are of major concern in this project.

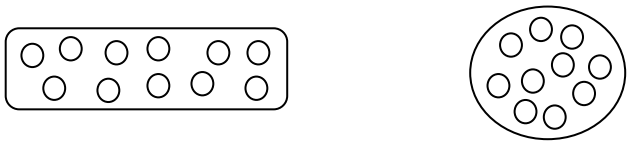


Figure 1.1: A simple schematic diagram that illustrates the final product appearance in either a capsule filled by medicated pellets (left), or a tablet contains the compressed medicated pellets and cushioning pellets (right), the diagrams drawn by the author.

1.2.4. Modified release (MR) drug delivery systems

Oral solids can be classified based on the drug release mechanism/s in the drug formulation design. Broadly, these are 1) immediate release drug formulations, where most of the drug is expected to be released into a liquid medium within one to two hours. 2) Modified release drug formulations, where the drug release profile is extended, delayed, or pulsatile. This approach have an initial high cost, owing to its technological complexity that requires an additional product and process optimisation and scale-up loads (Allen, et al., 2005), i.e. it is costly for a short term. However, this approach is considered superior to the immediate release system, owing to the reduced dosage regimen, increased safety, increased efficacy, and long-term cost-effectiveness (Allen, et al., 2005), as explained below.

By controlling the drug release profile from the dosage form, you can better ensure the plasma concentration to be in a steady state within the safe therapeutic window. This control can reduce and maintain the peak plasma concentration (C_{max}) and the time at which the peak plasma concentration is reached (T_{max}). Hence this control will reduce the curve fluctuations, where the over-dose or the under-dose incidents can be minimised, especially for the narrow therapeutic window drugs, such as theophylline. Also, modified release systems can reduce the cost for the long-term manufacturing and for the end user, the patients.

The reduction in the long-term cost was due to many aspects, profits obtained by the patentability. And by being more competitively advantageous in offering a dosage regimen that is more convenient, effective, safer, and cheaper for the patient to take for a long period of time. The latter advantage is owing to the less dose waste as the patient does not require frequent multiple drug loadings into the blood circulation, to re-gain effective drug concentration. The latter aspect is beneficial to patients as the total dose per day will be reduced (patients are less apt to neglect the regimen, increasing patient compliance), become less frequently taken, and less fluctuated in the plasma.

That is expected to result in minimising the over-dose and the under-dose events, and subsequently fewer hospitalisation events. That means fewer emergency loads, fewer nursing loads in administering drugs and for monitoring patients, and fewer dispensing loads regarding prescriptions. These long term benefits are expected to overweigh the initial higher cost of manufacturing the modified release system for the manufacturer and the patients alike.

The modified drug release systems can be broadly categorised into two systems, based on the formulation design that affect the drug release profiles. The first is the matrix system, which is also called the monolithic system, where the sustained release agent is mixed thoroughly with the active and the other inactive components of the drug formulation. The matrix systems are further sub-categorised into 1) soluble polymer

matrix systems, which are swellable systems that can be erodible as well, and 2) insoluble polymer matrix systems, which are intact systems based on pores formation and matrix tortuosity (McConnell & Basit, 2013). These systems are known to show inadequate or lack of in-vitro in-vivo correlation (IVIVC) when compared to membrane systems (Das & Das, 2003).

The second broad category is the membrane systems, also called the reservoir systems, where the sustained release agent is a semi-permeable membrane film, which allows the active component to move from the inner core or the sub-coat layer to the surrounding liquid, in a controlled fashion. The membrane used can be porous or non-porous. This approach can be modified to obtain the osmotic release systems (McConnell & Basit, 2013). The diffusion-controlled system is of particular interest in this project.

Similar to the matrix system, the membrane system can have drug release in a dissolution-controlled mechanism, or a diffusion-controlled mechanism. The dissolution is commonly controlled by diffusion. The diffusion is limited by the concentration gradient, membrane thickness, the drug solubility in the membrane, and the coefficient of permeability in the membrane (Porter, 2013). If the matrix system was used, the drug on the surface of the core will release at zero-order rate. Once the drug there is released, the drug in the centre of the core will start to migrate and at longer distances that takes more time to release the drug from the core. The latter drug release will not be in a zero-order rate. On the other hand, if the membrane system was used, the drug release will be at a constant gradient, where a zero-order rate can be obtained (Sinko, 2017). More mechanisms of the drug release can be applied including the dialysis-controlled, mechanical-controlled, and bio-responsive mechanisms (Sinko, 2017).

Modified drug release oral solid systems can be named based on their location of the drug release in the GIT (McConnell & Basit, 2013). Hence, they can be gastro-retentive, enteric, or colonic systems.

The gastro-retentive drug delivery systems (GRDDS) target the stomach for drug release, floating systems are one example of such a system, as seen in Figure 1.2. In this system, the drug formulation is actively retained in the stomach by its design performance. The GRDDS is a class of a sustained drug release systems (SDRS). The SDRS may also called extended drug release systems (EDRS) or prolonged drug release systems (PDRS). The SDRS is a broad category that mainly concerned with sustaining the drug release over time, with or without targeting a location of the drug release. Notably, the sustained drug release pellets are being discussed as an ideal dosage form of oral solids, owing to its large surface area, where the complete dissolution and absorption of the loaded drug can be more consistently achievable (Tan & Hu, 2015) and (McConnell & Basit, 2013).

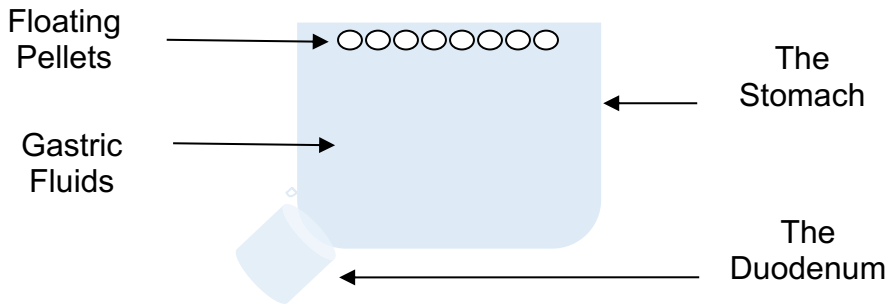


Figure 1.2: For illustration, this image shows pellets floating in the stomach.

1.2.5. Gastro retentive drug delivery systems (GRDDS)

The GRDDS are modified release systems that intended to remain in the stomach for a prolonged time. The floating drug delivery systems (FDDS) are a type of GRDDS, and they are well established in research, patent research and in the market for decades, see the marketed products in section 1.9. The distinctive feature of GRDDS lay in their design flexibility, where the candidate drugs and drug classes can be efficiently delivered, to provide an optimum bioavailability. After a specific time elapse, the GRDDS formulations are expected to get easily metabolised in the body. Hence, after the drug release, prolonged retention of the dosage form in stomach should be avoided during development. The gastric retention of a dosage form is for drugs, such

as theophylline that has an erratic absorption, and absorbed mainly at the upper part of the small intestine, the duodenum, with good absorption in the colon. Gastro-retention is also desired when the drug, such as alginates for heartburn are therapeutically acting on the stomach. It is also desired for diazepam, which is insoluble at high pH, and when the drug, such as captopril and ranitidine are degraded at high pH (Singh and Kim, 2000).

The erratic absorption of certain drugs can lead to variable absorption in the GI tract that results in variable plasma drug levels. However, the risk of not obtaining the required dose in the blood circulation becomes more pronounced when the drug molecules also having a narrow therapeutic window, like theophylline (Kang and Lee, 2009). This limited surface for absorption urges the consideration for more targetable delivery of such drugs.

In Figure 1.3, a variety of approaches can be taken for GRDDS (Singh & Kim, 2000) and (Lopes, et al., 2016), and are summarised as follows. Low-density or floating system (FDDS), it is the drug formulation design intended to be floated on the liquid surface of the stomach. A detailed literature review will be presented shortly for the types of floating systems and specifically, the floating pellets systems (mupFDDS), in the upcoming section. High-density system, it is the drug formulation design intended to sink into the stomach's groove, namely, to sink into the pyloric antrum groove, which located just before the pyloric sphincter. Bio-adhesive or muco-adhesive system, it is the drug formulation design intended to stick to the stomach's epithelium for a sufficient time. This system type can be co-designed with an effervescent floating system.

Swellable plug, super-porous hydrogel or largely swelling system, it is the drug formulation design intended to swell sufficiently enough, to be plugged away by the stomach's pylorus, and then eroded after sufficient time elapsed. It has an average pore size of more than 100 μm, to allow reaching the swelling equilibrium in one minute (Pawar, et al., 2011). This type of systems can also be a type of floating system. Hence, the

name; non-effervescent floating system is implying that as well. Modified shape or expandable system, it is the drug formulation design intended to unfold into a specified geometry of different shapes and sizes, where the peripheral parts of the system are erodible after sufficient time elapsed, that eases the elimination of the system. Magnetic system, it is the drug formulation design intended to be magnetically attracted to an object located outside of the body, near the stomach. Indigestible feed system, it is the drug formulation design intended to be co-administered with indigestible polymers and/or fatty salts to mimic the fed condition, which subsequently delays the gastric emptying time (Singh & Kim, 2000) and (Lopes, et al., 2016).

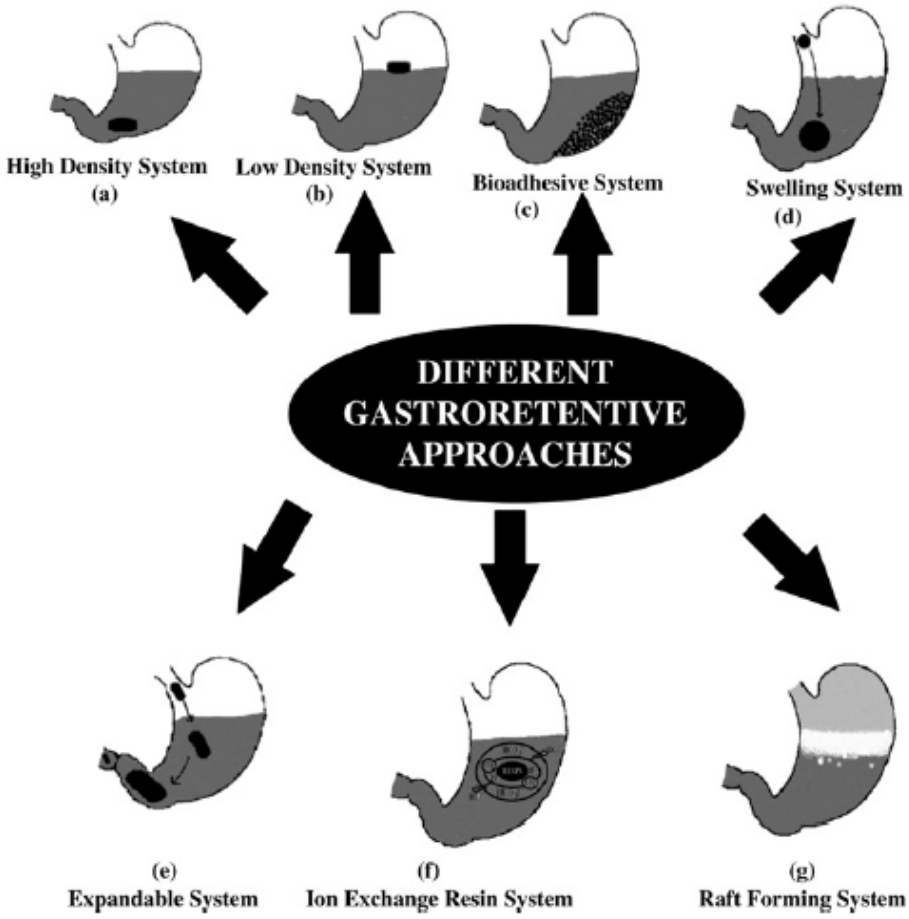


Figure 1.3: Illustrates most of the gastro-retentive systems. Apart from the high-density systems, the systems shown here are designed or can be designed to float. The graph is taken from (Prajapati, et al., 2013).

Interestingly, the specific FDDS reviews (at least 23) outnumber the GRDDS reviews (at least 15). The following reviews were consistently stating the pharmaceutical and the physiological aspects regarding the GRDDS designs (Chawla, et al., 2003), (Streubel, et al., 2006), (Garg & Gupta, 2008), (Bhardwaj, et al., 2011), (Mathur, et al., 2011), (Pandey, et al., 2012), (Siraj, et al., 2013), (Pant, et al., 2016) and (Tripathi, et al., 2019). Also, a recent and more focused review on the GRDDS in-vivo success brought by (Mandal, et al., 2016). Another GRDDS review was more focused on the applications against the *Helicobacter pylori*-induced ulcer by (Bardonnet, et al., 2006). Unique reviews for the expandable GRDDS was provided by (Klausner, et al., 2003) and for the super porous hydrogel GRDDS was provided by (Mayur, et al., 2012). A GRDDS review that was more focused on the FDDS, and where marketed GRDDS presented can be seen by (Pawar, et al., 2011). More presentation for the marketed products can be seen by (Chhetri & Thapa, 2014), (Lopes, et al., 2016). The latter is particularly recommended for a concise, comprehensive and recent update.

The following reviews were consistently stating the pharmaceutical and the physiological aspects regarding the FDDS designs (Singh & Kim, 2000), (Shaha, et al., 2009), (Hardenia, et al., 2011), (Chandel, et al., 2012), (Mukesh, et al., 2012), (Bhardwaj & Harikumar, 2013), (Meenakshi, et al., 2014), (Pooja, et al., 2015), and (Ishak, 2015). Other reviews that additionally presented the marketed FDDS products can be seen by (Arora, et al., 2005), (Patil, et al., 2006), (Narang, 2011), (Kaur, et al., 2013), (Patil & Saptarshi, 2013), (Kandwal, et al., 2014), (Sarawade, et al., 2014), (Gupta & Kothiyal, 2015) and (Rewar & Shakya, 2015). The (Goyal & Sharma, 2014) was focused more on the effervescent FDDS designs. (Avinash, et al., 2012) focused on the FDDS designs for drugs used in the cardiovascular diseases. (Solanki, et al., 2017) focused on the FDDS for Histamine 2 receptor antagonists, to relieve heartburn. (Prajapati, et al., 2013) focused on the raft forming FDDS designs, while (Foster, et al., 2013) focused on the pharmacokinetics aspects of the raft forming FDDS designs.

1.3. Floating Drug Delivery Systems (FDDS)

1.3.1. Floating drug delivery systems (FDDS)

The low density or floating drug delivery system (FDDS) is also known as the hydro-dynamically balanced system (HBS). Davis initially discussed such systems in 1968. Since then, the literature has heavily focussed on the single-unit floating systems, while the multiple-units floating systems like pellets have been discussed to a lesser extent.

Regardless whether single or multiple units, or whether matrix or membrane/coated systems being used, floating has been achieved via effervescent floating or non-effervescent floating systems. However, sometimes, mixed systems have been used and shown to be more reliable, as they provide synergistic floating mechanisms (Singh & Kim, 2000). For example, a muco-adhesion mechanism and/or swelling mechanism can be added to substitute the effervescent mechanism, to allow for more advanced gastro-retention functionality in the FDDS (Singh & Kim, 2000), see Figure 1.4. Unlike other GRDDS, floating systems do not affect gastrointestinal tract (GIT) motility/transit, resulting in no alteration of the gastric emptying rate. Also, as stated earlier, unlike other GRDDS, they have a well-established presence in the market, like Madopar® HPS, a single-unit capsule system that swells to float. Therefore, they were said to be one the most preferred approaches of GRDDS (Nadigoti, et al., 2011).

Tens of articles were seen during the last decade studying the single-unit floating systems (su-FDDS), primarily tablets. A relatively recent example can be seen by (Abdel Rahim, et al., 2015). Other examples are (Strübing, et al., 2008), (Sungthongjeen, et al., 2008) and (Guguloth, et al., 2011).

In addition to the advantages stated in MUPS section 1.2.2, the multiple-units FDDS (mu-FDDS) will have additional superiority to the single-units FDDS (su-FDDS) (Hendeles & Weinberger, 1983), (Shargel, et al., 2012), (Sungthongjeen, et al., 2006), (Rowe, et al., 2009) and (Reddy,

et al., 2011). Floating MUPS (also abbreviated as mupFDDS) tablets/capsules have a higher flexibility in regulation, as they are more likely to have consistent in-vitro in-vivo correlation (IVIVC). This is particularly evident when considering the overall advantages of the consistency of the sustained drug release and floating. The latter are owing to the small size and spherical shape properties of pellets (Singh & Kim, 2000).

Non-effervescent floating approach are better than the effervescent one. The latter approach may have premature CO_2 generation during processing and storage. This risk can increase if a citric acid co-exists in the formulation for the intention to provide a micro-acidic environment upon hydration. Premature CO_2 generation can impair the floating capacity of the design. Also, the effervescent system is a pH-dependent system, where a low pH medium is required to generate the gas to be entrapped for lowering the pellets density to float. The fasted stomach is a necessity if a micro-acidic agent is not used. These reasons may affect the IVIVC within the different systems of the floating pellets (mu-FDDS).

The following sections will discuss the fabrication and the development challenges of different FDDS approaches, followed by appropriate literature comparisons. An overview for the floating systems can be seen in Figure 1.4.

1.3.2. Effervescent floating drug delivery systems (effervescent-FDDS)

The effervescent FDDS is less preferred over the non-effervescent FDDS, due to that the former is a pH dependent system. Nevertheless, the effervescent FDDS is still being the most common approach seen in the literature and the market. The effervescent FDDS is primarily a gas generating system, which utilises a foaming agent or more commonly a gas-generating agent, such as the widely used sodium bicarbonate that produces CO_2. The latter causing air bubbles that can be embedded to

reduce the density of the dosage form, causing it to float. Its frequent use in formulation design is perhaps due to the prevailing view that the floating may not be readily achievable otherwise (Singh & Kim, 2000). The latter argument will be investigated in this project, to clarify this rationale for such carbonate salt.

Moreover, the CO_2 can do more than just floating to achieve optimum mechanism of gastro-retention. It creates an initial alkaline microenvironment that accelerates hydration. The latter aids the initiation of a bio-adhesive hydrogel structure (polymer gelation) that will be based on the adjacent constituents as well (Singh & Kim, 2000). The effervescent FDDS are listed below (Singh & Kim, 2000) (Gupta & Kothiyal, 2015) and (Ishak, 2015):

Foaming systems, where the formulation has an *effervescent agent*, like sodium bicarbonate, with or without an *acidifying agent*, like citric acid or tartaric acid. And with a *hydrocolloid gelling agent*, like the specific cellulosic polymers such as hydroxyl-propyl methylcellulose (HPMC), the polysaccharides such as chitosan, and the sodium alginate. The foaming system is also called swollen pills system, referring to floating tablets, here, the swollen word can be related to the swelling induced by gas-generation, and the swelling induced by the coating film and the cores materials.

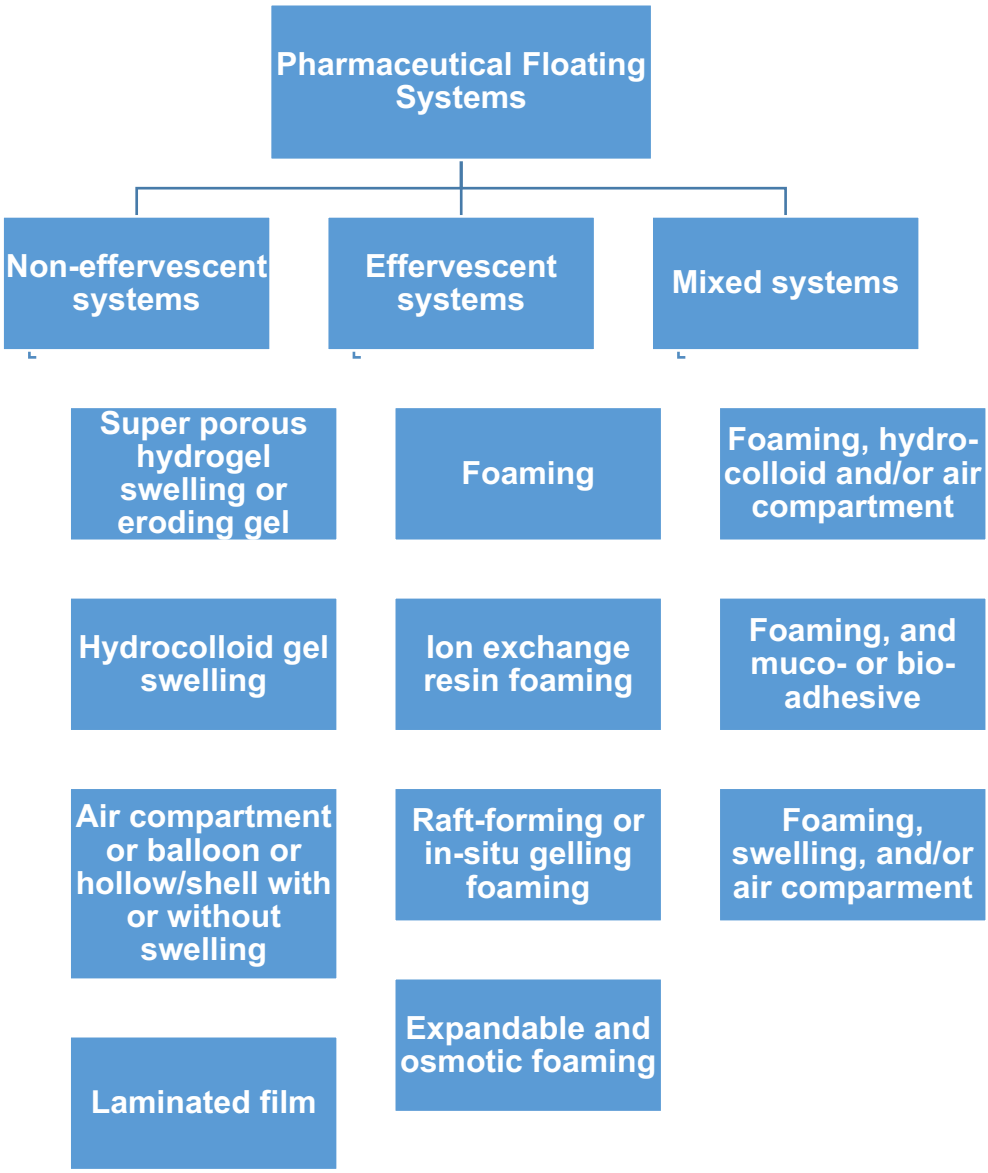


Figure 1.4: Technological approaches used in literature for single and multiple units floating systems, Mixed-systems being increasingly studied in literature. More details are seen in sections 1.3.2-3.

The dosage form is fabricated in a way that allows for controlled CO_2 generation and liberation. The typical final forms of FDDS are tablets, tableted pellets, or pellets in capsules. In this section, the details of specific layered pellets of interest, and the fabrications of materials involved will be addressed. Also, more information on the designs of interest in this project, see section 1.3.4. And more details on the floating mechanisms of floating pellets can be seen in section 1.4. It is good to mention here that if intended to be so, the following sub-systems can

also have the potential to float without a gas-generating agent, i.e. to be as fully non-effervescent FDDS systems.

Ion Exchange Resin Foaming System, where the *resin beads/pellets* formulation was loaded with an *effervescent agent* and attached to a drug of a negative charge, then encapsulated by semi-permeable or retard membrane that controls CO_2 liberation. Upon exposure to gastric content, bicarbonate ions get exchanged with the chloride ions of gastric fluids, results in partial liberation of CO_2, as the membrane trap the released CO_2. This controlled CO_2 release allows for the formation of the floating resin *beads* as a layer/seal (Atyabi, et al., 1996). The system is not widely used, time-consuming, and very expensive to formulate, as stated by (Prajapati, et al., 2013).

Raft-Forming or In-Situ Gelling Foaming System, where a *thick liquid* formulation that upon contact with gastric fluid will gel instantly, and that form a raft on the liquid surface as a barrier foam, that was along the use of bicarbonate salt to ease raft floating, a famous example of this type is the suspension of Gaviscon.

Expandable and Osmotic Foaming System, where a *folded device in a capsule* formulation that consists of a hollow deformable unit can convert from collapsed to an expanded position. Then after sufficient time, it returns to the collapsed position again. One chamber contains a drug, while the other contains a cyclo-pentane or ether, these are gassing/vaporising agents that are sensitive to the body temperature. The second chamber has a bio-erodible plug to allow the vapour to escape after time. The system is apparently complex and has safety issues, and these gases are of particular concern to smokers.

1.3.3. Non-effervescent floating drug delivery systems (non-effervescent FDDS)

Many of the non-effervescent floating systems involve swelling, which can differ in magnitude based on the type of design used, as it will be

explained shortly. Similar to the effervescent FDDS, these formulation designs here varied in their technological concepts.

These systems are summarised in the following papers (Ichikawa, et al., 1991), (Iannuccelli, et al., 1998), (Singh & Kim, 2000), (Waterman, 2007), (Hung, et al., 2014), and (Awasthi & Kulkarni, 2014):

Super Porous Hydrogel Swelling, Super Swollen Pill, Eroding Gel, or Plug System, which is obtained using *super-gelling/swelling agent*, such as purified shellac, with a channelling agent, and with or without the use of an effervescent agent. The pill size enlarges quickly to be plugged away by the pylorus sphincter and then to become floated as well. It is more applicable to large unit systems, like tablets or capsules, while pellets are not applicable as they will rupture upon vast expansion, and will not reach the desired size to be plugged away the pyloric sphincter. Plug systems can be designed as non-floated GRDDS as well.

Hydrocolloid Gel Swelling or Swollen Pill System, which is obtained using a *gel-forming hydrocolloid*, like HPMC, which creates a receding boundary upon hydration, induces surface gelation, followed by a gelatinous barrier that controls the diffusion process. A popular system was the floating capsule as su-FDDS obtained by Roche, in the brand name of Medopar HBS^{TM}. Hence, the name hydro-dynamically balanced system (HBS) was first used in the market (Singh & Kim, 2000).

Air Compartment, Balloon or Hollow/Shell System, with or without Swelling, which can be obtained using calcium alginate and poly-vinyl acetate (PVA). The PVA is acting like a channelling agent that increases membrane permeability and prevent the compartment collapse. It can be obtained using poly-styrene, ethanol and/or dichloromethane, to make the hollow globular shell in the core of the dosage form system. This system was reported to be prepared by ionotropic gelation, solvent evaporation or by the emulsion solvent diffusion methods. The term micro-balloons can be referred to the swollen micro-pellets/spheres intended for floating. As with hydrocolloid gel systems, these systems

can also be generally referred to as swollen pills systems. The term balloon sometimes can be referred to the swollen systems that have the potential to float. Moreover, balloons also may mean the largely swelling systems that cannot float or can float, like the plug and the floating plug systems, respectively. These terms, like the term air compartment, can also be referred for preformed low-density systems, i.e. during the manufacturing process, a gassing agent reacting to an acid, and the gas generated will provide air in the cores, resulting in low-density dosage form prior administration, like the pellets made by (Iannuccelli, et al., 1998). Those pellets floated immediately for more than 24 hours in the artificial gastric fluids, regardless of the pH. Laminated Film System, which is obtained through film overlaying, the resulting films provide small air pockets entrapment, which causes the films to float (Singh & Kim, 2000). More examples for non-effervescent floating systems are listed in Table 1.1.

Table 1.1: Examples of the non-effervescent floating systems.

Reference	**Design of formulation**	**Composition of formulation**	**Comments**
(Streubel, et al., 2003)	Micro porous foam pellets-Solvent soaking	Poly-propylene (PP)	Solvent soaking offers short processing times, no exposure of the ingredients to high temperatures, and high encapsulation efficiency
(Ichikawa, et al., 1991)	Pellets	Polyvinyl acetate (PVA) and purified shellac	Immersed pellets have a density much lower than 1.0 g/m
(Talukder & Fassihi, 2004).	Pellets	Calcium and low methoxylated pectin (LMP), which is an anionic polysaccharide and sodium alginate	The calcium-pectinate-alginate beads have faster drug release rates than the calcium-pectinate beads. As 100% and 50% drug released in 10 hours, respectively
(Awasthi & Kulkarni, 2014) and (Singh & Kim, 2000)	Pellets_ Ionotropic gelation	Low methoxyl pectin and HPMC	It could by-pass the housekeeping wave for pellets (esp. during fasted state). Pectin beads were shown to have higher incorporation efficiency than alginate-HPMC beads
(Iannuccelli, et al., 1998).	Pellets	calcium alginate/polyvinyl alcohol (PVA)	-

(Singh & Kim, 2000)	Agar molds	Agar 2% or more, with mineral oil	The oil prevent entrapped air from escaping, which avoided the bias of compaction

1.3.4. Effervescent and non-effervescent multiple units of pellets floating drug delivery systems (mupFDDS)

The effervescent and non-effervescent floating drug delivery systems of multiple units of pellets (mupFDDS) designs can vary significantly based on the methods of preparation, the number of coating layers, the intended floating mechanism/s, and the drug release profile. The design of floating pellets made using the extrusion and spheronisation method is of particular importance in this project. Previous work done in the literature regarding floating pellets designs that no coating or up to quadruple-coated pellets. This summarised below, and more information given in Tables 1.2 and 1.3 (Sinko, 2017).

Core Matrix Design, which may consist of drug-loaded pellets, with or without bicarbonate. The design is usually considered challenging, owing to many reasons, namely, the difficulty of processing the fully functional core pellets, and the difficulty of obtaining quality attributes within specifications. Single Layer Design, which may consist of cores loaded with drug and bicarbonate, with a single multi-functional polymeric layer, the layer is of gas-retard and drug-retard functions. Although this design is simpler than the designs below, it is more challenging to optimise floating and sustained drug release properties. As the following mechanisms become more difficult to optimise; the gas-generation from the cores, the gas-entrapment and gas-release by the single layer, and the drug-release by the single layer. Double Layer Design, which may consist of drug-loaded cores, with an inner sub-coat layer, of gas-generating function, followed by an outer polymeric layer, of gas-retard and drug-retard functions. Triple Layer Design, which may consist of drug-loaded cores, with an inner sub-coat layer, of a drug-retard function, followed by a second inner sub-coat layer, of gas-generating function, and finally, an outer polymeric layer, of a gas-retard function. Quadruple Layer Design, which may consist of sugar-loaded

cores for swelling and void formation, with an inner sub-coat layer of swelling-retard function, followed by a second inner sub-coat layer of drug and hydrocolloid function, followed by a third inner sub-coat layer of hydrocolloid function, and finally, an outer polymeric layer of drug-retard function. Although multi-layered designs may have more distinctive and predicted functionality, they are less cost-effective and more-time consuming when compared to the less layered designs. Therefore, the less-layered design can reduce the excipients where the remained layers have to do more functions. In this project, the latter is desired though it requires more optimisation work to obtain multi-functionality by the reduced-layer design. Upon layer reduction from triple to double layered design, the optimisation of the retard coating layer becomes more demanding. Because the former design has two retarding layers, one for retarding drug release and other for retarding gas release. While the later design has only one retard layer that retard both drug and gas release. The floating requires more water-soluble retard polymer, where the sustained drug release requires less water-soluble polymer. The optimisation work also depends on other various factors, such as the drug solubility, the compositions of the coating dispersion, and the coating process variables. Upon layer reduction from double to single layered design, the optimisation of the retard coating layer remained as demanding. However, the optimisation of the core pellets become more demanding. The latter because the additional addition of $NaHCO_3$ or other agent that reduce density in the core pellets. Hence, the powder sensitivity to the granulating liquid volume is expected to be increased during the wet massing process. Upon layer reduction from single layered to matrix design, the optimisation of all materials will be more demanding. Moreover, the drug release of the matrix system is often more variable than the coated/membrane system, as explained in earlier. An illustration in Figure 1.5 shows the layout of the single-coated floating pellets. The following section will further elaborate on the concepts of floating, with more reflection on the expected floating mechanisms of this project.

Table 1.2: The effervescent and non-effervescent mupFDDS designs made by the extrusion/spheronisation method. This table has an exclusive list so far, according to the best knowledge of the author.

Reference*	Drug and Water Solubility	Design and Method**	Compositions	Floating and SR Profiles	Relevance to this project, and comments
(Chen, et al., 2012)	Losartan potassium, freely soluble	Single layer, ext/sph (Shang Yuh Machine), rotor FB coater (GPCG-1 Glatt)	Cores: 25% Drug, 55% MCC, and 20% $NaHCO_3$. Coating layer: was of different GIT-soluble and GIT-insoluble polymers combinations.	A mixture of 5% Kollicoat SR and 5% PEG 600, where a 20% coating gain provide floating lag time of 15 minutes and maintained buoyancy for over 12 hours. And all of the drug released in 3 hrs, or it was delayed for >2 hrs to start sustaining the drug release for 6 hrs.	All coating efficiencies are over 90%.
(Hung, et al., 2014)	Losartan potassium, freely soluble	Single layer, RB extruder, and spheroniser of Shang Yuh®	Cores: MCC of Avicel® PH102, $NaHCO_3$ and L-HPC and fixed drug level. Coating layer: Eudragit® RL30D, RS30D, or NE30D, with di-ethyl phthalate (DEP) or tri-ethyl citrate (TEC), or Surelease® 25% with HPMC.	RS:RL 1:1 with 15% DEP can show potentially good SR and floating if the drug used was slightly soluble in water. Batches showed either >80% DR in 2 hrs, or SR for 4 hrs followed by an only ~10%DR for the next 20 hrs, or it will be delayed for >4-8 hrs to start the release that is sustained for 40%DR at 24 hrs. All batches showed >80% floating and remained floated for 24 hrs, lag time: ~5-30 min.	The NE30D grade results stated and analysed clearly in the surface tension study in the enhancment chapter, with an improved functionality. In the screening work for the single-coated pellets, use of PVP or cros-PVP instead of L-HPC. This reference was shown that L-HPC has superiority over MCC, regarding water absorption and swelling tendency.
(Qi, et al., 2015)	Famotidine	Single-coated pellets-non effervescent via swelling. Wet massing by 80 mesh sieve, RS extruder of 0.4 mm (JBZ-300), blow dryer, FB coater (Werner Glatt), flat-faced single	Powder mix of drug, MCC of Avicel PH101 and stearyl alcohol as low-density agent (1:1:10). Kneaded with 5% PVP k30 liquid binder.	The tableted floating pellets were floated immediately for more than 12 hours for non-compressed and compressed coated pellets (% of floating not stated) and SR was for up to 8 hours, though DR reach 80% in 4 hours (for both non-compressed and compressed coated pellets and comparable to PK data of	The enhanced formulations in this project are noticeably different in two means: (1) No combination of Eudragit RL30D and RS30D was used, (2) No alcoholic PVP as the liquid binder was used, instead an ethanol liquid binder was used. The PVP is rather in powder and

		punch/press (Shanghai Pharm Machinery Factory)		absorbed drug in animals). The medium used for drug release is not stated.	get wet without soaking or dissolving, which decreases the risk of no re-swellability.
(Sungthongjeen, et al., 2006)	Anhydrous theophylline, slightly soluble	Double layer, TM of Rotomixer Foster®, MWM, RB extruder of Caleva® 25 and RPRCHGS of Caleva® 250	Cores: MCC of Avicel® PH101. Sub-coat: $NaHCO_3$ and HPMC of Methocel® E15LV and PEG6000. Retard coat: Eudragit® RL30D, RS30D or NE30D, with DEP.	Only RL30D grade allowed floating. Higuchi is the best fit: linear with the squared root of time for 12 hrs (with low variation). The floating was less than 0.5 hr for the high concentration of $NaHCO_3$ batches, while, it was >24hrs for the low $NaHCO_3$ batches. (floating profiles of 24 hrs were not shown)	This is seen as the least challenging mupFDDS design in literature, as the number of layers provides distinctive and sufficient functionality, yet it is more time consuming than single-coated designs. In double-coated chapter, the double coated pellets mimic this design, and with the use of novel spheronisation aid; Avicel HFE102.
(Zhang, et al., 2012)	Ofloxacin	Triple layer**,** 80 mesh dry sieve, Extruder and Spheroniser (WL350, Wenzhou®), FB coater (FD-MP-01, Powrex®)	(1) Avicel PH105 and drug-loaded cores, (2) EC (10cp) strength of 3% w/v, with PVP k30 as pore forming and plasticiser, in 4:1 ratio, dissolved in 95% alcohol, (3) sodium bicarbonate with HPMC E5 (ratios of 1:4, 1:2, 1:1, 2:1, and 4:1) with PEG 6000 (in 10% w/w of HPMC solids). The weight gain was 12% w/w, (4) Eudragit RL30D plasticised by DEP (20% of RL30D solids). Weight gain was 15% w/w.	Successfully sustained the drug release. The floating was for at least 6 hours in vivo.	The design here is more complicated and more time-consuming. Therefore, the attempts to make something similar were avoided.
(Katakam, et al., 2013)	Alfuzosine Hydrochloride	Triple layer**,** 40-mesh sifting, RMG of HSMG10 Levin Process®, Extruder 20 and Spheroniser 250 of Caleva®, FB coater of	(1) MCC of Avicel® PH102, ultra micronised cros-PVP of poly-plasdone® XL10 and drug-loaded cores, (2) 8% wt gain of EC (7cp) dispersed in IPA, hydromellose of	Similar to Sungthongjeen, only the RS30D grade was shown successful floating, and with 6 hours floating in-vivo.	Similar to Hung, the Katakam work has no factors layout for the cores to allow further optimisation. Similar to Zhang's design, the

		GPCG Pamm Glatt® 1.1 Wruster.	Methocel® E5-LV Premium, (3) 12% wt gain of $NaHCO_3$ with the use of Methocel® E15-LV (in 2:8, 5:5, and 8:2 ratios) (4) 5, 10 or 15% weight gain of Eudragit® RL30D, RS30D, or NE30D, with DEP or TEC 20%		Katakam's design is complex as well.
(Setthachewakul, et al., 2011)	Tetrahydro-curcumin (THC), highly soluble	Matrix-non effervescent via self-emulsifying. The extruder was developed in-site using 2 mm pore size screen.	THC-SEDDS solution of four polymers, as a liquid binder, after pouring 5ml of water in the dried powder of other five polymers, including MCC.	Floating and drug release properties achieved from the self-emulsified matrix, and no coating applied.	They used ten polymers to achieve that, which is a bit of high cost, and complexity here arise from the potentially unfavourable hidden interactions.
(Biswas, et al., 2012)	Metronidazole	Matrix-non effervescent via swelling. Pellets made by the extrusion method.	Cores that have HPMC (as hydrocolloid agent) in different grades (K4M premium, and L100LV premium) in ratios of 2:1, 1:2, and 1.5:1.5. Where sodium alginate (as mucoadhesive) was used in 3.5g, 5.25g, and 7g, respectively.	One formulation has the best fit in Higuchi drug release model (r=0.994). Floating data not obtained due to lack of full access.	The ratios tested cannot be a full representation of factors' levels, yet full access is needed to confirm whether this was considered.
(Hwang, et al., 2016)	Cilostazol, a hydrophobic drug	Matrix-non-effervescent via air compartment. The pellets were lyophilised as well.	Cores have Cilostazol, glyceryl behenate as a matrix former and floating aid, hydroxyethyl cellulose as an additional floating aid, camphor as a sublimating agent.	The resulted porous structure offers immediate floating. The HEC addition increase the floating duration for an acceptable time. The hydrophobicity of the drug allows for an erosion-mechanism sustained release profile.	The lyophilisation along with excipient use is stated as a way to provide highly porous system for non-effervescent floating. Lyophilisation was not used in this project. No full access obtained; the % and duration of floating is not known. Also, the SR duration is not known.

(He, et al., 2017)	Bolo leaf phenols (BLPs)	Matrix-non effervescent via bio-adhesion and potential air compartment and/or swelling.	Cores have Bolo leaf phenols (BLP) and chitosan as a bio-adhesive. No full access obtained; not known whether the chitosan his responsible for the floating and the SR effects.	Floated immediately for >12 hrs, SR for >6 hrs and followed Higuchi model. ~73% adhesivity to the gastric tissue and >40% retention rate in rats after 6 hrs.	The chitosan bio-adhesion is responsible for gastro-retention. But not known what is causing an immediate floating. Bio-adhesion was not used in this project.
(Li, et al., 2014)	Dypridamole	Quadruple layer-non-effervescent via air compartment, WM by 80-mesh sieve, FB coater	(1) Water soluble excipients like mannitol, and Avicel® PH101in 4:1, (2) EC (10cp) and PVP k30, dissolved in alcohol/water (80:20 v/v), immersed in water for 12 hours to allow water channelling, then dried to allow voids formation, (3) drug, HPMC E5 and PEG 6000 (10% of latter), (4) HPMC and PEG 6000 (10% of latter), (5) Eudragit® NE30D.	Unlike other designs, the NE30D grade was shown successful floating.	The NE30D grade was selected based on this paper success, and PVP 44,000 g/mol selected as well. Although NE30D grade was not successful in other studies, but, owing to its neutral solubility in water, it is expected to allow for fine-tuning the balance between floating and SR profiles. As floating need hydrophilicity while SR needs hydrophobicity in the retarding polymer. Also, the paper gives insights for the fed state testing.
*References were ordered based on the number of layers in the studied design and the date of publication, followed by the type of floating system regarding the effervescent presence.					
** The equipment model configuration or the brand name is specified where possible. Abbreviations: FB: fluid bed, TM: tumbling mixer, MWM: manual wet mixing, RB: radial-basket, RPRCHGS: the rotational plate of regular cros-hatch geometry spheroniser, RMG: rapid mixer granulator.					

Table 1.3: Some of the effervescent and non-effervescent mupFDDS designs made by methods other than the extrusion/spheronisation method. Some more clear description about the methods is described elsewhere for convenience, in section 1.8.

Reference *	Drug and Water Solubility	Design and Method**	Compositions	Floating and SR Profiles	Comments
(Sawicki & Łunio, 2005)	Verapamil hydrochloride	Matrix, wet granulation followed by direct spheronisation: moist mass made rubbed through a metal sieve (Retsch®, Hann) of 1.25 mm mesh diameter. Spheroniser Caleva® 120. Spheroniser shield rotation speed measured by a Caleva tachometer. A blow-dryer was used as well.	Cores were having drug 20.0%, sodium hydrocarbonate 20.0%, Avicel® PH101 10.0%, Arbocel® P290 33.4%, lactose 12.3%, Povidone K-30 4.3%. Kollicoat® SR 30 D. Plasticisers were 10% propylene glycol, 10% triethyl citrate or 10% dibuthyl sebecate. The films' thickness for SR was 70 mm.	The most appropriate tablet mass for floating pellets was Avicel PH102, mannitol and Kollidon CL (as swelling agent). SR of tableted pellets was identical to non-compressed pellets, where nearly 70% of the drug was released in 6 hours.	It is an example of tableted coated pellets. The Kollidon CL is used in this project (In ch. 5) to compare with the enhanced PVP batches.
(Amrutkar, et al., 2012)	zolpidem tartrate	Triple layer, liquid layering method, a drug containing solution with various excipients, to be layered into non-peril sugar pellets/starter pellets, using bottom-spray fluidised bed coater (Pam Glatt®).	Cores were non-peril sugar pellets, drug layered, effervescent sub-coating layer; sodium bicarbonate, followed by a MR layer; Eudragit® NE 30D.	Floated completely within 5 min and for over 10 hours. Drug release was either zero-order or Higuchi's, and for up to 10 hours, but with initial burst, and with some fluctuations.	It describes that the gas generation inducing balloon or swollen pellets, owing to the gas generation rather than the effect of other swelling polymers. SEM shows that the smoothest surface was obtained by the 2nd layer. The Eudragit NE30D here is showing effects, which is showing some similarity to the effects in ch.3 of double-coated systems.
(Malode, et al., 2015)	Metoprolol succinate	Matrix, hot-melt extrusion: powders sifted by sieve 40, wet massing by manual mixing in a poly-ethylene bag, then extruded by HME (Thermo® Pharma 11 twin-screw	A molten mix of the drug, sodium bicarbonate, glycerol monostearate as the thermal lubricant, polyethylene oxide	Floating and SR achieved for up to 12 hours.	This method is the most current in research for developing novel mupFDDS designs with claims to be a superior method over other methods, in particular, it was claimed to be a superior over extrusion/spheronisation

		extruder), extrudates segmented in 5 mm length using a cutting blade.	(PEO) or Eudragit® RS PO with HPMC.		method, as HME have easier processing features and less time-consuming.
(Kumaran, et al., 2010)	Mosapride	Matrix, Ionotropic gelation, non-effervescent: mechanical stirrer, de-gassed by vacuum, then dropped by 26G-syringe needle, filtered, washed, freeze-dried.	(1) Drug, sodium alginate and HPMC (9:1 ratio), and $KHCO_3$ mix dropped to: (2) 1% w/v CaCl and 10%w/v glacial acetic acid, then beads will form in a solution.	All formulations were floated completely in both simulated gastric fluid, and in pH1.2 media, for 24 hours	After pellets formation, stirring will be continued, to improve pellets' mechanical strength, and to allow sufficient time for completing CO_2 generation inside the beads. HPLC testing of drug release, and swelling from such systems is explained.
(Vidyadhara, et al., 2015)	Stavudine	Matrix micro-pellets/ micro-balloons, emulsion solvent diffusion and evaporation, non-effervescent: sonicator, mechanical stirrer, filtration, and desiccator for drying at room temperature for 24 hours.	Micro-pellets made by HMPC E5, drug, and IPA as liquid binder. Micro-encapsulated by the emulsion evaporation, the emulsion is EC 7cps, Eudragit® S 100, and 1% PEG400.	SR profile was shown the first-order release over 12 hours, with as low floating lag time as 1 minute.	Among process factors, the stirring speed was found to be critical.
*References were ordered based on the number of layers in the studied design and the date of publication, followed by the type of floating system regarding the effervescent presence.					
**Other recent studies used for these methods were as follows: the ionic gelation method by (Bera, et al., 2015), hot-melt extrusion by (Vo, et al., 2016). Moreover, the liquid layering method where the Celphere®; MCC starter pellets were used by (Pagariya & Patil, 2013). Also, the emulsion solvent diffusion and evaporation by (Kumar, et al., 2017) where a slurry made by solvent addition, pellets formation by SLS addition and stirring, pellets collection by decantation, washing by n-hexane, and oven dried.					

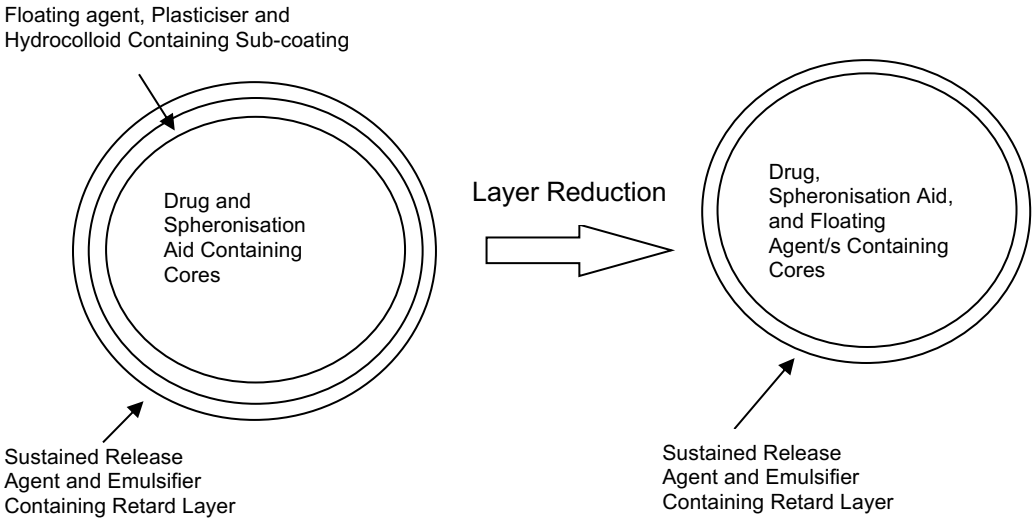


Figure 1.5: Schematic diagrams of mupFDDS used, where components of each stage of formulation preparation are identified.

1.4. Floating Mechanisms of the Floating Pellets

1.4.1. Floating mechanisms

When a floating dosage form is immersed in the dissolution medium, a lag time before the floating takes place is typically seen, this is followed by continual floating on the surface of the liquid, resulting in a *hydrodynamically balanced system* (HBS). In the effervescent floating system of pellets or tablets, gas generation and entrapment is vital (Solanki, et al., 2017).

Also, the floating mechanism of effervescent system can be elaborated as follows (Singh & Kim, 2000), (Sungthongjeen, et al., 2006) and (Solanki, et al., 2017). Specifically, the CO_2 generated leak into the existing pores in either the sub-coat layer or in the core pellets. The CO_2 entrapped by the retard-coat layer. This lowers the density of the overall dosage form system. Effective gas-retard agent, include the commonly used Eudragit RL30D. The latter is usually applied in an outer coating layer of the pellets.

In the non-effervescent floating system of pellets and of some tablets designs, the mechanism of floating can include swelling and/or muco-adhesion. The muco-adhesion mechanisms are based on numerous theories, include wettability, electronic, fracture, adsorption, and diffusion inter-locking theories. The muco-adhesion mechanism and its theories are beyond the scope of this project, nevertheless, the mechanisms involved in each theory are listed by (Lopes, et al., 2016). In this project, the focus was on the swelling mechanism for the non-effervescent floating.

After liquid uptake by the coated pellets in such systems, gradual relaxation of the cros-linked polymers will occur in the core pellets and the coating layer, resulting in a volume increase that supersedes the weight increase. The latter will result in a reduced density of the coated pellets. The time needed to achieve the latter can be called the lag time needed to initiate floating before the controlled swelling takes place. The flexibility of the polymer relaxation is controlled by the plasticiser. Controlled swelling is critical to avoid the excessive swelling, as this may make the system heavier, causing it to sink.

1.4.2. Water uptake and floating strength

In these floating systems, understanding the mechanism of water uptake is clearly important to understand both the floating profile, but also the drug release profile. A correlation study by (Chen, et al., 2012) showed that the water uptake of pellets explains their floating lag time and their drug release rate, while the tensile strength of pellets explains their floating duration. These findings were regardless of the coating level applied for the making of the polymeric film/membrane. The film controls water permeation. To sum up, at different coating levels, the water uptake by the film will affect the floating lag time. Floating strength was studied through a customised equipment, noticeably by (Timmermans & Moes, 1990), (Strübing, et al., 2008), (Hung, et al., 2014) and reviewed by (Solanki, et al., 2017). Their work provides additional, supportive, and unique information to the floating profiles.

The following section will discuss where the gastro-retention is most desired, based on some specifications that relate highly to the drug substance of interest.

1.5. Drug Candidates' Requirements for the GRDDS

1.5.1. General considerations in biopharmaceutics

There are several aspects of the drug substance need to be considered before selecting the suitable candidate to be formulated into a drug product. These considerations comply with the emphasis of the International Conference of Harmonisation (ICH) on with the concepts of the pharmaceutical quality by design (QbD), regarding obtaining pre-knowledge about the drug substance prior formulation. The drug bioavailability can be affected by the drug product and the physiological factors, see Figure 1.6

One of the important aspects is the “biopharmaceutics classification system (BCS)”, which was first introduced by (Amidon, et al., 1995). It classifies drugs according to their dosage strength, solubility, and permeability, see Table 1.4. Class I drug (drug of high solubility and high permeability) is safer and easier to formulate into a modified release (MR) drug delivery system than other BCS classes. However, if the drug is poorly soluble but highly permeable (class 2 drug), as with most drugs, the MR formulation success become more difficult.

Another classification system was introduced by (Wu & Benet, 2005), the “biopharmaceutics drug disposition classification system (BDDCS)”, where they found that the majority of high permeability drugs (class I and II drugs) get eliminated by metabolism. Hence, the rate of permeability can be extracted from the rate of elimination.

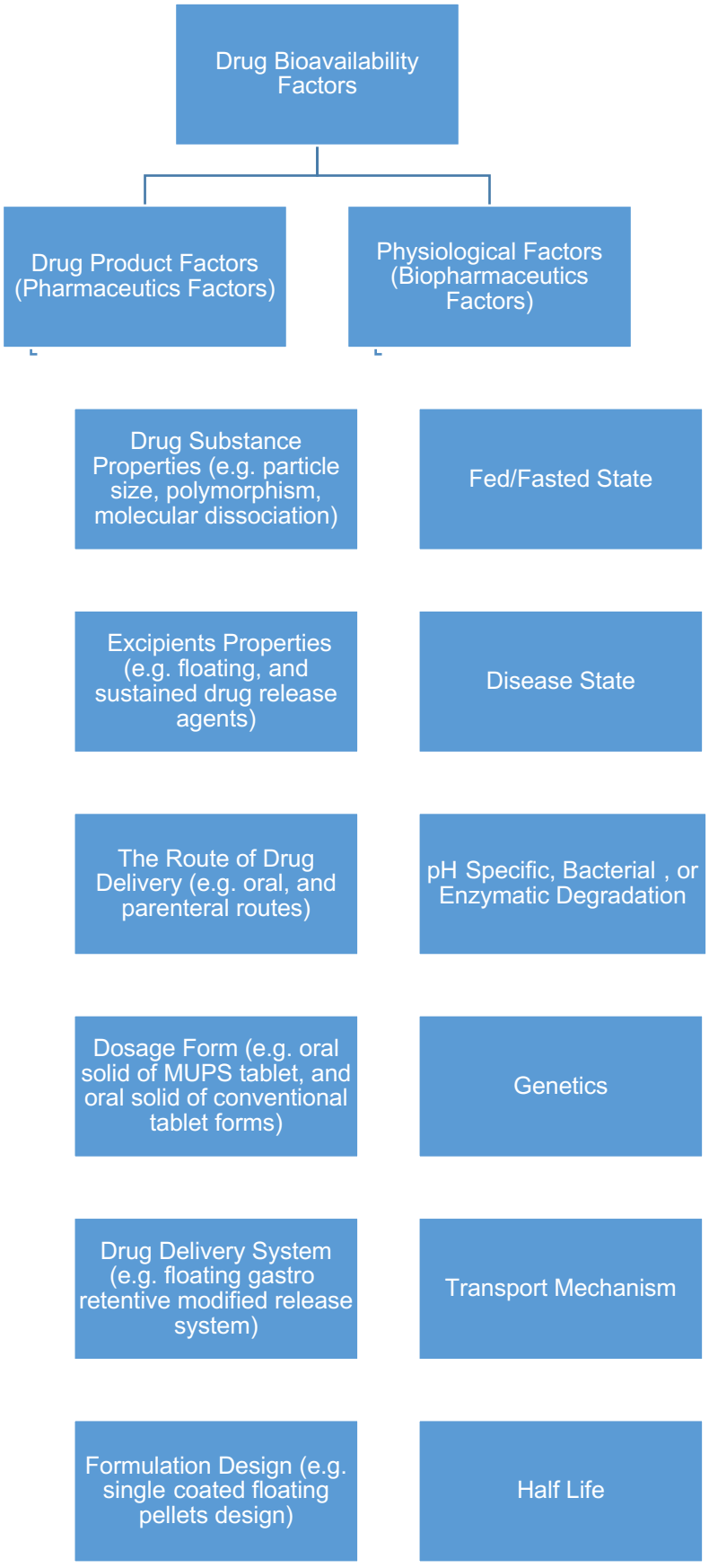


Figure 1.6: The drug product and the physiological factors that affect the drug bioavailability.

Another aspect considering the drug substance is the Lipinski's rule of five, to speculate drug permeability. This rule is used to predict the passive drug absorption from the GIT and to predict the overall drug properties. The state that a drug is more likely to show poor permeability through the bilayer membrane when the drug possess more than one of the following (Loftsson, 2015).

(1) More than 5 Hydrogen-bond donors,
(2) More than 10 Hydrogen-bond acceptors,
(3) More than 500 g/mole molecular weight (M.wt), and
(4) More than 5 $\log P_{octanol/water}$.

Table 1.4: The biopharmaceutics classification system (BCS), where drugs classified based on their solubility and permeability, which related to their water and lipid solubility, respectively (Wu & Benet, 2005).

Solubility vs Permeability	**High Solubility**	**Low Solubility**
High Permeability	Class 1 (Rapid Dissolution, Biowaiver)	Class 2
Low Permeability	Class 3	Class 4

1.5.2. Drug candidate requirements for the gastro-retentive drug delivery systems (GRDDS)

As an addition to the previous section considerations, the formulation of a drug as gastro-retentive system is encouraged when either of the following is evident, the candidate drugs are listed in Table 1.5.

The drug is insoluble at higher pH values, like the pH of the intestine (pH~ 5.7-7.4), which is evident for some acidic and basic drugs, such as diazepam, where GRDDS can minimise the drug precipitation in the intestine. Unstable drugs at high pH, such as captopril and ranitidine degrade at high pH, where the GRDD can minimise the drug degradation in the intestine. Drugs with an absorption window in the stomach or in the upper small intestine, drugs can have erratic absorption, which are good candidates for GRDDS, like theophylline. Drugs acting locally in the stomach diseases: a common product in mind is the floating liquid alginates (Gaviscon®), which relieve heartburn for longer times than non-floating alginates (Singh & Kim, 2000) and

(Hamman, et al., 2007). The following characteristics are the drug candidate requirements for drugs that sustained-release products (SRDDS), including GRDDS.

The rate of the drug absorption and excretion should be neither too high nor too low, which means at least two hours half-life is required. Because, a very high dose will be necessary if the drug has shorter than that half-life. And, also means that not more than six hours half-life is required. Because, an inherent sustained action over a long time can be obtained if the drug has longer than that half-life (Allen, et al., 2005), (McConnell & Basit, 2013) and (Prescott & Nimmo, 1979). In a specific occasion, the SRDDS can be pursued even if the half-life of the drug is high. This is when the purpose of SRDDS is to reduce the adverse effect of the drug. This is possible as the drug fraction absorbed is flattened, where a maintained efficacy within the safe therapeutic window can be obtained. For example, the L-hyoscyamine causes dry mouth and impaired vision as adverse effects, and it has a long half-life. The SRDDS pellets of L-hyoscyamine can be taken once daily, and it maintained the drug in the safe therapeutic window. The latter has reduced these adverse effects (Prescott & Nimmo, 1979).

The GIT absorption should be uniform. The varied absorption of drugs, like theophylline, can be due to their erratic absorption. Therefore, introducing GRDDS formulation will be necessary to resolve this issue. The GRDDS is an excellent approach to tackle the bioavailability problem, owing to the inconsistent drug absorption. As it offers a great control over the dosage form, in terms of both controlling the location and the timing of drug release (McConnell & Basit, 2013).

The drug should be administered in as relatively small dose formulation as possible to ease swallowability. Otherwise, the sustained release formulation will be too large to be easily swallowable, as the sustained release formulation requires typically higher dose than immediate release. Pellets, and specifically ensemble pellets are particularly is advantageous regarding swallowability. The drug should have a safe

therapeutic index (wide therapeutic window), which means that the therapeutic response will be less sensitive to change with a changing drug plasma level. Pellets are particularly advantageous when such a drug need to be formulated as SRDDS, owing to their dose distribution and uniform coating. The drug should be used for a chronic condition rather than an acute condition. The acute conditions will usually require a higher dose and resolved in a short term. Hence, it is not cost effective to formulate SRDDS formulation for a drug that treat only acute condition/s (Prescott & Nimmo, 1979).

Table 1.5: Examples of candidate drugs for GRDDS that have a problematic delivery for different reasons, resulting in their poor bioavailability profiles (Singh & Kim, 2000) and (Lopes, et al., 2016)

Therapeutic Class	**Candidate Drug**	**Therapeutic indication**	**Reasons for GRDDS**	**Resulting issues if taken in a formulation other than GRDDS**	**How can GRDDS/FDDS help**
Tea Alkaloids (xanthine derivatives)	Theophylline	Anti-COPD; a bronchodilator managing the chronic obstructive pulmonary disease	Absorbed preferentially from the stomach and the upper part of the small intestine	Large amount of the dose will skip the *absorption* site, owing to the limited and the variable transit time in the stomach	Increase the overall drug exposure to the site of absorption and the bioavailability
Calcium channel blockers (CCBs)	Verapamil	Anti-hypertensive, anti-angina	More soluble in the fasted stomach pH; acidic pH media	Large amount of the dose will skip the *dissolution* site, owing to the limited and the variable transit time in the stomach	Enhance the drug solubility and the overall bioavailability
Dopamine agonist + dopamine antagonist	Bromocriptine (BC) + metoclopramide	Anti-parkinson + anti-emetic	Bromocriptine cause nausea, and the anti-emetic acts in the stomach	Large amount of the dose will skip the *active* site, owing to the limited and variable transit time in stomach	Metoclopramide relieves nausea, especially when floated in stomach, reversing the adverse effect of BC
Narrow spectrum antibiotics	Metronidazole	Anti-microbial against *Helicobacter-pylori*	Resistant gastric infection	As above	Provide high drug concentration, sustained, and localised in the stomach to maximise efficacy

1.5.3. Theophylline as a suitable candidate model drug

i. The therapeutic indications of the drug theophylline

Theophylline (1,3-Dimethylxanthine) drawn in Figure 1.7, is a well-known bronchodilator. It belongs to the tea alkaloids group drugs and acts as a nonselective phospho-di-esterase (PDE4) inhibitor. Also, it was shown to have a muscle relaxant effect, a cardiac stimulant effect, and a diuretic effect. Hence, it is used to relieve asthma, chronic obstructive pulmonary disease (COPD) and bronchopulmonary dysplasia (BPD) (Koda-Kimble, et al., 2007).

ii. The drug theophylline as a GRDDS drug candidate

Table 1.6 is shown the descriptive terms of aqueous solubility, classified based on the USP solubility criteria. The properties of theophylline are appropriate for GRDDS, as shown in Table 1.7. Based on the USP solubility criteria, theophylline is slightly soluble in water (8.3 mg/ml) (BASF, 2009, and Sigma-Aldrich, 2014).

Based on the biopharmaceutics classification system (BCS), the maximum oral dose of theophylline in the market (600 mg) need to be considered as well. The latter dose need to be soluble in 250 ml or more in aqueous media over a pH range of 1-8, for the drug to be as highly soluble. The 600 mg of theophylline requires only 72.3 ml of water to be soluble. Moreover, theophylline dose need to have >90% absorption through lipid bilayer membrane, to be considered as highly permeable drug (Ashford, 2013). Theophylline did not violate any condition regarding the rule of five. Therefore, it was considered as highly permeable. Hence, according to BCS, theophylline is considered highly soluble and highly permeable drug (class 1) (Vo, et al., 2016).

Theophylline (as a Bronsted-Lowry acid) is fully ionized at high pH (≥10.81), based on its pKa value of 8.81. Theophylline (as a Bronsted-Lowry base) is fully ionized at pH of -1.3 or lower, based on its pKa value of 0.7. The latter situations will provide the maximum solubility of the drug, yet, the complete ionization is not fully desired in the physiological

conditions, because the unionization is desired for the permeability of the drug. That's why the drug (as a Bronsted-Lowry base) is partially unionized and only slightly soluble at a pH of 1.2 (when the 0.1 HCl is used). While the distilled water pH of 5.8 indicates that the drug (as a Bronsted-Lowry acid) is completely unionized (Aulton, 2013), indicating a further decrease in solubility. The latter may render the 1.2 pH medium to show better dissolution profiles for the drug theophylline, when compared to the 5.8 pH medium.

It has rapid absorption orally, and high bioavailability if taken after food. Hence, food delays gastric transit, resulting in a food-induced gastro-retention. This food-induced retention is favourable for the drugs of erratic absorption, such as theophylline, to improve its bioavailability profile. Nevertheless, It has an erratic absorption from the duodenum (Kadono, et al., 2002) and from colon (Mura, et al., 2003), it. It has a narrow therapeutic window. Sustained release pellets formulation will significantly reduce the risk of dose dumping. It has no receptor desensitisation by its prolonged exposure when used for controlling asthma or COPD conditions. The floating system will ensure most of the drug released to be consistently and primarily absorbed by the duodenum, to ensure consistent bioavailability.

Drug absorption and bioavailability of drugs, including theophylline, will also be affected by various physiological and formulation factors, as summarised in Figure 1.6. The order of drug release from the dosage form, like pellets, affect the pattern/mechanism of drug absorption. Usually, it can be in either a zero-order rate or first-order rate, according to the administered dose (Ashford, 2013). The former is concentration in-dependant owing to the fact that the concentration is dependent on a retard polymer, while the latter is concentration dependant. The rate of drug escaping the stomach toward the small intestine will be dependent on the drug release rate of the GRDDS formulation. The surface area of the absorption site will affect the drug absorption as well. The common site, the small intestine, has a high surface area that is desired for absorption (Ashford, 2013).

All of these characteristics of theophylline make it as suitable candidate model in optimising the floating pellets formulations. Theophylline properties can be highly suitable regarding the many advantages of floating pellets. The following section will address the physiological challenges that are facing the GRDDS, particularly the FDDS.

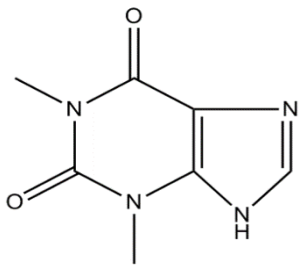


Figure 1.7: The chemical structure of anhydrous theophylline (empirical formula: $C_7H_8N_4O_2$, the chemical name: 1,3-Dimethylxanthine, molecular weight 180.16). The compound is drawn by the ChemDraw.

Table 1.6: The water solubility table, where part per part (ppp) concentration unit describes the solubility limitation in water for the corresponding solubility term (Aulton, 2013).

Solubility descriptive term	**Parts/grams of solvent required per one part/gram of solute**	**Solubility range (mg ml^{-1})**
Very soluble	Less than 1	≥1000
Freely soluble	1-10	100-1000
Soluble	10-30	33-100
Sparingly soluble	30-100	10-33
Slightly soluble	100-1000	1-10
Very slightly soluble	1000-10000	0.1-1
Practically insoluble	More than 10000	≤0.1

Table 1.7: the drug theophylline properties that impact its bioavailability.

Property	Value	Comments	Reference
pKa	8.81	it act as both Bronsted acid and Bronsted base, that means, it has flexibility in the ion exchange	(DrugBank, 2019)
Saturated solubility (of the anhydrous form)	8.3 mg/ml in water	Slightly soluble	(BASF, 2009) and (Sigma-Aldrich, 2014)
	7.36 mg/ml in water, at 25 C^o	Slightly soluble. Resulting in a faintly acidic solution	(PubChem, 2019)
	12.5 mg/ml in alcohol	Sparingly soluble.	(Rowe, et al., 2009)
	33-100 mg/ml in 0.1M HCl, 0.1M NaOH, and 1M NH_4OH	Soluble. A clear and a colorless solution	(Sigma-Aldrich, 2014)
Polymorphism	After 10 seconds of dissolution: ~12.7 mg/ml of anhydrous/ metastable form, and ~6 mg/ml of hydrous/stable form	Anhydrous form act as a pseudo-polymorph. A super-saturated solubility, also called meta-stable or kinetic solubility will last for less than a minute, and it is not likely to affect the extent of dissolution (true solubility).	(Buckton, 2013)
Partition Coefficient (LogP)	-0.02	The latter value is nearly zero, indicating a balance between hydrophilicity and hydrophobicity. Less than 5. Obey the rule of five.	(DrugBank, 2019)
Molecular weight (Mwt)	180.164 g/mol	It has less than 500 M.wt chemical structure. Obey the rule of five.	(PubChem, 2019)
Hydrogen (H) donors	1 H-bond donor	Less than 5 H-donors. Obey the rule of five.	(DrugBank, 2019)
Hydrogen (H) acceptors	3 H-bond acceptors	Less than 5 H-acceptors. Obey the rule of five.	(DrugBank, 2019)
Absorption window	2 sites of absorption	Duodenum (mainly), and colon (partly). It has an erratic absorption and claimed to have a	(Kadono, et al., 2002), (Mura, et al., 2003), (Kang

		narrow therapeutic window	and Lee, 2009).
volume of distribution (Vd)	0.45 L/kg in adults and 1.0 L/kg in neonates lipid tissues	It has a low Vd. The lower the half-life, because a low Vd means the drug is expected to stay for a shorter period in the blood circulation.	(Koda-Kimble, et al., 2007).
Protein binding	50-65% in adults, and 45-50% in neonates	The protein binding is considered moderate. It was mostly by the albumin.	(Koda-Kimble, et al., 2007).
Half Life (t half)	6-12 hours in adults and 20-60 hours in neonates.	A moderate and long half-life, respectively.	(Koda-Kimble, et al., 2007).
Therapeutic Range	10-20 mg/L	The dose regimen should provide a plasma drug profile within this range	(Barnes, 2010)
Dose tolerance	Not observed	It has no dose tolerance/dose desensitisation if used for inducing the bronchodilation effect.	(Barnes, 2010)
Food Effect on the Half Life	Protein-rich diet and low-carbohydrate, and charcoal made beef.	Reduced half-life from 7.6 up to 5.2 hours. Charcoal contains poly-cyclic aromatic hydro-carbons that interact with the drug	(Shargel, et al., 2012).

1.6. Physiological Challenges for the GRDDS in the Gastro-Intestinal Tract (GIT), with Focus on the Considerations of Floating Systems

1.6.1. General considerations in biopharmaceutics

For the erratic absorption drugs, the control of the dosage form transit is critical, as the dosage form is desired to stay in the stomach for longer hours. To achieve that, a gastro retentive formulation design is needed. However, to avoid foreseeable risks in the formulation design, it is important first to identify what can possibly happen to this formulation when it gets administered by the patient. The optimum GRDDS should

have sufficient retention time in the stomach and should overcome the gastric motility problems. A common problem is the short mean gastric residence time (GRT) of 2-3 hours. Hence, the latter short GRT will not provide the sufficient time to allow for the drug to experience sufficient duodenum exposure, the desired absorption site for theophylline. That will result in a variable absorption, and subsequently, in a variable bioavailability. The gastric emptying time (GET), the gastric resident time (GRT), and the gastric emptying rate (GER) are all synonyms for the resident time of the dosage time in the stomach (Singh & Kim, 2000).

Moreover, the GRT can be largely varied with many co-occurring factors. For instance, the occurrence of the fasted state and/or the diseased state may largely increase the GRT. Hence, this will provide unpredictable gastric emptying times that vary from few minutes to 12 hours. Therefore, the introduction of a GRDDS formulation design will control the transit time of the drug product, and subsequently, the transit of the drug substance. That will control the drug release in terms of location and timing. The poor bioavailability risk related to the latter problem can be tackled and mitigated (Pawar, et al., 2011). Hence, the FDDS dosage form should be floated within 15 minutes, and optimally within 3 minutes, and should be reached the expansion equilibrium within 1 hour (Hung, et al., 2014).

1.6.2. Gastric emptying process

The gastric emptying time (GET) is highly variable, which is owing to the following reasons (Ashford, 2013). The various anatomy of the tissue walls throughout the GIT: the different level of blood supply, types and level of pores/channels/transporters, and the presence of microvilli, will all affect the extent and the rate of absorption. Based on the drug substance, the absorption is dictated by either the passive or the active permeability mechanisms, according to the transport type that the drug prefers through the cells. The permeability and the transport

mechanisms with the basic pharmacokinetics involved are detailed sufficiently by (Loftsson, 2015).

The various chemical and the microbiological constituents throughout the GIT. The different concentration of surfactants, acids, enzymes, and microflora in different locations, will affect the solubility and/or the degradation of the drug prior absorption. For instance, the presence of the CYP3A4 enzyme in the gut wall is considered an issue that affects some drugs, like docetaxel, where the drugs' stability can be highly affected prior absorption in the GIT (Thummel, 2007). The fed/fast state effects (more details are below), the disease state, the genetic make-up, and gender, will also have an effect on the drug absorption in many ways. Also, the difference in the formulation design, dosage form, the excipients, will all affect the dosage form emptying, and the subsequent drug dissolution, and drug permeation/absorption.

In the fasted state, the stomach will follow the inter-digestive myoelectric cycle, which is more commonly called the migrating myoelectric complex (MMC), which consists of four phases that altogether takes about 1.5-2 hours to complete, see Table 1.8. In the fed state, the pattern of gastric motility differs significantly during the emptying of the gastric contents. It is due to that MMC phases will no longer be relevant, as the stomach will not be emptied in the fed state to allow the digestion of its contents. The housekeeping wave in the MMC cycle will take ~1.5-2 hours to be reached. However, this housekeeping wave will be delayed in the fed state until the food digested are emptied as liquid or semi-solids. That is, the housekeeping wave will be delayed for 4-10 hours, based on the meal contents, where a fat meat will delays the wave the most (Singh & Kim, 2000) and (Ashford, 2013). Moreover, the ionic content of the GIT can has an effect on the drug release in either fasted or fed conditions (Asare-Addo, et al., 2011).

Table 1.8: Migrating myo-electric complex (MMC) phases and the GIT in different states.

MMC phases	Stomach transit time in the fasted state (pH 1-2)*	Stomach transit time in the fasted state with the floating pellets
1. Quiescent period	40-60 minutes with rare contractions	Optimally, pellets should remain floated in the stomach for >4 hours. i.e. Meanwhile, these MMC phases in the fasted state are expected to be repeated more than twice.
2. Intermittent action potentials period	40-60 minutes with gradual intensity of contractions	
3. Housekeeping period	4-6 minutes with intense, large and regular contractions	Optimally, more than two housekeeping waves will occur in the fasted state without sweeping off the floated pellets.
4. Transitional period	A brief period occurs between phase 3 and 1	-
*The total transit time in the stomach is approximately 1.5-2 hour (fasted state), approximately 4-10 hours (fed state; pH 4-7), and >4 hours for the floating pellets.		
The total transit time in the whole gastro-intestinal tract (GIT) is approximately 8-12 hours (fasted state), approximately 16-24 hours (fed state), and an estimated 16 hours for the floating pellets mimicking the fed state transit time.		

1.6.3. Food-induced variability in gastric emptying

As evident in the previous section, the food is considered to be a major factor in delaying the GRT and could be even more detrimental than the floatability of the formulation and its gastro-retention. Unlike floating tablets, the floating pellets, once sink, they will escape to the small intestine when the stomach is under the inter-digestive state; the fed state. The latter is because that the pylorus sphincter opening will be smaller in the fed state, but not entirely closed, allowing for the small units of <2 mm to escape as the liquid transit (Padfield, 1989) and (Davis, 2005). Therefore, the emptying of pellets from the stomach is not seemed to be affected by the fed/fasted state. In conclusion, the pellets will allow the dosage form to have a superior self-control on its transit, and the emptying will not be limited by the fed state presence.

Also, the latter advantage of pellets is more of particular importance to the enteric delivery of a drug, to avoid the premature drug release as the dosage form is interacting with the less acidic medium of the food (Padfield, 1989). Food can also interfere indirectly, raising the pH of the stomach will adversely affect (1) the dissolution of alkaline drugs, and

(2) the effervescence reaction of FDDS. These problems can be mitigated by incorporating an acidifying agent. Alternatively, starter inert core pellets of citric acid or tartaric acid can be used instead of the sugar-pellets. These options will provide an acidic microenvironment inside the dosage form.

Moreover, if the floating formulation is of non-effervescent type, then it will have food independent property. It will allow the dosage form to float in the stomach in either the fed state or fasted state. That will improve the patient compliance, especially for patients with irregular eating habits. Therefore, in this regard, the effervescent mupFDDS design will be compared to the non-effervescent mupFDDS design, using acidic-pH and water-pH media as seen in this project. The food also delays the onset of peristaltic contraction in the stomach, ensuring that there is a no-premature emptying of floating pellets. That is because the nervous system has an effect on the stomach emptying process, based on the fast/fed state (Singh & Kim, 2000) and (Ashford, 2013), as seen by the MMC phases in Table 1.8. The following section will address the materials used in the project for composing the floating pellets.

1.7. Introduction to Materials as the Excipients in Floating Pellets

Microcrystalline cellulose (MCC) is a non-disintegrating excipient that is commonly used to produce pellets. During the wet mixing, the MCC polymer can enhance the water distribution in the moist mass, that result in a consistent wet mixing process (DFE-Pharma, 2011). The water distribution enhancement is due to many desirable properties that MCC possess; namely, it induces consistent cohesiveness, water retention, and water release. That is favourable for high binding property that allows for high drug loading. Also, that makes it a water retentive material that tolerates various stresses of processes after the wet massing and/or granulation step. That is, it provides sufficient rheological properties like plasticity, which allow for consistent re-shaping and densification mechanisms to occur upon a compaction

process, such as extrusion and spheronisation processes (Jain, et al., 2010). Although MCC is still considered the most desired spheronisation aid, it has some limitations, thus other alternative aids like the co-processed MCC and cros-PVP are used. The limitations claimed are the adsorption of drugs, deactivation of drugs like ranitidine, and may incur long dissolution time (Jain, et al., 2010). Most drugs have the ability to be loaded in MCC at a loading of 40-60%. To justify the MCC use as a cushioning material, the literature stated that the lyophilised pellets of high MCC content were shown to be protective, inert, and highly compressible cushioning aid (Habib, et al., 2002). Also, blending an organic solvent with an aqueous solvent, such as ethanol with water, to be used as a liquid binder was previously shown to form MCC granules that cushion and better protect the coated pellets (Vladyka, et al., 2005).

In hydroxyl propyl methyl cellulose (HPMC) polymers, a low molecular weight HPMC can be used in coating solutions as a binder. It ensures the deposition of other accompanied and functional molecules is achieved. For instance, it allows the deposition of drug molecules on the surface of the solid agglomerates or compacts (Sungthongjeen, et al., 2006). On the other hand, the high molecular weight HPMC, which is a highly cros-linked polymer, tends to be more viscous and less soluble in water. In this project, it is used in the swelling system as a hydrocolloid swelling agent. During wet massing, it ensures that the cores can have a higher swelling capacity that may potentially provide a non-effervescent floating aid (Sungthongjeen, et al., 2006). Also, it is known that as its viscosity increase, the gel-forming ability increase, resulting in more prolonged drug release (Kadajji & Betageri, 2011). The poly-ethylene-glycol (PEG) polymers are used for various functions, and some were used for advanced purposes, like the so-called PEGylayation, which was first proposed in the late 1970s, to improve the selectivity of the drug to the desired physiological receptors (Kadajji & Betageri, 2011). The one of interest here for floating pellets is PEG 6000 polymer, which was prepared with the HPMC polymer, to improve the plasticity of the latter, to make the HPMC polymer more flexible to

withstand the volume expansion upon fluid absorption. That is, it is used as a plasticiser in the coating solution (Sungthongjeen, et al., 2006).

Sodium bicarbonate ($NaHCO_3$) is a carbonate salt, which upon exposure to an acidic medium, will undergo a neutralisation reaction, results in the generation of a gas, the carbon dioxide (CO_2). Hence, it is used as a gas-generating agent, where it first mixed with a non-acidic coating solution, then sprayed on the surface of the core pellets, to make a sub-coat layer. Alternatively, it can be wet-mixed in a non-acidic wet massing liquid along with other powders to make the core pellets (Sungthongjeen, et al., 2006). The low molecular weight poly-vinyl pyrrolidone (PVP) is commonly used in the wet granulating liquid as a binder for the powder bed, or in the coating solution for the coating materials (Kadajji & Betageri, 2011). It is also used in the wet massing liquid as a liquid binder (Qi, et al., 2015). In this project, a low molecular weight grade has been used, the 44,000 g/mole, to potentially allow for the PVP swelling to occur in the core pellets. The crospovidone (cros-PVP) is used as a super-disintegrant to allow for a fast disintegration of a tablet. Also, it is used as a solubiliser, a swelling agent, an alternative spheronisation aid, and many other functions (Jain, et al., 2010). Here, it is used as a swelling agent, to examine whether there are any differences in the resulting pellets quality.

The poly-meth-acrylates (PMAs) is a polymer can be made in a wide range of grades of different quaternary ammonium groups, which will allow for different water permeability. There are closely related derivatives of polymers that have different properties, like the different pH-dependant solubility, that can allow for an enteric drug delivery (Evonik, 2017). It is used here to restrict the gas release and the drug release, to allow for gastro-retention and sustained drug release, respectively (Sungthongjeen, et al., 2006).

1.8. Introduction to Preparation Processes of Floating Pellets

The techniques have various technological concepts, many of which were long used in literature and the pharmaceutical industry. The aim here is only to shed light for some of the conventional and available pelletisation techniques. An overview for the processes involved is seen in Figure 1.8. The several aspects of some of these methods on the floating pellets systems will be elaborated in the results chapters. As with many other dosage forms, during the floating pellets development, the drug dissolution is considered a major characterisation process. The dissolution science itself has an origin since the late 19th century.

1.8.1. The related granulation techniques

Granulation processes are divided into two main categories, dry and wet granulations. The wet granulation is also sub-classified into fluid bed and shear granulations. Moreover, the shear granulations are either high or low shear granulation methods. The interest in this project is the low-shear granulation method, as seen next page.

i. Wet granulation processes

The wet granulation processes are classified into two main categories, as follows. Fluid bed granulation, is where the mechanism of granulation is through the nucleation and granule growth. The viscosity of liquid binder should be low and thus more fluid is needed, due to the spraying requirements. Shear granulation, is where the mechanism of granulation is through wet massing and granule growth. The viscosity of liquid binder should be higher and thus less fluid is needed. The high viscosity liquid increases the shear stress during wet massing, to improve granule properties and powder mixture homogeneity. It can be regarded as either high or low shear granulation, based on the mixing speed applied (Aulton & Summers, 2013).

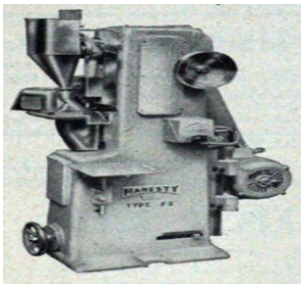
Planetary Mixer (Kenwood)

Radial Extruder (Caleva)

Top-Bench Spheroniser (Caleva)

Oven Drying

Top-Spray Mini Coater/Drier (Caleva)



Single-Punch Tabletting Machine (Manesty)

Oven Drying

Filling into Gelatine Shell Capsule*

Figure 1.8: summarises the steps that conducted in this project for the overall process of making the coated pellets, where the pellets will be either filled into a capsule or compressed into a tablet. The shown images are similar to the equipment used in this project. *The scale-up of the capsule filling should consider the pellets feeder attached to the capsule filling machine. (Images were taken from the respective companies, except that the tabletting machine image is taken from the gracesguide.co.uk, and the capsule image from www.naturalmedicines.co.uk).

ii. Low shear wet granulation process

The low shear granulation process consists of two main mechanisms, as follows. The ‘wet massing’ is where the moist-sand wet bed will be formed. The wet mass can be produced using mixers with kneeling ability. That is, it can be obtained by a mixer of a convective mechanism, such mixers are the planetary, ribbon, screw, or paddle mixers. The ‘densification and granulation’ are where the agglomeration will result in the granule growth. The granules can be produced using an oscillating granulator or gear role granulator. Granules are slightly elongated in shape with a smooth, but porous surface (Aulton & Summers, 2013).

1.8.2. The pelletisation techniques

Pelletisation process can be considered as a specialised wet granulation technique. The word pelletisation in the context of the pharmaceutical manufacturing was defined by (Ghebre-Sellassie, 1989) as follows: “It is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets”. Historically, the interest in pelletisation or spheronisation for the pharmaceutical use can be traced back to the late 9th century.

However, in the late 19th century, the advent of tablets and capsules supersedes the spheres making to a great extent. In the mid of the 20th century, the spheres become an interest again for the pharmaceutical use. Although the extrusion and spheronisation method was used in other industries, the pharmaceutical industry took time to apply it. The interest in pelletisation re-emerged in 20th century due to the increasing demands for efficient sustained drug release systems (Ghebre-Sellassie, 1989). The pelletisation mechanisms including relevant techniques/methods are summarised in Figure 1.9 (Muley, et al., 2016) and (Ghebre-Sellassie, 1989).

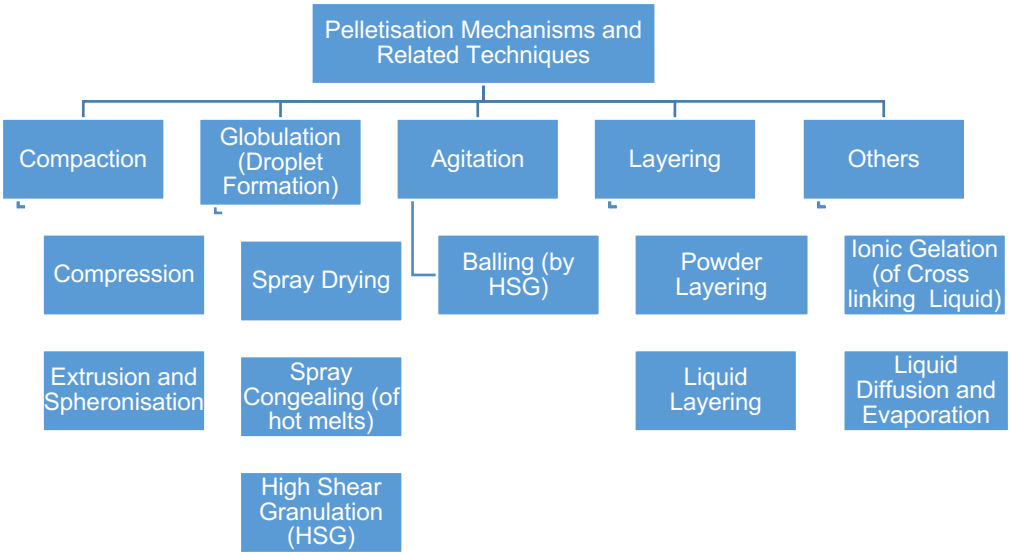


Figure 1.9: shows the pelletisation mechanisms (like compaction) and the relevant techniques (like compression).

The used pelletisation techniques or methods for making the pharmaceutical floating pellets, are described below, but not necessarily limited to the following (Kumari, et al., 2013).

i. Extrusion and spheronisation: this is where the wet mass will be extruded, then extrudates will be spheronised. It is the most popular and well-established method for making the pharmaceutical pellets, and arguably, one of the most desired methods. It is widely used in industry, as it simplifies plant procedures and reduces cost (Caleva, 2015). In this method, the optimisation of the liquid binder is considered highly challenging (Chu & Chaw, 2012), (Puah, et al., 2013) and (Garekani, et al., 2013). This method is used in this project. Therefore, more details about this method will be seen in the upcoming section.

ii. Direct spheronisation or high-shear granulation: this is where agglomerates are formed from the wet powder through the use of rotary fluidised bed granulator, or formed from a suspension by a spray dryer. Then, followed by a subsequent size enlargement until these agglomerates reach the size range of a micro-pellet (<500μm) or a milli-pellet (0.71-1.18 mm) (Aoki, et al., 2015) and (Srivastava & Mishra, 2010). Direct spheronisation can also be obtained by placing the

granules in a spheroniser, skipping the extrusion process (Sawicki & Łunio, 2005).

iii. Hot melt screw extrusion: this is where powders are melted and mixed gradually with the use of a screw, then the homogeneous melt is extruded as a thin and long thread-like melt. A cutter is used to chop the melt into spherical pellets. This method is increasingly common in the research, as it claims easier processing (Vo, et al., 2017), which will ease the pilot scale formulation development (Hossain, et al., 2017).

iv. Inert sphere layering: this is where inert starter pellets, which are the commercially pre-made pellets, will be used for drug and functional coatings. The formulator here will only focus on optimising the coating of these pellets. Because the drug has to be layered on these inert cores, this method usually requires at least double-layers design, regardless of the drug delivery system required. It is also considered a common method of pelletisation (Pagariya & Patil, 2013), (Amrutkar, et al., 2012) and (Hosseini, et al., 2013).

v. Emulsion-solvent diffusion and evaporation: this is usually by evaporating solvent from either emulsion/suspension of microparticles or soaked microparticles (Streubel, et al., 2006). It is usually by forming an oil in water (o/w) emulsion, then forming a shell through the rapid out-diffusion of ethanol, followed by generating a gas phase through the diffusion and evaporation of dichloromethane. Finally, micro-balloons will be formed because of the hollow sphere formation (Streubel, et al., 2006).

vi. Cross-linking, ionic gelation or coacervation, with or without lyophilisation: this it is where a heterogeneous polymeric solution and drug solution were mixed, then poured in a drop-wise manner into a cross-linking solution of, e.g. calcium hydroxide, resulting in the formation of the wet matrix pellets. Those pellets can be frozen, then undergone into the condensation phase, and subsequently, undergone

into the sublimation phase, resulting in the lyophilised pellets (Murphy, et al., 2012) and (Thomas, et al., 2012).

1.8.3. The extrusion and spheronisation

i. Packability of particles

In the extrusion and spheronisation process, water/liquid binder uptake by the powder during the wet massing is known to be critical. A study by (Sarkar, et al., 2013) showed that during the wet massing process, a critical factor was found to be evident, the *particles packability*, which is the arrangement of particles components. Packing was correlated to the cohesive strength of the agglomerates. As the shear forces applied to the wet mass, the coalesced particles integrity and re-shaping ability can be determined. Packability was found to be affected by and affected on the spheronisation of the extrudates into pellets. Hence, it affects the production yield of the narrow size distribution of pellets.

ii. Growth mechanisms of pellets by the high shear wet granulation

There are different proposed mechanisms for pellets growth/formation, some of which can happen simultaneously. The mechanisms involved in the high shear granulation methods are of some to little relevance to the other methods of palletisation, like the extrusion and spheronisation method. Nevertheless, the latest view for the high shear granulation proposes several steps for pellets formation, which are nucleation, coalescence, layering, and abrasion/mass transfer. In contrast, the pellets size reduction mechanisms include attrition, breakage, and/or shatter (Muley, et al., 2016), see Figure 1.10. The size reduction in pellets should not exceeds the pellets growth, to allow for producing sufficient yield of pellets.

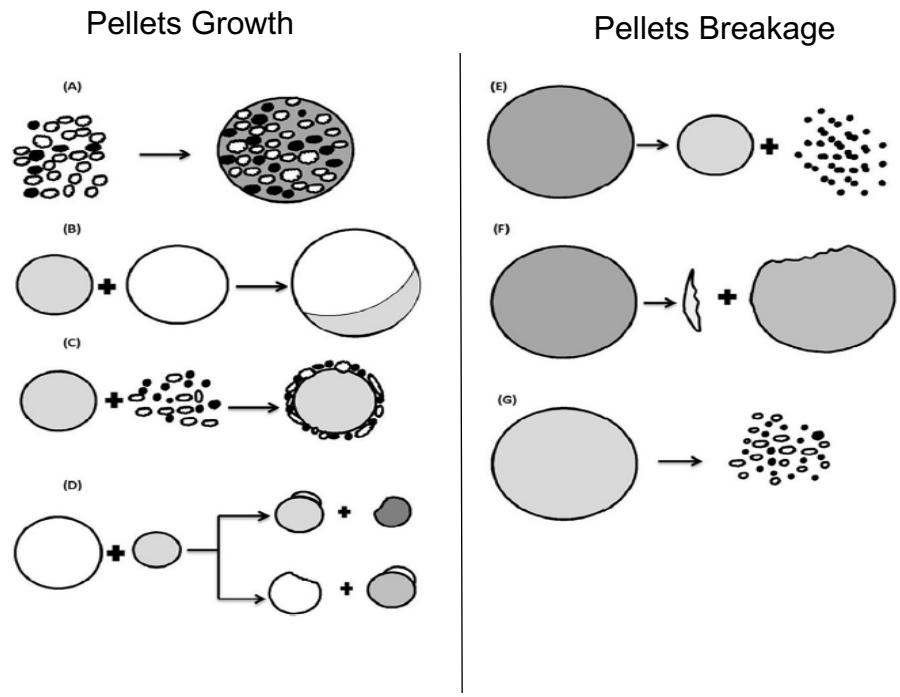


Figure 1.10: Pellets formation mechanisms (a. nucleation, b. coalescence, c. layering, d. abrasion transfer) and size reduction mechanisms (e. attrition, f. breakage, g. shatter) from the high-shear granulation methods (Muley, et al., 2016).

iii. Wet massing (a low shear wet granulation process)

The wet massing was undertaken by the use of a planetary mixer, or less commonly by the use of a screw mixer (Puah, et al., 2013) and (Chu & Chaw, 2012). The phases of wet massing involve the solid-liquid interactions, namely, the pendular, funicular, capillary, and droplet phases, see Figure 1.11. The pendular phase has the lowest spreading of liquid binder, while the droplet phase has the highest (Sakr, et al., 2012). The capillary phase is considered the optimum phase for a consistent wet mass (Muley, et al., 2016). The wet mass consistency can be measured qualitatively by the hand squeeze method, and quantitatively by the powder torque rheometer.

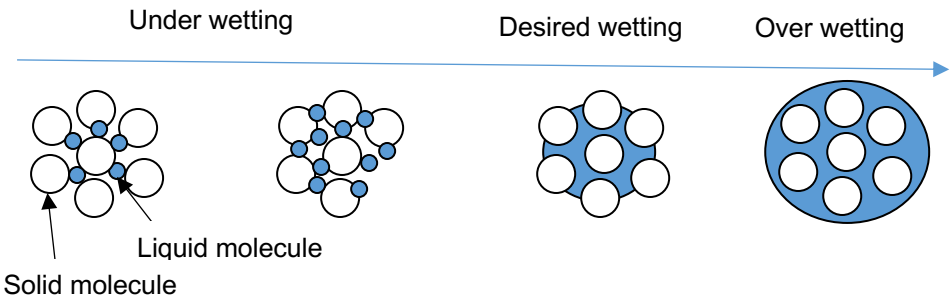


Figure 1.11: The solid-liquid phases during wet massing, prior extrusion and spheronisation. Left to right: pendular, funicular, capillary, and droplet phases. The image drawn by the author.

iv. Extrusion (a special type of wet granulation)

The pharmaceutical extruders come with different configurations that can have different effects on the intermediate and the final product attributes. Figure 1.12 summarises the common extruder configurations. Main configurations are listed, but not necessarily limited to the following (Muley, et al., 2016), (Aulton & Summers, 2013), (Mehta, et al., 2005) and (Ghebre-Sellassie, 1989).

Basket or gravity-feed extruders, where the wet mass is fed into rotating roll or radial arm, which compresses the bed against an oscillating cylinder roll, gear roll, or a ring screen that configured for a specific perforations size. The gravity-feed rotating radial arm extruder of two oscillating rolls was used in this project. The two oscillating rolls oscillate against the perforated ring screen. The screen comes with or without a cutter, to cut extrudates into even lengths. Radial extruder may be seen as a sieve extruder, owing to the specific and even dimeter of the screen openings. In addition to the gravity-feed design, a radial extruder can be also configured as a screw-feed design.

Screw-feed extruders, where the powder is mixed with a liquid binder, then the wet mass was forced by a single- or twin- screws against uniform openings. It comes with different designs like the axial, the dome, and the radial designs. It also comes with different blades, axial blades like the non-continuous and continuous blades. And radial blades like the conical-blade and the intermeshing-blade. Ram or piston-feed extruders, where the wet mass is fed into a piston inside a cylinder or channel, where the piston compresses the bed against orifices.

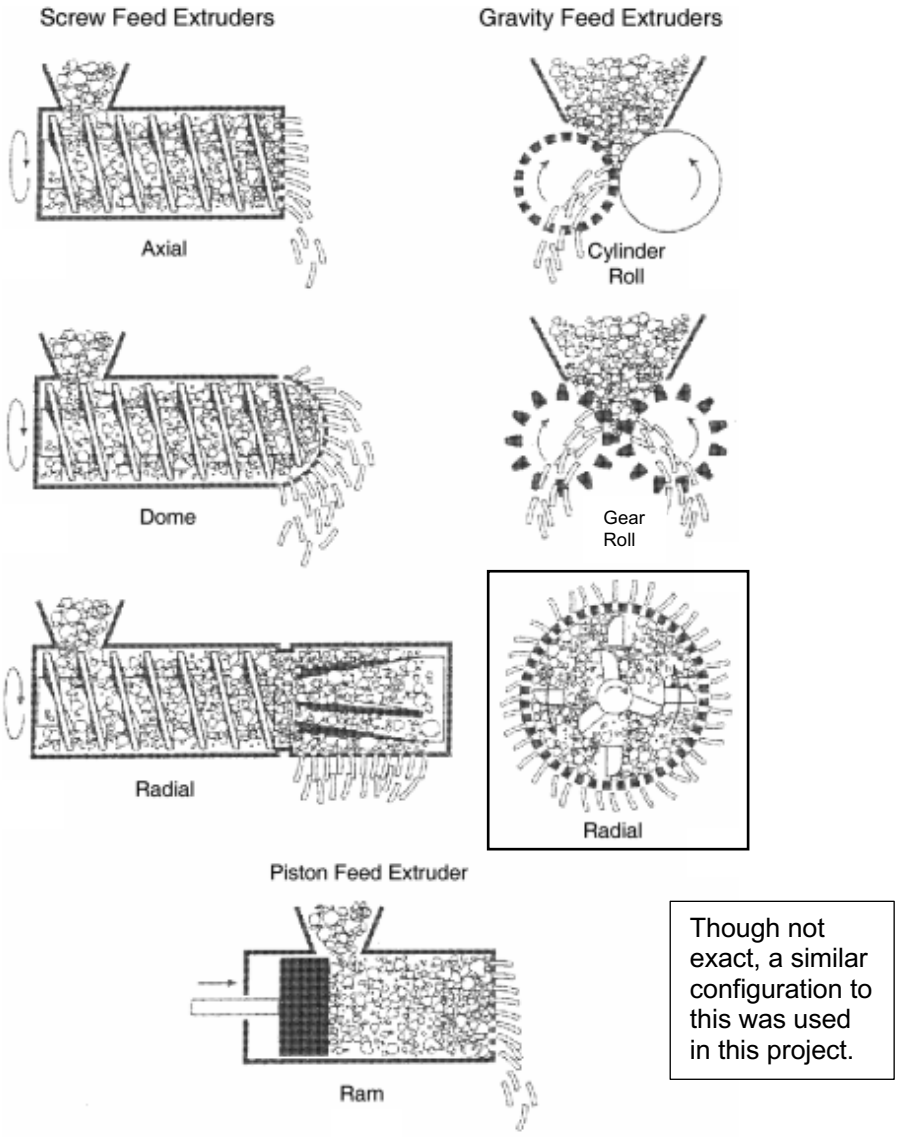


Figure 1.12: The extruder configurations used in the extrusion/spheronisation method. Gravity-feed radial configuration was used in this project. The one shown here has some differences from the actual one used, the latter stated in the text. The image obtained from (Mehta, et al., 2005).

v. Spheronisation (a special type of wet granulation)

The typical pellets size is 0.71-1.4 mm. A disc/plate with a rotating drive shaft is used. It can be called as round, spinning, or friction plate. It spins at a high speed in the bottom of a cylindrical bowl. The plate has grooves from its cross-hatched (waffle iron) or radial designs of different sizes. These grooves allow for an increasing friction against the extrudates, where the spheronisation occurs (Caleva, 2015), (Aulton & Summers, 2013) and (Ghebre-Sellassie, 1989), see Figures 1.13-14.

The rod-like extrudates (maybe also called as granules, or cylinders) were placed on the plate, and cut into segments as the plate spins. Then the segments collide with the bowl wall and then thrown back to the centre. Hence, the latter movement will likely result in the rope-like motion along the bowl wall. The segments will be gradually rounded by the collisions with the bowl wall and the plate, and of each other (Caleva, 2015). The rope-like motion around the edge of the bowl is needed to facilitate the friction, which is required for the spheronisation to occur (Caleva, 2015).

The extrudates are expected to be plastic enough to allow the deformation into spheres. The extrudates deformation is expected to occur upon the impact and collisions they receive during spheronisation. Powdering or dusting can occur if extrudates were too plastic, while sticking and dumbelling can occur if extrudates were not plastic enough. The mixer torque rheometer can easily, accurately, and quickly measure and optimise the plasticity of the wet mass prior extrusion and spheronisation (Caleva, 2015). The spheronisation mechanism of extrudates was proposed with different variations, where the common phases are the cylinder, dumbbell, and spheres formations (Muley, et al., 2016) and (Sakr, et al., 2012), see Figure 1.15.

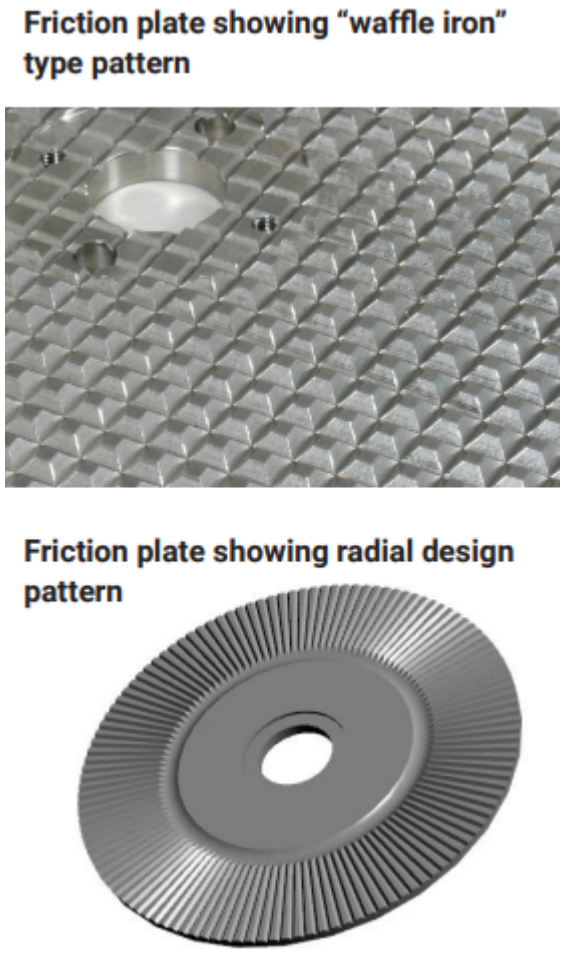


Figure 1.13: The sphernisation plates used in the extrusion/spheronisation method. Waffle iron pattern was used in this project. The image obtained from (Caleva, 2015).

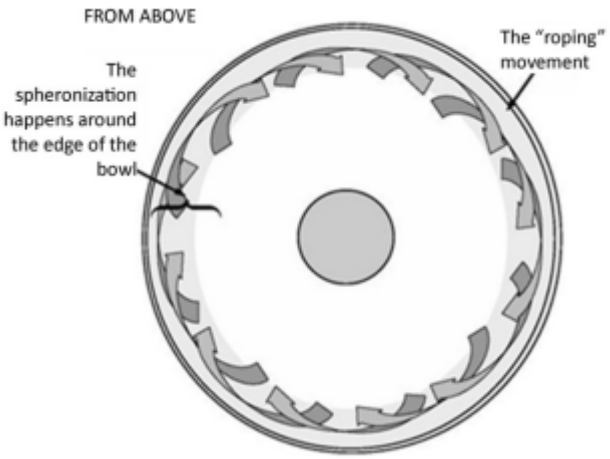


Figure 1.14: The site of sphernisation in the spheronisation plate. The image obtained from (Caleva, 2015).

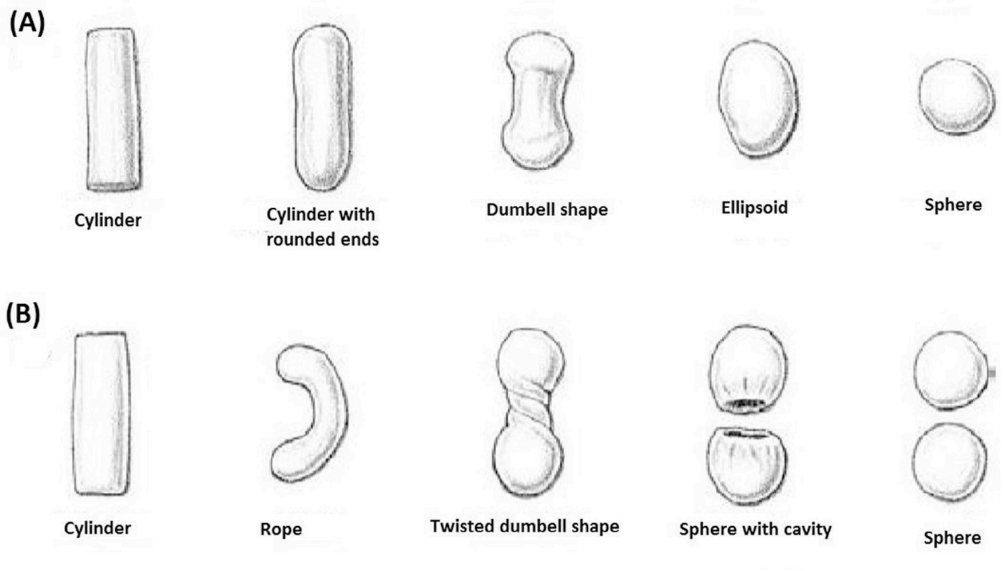


Figure 1.15: The spheronisation mechanism of extrudates, where shape evolution into pellets is illustrated. (A) proposed by (Rowe, 1985), while (B) proposed by (Baert & Remon, 1993).

1.8.4. The coating techniques

Different coating techniques are available for coating pellets, they are listed, but not limited to the following (Srivastava & Mishra, 2010):

i. Fluidised bed (FB) coating

The fluidised bed coaters can come with different spray configurations that greatly dictate the coating process efficiency. The most commonly known configurations are as follows. Top spray, using, e.g. Caleva mini coater/dryer, which is used in this project. Among other variables, the variables involved in the top-spray FB coating process were of high importance in obtaining fully functional pellets. Most factors involved in the top-spray fluidised bed coating process are important to the coating efficiency as well as to the function of the floating pellets. To examine the importance of the coating process factors and all the other factors involved in the making of the floating pellets, see the risk analysis section 3.2 in chapter 3. Bottom spray, also called Wurster spray, it is where the first film-coated tablet was made. Wurster is the configuration of choice for pellets coating, using, e.g. a Glatt Wurster HS coater, or Precision and Supercell™ coater of GEA. The third configuration of FB coater is the tangential spray. The FB coating is more relevant for the pellets applications when compared to pan coating, as it is

advantageous in terms of providing a discrete coating. The latter can decrease the agglomeration risk and provide a uniform deposition of the droplets on the pellets' surfaces (Porter, 2013).

ii. Pan coating

Similar to the fluid bed coaters, the pan coaters can come with different spray configurations that greatly dictate the coating process efficiency. The most commonly known configurations are as follows. Tapered cylindrical pan, where spray guns are mounted in the front opening, while the drying and exhaust air are from the rear opening, using, e.g. Pellegrini coater. This type suffers from poor thermal contact and poor coating finish (Cole, et al., 2002). Perforated rotary or side-vented rotary pan, where both spraying and aeration are from the same opening, which provides better heat and mass transfer, and better coating finish, using, e.g. Manesty Accelacota, Driam Driacoater, and a Glatt coater (Cole, et al., 2002). Also, another example in the market is the Premier 500 coater of Bosch.

iii. Dry powder coating

This will eliminate or largely eliminate the need for the liquid in coating, resulting in reduced operational cost, safer processing for the moisture-sensitive materials like the amorphous solids, and allow for better identification of counterfeit medicine (Sauer, et al., 2013). Recent advances in this field are evident, as the introduction of the novel one-step micro/nano-particle coating technology, which is now in the market by (Smith, et al., 2016). Several types belong to the dry powder coating category (Sauer, et al., 2013), such as liquid-assisted coating, thermal-adhesion coating, and electrostatic coating.

Different coating techniques and configurations, along with other coating process factors and coating solution factors, can greatly affect the tendency toward coating defects. Defects can be in the form of blisters, flakes, cracks, and pinholes. The coating defects can result in pre-mature/sudden drug release from the cores upon exposure to the dissolution medium (Xu, et al., 2015). Hence, floating profiles will also

be at high risk when such defects present in the coated dosage form. The thermal effects of the curing process are controversial, as some studies showed that curing of coated dosage form might increase, decrease, or have no effect on the drug release profiles (Bhattacharjya & Wurster, 2008).

1.8.5. The tabletting techniques

Different tabletting techniques are available for tabletting the coated pellets. They are listed, but not necessarily limited to the following (Alderborn, 2013). Eccentric tabletting, where a single-punch press is used, and has one die and one pair of punches. It is used during the formulation development and for the clinical trials production, with up to ~200 tablets per minute when automated. This method was of particular interest, as this project involve using small samples, which justify its use in this project. The compression force is considered the most important factor in the tabletting of the floating pellets. The compression force in the tabletting process is considered an essential process variable that can significantly affect the quality attributes of the final formulation (Alderborn, 2013). Rotary tabletting, where a rotary press, which is also called a multi-station press. It is used during the scale up with as minimum presses as three, and used during the large production with as many presses as 60 or more, with over 10,000 tablets per minute. It results in fast and cost-effective production.

Hydraulic tabletting, where a computerised hydraulic press is used, which is also called a compaction simulator. It is used in the research, where it can mimic the loading pattern of the production presses. Hence, it will further facilitate the tabletting scale-up for proactive risk mitigation. Hand-held tabletting, where a hand-size press is used. It can be used in the early risk assessment stage, but, there is no evidence yet for its use as a reliable and an accurate method of prediction. The method lack control on the compression force, as it only relies on the hand strength. Example is the Vice handheld press (LFA, 2017). The following section will present the marketed dosage forms of interest.

1.9. The Marketed GRDDS, MUPS Tablets, and MUPS Capsules

There are several marketed gastro-retentive systems, and more noticeably, the floating systems. Most of the floating systems on the market are based on the presence of an effervescent, see Table 1.9. Also, other marketed gastro-retentive systems and pellets systems are seen in Tables 1.10-11, respectively.

As seen in Tables 1.9-10, there is no clear statement that these dosage form contains pellets intended for floating or for any other gastro-retentive mechanism. Moreover, there is no marketed gastro-retentive dosage form for the drug theophylline in the market. As seen in Table 1.11, there are dosage forms that contain pellets for the drug theophylline, which are filled into capsules or compressed into tablets. However, the manufacturers of the latter dosage forms did not clearly state whether these pellets are intended for gastro-retention or not. Examples of the marketed products of theophylline loaded pellets intended for the sustained drug release are the Theo-Dur and the Elixophyline.

Table 1.9: Marketed floating systems.

Brand name	Generic name	Therapeutic indication	Formulation design	Manufacturer	Reference
Zanocin OD	Ofloxacin	Infections	Effervescent floating system	Ranbaxy, India	(Pawar, et al., 2011)
Riomet OD	Metformine HCl	Diabetes	Effervescent floating system	Ranbaxy, India	(Pawar, et al., 2011)
Cifran OD	Ciprofloxacin Ranbaxy India	Infections	Effervescent floating Form	Ranbaxy India	(Pawar, et al., 2011)
Prazopress XL	Prazosin HCl	Hypertension	Effervescent and swelling-based floating system	Sun Pharma, Japan	(Pawar, et al., 2011)
Metformin HCl LP	Metformin HCl	Diabetes	Minextab Floating®	Galenix, France	(Pawar, et al., 2011)
Cafeclor LP	Cefaclor	Infections	Minextab Floating®	Galenix, France	(Pawar, et al., 2011)
Tramadol LP	Tramadol	Severe pain	Minextab Floating®	Galenix, France	(Pawar, et al., 2011)
Baclofen GRS	Baclofen Sun	Muscles Relaxant	Coated multi-layer floating & swelling system	Pharma, India	(Pawar, et al., 2011)
Madopar HPS, or Prolopa HPS	Levodopa and Benserzide	Parkinson disease	Floating, CR capsule. Its advantage: reduce motor fluctuations.	Roche, UK	(Singh & Kim, 2000), (Pawar, et al., 2011)
Liquid Gaviscon	Alginic acid and Sodium bicarbonate	Heart burn	Effervescent floating liquid alginate preparation. Alginates act as floating and SR agents	Reckitt Benckiser Healthcare, UK	(Singh & Kim, 2000), (Pawar, et al., 2011)
Valrelease	Diazepam	Anxiety	Floating capsule	Roche, UK	(Singh & Kim, 2000), (Pawar, et al., 2011)
Cytotec Bilayer	Misoprostol	Stomach ulcers	floating capsule	Pharmacia Limited, UK	(Pawar, et al., 2011)
Topalkan	Aluminum magnesium and alginic acid	Heart burn	Floating liquid alginates. Its active act as a floating agent.	Pierre Fabre Medicament, France	(Singh & Kim, 2000), (Pawar, et al., 2011)
Conviron	Ferrous sulfate	Iron deficiency	Colloidal gel forming FDDS	Ranbaxy, India	(Pawar, et al., 2011)
Almagate Flatcoat	Aluminum magnesium	Heart burn	Floating liquid form. Its active act as a floating agent.	-	(Singh & Kim, 2000), (Pawar, et al., 2011)
Inon Ace Tablets	Simethicone	Gastric bloating	Foam based floating system	Sato Pharma, Japan	(Pawar, et al., 2011)

Table 1.10: Marketed gastro-retentive systems other than or not clearly stated as floating systems (Pawar, et al., 2011).

Brand name	Generic name	Therapeutic indication	Formulation design	Manufacturer
Gabapentin GR	Gabapentin	neuropathy	Polymer-based swelling technology: AcuForm™ (In phase three clinical trial)	Depomed, USA
proQuin XR	Ciprofloxacin	Infections	Polymer-based swelling technology: AcuForm™	Depomed, USA
Glumetza	Metformin HCl	Diabetes		Depomed, USA
Metformin GR™	Metformin HCl	Diabetes		Depomed, USA
Kadian	Morphine sulfate	Severe pain	—	Sumitomo Pharma, Japan
Cipro XR	Ciprofloxacin hydrochloride and betaine	Infections	Erodible matrix based system	Bayer, USA
Accordion Pill TM	-	-	Expandable film filled in capsule	Intec Pharma
Coreg CR	Carvedilol	Heart disease	Gastro retentive osmotic system	Glaxosmithkline, UK

Table 1.11: Marketed pellets-containing tablet or capsule (MUPS tablets or MUPS capsules).

Brand name	Generic name	Therapeutic indication	Formulation design	Manufacturer	Reference
Losec MUPS	Omeprazole magnesium	Peptic ulcer, gastro-esophageal reflux disease (GERD)	Enteric release tablet	Astrazeneca	(Tan & Hu, 2015) and (Chen, et al., 2017)
Nexium	Esomeprazole magnesium	Peptic ulcer, GERD	Enteric release tablet	Astrazeneca	
Prevacid	Lansoprazole	Peptic ulcer, GERD	Enteric release tablet	Takeda	
Betaloc ZOK	Metoprolol succinate	Hypertension (HTN)	tablet	Astrazeneca	
Harnal D	Tamsulosine HCl	Prostate hyperplasia and HTN	- tablet	Astellas	
Moxatag	Amoxacillin	Tonsillitis, pharyngitis	Prolonged-release pulsatile system	MiddleBrook Pharmaceuticals	(Chen, et al., 2017)
Antra MUPS	Omeprazole	Antispasmodic, antiulcer, GI inflammatory/bowl disorders	Delayed-release orally disintegrating system	Astrazeneca	
Theo-Dur*	Theophylline	Asthma, bronchitis and emphysema	-	Key Pharmaceuticals	
Liallda	Mesalamine	Ulcerative colitis	-	Shire	
K-Dur	Potassium	Hypokalemia with or without metabolic alkalosis in digitalis intoxication or in familial periodic paralysis	Sustained release	Key Pharmaceuticals	
Naprelan	Naproxen sodium 750mg	Peptic ulcer, GERD	Pulsatile release tablet	Alvogen Malta Operations Ltd	(Kallakunta, et al., 2017)
Prilosec	Omeprazole Magne sium	Peptic ulcer, GERD	Delayed release tablet	AstraZeneca	
Toprol-XL	Metoprolol succinate	Heart disease, hypertension	Extended release tablet	AstraZeneca	
Clarinex-d 24 hour	Desloratidine and Pseudoephedrine	Nasal congestion	Extended release tablet	Merck Sharp and Dohme Corp	
Oracea	Doxycycline	Infections	Delayed release capsule	Galderma Laboratories Lp	
Elixophyline*	Theophylline	Asthma, bronchitis and emphysema	Sustained release capsule	Actavis plc	(Hamman, et al., 2017)
*These are theophylline loaded pellets filled into capsules or compressed into tablets. It is unclear whether any of these products intended for gastro-retention.					

1.10. Pharmaceutical Quality by Design (QbD)

In this project, only the risk identification and the risk analysis (sub-categories of the risk assessment) were conducted per QbD, where the risk evaluation was based solely on the minimal approach of development. Hence, no statistical design of experiments (DoE) studies were conducted in the thesis. For future remarks, the DoE section 1.10.3 will serve as a guidance for the optimisation work during scaling-up manufacturing.

The total quality management (TQM) provides a plethora of concepts, where the QbD is seen as a sub-topic. The TQM is noticeably resourced by the collaborative approach of Six Sigma (6Q) movement, which is known for its business advantage across the various industries. One useful resource that widely recommended for a brief understanding of 6Q is the pocketbook of (George, et al., 2005). For the QbD in pharma, many resources are available from regulatory documents, quality books, published quality papers, as well as from the advanced software knowledge that applies the quality concepts and tools. A recent book that give a practical approach to the pharmaceutical QbD is (Schlindwein & Gibson, 2018).

1.10.1. An overview of the QbD approach for the pharmaceutical development

Quality by design can be defined merely as a strategic approach to quality, where a proactive thinking is paramount. Although the QbD implementation will be of high cost initially, it is expected to reduce the long-term costs, as the needs for the troubleshooting are expected to be minimised (Zhang & Mao, 2017). Unlike end-testing the quality, the QbD concerns with the continuous improvement, via a continuous and structured understanding of process attributes and product attributes. This proactive quality work will provide the privilege of being more informative about the unforeseeable risks (Zhang & Mao, 2017). In 2003, the US Food and Drug Administration (FDA) launched the current Good Manufacturing Practices (cGMPs) for drugs, which is a

comparable version to the International Conference of Harmonisation Quality 6 document (ICH Q6). The cGMP launch along with other quality documents have increased the awareness toward obtaining the higher level of quality assurance in all stages, from the research and development to the large-scale manufacturing. Some common and some tailored tools can be used in accordance with the stage of the product lifecycle (Zhang & Mao, 2017). After that, the ICH set up the so-called the enhanced quality by design (QbD) approaches for the pharmaceutical development and manufacturing. Where the ICH encourages the adoption of the QbD approaches over the minimal/traditional approaches, for the pharmaceutical development (ICH, 2009), see Figure 1.16 The main documents of interest in the ICH quality guidelines for the QbD initiative are as follows:

i. ICH Quality 8 (Q8): Pharmaceutical Development (PD) guidelines.
ii. ICH Quality 9 (Q9): Quality Risk Management (QRM) guidelines.
iii. ICH Quality 10 (Q10): Pharmaceutical Quality System (PQS) guidelines.

The QbD defined by the Q8 as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (QRM)". The detailed implementation of QbD was discussed by Q9 (ICH, 2005) and Q10 (ICH, 2008). The quality risk management process (QRMP) summarises the major umbrellas of the QbD work, see Figure 1.17. The QRMP also involves the application of the process analytical technology (PAT) tools. The QRMP categories consists of the following:

i. The risk assessment: for the process and product development, which is the main focus in the work of this project.
ii. The risk control: for the control strategy development.
iii. The risk review: for the continual improvement.

The risk assessment defined by the Q9 as “an assessment that consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards” (ICH, 2005). The risk assessment consists of the following:

i. Risk identification: for identifying all potential factors, using, for instance, the Fishbone diagram tool.
ii. Risk analysis: for analysing all potential factors, to select high-risk factors, using, for instance, the failure mode effect analysis (FMEA) tool.
iii. Risk evaluation: for evaluating the outcome of high-risk factors, using, for instance, the design of experiment (DoE) tool.

The various process and formulation factors in the cores making, coating and tabletting of floating pellets will urge the needs for risk assessment study per QbD, that will not only offer systematic understanding but also will ease the scale-up of the floating pellets for the pilot and production scales. The risk assessment will be based on the literature and the preliminary/screening experiments, in attempts to select and initially assess the high risk factors. These factors to be further tested in the enhancement and optimisation studies, where the updated risk assessments can be obtained (ICH, 2009). The aspects of early on planning and the set-up of experiments in the risk assessment stage are considered the backbone of the QbD. It is where the proper risk analysis can be ensured as viewed by many regulatory agencies, like FDA and ICH, as the most important stage. Therefore, collecting good data from pre-knowledge in literature and preliminary experiments is vital for obtaining a solid risk assessment (Hand, 2008) and (Eriksson, et al., 2008). The risk analysis will allow the selection of best factors and factors settings to build the DoE model. The DoE model will provide an experimental worksheet, where then it allows for the results from these experiments to fit in it, which provides a prediction for the design space (DS). Here is where the risk evaluation leverages the risk analysis (Zhang & Mao, 2017). The FMEA and DoE will be introduced in the

upcoming sections. Some elaboration on the concepts of risk assessment will be particularly seen in chapters 2 and 3.

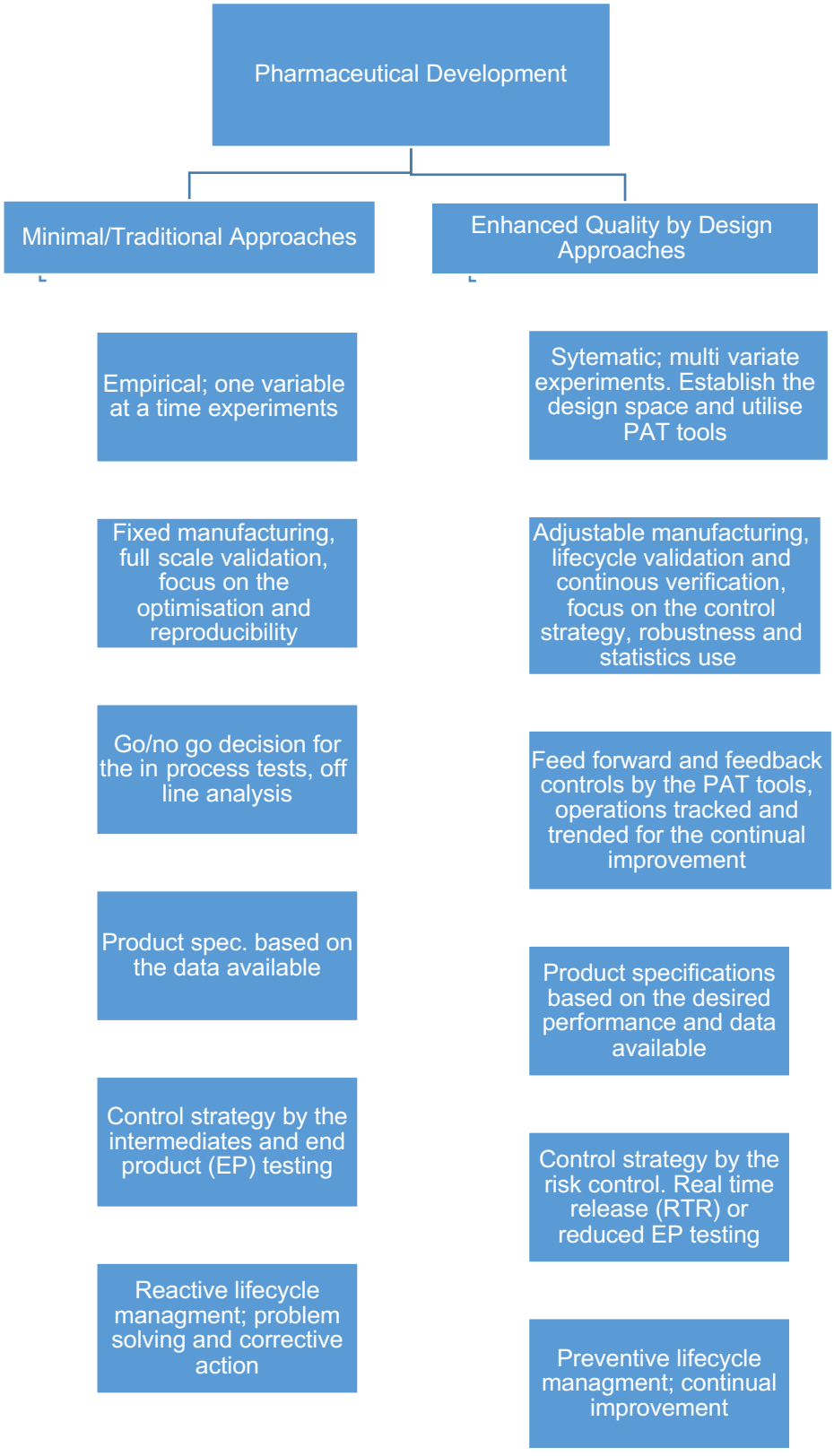


Figure 1.16: A comparison of the different pharmaceutical development approaches based on and adapted from ICH-Q8 guidelines.

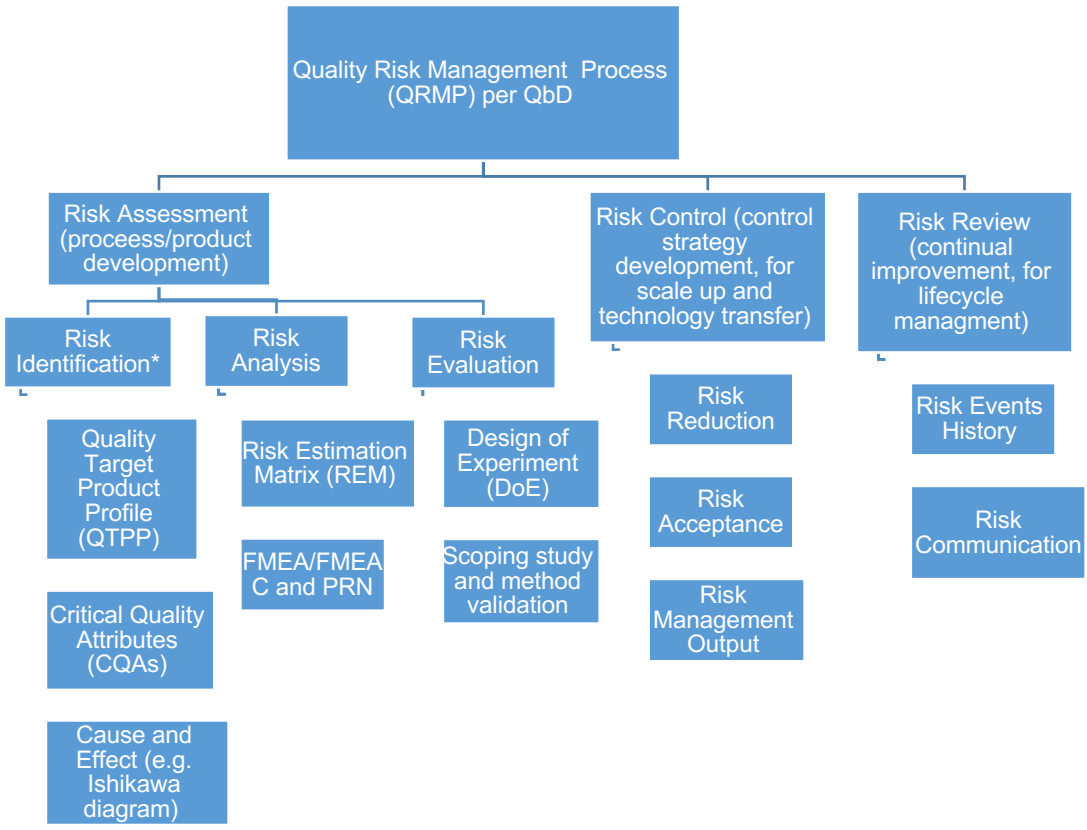


Figure 1.17: Quality risk management process (QRMP) that comprise most of the quality by design concepts stated by ICH-Q8, Q9, and Q10 guidelines. *All of these risk identification tools are needed to be used in the QbD work, while other risk assessment categories will require at least one tool per the category.

1.10.2. An overview of the failure mode effect analysis (FMEA)

This tool requires that all factors be identified first prior its application. Then all factors will be intensively investigated for their tendency toward failure in the overall outcome of the product and/or the process.

The failure descriptors will be as follow: (1) failure severity, (2) failure probability and (3) failure detectability. Semi-quantitatively, each of these failure descriptors will be risk numbered as low risk/1, medium risk/2, high risk/3, or very high risk/4 against each factor. The risk numbering is based on the analyser/s pre-knowledge. After that, these numbers of each factor will be multiplied by each other, to obtain the so-called the risk priority number (RPN) (Zhang & Mao, 2017) and (George, et al., 2005).

A threshold RPN value will be set based on the pre-knowledge, the experimenter knowledge and the preliminary studies. Beyond that threshold, the potential high-risk factors are identified. The pre-knowledge is primarily from the literature and from the expertise of the analyzer/s, while the preliminary studies are from the initial risk evaluation (Wang, et al., 2015).

This knowledge will be updated and reviewed as the risk evaluation advance, particularly, during the enhancement work. Hence, these updates will allow the establishment of the risk control and the risk review. The latter two stages of QRMP are more relevant to the pharmaceutical industry (ICH, 2005) and (ICH, 2008).

1.10.3. An overview of the statistical design of experiments (DoE)

During the last decade, the statistical DoE has increasing applications in the pharmaceutical sciences, like in (Qi, et al., 2015). The statistical DoE science is counted as an established sub-field of statistics. However, only some relevant information will be stated here. The QbD initiative is using this science to meet the needs for the high-quality development of various pharmaceutical processes and products. The DoE is considered one of the well-known tools in the risk evaluation stage of the QbD. The record for early DoE usage was linked back to the 18th century, where the physician James Lind used a form of DoE in his clinical trials. Some of the known contributors to the modern DoE field in the 20th century and beyond are seen in four eras as follows (Montgomery, 2013): A) the agricultural DoE era, primarily by Ronald Fisher contribution in the 1920s and early 1930s. B) The industrial DoE era, mostly by the input of Box and Welson in 1951, and Kiefer and Wolfowitz in 1959. C) The discrete-parts industrial DoE era, primarily by Genichi Taguchi and Wu in 1980, Kackar in 1985, and Taguchi in 1987 and 1991. D) The modified Taguchi and computer-assisted DoE era, by various contributors worldwide, the work of Douglas Montgomery and Anderson-Cook in 2009 is one example.

The pharmaceutical scientists and the pharmaceutical industry will be able, by the use of DoE, to define a robust region of operability in preparing the floating systems. The DoE will allow the systematic screening of materials and/or processes factors, at different levels. Then that will enable the systematic optimisation for the region of the best factors levels' combination. Hence, it potentially helps in producing robust and standardised specifications of mixture and/or process factors' levels, to be used for such formulations. That is, the DoE consolidates the QbD concepts in the pharmaceutical formulation development (Eriksson, et al., 2008).

To sum up, the DoE is an innovative approach for risk evaluation, as it elucidates more information than the traditional/intuitive approach of one at a time experiments. It runs factors' levels simultaneously through a mathematical model, usually through the use of statistical software. The DoE designs are mainly classified into two distinctive categories, the full factorial designs, and the fractional factorial designs (Zhang & Mao, 2017) and (Eriksson, et al., 2008), see Figure 1.18.

The DoE designs listed in Figure 1.19 are based on the DoE objective, the design class, and design family. Also, the DoE use for either mixture or process factors or both was noted there.

Figure 1.18: Showing diagrams for (A) the full factorial design; 2^3, and (B) the half fractional factorial design; 2^{3-1}. These designs are for 3 factors, 2 levels each, but the second model is taking only the half of the experiments in the first model. The diagrams were drawn by the author, similar ones are seen in the Minitab website (Minitab, 2017).

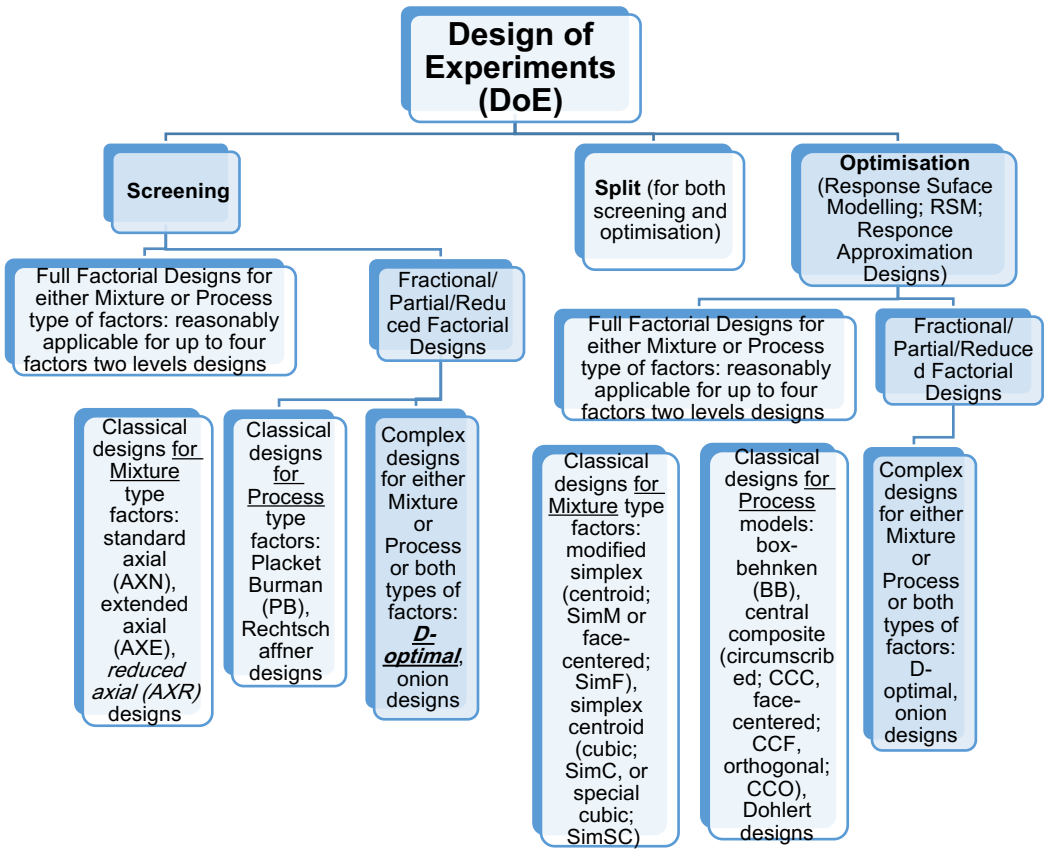


Figure 1.19: The DoE objectives and the statistical models involved as per objective and as per the design category (Erikson, 2012).

1.10.4. The use of the QbD in the floating dosage forms development

Although certain floating pellet systems have been proven to be promising, they are yet complex and prone to high variability as seen in the literature. That may discourage their transfer to the industry. Additional scalability issues include the multiple stages of manufacturing, the longer processing time, and the technically tedious processes that are prone to errors. Also, a skilled and knowledgeable formulator is necessary to develop the formulation and to oversee the entire manufacturing process.

Therefore, quality by design (QbD) approach for the floating pellets development is largely needed. The use of DoE in floating systems (FDDS), including floating pellets systems (mupFDDS) and tableted mupFDDS was evident by numerous studies. It is recently evident by those making the pellets using the extrusion and spheronisation processes, like (Li, et al., 2014) and (Qi, et al., 2015). A region constraint (irregular region) can be tried for trouble-shooting using the D-Optimal design. That can result from the use of largely different factors' ranges of mixture type. This issue was of relevance to this project, namely, for the core pellets (risk evaluation results per the statistical DoE are not shown). Apart from the use of DoE, the other risk assessment tools were not studied before for the floating pellets systems. Therefore, the aim here is to explore the benefit of the other risk assessment tools as well, like the use of cause and effect diagram (Fishbone diagram) and the failure mode effect analysis (FMEA) tools for the floating pellets development.

1.11. Aims and Objectives

i. Aims:

(1) Assess the feasibility of making “double-coated, then the single-coated” floating pellets drug formulations, and assess their feasibility for tabletting.

(2) Obtain enhanced and novel floating pellets, which confirm the suitability (in terms of floating and drug release) of a simplified formulation (single coat as opposed to double coat) for product design and development of modified release oral solid dosage form.

ii. Objectives:

(1) Prepare core pellets, coated pellets, and ensemble pellets of the double-coat and single-coat floating pellets designs. That using the processes of extrusion and spheronisation, top-spray fluidised bed coating, and single-punch tabletting, respectively.

(2) After the making processes, analyse core pellets, coated pellets, and ensemble pellets of the double-coat and single-coat designs. That is mainly through image, drug release, and floating studies.

(3) Assess the feasibility of using a new spheronisation aid (Avicel HFE 102) in the core pellets making of the double-coat floating pellets design.

(4) After the latter objective is confirmed, assess the feasibility of incorporating various materials during the core pellets making of the single-coat floating pellets design, like incorportaing povidone (PVP), and sodium bicarbonate ($NaHCO_3$).

(5) Once the latter objective found feasible, enhance the core pellets and the film of the single-coat floating pellets design.

(6) For further processing, like pellets tabletting, use cushioning excipient to protect the film integrity of pellets and to ensure a sufficient binding to the coated pellets. That is to minimise film damage and to form strong tablets that are not friable.

Chapter Two:

Materials and Methods

2.1. Materials used for the Production of Floating Pellets

2.1.1. Excipients for the coated pellets (double-coated and single-coated pellets)

The chemicals (materials) used in this project, their roles, and suppliers are listed in the Table 2.1. For preparation of the double-coated pellets, the core pellets were loaded with anhydrous theophylline, and with Avicel PH101 or Avicel HFE102. Distilled water was the liquid binder. The sub-coat or effervescent layer (inner layer) was made with either 3.33 or 6.66 w/w% sodium bicarbonate, and with hydroxy propyl methyl cellulose (HPMC) of 80-120 centimetre Poiseuille (cP) viscosity grade The targeted coating weight gain is 11±1%. The retard coated layer (outer layer) was made of the polymethacrylates. The coating dispersion was diluted to 15% strength. The targeted coating weight gain is 11±1%. Eudragit NE30D is pre-plasticised by the manufacturer, and this grade is a form of polymethacrylate dispersion that has pH-independent solubility.

For preparation of the single-coated pellets, materials were incorporated the core pellets were loaded with anhydrous theophylline, Avicel HFE102, sodium bicarbonate, polyvinylpyrrolidone (PVP) 40,000 g/mol, and/or micronised crospovidone (Cros-PVP). Either distilled water or 10 w/w% ethanol was used as a liquid binder during the wet massing. The ethanol containing liquid binder was used in the enhancment work. The retard coat was also made of the Eudragit NE 30D. The dispersion was diluted to 15 w/w% strength. The targeted coating weight gain is 15.6±1%. In the enhancment work, the total volume of dispersion contains 25 w/w% ethanol, and the targeted coating weight gain is 6±0.5%

Table 2.1: The chemicals (materials) used in this project, their roles, and suppliers.

Chemical	Role (in this project)	Supplier
Anhydrous theophylline	Model drug	BASF, Ludwigshafen, Germany
Microcrystalline cellulose (MCC); Brand name: Avicel PH 101	Spheronisation aid	FMC BioPharma Philadelphia, USA (gift)
MCC co-processed with mannitol content of ~10%; Brand name: Avicel HFE 102	Novel spheronisation aid, cushioning agent	FMC BioPharma, Philadelphia, USA (gift)
Sodium bicarbonate ($NaHCO_3$)	Floating agent: carbon dioxide generating agent (pH-dependent)	Sigma-Aldrich, Gillingham, UK
Hydroxyl propyl methyl cellulose (HPMC) of 80-120 centimetre Poiseuille (cP)	Floating aid and binder	Sigma-Aldrich, Gillingham, UK
Polymethacrylates; Brand name: Eudragit NE 30D. It contains 1.5% nonoxynol as an emulsifier	A sustained drug release agent, a gas retarding agent, and a swelling-control agent	Evonik Industries, Darmstadt, Germany (gift)
Polyvinylpyrrolidone (PVP or Povidone) 40,000 g/mol	a hydrating agent as a swelling aid	Sigma-Aldrich, Gillingham, UK
Micronised cros-povidone; Brand name: Kollidon CL-M	a hydrating agent as a swelling aid	BASF, Ludwigshafen, Germany

2.1.2. Excipients for the ensemble pellets

The ensemble pellets were formed mainly by the compression of the pre-prepared drug-loaded coated pellets, along with either cushioning pellets or cushioning powder. The cushioning agent used was the Avicel HFE102 grade only, with or without using a 10% ethanol during the wet massing stage of pelletisation, more details will be in the preparation section 2.2.

2.2. Preparation of the Floating Pellets

Table 2.2 summarises codes used for floating pellets batches. The preparation process parameters for the pelletisation, coating, and tabletting were listed in Table 2.3-4. The process parameters during preparation were listed in Table 2.5.

Table 2.2: Codes used for floating pellets batches*

Batch Code**	Key Differences in Compositions	Location in Text
B1D-PH,40,6	Avicel PH101, 40% drug loading, 6.6% $NaHCO_3$***	Chapter 3 (Double-Coated Floating Pellets, and Tabletting Feasibility)
B2D-PH,40,3	Avicel PH101, 40% drug loading, 3.3% $NaHCO_3$	
B3D-HFE,40,6	Avicel HFE102, 40% drug loading, 6.6% $NaHCO_3$	
B4D-HFE,40,3	Avicel HFE102, 40% drug loading, 3.3% $NaHCO_3$,	
B5D-PH,60,6	Avicel PH101, 60% drug loading, 6.6% $NaHCO_3$	
B6D-PH,60,3	Avicel PH101, 60% drug loading, 3.3% $NaHCO_3$	
B7D-HFE,60,6	Avicel HFE102, 60% drug loading, 6.6% $NaHCO_3$	
B8D-HFE,60,3	Avicel HFE102, 60% drug loading, 3.3% $NaHCO_3$	
B7D2-HFE,60,6, 15.3	Avicel HFE102, 60% drug loading, 6.6% $NaHCO_3$, 15.6% weight gain Eudragit NE15D	
B7D2CPowder	B7+ 47.3%**** cushioning powder	
B7D2CPellets	B7+ 47.3% cushioning pellets	
B1S-25P	25% PVP	Chapter 4 (Single-Coated Floating Pellets)
B2S-25N	25% $NaHCO_3$	
B3S-20P	20% PVP	
B4S-20N	20% $NaHCO_3$	
B5S-22.5N	22.5% $NaHCO_3$	
B6S-22.5P	22.5% PVP	
B7S-12P,12N	12.5% PVP, 12.5% $NaHCO_3$	
B8S-11P,11N	11.25% PVP, 11.25% $NaHCO_3$	
B9S-8P,3N,10E	8.6% PVP, 3.5% $NaHCO_3$, 10% ethanol	Chapter 5 (Enhancment of Single-Coated Floating Pellets)
B10S-12P,47HF,10E	12.5% PVP, 0% $NaHCO_3$, 10% ethanol	
B11S-12CP,47HF,10E	8.6% cros-PVP, 3.5% $NaHCO_3$, 10% ethanol	
B12S-12P,47PH,10E	12.5% PVP, 0% $NaHCO_3$, 47.5% Avicel PH101, 10% ethanol	
B13S-60DL,10E***	0% PVP, 0% $NaHCO_3$, 60% drug loading, 10% ethanol	
B14S-2P,17N,10E	2.5% PVP, 17.5% $NaHCO_3$, 10% ethanol	
B15-Cushioning Pellets	100% Avicel HFE102	Chapters 3, 5 and 6
B9SLow	B9S + 33.3% cushion powder	Chapter 6 (Tabletting the Enhanced Single-Coated Floating Pellets)
B10SLow	B10S + 33.3% cushion powder	
B11SLow	B11S + 33.3% cushion powder	
B12SLow	B12S + 33.3% cushion powder	
B12SHigh	B12S + 66.6% cushion powder	
B13SLow	B13S + 10% cushion powder	
B13SHigh	B13S + 65% cushion powder	
B14SLow	B14S + 33.3% cushion powder	

B14SHigh	B14S + 66.6% cushion powder	
*All compositions will be detailed in the following tables of this chapter. Hence, here only the key compositions that help differentiating the batches were stated, to better guide the reader throughout the results chapters.		
**The number of all pellets and pellets containing batches made and analysed in the thesis are 34 batches.		
***The strength of e.g. the $NaHCO_3$ refers to the strength in the coating dispersion, where the actual amount of $NaHCO_3$ can be known when correlating to the obtained weight gain of the films. Other main fixed components in the double-coated pellets: 62.5% distilled water, and Eudragit NE (0% ethanol). The 0% ethanol in Eudragit is also used in the screening for the single-coated pellets. Another main fixed component in the enhanced single-coated pellets: Eudragit NE (25% ethanol). The single-coated pellets have varied water content, and that will be explained in the respective chapter.		
****The percentage of cushioning excipient is based on the total weight of the tablet.		

Table 2.3: Summary of the complete formulations' compositions for the double coated floating pellets.

Batch code	Core pellets compositions for the 80 g powder batch size*		% Liquid binder (distilled water) (with regards to the powder batch size)	Sub-coat layer compositions for 11±1% coating weight gain		Retard coat layer compositions for 11±1% coating weight gain	Compressed double coated pellets in 400mg tablet
	Grade and % of the spheronisation aid	% Anhydrous Theophylline		Sub-coating $NaHCO_3$: HPMC w/w%**	Plasticiser (PEG6000) w/w%	Retard coating	Cushioning excipients to drug loaded pellets w/w%
B1D-PH,40,6	Avicel PH101; 60%	40	62.5	6.66: 3.33	1.5	Aqueous Eudragit NE30D (ethyl-acrylate-methyl-meth-acrylate (EAMMA)) diluted to 15% strength	-
B2D-PH,40,3	Avicel PH101; 60%	40	62.5	3.33: 6.66	3.0		
B3D-HFE,40,6	Avicel HFE102; 60%	40	62.5	6.66: 3.33	1.5		
B4D-HFE,40,3	Avicel HFE102; 60%	40	62.5	3.33: 6.66	3.0		
B5D-PH,60,6	Avicel PH101; 60%	60	62.5	6.66: 3.33	1.5		
B6D-PH,60,3	Avicel PH101; 60%	60	62.5	3.33: 6.66	3.0		
B7D-HFE,60,6* **	Avicel HFE102; 60%	60	62.5	6.66: 3.33	1.5		47.3: 52.7
B8D-HFE,60,3	Avicel HFE102; 60%	60	62.5	3.33: 6.66	3.0		-
CP-cushioning pellets	Avicel HFE102; 100%	-	100	-	-	-	-
*10g from the narrowed size of 1-1.18 mm core pellets were subjected to the coating process.							
**All coating dispersions were freshly prepared in a total volume of 300ml prior the start of the coating process. Regarding the coating materials, the w/w percentages represent the concentration in the coating dispersions. Hence, the coating solids in the coated layers of B1 are the coating gain solids. Therefore, if 10% is the weight gain, and the core pellets intended for coating were 10g, then the coating solids are 1g.							
*** For tablets, the cushioning excipient was either the Avicel HFE102 powder (B7DCPowder) or Avicel HFE102 pellets (B7DCPellets).							

Table 2.4: Summary of the complete formulations' compositions for the single coated floating pellets.

Phase of formulation development	Batch ID	Core pellets compositions for the 80 g powder batch size*				Liquid binder (with regards to the powder batch size)	Retard coat layer compositions for 15.6±1% and 6±0.5% coating weight gain, respective to the development phase	Compressed double coated pellets in 400mg tablet
		PVP	Avicel HFE 102	$NaHCO_3$	Drug loading		Retard coating	Cushioning powder to drug loaded pellets ratio**
Screening phase	B1S-25P	25.00%	35.0%	00.00%	40%	18.75%	Fully aqueous Eudragit NE30D (ethyl-acrylate-methyl-meth-acrylate (EAMMA)) diluted to 15% strength +1.5% Nonoxynol 100 emulsifier (15Eud0Eth)	-
	B2S-25N	00.00%	35.0%	25.00%	40%	43.75%		-
	B3S-20P	20.00%	40.0%	00.00%	40%	31.25%		-
	B4S-20N	00.00%	40.0%	20.00%	40%	50.00%		-
	B5S-22.5N	00.00%	37.5%	22.50%	40%	50.00%		-
	B6S-22.5P	22.50%	37.5%	00.00%	40%	25.00%		-
	B7S-12P,12N	12.50%	35.0%	12.50%	40%	43.75%		-
	B8S-11P,11N	11.25%	37.5%	11.25%	40%	43.75%		-
Enhancment phase	B9S-8P,3N,10E	08.60%	47.9%	03.50%	40%	37.50%	Eudragit NE30D (ethyl-acrylate-methyl-meth-acrylate (EAMMA)) diluted to 15% strength and to 25% ethanol strength +1.5% Nonoxynol 100 emulsifier (15Eud25Eth)	33.33:66.66
	B10S-12P,47HF,10E	12.50%	47.5%	00.00%	40%	50.00%		33.33:66.66
	B11S-12CP,47HF,10E	12.50%(Cros-PVP)	47.5%	00.00%	40%	100.00%		33.33:66.66
	B12S-12P,47PH,10E	12.50%	47.5% (PH101)	00.00%	40%	56.25%		33.33:66.66, and 66.66:33.33
	B13S-60DL,10E***	00.00%	40.0%	00.00%	60%	62.50%		90:10, and 55:65
	B14S-2P,17N,10E	02.50%	40.0%	17.5%	40%	50.00%		33.33:66.66, and 66.66:33.33

	B15-cushioning pellets	00.00%	100%	00.00%	00%	100%		Not Applicable
*5g from the narrowed size of 1-1.18 mm core pellets were subjected to the coating process.								
**The cushioning powder ratios were selected to 1) allow for a sufficient binding and cushioning, 2) ensure that the drug-loaded pellets are meeting the required dose loading in the tablet.								
***B13S batch was of different cushioning powder ratio, due to that the medicated pellets were having higher drug loading (i.e. 60% instead of 40%). The tablets batches codes were B9SLow, B9SHigh, and likewise for the enhanced pellets.								

Table 2.5: Summary of process parameters for the development double and single coated floating pellets that includes (pelletisation, coating and tableting).

Mixing parameters	**Value/ type used**	**Extrusion parameters**	**Value/ type used**	**Spheronisation parameters**	**Value/ type used**	**Coating parameters**	**Value/ type used**	**Tableting parameters**	**Value/ type used**
Mixing load	80g powder+ specific amount of water	**Extrusion load**	125 g*	**Spheronisation load**	~80 g*	**Coating load**	6-10 g	**Tablet feed size**	400mg
Mixing time	10 min	**Extrusion time**	5 min	**Spheronisation time**	10 min	**Coating time**	1.5-2 hr	**Die depth**	5-5.5 rounds
Mixing speed	3	**Extrusion speed**	30 rpm	**Spheronisation speed**	2500 rpm	**Coater nozzle size**	0.8 mm	**Compression force**	21.5 kN**
Mixer type	planetary	**Extruder type**	Radial	**Spheronisation disc design**	Cross-hatched	**Coater type**	Top-spray fluidised bed	**Tebletting machine type**	Single-punch
-	-	**Extrusion screen size**	1.2-1 mm	**Spheronisation disc cross hatch pyramid diameter**	3 mm	**Coating liquid tube diameter**	0.8 mm	**-**	-
-	-	**-**	-	**Spheronisation disc diameter**	120 mm	**Others**	See Tables 2.4-5	**-**	-
*The extrusion load was divided into nearly 5 proportions of 25g -dependent on the liquid binder amount-, which were fed one at a time. The typical spheronisation load is 100g for this disc diameter (120 mm), This load or less will provide a desired robe-like movement (Caleva, 2015).									
**The desired compression force was found to be at 21.5 kN, it was obtained by trial and error (data not shown).									

2.2.1. Pelletisation/core pellets making process

The powder was wet mixed by a process called wet massing. The pelletisation process was conducted using the extrusion/spheronisation method. The obtained wet core pellets were dried on the top of the oven at a surface temperature of 52 °C. Dried core pellets were stored in glass jars ready for the core pellets analysis and the subsequent coating and tabletting processes. The pelletisation process is shown in Figure 2.1. The process can be understood from (Sungthongjeen, et al., 2006), (Politis & Rekkas, 2011), (Korakianiti, et al., 2000), (Mehta, et al., 2005), (Puah, et al., 2014), (Chu & Chaw, 2012), (Low & Chaw, 2012) and (Koester & Thommes, 2010).

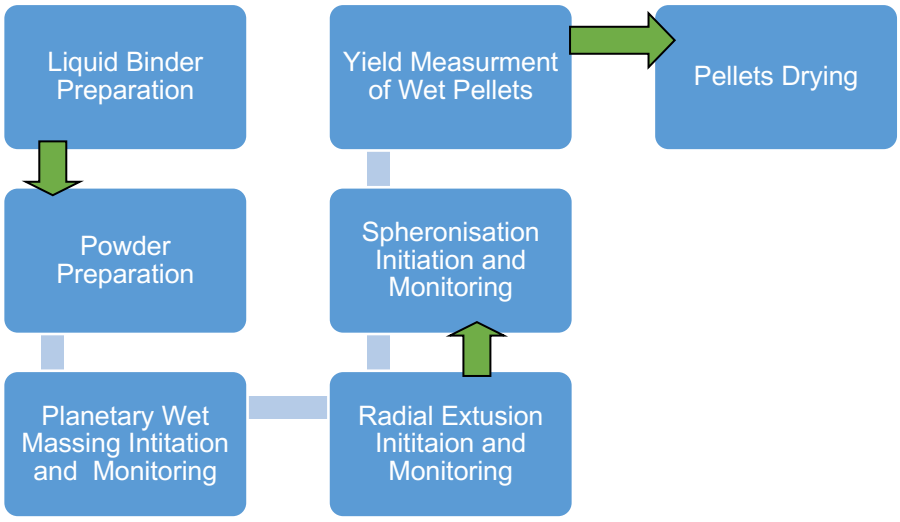


Figure 2.1: A summary of the pelletisation method for the pharmaceutical core pellets at a lab scale.

i. Weighing the raw powders

The powders for making the core pellets (for making the intra-granular compsitions) were weight using Precisa analytical balance (four decimal places). For de-clumping, pre-sieving theophylline powder in an appropriate sieve size was performed.

ii. Planetary mixing

After sieving the theophylline powder, all powders were transferred into the planetary mixer (Kenwood Chef®; a simple 3-way-blade). The mixer was closed by its plastic cover, to avoid dusting out during dry-mixing

(pre-mixing) and wet massing. The planetary mixer has a. Pre-mixing was performed for 3 minutes at a speed setting of 3, then the wet mixing/granulation process was performed for 10 minutes at a speed setting of 4 (Puah, et al., 2014). Liquid binder was added in 5ml fractions every 1-2 minutes, until the required wet mass consistency was reached (Puah, et al., 2014). The consistency of the wet mass was checked using the hand-squeeze test. It was checked prior and after the last liquid binder additions, where the capillary state of the solid-liquid phase is expected to be near. The mixture's fluffiness was visually checked. When pausing the mixer, the sticky clumps on blades were scratched.

iii. Radial extrusion

The wet mass was extruded straight after reaching the required consistency, using Caleva® Extruder 20, with screen sizes of 1.2 mm or 1 mm. The run time was about 5 minutes, and the extrusion speed was set at a speed of 30 rpm, as recommended by Puah, et al., (2014). The extrudates size and structure was visually observed after the extrusion. The extrudates were stored in a light-protective and air-tight container/jar for no more than 30 minutes prior the spheronisation process (Puah, et al., 2014). It should be noted on the rollers of the extruder, if a thick layer appeared, it would be an indication that the wet mass was too wet. Upon spheronisation, that may form either dumbbells or enlarged pellets. On the other hand, if the wet mass was overly dry, dry and porous extrudates will be produced. Upon spheronisation, that may cause powdering (Caleva, 2015).

iv. Bench-top spheronisation

Extrudates were fed into the top-bench spheroniser of Caleva® Spheroniser (Model 120). The speed set was high at 2500 rpm with 10 minutes residence time. The latter was recommended by Pauh, et al., 2014) to achieve AR values ≤1.2. The pellets size and roundness was visually observed after the spheronisation.

v. Oven-top drying

After spheronisation, the product (pellets, or dumbbells, etc) was discharged into a collection tray. Then the product was oven dried at 52 °C for 2 hours until a constant weight was reached. The latter was determined by re-weighing (data not shown). The percentage yield was calculated after sieving, based on the weight before and after drying. The usable yields of pellets were stored in glass jars for later processing (Puah, et al., 2014).

2.2.2. Coating of the core pellets

The coating method is shown in Figure 2.2.

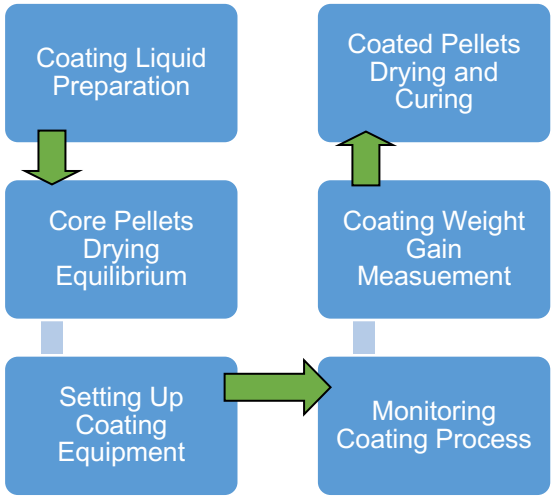


Figure 2.2: A summary for the fluidised-bed coating method for the pharmaceutical core pellets at a lab scale.

i. Coating liquids preparation

The compositions of all coating liquids used in this project are listed in Tables 2.2-3. The coating process parameters were listed in Tables 2.5-7.

Hydroxyl propyl methyl cellulose (HPMC) dispersion:

HPMC solutions were prepared using the cold blending method in a low shear paddle mixer (Heidolph RZR 2041). At RT, distilled water (of two third the targeted amount) was weighed and added to the intended glass container. The mixer speed was set at 300 rpm (Dow, 2002), and the

duration of mixing is 2 hours. The smallest amount of powder was added first to the liquid as follows, the polyethylene glycol (PEG) 6000 plasticiser, then sodium bicarbonate, then HPMC 80-120 cP. The HPMC addition will need at least 10 minutes. A cautious and gradual addition of HPMC into the liquid is needed, to ease de-clumping. During the HPMC addition, the viscosity of coating liquid increases, thus the speed of mixing was gradually increased from 300 to 600 rpm.

Poly-methacrylate dispersions:

The original Eudragit NE30D contains 30% poly-methacrylates. It was diluted to 15% poly-methacrylates prior its use. The dilution for less than 20% strength is recommended by (Evonik, 2016). The dilution liquid was either a distilled water only or a distilled water with 10 or 25% ethanol. That is, the final dispersion should be of 15 w/w% solids and 10 or 25 w/w% ethanol content.

ii. The coating process

An overview of the coating process:

The coating procedure was adapted from (Evonik, 2016) as possible. Depending on the design of the formulation made, the coating was performed for either one or two coating layers, using the top-spray fluidised bed coating of Caleva Mini Coater/Drier 2, see Figure 2.3. The fluidisation should result in a ring-like movement of pellets that can be checked visually. The coating process parameters were as seen in Tables 2.6-8. The targeted weight gain in mg= (weight of batch size* weight gain %)/ 100. The obtained coating weight gain %= (the obtained weight gain in mg* targeted coating weight gain %)/ targeted weight gain in mg). The WG was checked in 15-30 minutes intervals, to ensure that the obtained WG is not largely varied from the targeted WG.

For the double-coated pellets system, two subsequent coating layers with an intermediate drying step of 30 minutes at 60^{o}C were performed. Then, the wet coated pellets dried at 52 °C for at least 2 hours, until a constant weight was reached.

For the single-coated pellets system, one coating layer was made, then finally dried at 52 °C for 2 hours, to obtain <5% liquid content. Additionally, the curing was performed for 22 hours at 52 °C. Hence, the drying was extended to include static curing for 24 hours in the single-coated systems. The latter was because that the curing ensure complete plasticisation of the retarding polymer, which will avoid changes in the system's functions with time upon storage. Besides, the additional curing time of 22 hours was not showing a difference in the drug release and floating profiles.

Free films preparation

Approximately 10 ml of the pre-prepared coating solution was poured into a flat glass dish, then placed on the top of the oven at 52 °C, for two hours or until no change in weight loss was recoded. The film's thickness was 0.2 mm, using a micrometre of Moore and Wright Metrics (Sheffield, UK)

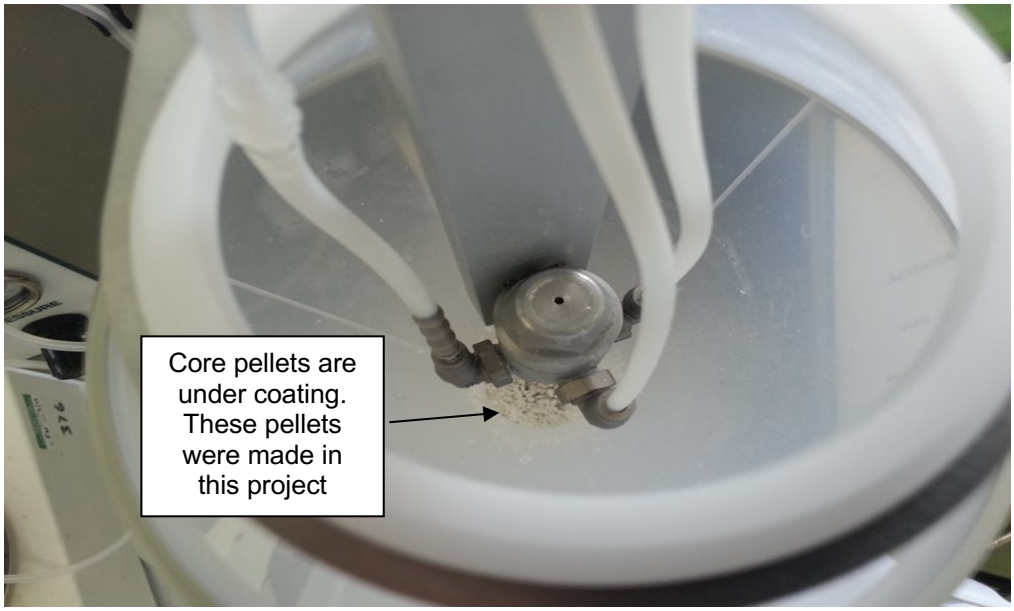


Figure 2.3: A top view for the coater's cone, where it shows the fluidised pellets during the top-spray coating process.

Table 2.6: Coating process parameters used for the double-coated system, enhanced by trial and error.

Coating solution*	**Coating liquid temp (°C)**	**Flow rate Pump speed (rpm)**	**Air pressure atomiser (bar)**	**Nozzle height ** (cm)**	**Pellets feed (g)**	**Fan air velocity (m^3/hr) *****	**Heater (°C)**	**Agitator frequency (Hz)**	**Coating solution flowrate (ml/hr)**
HPMC:$NaHCO_3$ of 3.33:6.66% w/w, with distilled water	RT	3.1	0.25-0.5 bar****	~10	6-10	135.73	35-45	10-11.7	~12
HPMC:$NaHCO_3$ of 6.66:3.33% w/w, with distilled water	RT	3.1	0.25-0.5 bar	~10	6-10	135.73	35-45	10-11.7	~12
Eudragit NE30D, diluted into 15% strength, with distilled water (15Eud0Eth)	RT	3.1	0.25-1 bar	~12	6-10	180.96-199.06	25	10-14.5	~12
*A magnetic stirrer was used to ensure the liquid homogeneity during coating.									
**The nozzle height was the measured distance between the pellets' bed and the nozzle's opening.									
*** The pipe's circular orifice diameter is 40 mm. Therefore, the air flow speed/velocity can be expressed from 108.58 m^3/hr to 289.53 m^3/hr, that correlates to the range of 6 to 16 mm/sec air flow speed (Engineering.com, 2017).									
****The pressure of 0.5 bar is the default one that usually used for this coater. The pressure unit of PSI stands for the pounds per square inch.									
Note: the full scales are as follows: 6-16 mm/s fan airflow, 10-25 Hz agitator frequency, 20-60 C heater, 1-4 RPM pump speed (peristaltic pump of 4 rolls), 0-2 bars (0-30 PSI) atomising air pressure. While the nozzle height against the product support mesh is typically 10-20 cm. The coating solution flow rate when 0.8 mm tube diameter used is 3.9-15.2ml/hr, which is based on the pump speed of 3.1 rpm (Caleva, 2015).									

Table 2.7: Coating process parameters used for the screening work in the single-coated system, enhanced by trial and error.

Coating solution	Coating liquid temp (°C)	Flow rate Pump speed (rpm)	Air pressure regulator; atomiser in bar (PSI)	Nozzle height (cm)	Pellets feed (g)	Fan air velocity (m^3/hr)	Heater (°C)	Agitator frequency in Hz (%)	Coating solution flowrate (ml/hr)
Eudragit NE30D, diluted into 15% strength, with distilled water (15Eud0Eth)	RT	3.1	0.25-1 bar (3.75-15 PSI)	~12	2-5	180.96-199.06	25	10-14.5	~12

Table 2.8: Coating process parameters used for the enhancment work in the single-coated system and in the tableted system, enhanced by trial and error.

Coating solution	Coating liquid temp (°C)	Flow rate Pump speed (rpm)	Air pressure atomiser (bar)	Nozzle height (cm)	Pellets feed (g)	Fan air velocity (m^3/hr)	Heater (°C)	Agitator frequency (Hz)	Coating solution flowrate (ml/hr)
Eudragit NE30D, diluted into 15% strength, with 25% ethanol (15Eud25Eth)	RT	3.55	0.625	~7	5	162.87	25	10.7	~13.5

2.3. Preparation of the Ensemble Pellets

The ensemble pellets consisted of drug-loaded pellets, and cushioning materials of either powder or pellets forms. The cushioning pellets consisted of Avicel HFE 102 (Microcrystalline cellulose; MCC, co-processed with ~10% mannitol) were made as described in section 2.2.1, where 10% ethanol was used as liquid binder. The used size fraction of the cushioning pellets was similar to the used size fraction of the drug-loaded core pellets (1.0-1.18 mm). Each tablet's components were weighed separately for each tablet. After which, the tablets were made, using a single-punch tabletting machine (Manestry Type F3, Liverpool, UK). Fitted with a flat-faced punch of 9.6 mm, to reach a target mass of 400 mg with a tablet thickness of 4.65 mm and a diameter of 9.6 mm. The compression force was adjusted to achieve a targeted crushing force of ~5 to 7 KgF (49.03-68.65 N).

2.4. Characterisation Methods for the Floating Pellets and the Ensemble Pellets

All of the characterisation methods used in this study are listed in Figure 2.4. It summarises how the compositions of the floating pellets were tested at all stages of perpetration (upon preparing raw materials, core pellets, coated pellets, and ensemble pellets). Hence, the formulation development will be started with the pre-formulation testing followed by the intermediate-product testing, and finally by the end-product testing. It is important to state here that not all of the characterisation methods were used in all chapters. Also, to minimise repetitions, once a test is stated for the core analysis, it will not re-stated for the coated pellets and ensemble pellets analysis. Based on the literature and by the trial and error, the preparation processes were analysed to a certain extent in this project (data not shown). All parameters of the characterisation processes were fixed based on the literature values.

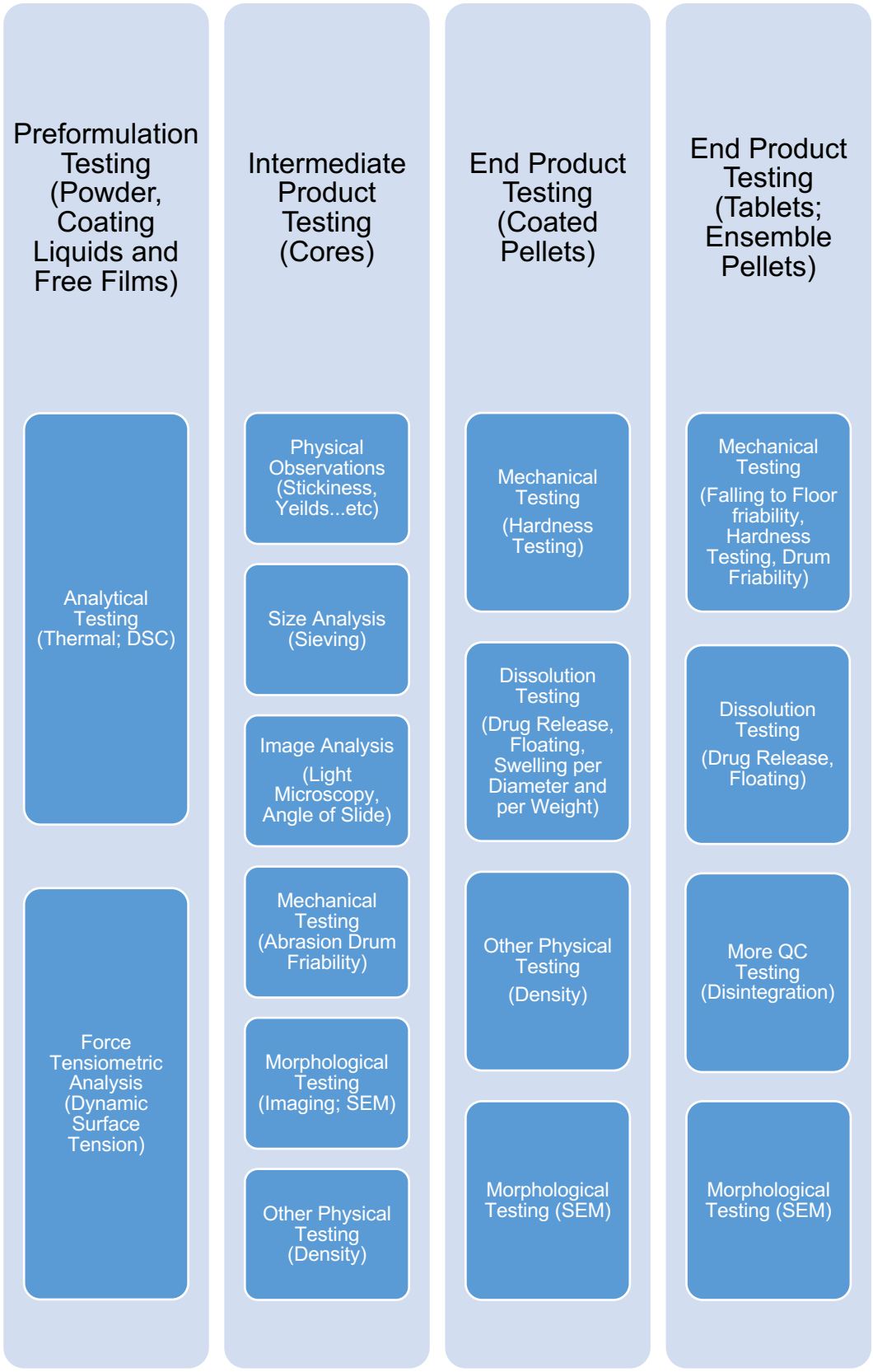


Figure 2.4: Showing the used characterisation methods in this project.

2.4.1. Pre-formulation testing

The results of pre-formulation testing are included in chapter 5.

i. Differential scanning calorimetry (DSC)

The DSC was used to determine the thermal properties of used powders and free films made from the coating liquids. The DSC was succinctly defined by (Chiu & Prenner, 2011) as a technique that "measure the specific heat capacity of thermally induced events as a function of temperature". The DSC is known to measure the melting (MP) and glass transition (Tg) of a polymeric sample upon melting and softening, respectively. Although both of which are energy-absorbing processes, the MP peak is an endothermic sharp peak that indicates crystal melting, while the Tg step change is an endothermic step that indicates amorphous softening. Hence, on the other hand, crystallisation and amorphosisation are exothermic processes that release energy. Crystal melting peak can be seen in (Bhattacharjya & Wurster, 2008).

Sample preparation for DSC

An automatic thermal analyser system was used (TA instruments Q1000). Samples of 3-4mg were weighed by the Mettler MT5 micro-balance of six decimal places (SNR-N86550). Samples were placed in an aluminium pan with an aluminium lid (Hermetic pan type), which is sealed by the pan press (Abdel Rahim, et al., 2015). Temperature calibrations before and after sample runs were performed using the indium standard. One emptied pan was sealed to be used as a reference, for a simultaneous measurement with each sample's measurement (Prasad, et al., 2013).

Software use for DSC

The refrigerated cooling system (RCS) was turned on. The mode of the run was set to a standard type, and the test was set to a ramp type. The run set to scan at 10 °C/min, from 0 to 300 °C. The latter range was selected based on the melting points of the materials tested (Abdel Rahim, et al., 2015). The test was under nitrogen atmosphere (50

mL/min), and s runtime of ~30 minutes for each sample (Mazurek-Wadołkowska, et al., 2013). The generated graphs were analysed using the Q1000 Analyser software (Abdel Rahim, et al., 2015).

Temperature calibration for DSC

The standard indium runs were performed before and after all samples runs to calibrate the temperature in the DSC equipment. The melting points (T_m=157.43-157.86 °C for before and after measurements) obtained were close to the literature T_m of the indium (T_m=156 C°) (TA-Instruments, 2009). The indium peak change after testing the film samples by 0.43 °C. The latter implies that the temperature of thermal events in the thermograms of films can varies by ±0.43 °C.

ii. Density of solids

The density of solids was obtained through the use of the multi-pycnometer (Quantachrome Instruments, MVP-D160-E, Boynton Beach, Florida, USA). This was used to derive the density values for powder materials, core pellets and coated pellets. The instrument was used to determine the pressure values required for calculating the apparent volume (V_p). A fixed amount of sample, typically 2 to 4 g was weighed, using Precisa analytical balance (four decimal places). The density of the samples was then derived from the apparent volume (V_p) value (Abdel Rahim, et al., 2015). Before the sample measurement, the equipment was calibrated according to (Mustafa & Chaw, 2016). The purpose of the calibration was to obtain the reference volume (V_R) and the total volume of the system (V_C). The equation used to determine V_P was as follows; $V_P = V_C - V_R [(P_1/ P_2)-1]$, where P_1 and P_2 are the pressures determined in the reference and sample cells, respectively.

iii. Force tensiometric analysis

It is a system for measuring various physical properties, including surface tension of liquids. The force tensiometer (Attension and One-Attension software, Sigma 700, Helsinki, Finland) was used to determine the physical characteristics of the coating dispersions. The following procedures were adapted from (Atension, 2014). The type of

force tensiometric study conducted in this work is the surface tension. The lower is the surface tension, the better are the spraying efficiency, wetting, and the spreadability of the coating liquid during the coating process. The samples were analysed using the Du-Nouy ring probe. The ring will be immersed and detached from the liquid surface, while the measurements are taken automatically.

2.4.2. Intermediate product testing: core pellets

i. Sieve size analysis

A nest of 9 sieves (pore sizes=0.25-2 mm) were placed on a vibratory sieve shaker (British Standard; BS sieves of Endecottes® EFL 2000). The shaker was used to sieve the dried core pellets for 10 minutes. Then, the pellets in each sieve were weighed, to determine the size distribution of pellets (Sungthongjeen, et al., 2006). For the purpose of further testing, the desired size range of core pellets is in the narrowed size fraction of 1-1.18 mm.

ii. Sphericity and swelling testing using image analysis

The core pellets were analysed for shape, using Feitz Dialux 22 light Microscope, with an attached camera (AxioCam MRc5, Magnification is 40X, Zeiss software). Thirty core pellets where captured from each batch, processed and analysed for each batch (Gupta, et al., 2011). The parameters determined from the software are Feret diameters, perimeter, circularity, area, and aspect ratio.

The swelling per diameter study was also based on image analysis. It uses the diameter, Dvolume, and surface area values. The individual coated pellet was placed in a glass dish and mounted on the microscope's stage. The images were captured at fixed intervals (0, 0.5, 1, 2, and 4 hours) before and after immersion in either medium of distilled water or 0.1N HCl. Then, the percentage increase in pellet's diameter (D) was determined, n=3.

iv. Friability study using the abrasion drum

The friability of the core pellets was measured by a friabilator (Copley®), where the core pellets were used (10 g). The abrasion drum is designed specifically for the pellets friability testing. The rotation speed was set for 200 rpm (Sungthongjeen, et al., 2006). The mechanical strength index (MSI) was calculated as follows; $MSI\%=(W_2/W_1)*100$. While the weight loss % was calculated as follows; $WL\%= [(W_1-W_2)/W_1]*100$. The W_2 is the remaining integrity of the core pellets after the test, W_1 is the total weight of the core pellets before the test.

v. Scanning electron microscopy (SEM)

The pellets were captured for images and analysed using scanning electron microscopy (SEM) (Hitachi, S-3000, 2^{ry} electron detector). The SEM was used to analyse the core pellets, coated pellets before and after dissolution. Also, the SEM was used for the coated pellets after crushing the ensemble pellets, and after the dissolution of the dis-assembled tablet. The procedure below was adapted from (Sungthongjeen, et al., 2006) as possible.

The dry coated pellets samples were mounted onto stages. The stages were glass stub with a double-sided adhesive tape. Some of the coated pellets were bisected into two halves by a sharp blade, where a thin wax piece was placed underneath the pellet before suctioning, to avoid squashing the pellets. The mounted pellets were coated with gold-palladium, using the Quorum Mini Sputter Coater (SC 7620), under a vacuum of an argon atmosphere (specifications not shown). Then, the samples were ready to be observed under the SEM.

That is the SEM image analyser software was used, where a manual ruler tool was used to measure the coating thickness of the bisected coating pellets. At the 500 μm capture magnification, the smallest and the largest coating thickness regions were visually observed as possible (n=3 pellets).

2.4.3. End product testing: coated pellets

i. Dissolution study

The procedure below was adapted from (Sungthongjeen, et al., 2006) as possible.

Theophylline absorbance calibration

The absorbance was measured using Single Beam UV/Vis Spectrophotometer (Camspec, M501). To enable the quantification of the drug theophylline, a calibration curve was produced. First, the concentrated drug solution or the stock solution of 200 mg/L was made. Subsequently, dilutions were made separately from the stock solution (20, 16, 8, 4, 2, 0.4, and 0.2 mg/L). The absorbance was determined at 268nm λ (USP25, 2002). The latter value was determined as the λ_{max} by an equipment scan.

Dissolution procedure

USP type 2/ paddle apparatus (Copley DT6) was used for the dissolution process of the coated pellets and ensemble pellets (37.0±0.5 °C, 50 rpm, 900 ml, 0.1N HCl, n=3). Based on the 200 mg dose of theophylline, drug loading (DL), and the coating weight gain (WG), the coated pellets were weighed. The drug loading is based on the initial amount of drug powder. It was assumed that any loss of the drug amount during the making of core pellets is comparable to the loss of the other compositions. Weight of core pellets in mg (for 40% DL)= [(targeted drug dose in mg*1000 mg)/ 400 mg= 500 mg. Weight of coated pellets in mg (for 6% WG)= [(weight of the core pellets in mg* targeted WG in %)/100] + dose of the core pellets in mg= 530 mg. The latter weight is used.

Also, the tablets of the corresponding dose were directly placed in the dissolution vessels. The absorbance measurements were at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours. The 5 ml samples were filtered through 0.25 μm membrane filter, then diluted with 0.1 N HCl to reach the required dilution of samples, where the maximum concentration can reach an

absorbance value of 1. The value of 1 is based on the calibration run. The dissolution equipment used is shown in Figure 2.5.

Model-dependent approach to compare dissolution profiles

For analysing the dissolution kinetics of the coated floating pellets in literature, the zero-order and Higuchi kinetics are commonly used (Sungthongjeen, et al., 2006). In this project, only the zero-order kinetics applied. From the calibration curve, the regression equation was used to determine the drug concentrations and the drug cumulative percentage of release from formulation at a specific time. If data fitting - of all time points shown in the results- produced a straight line, a regression value >0.9 should be confirmed to indicate high linearity that implies a high accuracy for calculating the slope. The slope here is the rate constant of the zero-order reaction, which determine how much drug dissolved over time. The rate-limiting mechanism of the sustained drug release from the dosage form can be a zero-order kinetics rate (Sungthongjeen, et al., 2006), (Allen, et al., 2005) and (Shargel, et al., 2012). The equation; $[A]_t$-$[A]_0$= -kt, is a form for the integrated rate law of the zero-order reaction (Pugh, 2013). It can be re-written as follows; $[A]_t$= -kt + $[A]_0$, which is in a similar form for the straight line (the regression line) equation; y=mx+b. Hence, $[A]_t$ is the concentration of the drug at a specific time on the y axis, -k is the slop of the line, t is the time on the x axis, and $[A]_0$ is the concentration of the drug at a zero time on the y intercept.

ii. Floating study

The procedural set up of floating study was below was adapted from Li, et al., (2014), which is similar to the dissolution procedure above. The onset of floating/floating lag time/time to float (TTF) and the duration of floating were all measured by visual observation. The percentage of floating pellets was calculated as follows, % of floating pellets = the number of floating pellets at the measured time/the initial number of the pellets)×100 (Hung, et al., 2014). The floated pellets were counted on the surface of the liquid as seen in Figure 2.5.

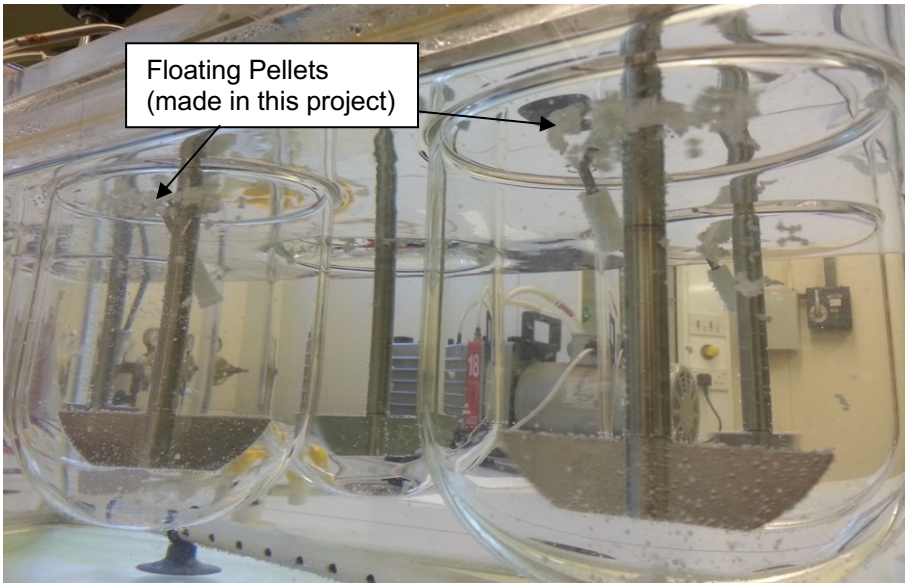


Figure 2.5: It shows the traditional dissolution type 2 USP paddle apparatus, where the floating pellets were either on or approaching the surface of the dissolution medium. The author took the image during the enhancement phase of the single-coated pellets systems.

iii. Surface tensile strength (STS) study

The procedure below was adapted from Bashaiwoldu, et al., (2004). The coated pellets were tested for their mechanical strength, prior compression into tablets. To ease the coated pellet positioning, the test position was set to 1.7 mm, the return position was set to 1.1 mm, and the Z-distance was automatically set to 5.4. The speed of 5 kg load was set to 1 mm/min (Puah, et al., 2014). After zeroing the force, one coated pellet at a time was carefully placed in the middle of the stage, and then the force was loaded. Then, the force was recorded in kg. This force was applied to cause deformation of the surface/film of the pellet, which was converted into Newton (1kg=9.80665N).

v. Swelling study per weight

One hundred milligrams of the coated pellets were poured in 300 ml beaker in the dissolution medium of either distilled water or 0.1N HCl. At pre-determined times (0, 0.5, 1, 2, and 4 hours), pellets' weight was checked. The pellets were removed and gently blotted with tissue papers, to remove the excess amount of the liquid found on their surfaces before being weighed. The pellets then returned to the beaker. The equation used to calculate the percentage of dissolution medium

uptake (DMU) was as follows; DMU= (weight after immersion- weight before immersion)/weight before immersion) × 100%. The DMU is also referred to as the swelling index (Ishak, 2015). In the project, the term swelling will be used instead of swelling index.

2.4.4. End product testing: ensemble pellets

i. Apparent porosity test

The apparent tablet density (g/cm^3) was calculated as follows, density=the tablet's mass/tablet's volume. The tablet's volume was based on the volume of the cylinder, which equals to πhr^2, where π is the circular constant that equals to ~3.14, and h is the tablet's thickness in mm. The r is the tablet's radius, which is the half of the tablet's diameter in mm. The tablet's thickness (h) and the tablet's diameter (d) were measured (n=12), using a micrometre (Moore and Wright Metrics, Sheffield, UK) (Abdel Rahim, et al., 2015). The apparent tablet porosity (unit-less) was calculated as follows, porosity=1-(density/1.4). While the percentage of the apparent tablet porosity was calculated as follows, porosity %=(apparent tablet porosity/true tablet's porosity)*100. The true tablets porosity was calculated from the tested volume of the tablet's composition, using the multi-pycnometer (Abdel Rahim, et al., 2015).

ii. Hardness and tensile strength test

The hardness tester of LabX Schleuniger was used (2E, Midland, Ontario, Canada), to examine the tablet's mechanical property (n=6). Breaking loads in kilograms-force (KgF) were recorded and were used to calculate the tensile strength (σ_t), according to the equation described by (Fell & Newton, 1970). The tensile strength (N/m^2) was calculated as follows; $\sigma_t = 2P/\pi dt$, P is the crushing load in Newton (N), d is the diameter in meter (m), and t is the thickness in meter (m). A unit conversion to mega Pascal (MPa) is needed as follows; MPa=Pascal or N/m^2/10^6 (Fell & Newton, 1970).

iv. Disintegration test

The disintegration of tablets was determined using Copley tester (DTG2000IS, Nottingham, UK), where the disintegration time was recorded. The disintegration basket consists of six tubes, each tube was used for one tablet (n=6). A vessel was filled with 800 ml distilled water and heated to 37±2 °C, where the basket was moved in and out. If 1 or 2 tablets failed to disintegrate, then the test will be repeated for 12 new tablets, where 16 tablets out of 18 tablets tested should disintegrate to pass the test (British-Pharmacopoeia, 2017). The tablets in the basket's tubes have ~1-4 cm depth of immersion into the disintegration vessel. The dipping rate was 30 dips per minute.

v. Friability study

Based on BP, 6.5 g of tablets were used. The de-dusting of tablets was before the initial weighing and before the final weighing. The drum speed was set at 25 rpm. The drum rotations were of 100 rounds/revolutions. If the pellets disassembled after tumbling, then the test was failed. If the powder loss was more than the targeted 1%, then the test will be repeated twice, and a mean of three values to be determined (British-Pharmacopoeia, 2017). The MSI and weight loss were calculated as in the friability test of core pellets.

2.5. Statistics

Independent two samples t-test was used, using Excel of Microsoft Office (Redmond, WA, USA), to obtain the p-values of various responses of the selected factors combinations (Sungthongjeen, et al., 2006). The statistical significance was tested using the t-test, unless if specified otherwise in the results. The scoping studies were performed for selecting the liquid binder amount, where the cubic-regression was applied, using the SPSS 21 software. The latter is to test the significance of water level interactions with other formulation factors in the core pellets. That is, the latter is to provide critical insights for the water level effect during the wet massing stage, to allow for determining the applicable water level of each factors combination in the core pellets.

2.6. Risk Assessment for the Floating Pellets Development

Within the scope of this project, the risk assessment was the appropriate QbD category of choice. See the risk assessment framework used in this project, in Figure 2.6. The risk assessment work in this project will identify all risks, analyse the level of risk for each factor, and to evaluate some of the high risk factors in details.

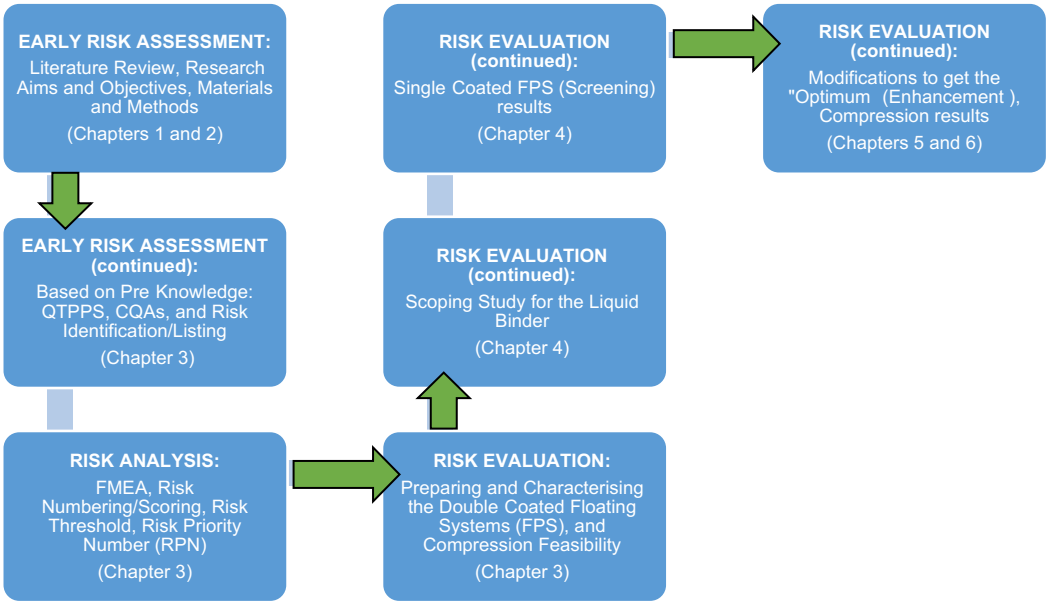


Figure 2.6: Show the framework for the risk assessment used in this project, with regards to the floating pellets development. This risk assessment framework summarises most of the spent efforts in making the story of this thesis journey.

The risk assessment is the bases for the subsequent QbD investigations, namely, for the risk control and the risk review categories of the QbD. The latter two risks activities are more relevant to the pharmaceutical industry. Hence, the risk assessment will ease the scale-up of the enhanced formulations, owing to its virtue of being the backbone of the QbD.

2.6.1. Risk identification

The quality target product profile (QTPP) was filled, to identify all attributes for the best product. The best product will consider the patient factors, like compliance and drug deliverability, the manufacturer factors, like cost-effectiveness and patency, as well as any other important considerations, which appear during the risk assessment. The

critical quality attributes (CQAs) or the product quality attributes (CPAs) were determined (based on literature as possible), to define the most critical attributes in QTPP table. The CQAs are defined based on the preliminary knowledge from literature. After then, the product, the process, the environment and the operator factors were identified and illustrated in the Ishikawa/Fishbone diagram (Wang, et al., 2015).

2.6.2. Risk analysis

The failure mode effect analysis (FMEA) tool was used, which can imply the risk estimation matrix (REM) tool as well. It was used to semi-quantitatively analyse the factors listed in the Ishikawa diagram, based on the preliminary knowledge from literature and preliminary studies (Wang, et al., 2015). After the literature review, the severity/impact of failure (S), the probability of failure (P), and the detectability of failure (D) were all explained for each factor, based on the risk definitions in Table 2.9. This explanation was further edited after preliminary studies (Wang, et al., 2015). Based on the provided explanation, each failure category was risk numbered. Then the numbers for each factor were multiplied by each other, to bring about what so-called the risk priority number (RPN). The numbering will be based on the risk definitions as well (Wang, et al., 2015). An intuitive threshold score for the RPN was set, where any factor exceeding this value was considered as a potentially high-risk factor. Hence, the critical process parameters (CProcPs) and critical product parameters (CProdPs) were then determined (Wang, et al., 2015).

Table 2.9: Shows the risk definitions for explaining, scoring and labelling the risk.

Risk Measure	Risk Score	Risk Definition	Risk Label*
Severity (S)	1	No impact or influence on product quality	No S
	2	Low impact or influence on product quality	Low S
	3	Moderate impact or influence on product quality	Medium S
	4	High impact or influence on product quality	High S
Probability (P)	1	Rare failure can happen	Low P
	2	Occasional failure can happen	Medium P
	3	Frequent failure can happen	High P
Detectability (D)	1	At all times, failure can be detected	High D
	2	In some cases, failure can be detected	Medium D
	3	Rarely, failure can be detected	Low D
	4	At all times, failure cannot be detected	No D
*Risk labels can be used to build the so-called the risk estimation matrix (REM). However, in this project, the risk scores will be used instead, to obtain the priority risk number (PRN). This allows a semi-quantitative analysis of the risk measures.			

2.6.3. Risk evaluation

During the risk evaluation, the statistical design of experiments (DoE) was not used. Rather it is the traditional (non-QbD) approach of development was conducted during the risk evaluation stage. Some of the high risk factors, in particular the composition factors of the core pellets were evaluated, which have the highest PRNs. Also, some other statistical testing were conducted as seen in section 2.5.

Chapter Three:

Screening Study for the Double-Coated Floating Pellets, and Tabletting Feasibility

3.1. Introduction

The gastro-retentive drug delivery systems (GRDDSs) are a type of the sustained release drug delivery systems (SRDDSs). The SRDDS is a major category in the modified release (MR) drug delivery systems. The GRDDS intended for slowly releasing the drug in the stomach. Floating drug delivery systems (FDDSs) are a type of GRDDS. The FDDSs have three categories, the effervescent system, non-effervescent system, and the mixed- system. The FDDS can be a single-unit or multiple-units of particulates (MUPS) system. The most common multiple units of particulates (MUPS) system is the millimetre sized pellets. Floating pellets (mupFDDS) will be buoyant on the gastric fluids, owing to its decreased bulk density when compared to the liquid's density. Floating pellets achieve floating as they contain floating agents and retard polymeric agents, usually through the application of coating layer/s. Using the extrusion and the spheronisation method, there are various designs for the floating pellets, ranging from no coating or matrix design to quadruple coating design. These layered designs are described in detail in section 1.3.4. The floating pellets formulations design used in this chapter is the double-coated design. The drug bioavailability is a major concern during the drug product development. It is affected by many drug products factors and physiological factors. Example of an important physiological factor is the gastric residence time (GRT). If the GRT is short and variable, then the drug release is incomplete above the absorption zone. The latter can cause reduced drug efficacy. The GRDDS prolong the GRT, to improve drug absorption, and the subsequent drug bioavailability (Sungthongjeen, et al., 2008).

In literature, the reason why more coating layers were added to the core pellets is to better control the performance of floating and the sustained drug release, and also to differentiate the drug product for increasing innovation. However, applying multiple coating layers is time consuming and not cost-effective. The development of floating pellets was intended first to be in the double-coat design, because the two layers system was found to be clearly successful in literature, and hence, it was perceived

to be a logical option to start with, where each layer has a distinctive and critical function. In this work, all attempts for making the matrix design failed as early as during the wet massing process of pelletisation. The results obtained in this chapter will be considered as a preliminary work for increasing the understanding and to uncover challenges prior to making a more intricate design (the single-coat design). Because the single layer will need to provide floating and drug release properties, which usually require hydrophilicity and hydrophobicity by the same retarding polymer, respectively. Hence, two opposing functions will need to be enhanced by only one layer of coating. The aim in this chapter is to screen for the feasibility of making the double-coated floating pellets systems, using a new spheronisation aid (Avicel HFE102). Screen for the feasibility of tabletting the obtained double-coated floating pellets systems. The objectives are to obtain new functionality for the Avicel HFE102 grade (as a spheronisation aid), by obtaining the drug-loaded pellets with an acceptable sphericity, and high usable size yield. Also, to understand the complications in the development of the double-coated floating pellets and the tabletted systems. For the tabletting studies here, the form of the cushioning agent will be addressed for the double-coated floating pellets, regarding the effect of the cushioning form on the tableting efficiency of pellets binding and film protection. Prior to conducting experiments, some early risk assessment is needed to ensure the selection of the high risk factors. When compared to less important factors, the high risk factors are expected to highly affect the quality of the floating pellets.

This chapter start with an early risk assessment work, to identify and analyse the risk factors involved in the development of the single-coated floating pellets. The risk assessment work is in line with the quality by design (QbD) initiative or methodology. The QbD is a development approach to the pharmaceutical formulations. This approach has relatively new concepts and tools to the pharmaceutical industry that oversees and improves the quality of the pharmaceuticals. It gives a new dimension to the pharmaceutical quality, as it sees the quality in a

proactive manner and in a patient-centric view. Therefore, it recognises the shortcomings, and consequently, increases understanding, cost effectiveness, and the total quality. It will complement the basic quality requirements regarding efficacy and safety in the pharmaceutical industry. First, the quality target product profile (QTPP) table was constructed, out of which, the critical quality attributes (CQAs) were identified. The number of factors listed and analysed were 95, out of which, 27 factors were identified as potentially very high risk factors. Some of the high risk factors were studied intensively as seen in this part of the chapter and subsequent chapters. However, the floating pellets will finally be enhanced in chapter 5.

3.2. Early Risk Assessment of Floating Pellets

This section will discuss the risk identification and the risk analysis of the floating pellets, regardless of the formulation design made in this thesis. Hence, the information here is also applicable to the single-coated pellets design as well. The risk evaluation per DoE is not conducted in this work. The risk evaluation was conducted through the characterisation tests in all results chapters, where various statistical analysis made (t-testing, and non-linear cubic modelling). However, the statistical design of experiment (statistical DoE) was not conducted.

3.2.1 Defining the Quality Target Product Profile (QTPP) and the Critical Quality Attributes (CQAs)

As recommended by FDA and ICH (ICH, 2009), the risk assessment per QbD was conducted by considering three risk sub-categories; risk identification, risk analysis, and risk evaluation. Quality target product profiles (QTPPs) were used to identify all the attributes of the best product characteristics, while the critical quality (product) attributes (CQAs/ CPAs) were determined from QTPPs, based on preliminary knowledge obtained from the floating pellets literature. The QTPP table, see Table 3.1, lists all of the desired attributes in the dosage form. These desired attributes are of benefit to the pharmaceutical industry and to the intended patients alike. The CQAs are the most challenging QTPP

attributes, which needed more efforts to optimise and to control. The CQAs were selected from the QTPP table as follows; >60% yield of cores, >90% yield of 0.71-1.4 mm size, ~1.1 aspect ratio (AR) for shape, 12-24 hrs sustained drug release, 6-12 hrs floating on liquids' surface, <1% weight loss of the tablets' friability, and 6-8 KgF (58.84-78.45 N) crushing force of the tablets' hardness.

Table 3.1: Shows the QTPP for the theophylline-containing floating pellets, where the CQAs are highlighted in grey*.

Attribute	**QTPP**
Dosage Form	Pellets in capsule
Route of Administration	Oral
Shape	Spherical, <1.2 aspect ratio (AR)
Strength	200 mg
Manner of drug release (membrane matrix)	Membrane-controlled system
Mechanism of drug release	Diffusion-controlled system
Dissolution specifications	12-24 hrs with R^2>0.9 regarding a zero-order drug release. (8 hrs drug release is acceptable).
Spheronisation yield	>60% after drying
Sieving yield	>90% 0.71-1.4 mm size range
Floatability	>50% floating for >4 hrs (preferably >90% floating for 6-12 hrs), floating lag time <15 min (preferably <3 min, and acceptable <30 min).
Surface hardness of coated pellets	>0.2 and <1.2 KgF (>1.96 and <11.77 N)
Mechanical Strength Index (MSI) coated pellets	>99%; <1% weight loss
Mechanical Strength Index (MSI) tablets	>99%; <1% weight loss
Hardness of tablets	6-10 KgF (58.84-98.06 N) crushing force**
Disintegration time of tablets	<5 min
*The hardness and friability of pellets were not studied in this results chapter. The enhancement chapter for the single-coated pellets addressed all of these attributes.	
**Fixed by trial and error, to ensure sufficient tablet strength with an acceptable friability.	

3.2.2. Risk Identification by the Fishbone Diagram

The product, process, environment and operator factors were identified and illustrated in the Fishbone diagram similar to (Wang et al., 2015). Factors of 95 were identified during the literature review process that have potential risk effect on the identified CQAs of floating pellets, see Figure 3.1. The variables of characterisation process parameters can also be important, especially, the dissolution process parameters. However, the optimisation of the characterisation process parameters is out of the scope in this project. Therefore, the characterisation parameters will be fixed as per literature.

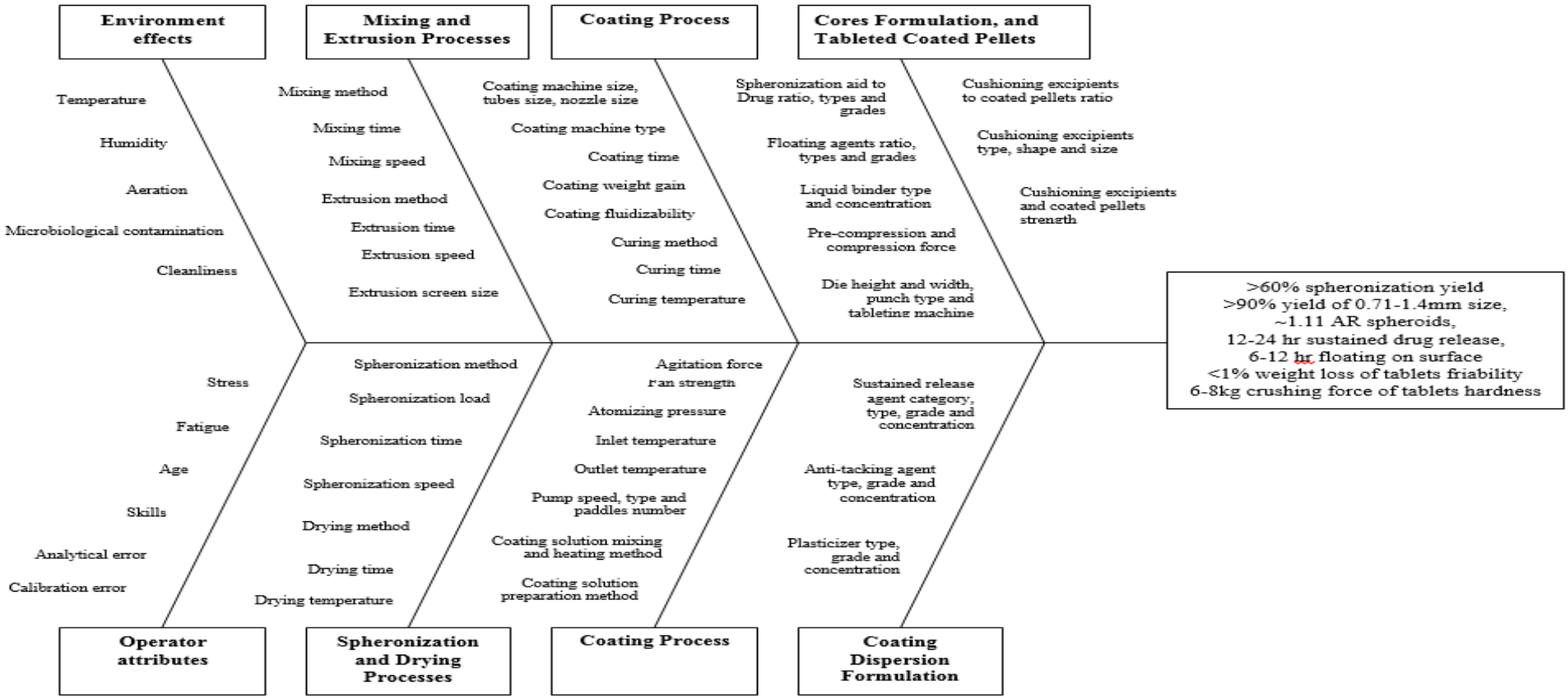


Figure 3.1: Fishbone (Ishikawa; Cause and Effect) diagram, where most possible causes/factors that contribute to the quality of multiple units of pellets as a floating drug delivery system (mupFDDS) are stated. Namely, the variables of the formulation components and the preparation processes, that leads to the effects/responses of the critical quality attributes (CQAs). The CQAs are seen in the far right box (fish head).

3.2.3. Risk Analysis by the Failure Mode Effect Analysis (FMEA)

After identifying all the contributory factors in the previous section, failure mode effect analysis (FMEA) was used to semi-quantitatively analyse each factor for the severity, probability and detectability of failures. The risk was assessed by obtaining the risk priority number (RPN) (Wang et al., 2015). After identifying all the contributory factors, an intensive and critical risk analysis of all factors was undertaken using FMEA, to reduce the number of factors to the most important ones only. The FMEA will semi-quantitatively analyse each factor for the severity, probability and detectability of failures. The risk was assessed by obtaining the priority risk number (PRN) (Wang et al., 2015). Based on the PRN threshold of 15, factors of 48 out of 95 exceeded the threshold and were identified as potentially high-risk factors. However, this number of factors is still high to investigate in the scope of this project. Therefore, a second PRN threshold of 20 was set, and 27 out of 95 factors were obtained as potentially very high-risk factors, see Figure 3.2. From the FMEA outcomes, the coating process variables are most numerous, and most of which are potential high-risk factors. This is owing to complexity of the coating process, regarding scale, operation and the other numerous critical variables involved, like coating liquid and core pellets variables.

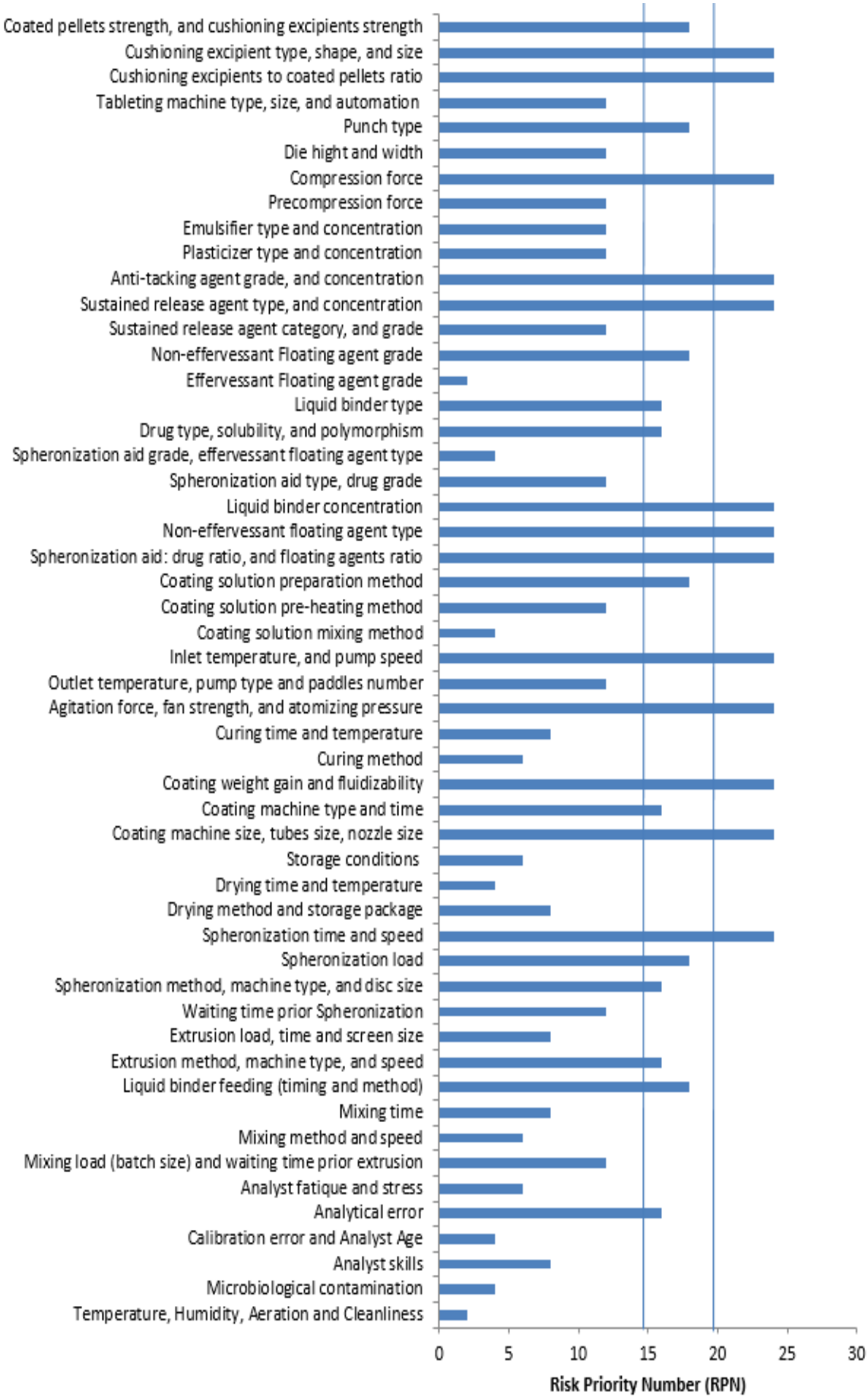

Coated pellets strength, and cushioning excipients strength
Cushioning excipient type, shape, and size
Cushioning excipients to coated pellets ratio
Tableting machine type, size, and automation
Punch type
Die hight and width
Compression force
Precompression force
Emulsifier type and concentration
Plasticizer type and concentration
Anti-tacking agent grade, and concentration
Sustained release agent type, and concentration
Sustained release agent category, and grade
Non-effervessant Floating agent grade
Effervessant Floating agent grade
Liquid binder type
Drug type, solubility, and polymorphism
Spheronization aid grade, effervessant floating agent type
Spheronization aid type, drug grade
Liquid binder concentration
Non-effervessant floating agent type
Spheronization aid: drug ratio, and floating agents ratio
Coating solution preparation method
Coating solution pre-heating method
Coating solution mixing method
Inlet temperature, and pump speed
Outlet temperature, pump type and paddles number
Agitation force, fan strength, and atomizing pressure
Curing time and temperature
Curing method
Coating weight gain and fluidizability
Coating machine type and time
Coating machine size, tubes size, nozzle size
Storage conditions
Drying time and temperature
Drying method and storage package
Spheronization time and speed
Spheronization load
Spheronization method, machine type, and disc size
Waiting time prior Spheronization
Extrusion load, time and screen size
Extrusion method, machine type, and speed
Liquid binder feeding (timing and method)
Mixing time
Mixing method and speed
Mixing load (batch size) and waiting time prior extrusion
Analyst fatique and stress
Analytical error
Calibration error and Analyst Age
Analyst skills
Microbiological contamination
Temperature, Humidity, Aeration and Cleanliness
0
5
10
15
20
25
30
Risk Priority Number (RPN)

Figure 3.2: Risk priority number (RPN) graph of the identified 95 factors for floating pellets formulation components and preparation processes. The risk score of each factor was determined semi-quantitatively through the failure mode effect analysis (FMEA), two thresholds were set for these RPN values; at 15 and 20, above which potentially high risk and very high-risk factors were identified, respectively.

3.3. Characterisation of the Core Pellets

The compositions of floating pellets are succinctly outlined in the codes table of pellets batches (Table 2.2) and detailed in Table 2.3. The preparation process parameters for the pelletisation, coating, and tabletting listed in Table 2.5.

The double-coated systems are expected to have floating and sustained drug release profiles that highly controlled by their coating layers. Hence, the variation in the size of the core pellets is expected to have low significance to the floating profile, as the floating will be highly controlled by the two layers. Hence, unlike the single-coated systems, the floating here is more dependent on the efficiency of the sub-coated layer rather than the swelled core pellets. Note that, a decrease in the core pellets size to 0.71 mm can reduce floating of a swelling system (data not shown).

3.3.1. Formulation and process variables for the core pellets

Core pellets were prepared according to the formulation and process parameters as outlined in chapter 2. The extrusion and spheronisation method of pelletisation is considered of a compaction mechanism. During preparation, long mixing time and higher mixing speed were avoided, as an increased swelling may result, where a reduced compactibility of the MCC can be obtained. The latter can affect the quality of the core pellets (DFE-Pharma, 2011) and (Muley, et al., 2016). Therefore, as recommended by Pauh, 2013, the mixing time, mixing speed and the extrusion time were at medium values, while the extrusion speed, spheronisation speed and spheronisation time were kept at high values (parameters shown in chapter 2). According to the initial screening trials and as stated by (Dwibhashyam & Ratna, 2008), the

extrusion and the spheronisation processes are more critical to changes in the formulation when compared to the tabletting process, like changes in water: MCC ratio and drug: MCC ratio. Therefore, the water level was maintained fixed at (62.5%), as it was fixed after some trial and error.

3.3.2. Coating weight gain as the coating yield

The coating yields for the sub-coating and the retard-coating layers are seen in Tables 3.2-3, respectively. In this work, the sub-coating dispersion of 11±1 % solids produced about 11±1 % weight gain within 90-135 minutes (i.e., 1.5-2 hours). Also, the retard coating of the aqueous Eudragit NE15 for ~11% weight gain takes 90-135 minutes (i.e., 1.5-2 hours). The approximate quantity used for the coating liquid was about 21±3 ml/batch, as the flow rate of the coating liquid was 12ml/h.

Table 3.2: Shows a summary of the coating process worksheet for the first layer (sub-coating layer of the HPMC and $NaHCO_3$), where the coating weight gain values (the coating yields) are seen.

Batch code	**Sub-coating dispersion**	**Weight loss of core pellets after 20 minutes drying at 50 °C (%)**	**Weight of core pellets (coating batch size) (g)**	**Weight gain (coating yield yield) after 135 minutes of coating and 45 minutes of drying at 50 °C (%)**
B1D-PH,40,6	HPMC: $NaHCO_3$ 3.33:6.66 %	0.20	10.08	10.0
B3D-HFE,40,6		0.57	07.01	10.1
B5D-PH,60,6		5.00	10.01	10.0
B7D-HFE,60,6		1.40	07.00	10.5
B2D-PH,40,3	HPMC: $NaHCO_3$ 6.66:3.33 %	0.30	10.01	10.5
B4D-HFE,40,3		1.30	10.02	20.0
B6D-PH,60,3		0.40	10.01	11.5
B8D-HFE,60,3		1.00	07.00	10.0
Notes: (1) The weight equilibrium step was used prior the coating to minimise the false negative weight gain effect during coating. Nevertheless, the weight loss during the coating can also result due to other reasons, as observed with 0.725-1 mm core pellets size, which can escape the cone upon spraying owing to their small size.				

(2) The pump was set to 100% to clean tube and the nozzle with the distilled water after 2-3 batches and for 20-30 minutes. The isopropanol (IPA) was used as well to clean the blocking caused by the polymethacrylates dispersion.

Table 3.3: Shows a summary of the coating process worksheet for the second layer (retarding layer of Eudragit NE), where the coating weight gain values or the coating yields are seen.

Batch code	Retard coating dispersion	Weight loss of core pellets after 20 minutes drying at 50 C (%)	Weight of core pellets (coating batch size) (g)	Weight gain (coating yield yield) after 135 minutes of coating and 45 minutes of drying at 50 °C (%)
B1D-PH,40,6	Eudragit NE30D, diluted into 15% strength, diluted with distilled water only	0.50	07.72	10.30
B3D-HFE,40,6		1.00	11.02	11.54
B5D-PH,60,6		1.16	06.88	10.13
B7D-HFE,60,6		0.23	08.80	11.27
B2D-PH,40,3		0.00	08.70	10.00
B4D-HFE,40,3		1.00	11.05	11.80
B6D-PH,60,3		1.00	06.52	10.00
B8D-HFE,60,3		1.00	09.10	10.00

3.3.3. Visual characteristics of the core pellets during preparation

The physical appearance, spheronisation yield, and the used narrowed size range of the different batches are presented in Table 3.4. The extrudates can show different visible thicknesses and surfaces (thick or thin, and smooth or perforated). The core pellets can show different visible shapes as well (dumbbell, irregular, rounded or round pellets). In this study, no dumbbell or irregular shapes were obtained. The batches (B1D-B14D) of high microcrystalline content (60%) showed thick and smooth extrudates, which is owing to the increased MCC content that increases the swelling of extrudates.

For the first time, a new functionality was discovered for the mannitol-containing Avicel HFE102 grade (as a spheronisation aid), which was successfully applied to make pellets using the extrusion and the spheronisation processes. Results revealed that the Avicel HFE102 grade can be at least as efficient as the Avicel PH101 grade.

The Avicel HFE102 consistently provide higher spheronisation yield and more narrowed size range (1-1.18 mm sieve yield) that reaches for up to 100%, and 44%, respectively. Regardless of the Avicel grade, the batches of higher MCC content (60%) can results in lower spheronisation yield 76.1-83.3% when compared to the batches of the lower MCC content (40%). Although that the high Avicel HFE102 content (60%) showed relatively less spheronisation yield (76.1%), the yield of the used narrowed size range (1-1.18 mm sieve yield) was higher than any other batch (44.2%). The latter may be owing to the mannitol content -in addition to the MCC content-, which could further increase the absorption of the distilled water, resulting in a better consistency for the wet mass.

Table 3.4: Summary of the visual observations of the core pellets during preparation and the total yield of the core pellets after spheronisation, drying and sieving.

Batch code* **	**Extrudates**		**Core Pellets**	**Core Pellets Yields (%)***	
	Appearance	**Notes****	**Appearance**	**Spheronisation Yield**	**Narrowed size range (1-1.18 mm Sieve Yield)**
B1D and B2D (PH,40)	Thick and smooth	Very high content of water	Rounded	83.33	24.82
B3D and B4D (HFE, 40)	Thick and smooth	Water content is a bit high	Round	76.05	44.21
B5D and B6D (PH, 60)	Thin and Smooth	Water content is a bit high, medium length (~1cm)	Round	94.55	20.16
B7D and B8D (HFE, 60)				100.00	27.00

Cushioning pellets	Wet sand-like	Smooth no stickiness, medium length (~1cm)	Round/ Spheres	56.00	32.20
***The spheronisation yield**: is the dry core pellets yield after spheronisation that based on the weight of the wet core pellets and the weight of the starting materials (powders). **The sieving yield**: is the size fraction yield of the 1-1.18 mm core pellets that based on the weight of the latter size fraction and the total dry core pellets.					
****The extrudates appearance had a medium length (~1cm).					
*****Batches codes can be defined in Table 2.3.					

3.3.4. Particle size analysis

A set of nine sieve stacks ranging from 0.25-2 mm were used to separate the sizes of the core pellets. The summary of the core pellets' size analysis is seen in Table 3.5 and Figure 3.3. In the size analysis of the core pellets, different fractions were calculated, including the used narrowed size range, the useable yields, and the fine and the coarse fractions. Also, the inter-quartile range (IQR) and the median class were calculated. For all batches, the IQR values were less than 0.4 mm, indicating that the variation from the mean is not highly skewed. The median values were about 1mm, which is within the usable range (0.72-1.4 mm), and highly close to the used narrowed size range (1-1.18 mm). Moreover, the coarse and the fine fractions were low (<15%), as desired, because these fraction are not usable for the subsequent coating.

Large usable yields (83-95.4%) and negligible coarse fraction (0-1.4%) were obtained for Avicel HFE102 containing core pellets, regardless of the drug loading level. In particular, when the Avicel HFE102 was used, a higher yield of the 1-1.18 mm size (27-44%) was obtained, while a slightly smaller yield of 0.71-1.4 mm core pellets was obtained. These findings were in comparison with the Avicel PH101. The Avicel HFE102 containing core pellets showed IQR values in the range of 0.28-0.3 mm, which indicates that the size distribution of these pellets is less scattered when compared to the core pellets of the Avicel PH101 grade (IQR=0.29-0.39 mm), especially seen in Figure 3.3 with the higher drug

loading batches (B7 and B8). This low scattering may indicate that the mannitol could slightly lower the overall spread of the core pellets' size during the spheronisation process, especially at higher drug loading. As complied with the latter finding, slightly higher usable yields (83-95.4%) with maintained sphericity were obtained. Hence, the mannitol in the Avicel HFE102 grade can provide a comparable or further aid in the spheronisation process, indicating that the Avicel HFE102 provided better plasticity for the wet mass.

The above quality attributes of the usable yields and aspect ratio are highly desirable during the pellets making using the extrusion and the spheronisation processes (Chu & Chaw, 2014). Besides, owing to the mannitol pore forming ability, this grade of mannitol-containing MCC may have a potential aid in floating, as it will be seen later in this chapter. Moreover, the core pellets of the Avicel PH101 with 40% drug loading showed an IQR value of 0.29 mm. In the first instance, this could indicate that a small fine fraction and a small coarse fraction were obtained. However, these fractions were found to be more than 14% of the spheronisation yield. Therefore, the low IQR value was not due to the small fine fraction and/or the coarse fraction. Instead, the low IQR was due to the large yield of the 1.18-1.4 mm core pellets (>45%).

Table 3.5: Shows the summary of the core pellets size analysis.

Batch code*	**1-1.18 mm yield (%)**	**0.72-1.4 mm yield (%)**	**Fine fraction (%)**	**Coarse fraction (%)**	**IQR (mm)**	**Median class**
B1D and B2D	24.82	85.73	10.26	4.01	0.29	1.18 mm (45.17%)
B3D and B4D	44.21	82.96	15.78	0.03	0.30	1.00 mm (44.87%)
B5D and B6D	20.16	82.80	12	5.20	0.39	1.18 mm (41.12%)
B7D and B8D	27.00	95.40	3.42	1.42	0.28	1.18 mm (46.8%)
* Batches codes can be defined in Table 2.3.						

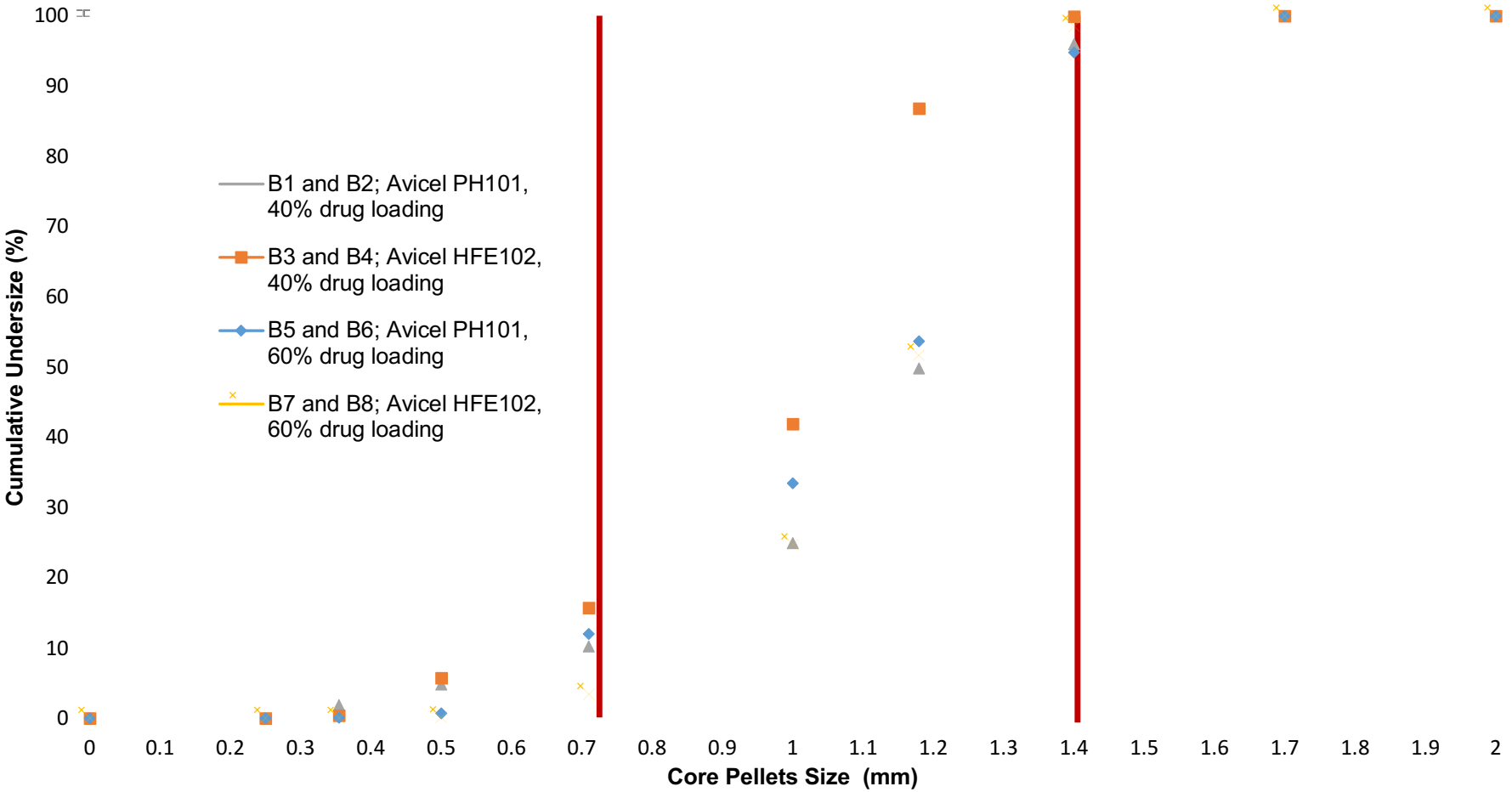


Figure 3.3: Shows the particle size distribution based on the cumulative undersize (%) of the sieved core pellets (n=1) intended for double-coating. The red vertical lines represent the range of the usable size fraction that suitable for the subsequent processes of coating and tabletting.

3.3.5. Sphericity testing by the image analyser

The core pellets were quantitatively analysed using the images from the light microscope, where the shape-related parameters were calculated. These parameters were the Feret diameters, the perimeter, the circularity, the area, and the aspect ratio. The core pellets (n=30) showed an average aspect ratio (AR) of 1.07-1.11, with <4% relative standard deviation (RSD%), where the average circularity values were close to a value of 1. As complied with (Chu & Chaw, 2014), these values are desired for achieving high sphericity of the core pellets, see Table 3.6. It is because that if the AR increase for more than 1.2, it means that the difference between the F_{min} and F_{max} diameters of the same core pellet is large enough to violates the spherical shape. The circularity of a sphere is equal to one, which means that the core pellets should approach the circularity value of one to ensure sphericity. The feasibility of the Avicel HFE102 grade as a new spheronisation aid was evident according to this core pellets studies, and it was at least as efficient as the Avicel PH101 grade.

It was encouraged in literature to find alternative spheronisation aids that are co-processed with other materials (Jain, et al., 2010). This alternative and new spheronisation aid may help in addressing the drawbacks of the MCC, which encourages more studies to be made in this grade of Avicel. The drawbacks of MCC claimed in the literature are the absorption/adsorption of drugs, deactivation of drugs like ranitidine, and inducing long dissolution time due to the non-disintegration of pellets (Jain, et al., 2010).

In this project, the latter issue was not evident in the preliminary study of Avicel PH102 and HFE102 grades done, because the uncoated core pellets showed complete drug release in one hour (data not shown).

Table 3.6: Shows the core pellets analysed using the light microscopy*.

Batch code	Feret-Min (F_{Min}) mm	Feret-Max (F_{Max}) mm	Feret Ratio	Perimeter mm	F-Circle or Circularity	Aspect Ratio (F_{Max}/F_{Min})
B1D and B2D (PH,40)	1.11 ± 0.05	1.23 ± 0.08	0.91 ± 0.03	3.91 ± 0.23	0.96 ± 0.02	1.1 ± 0.04
B3D and B4D (HFE,40)	1.11 ± 0.05	1.21 ± 0.07	0.91 ± 0.03	3.88 ± 0.19	0.96 ± 0.01	1.11 ± 0.04
B5D and B6D (PH,60)	1.05 ± 0.05	1.13 ± 0.05	0.93 ± 0.02	3.66 ± 0.18	0.96 ± 0.02	1.07 ± 0.02
B7D and B8D (HFE,60)	1.07 ± 0.06	1.14 ± 0.06	0.94 ± 0.02	3.69 ± 0.20	0.97 ± 0.01	1.07 ± 0.02

*Values were entered in the following format: (Mean±SD), n=30. Definitions and equations are seen in the Abbreviation page. Batches codes can be defined in Table 2.3.

3.4. Characterisation of the Sub-Coated Pellets

For the sub-coated pellets, only the floating study was performed.

3.4.1. The floating study

According to the preliminary work, when the MCC was used alone with the drug in the core pellets, it could neither provide sustained drug release nor maintain the floating, until a suitable coating was applied to the core pellets. Therefore, the sub-coating layer was applied solely to initiate and maintain the floating. However, the sub-coating layer alone will not be sufficient for fulfilling the purpose of floating, as seen in the next paragraphs.

The sub-coated pellets were tested for their floating in a 0.1N HCl medium, see Figure 3.4. The floating duration for each batch was recorded (n=100 pellets), and the floating duration started once the sub-coated pellets were introduced into the beaker. For the floated sub-coated pellets, no floating lag time was seen. For the sunken ones, there was no ability to rise again to the surface, due to the lack of the controlled swelling and the gas entrapment mechanisms. The lack of the latter mechanisms resulted in an excessive swelling and quick gas release, which substantially impaired the sub-coating layer.

The sub-coated pellets containing the film of the 3.33: 6.66 w/w% $NaHCO_3$: HPMC dispersion showed a prolonged floatation when compared to the film of the opposite ratio (p-value<0.001). That could be due to the binding ability of HPMC that may relatively reduce the gas escape from the pellets. This gas is responsible for lowering the density of the pellets. This finding is consistent with the relationship obtained by (Sungthongjeen, et al., 2006). This was caused by the higher HPMC ratio, which may indicate an aid in the entrapment of the gas generated in the floating process. Subsequently, the relatively prolonged entrapment of the gas will maintain the lowered density status of the sub-coated pellets, resulting in an increased floating duration.

None the sub-coated pellets showed satisfactory floating duration. Nevertheless, it was found that the higher the HPMC, the better the synergistic effect in prolonging the floatability. According to (Treesinchai, et al., 2016), the HPMC K100LV + >10% foam powder of the polypropylene will allow the tablet to float immediately upon contact with the liquid surface and for a duration of >12 hours (remained floated when the last measurement was taken). The latter in that study was achieved without the addition of a retarding polymer and without applying any coating layer on the tablets.

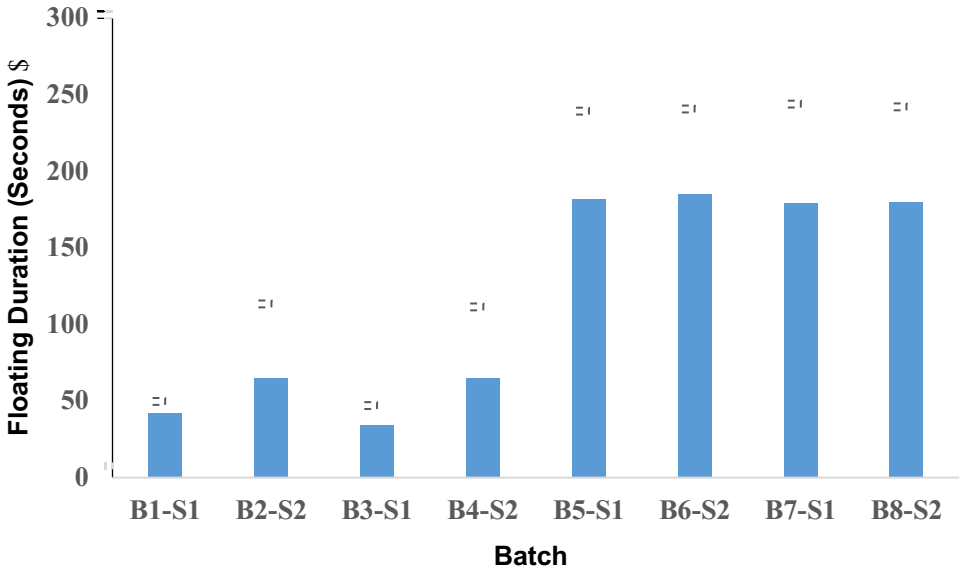


Figure 3.4: Summary of floating study for the sub-coated cores*.
*Values were entered in the following format: (Mean±%SD). The runs were under no mixing and no control of temperature; i.e. under an ambient room temperature of 22°C. *"6" stands for a sub-coating film made of the dispersion strength of 6.66: 3.33 w/w% $NaHCO_3$: HPMC ratio, while "3" was a vice versa. All batches have a second layer; the retard coating film of the Eudragit NE15D without ethanol. N=100 pellets. The Batches defined in Table 2.3.

3.5. Characterisation of the Double-Coated Pellets

The double coated pellets were initially studied for their floating profiles, then for their sustained drug release profiles and morphological features.

3.5.1. The floating study

The double-coated pellets were tested for floatability, i.e., floating lag times, floating duration, on-surface floating, and redundant floating. Batches were all tested in triplicate; see Table 3.7 and Figure 3.5. For all batches, the floating lag time was 0-7 minutes, floating duration for 3 to >12 hours, the floating % of the coated pellets counted on surface was 34-98%. Where most of the coated pellets (>85%) maintained the floating on the liquid surface for a minimum of four hours. The floating profiles preferred the high-level drug loading of 60% (p-values<0.01), then to the lesser extent, for the presence of the mannitol-containing Avicel grade (Avicel HFE102) (p-values>0.05). The floating was maintained for a minimum of 4 hours, where >50% of the pellets floated without a lag time to start the floating upon immersion in the liquid.

To lesser extent, the channel formation can also increase when the MCC is being co-processed with the 10% mannitol (Avicel HFE102 grade). It is worth noting here that the MCC only can swell, hence, that can also accommodate for the generated gas. The channel formation provided larger space for the generated CO_2 gas to be entrapped, resulting in the decreased pellets' density, followed by a better buoyancy/floatability. This discussion is also described by (Sungthongjeen, et al., 2006). Upon the gas generation, the presence of Avicel PH101 along with the lower drug loading (40%), and higher $NaHCO_3$: HPMC ratio sub-coat layer will ease the escape of the air bubbles, as seen for B1. Hence, the quick gas release or escape to the outside of the coated pellets resulted in poor floating profiles.

The floating is due to the immediate gas/air generation and entrapment upon pouring to the dissolution medium. This immediate gas generation

is owing to the nearby sub-coating layer that is concentrated with the gas-generating agent. Another explanation for the immediate floating can be attributed to the coating process. The sprayed dispersion that contains the gas generating agent ($NaHCO_3$) may had interacted with some of the slightly acidic drug molecules on the surface and in the inside of the core pellets. This possible salt-acid interaction or neutralisation reaction will generate some entrapped gas that induced the low-density of coated pellets for an immediate floatability. Therefore, the use of Avicel HFE102 along with the higher drug loading, supplemented with a double coating system is a promising design for the floating pellets and the subsequent gastro-retention of pellets. However, the dissolution results were not sufficient as most of the coated pellets showed a complete drug release in four hours. Therefore, further investigations were conducted to lengthen or to sustain that period for longer hours.

Table 3.7: Summarises the floating duration and floating percentage of the double coated pellets (n=3, based on mean values, SD of total floating shown in Figure 3.5).

Batch code	Floating lag time (min) **	Floating duration (hr)***	On-surface floating (%)****	Suspended pellets (%)	Total floating (%)*****
B1D-PH,40,6*	5	3	34	10	44
B2D-PH,40,3	5	6	57	8	65
B3D-HFE,40,6	5	6	69	16	85
B4D-HFE,40,3	7	8	72	14	86
B5D-PH,60,6	0	8	97	3	100
B6D-PH,60,3	0	8	96	3	99
B7D-HFE,60,6	0	>12	98	2	100
B8D-HFE,60,3	0	>12	97	3	100
*"6" stands for a sub-coating film made of the dispersion strength of 6.66: 3.33 w/w% $NaHCO_3$: HPMC ratio, while "3" was a vice versa. All batches have a second layer; the retard coating film made of the Eudragit NE15D dispersion without ethanol.					
**The lag time was recorded when >40% total floating of the double coated pellets was obtained (by counting).					
***The values were selected based on the period that maintains 40-100% total floating (by counting).					
****All percentages were averaged for the period of 4hrs floating. On surface floating % was calculated based on the counting method (Sungthongjeen, et al., 2006). The number of the double coated pellets tested was calculated based on the 200mg drug dose.					

*****Total floating %= on surface floating % + suspended pellets %. The suspended pellets term relates to when the pellets show a tendency of floating, but, yet suspended between the surface and the bottom of the vessel.

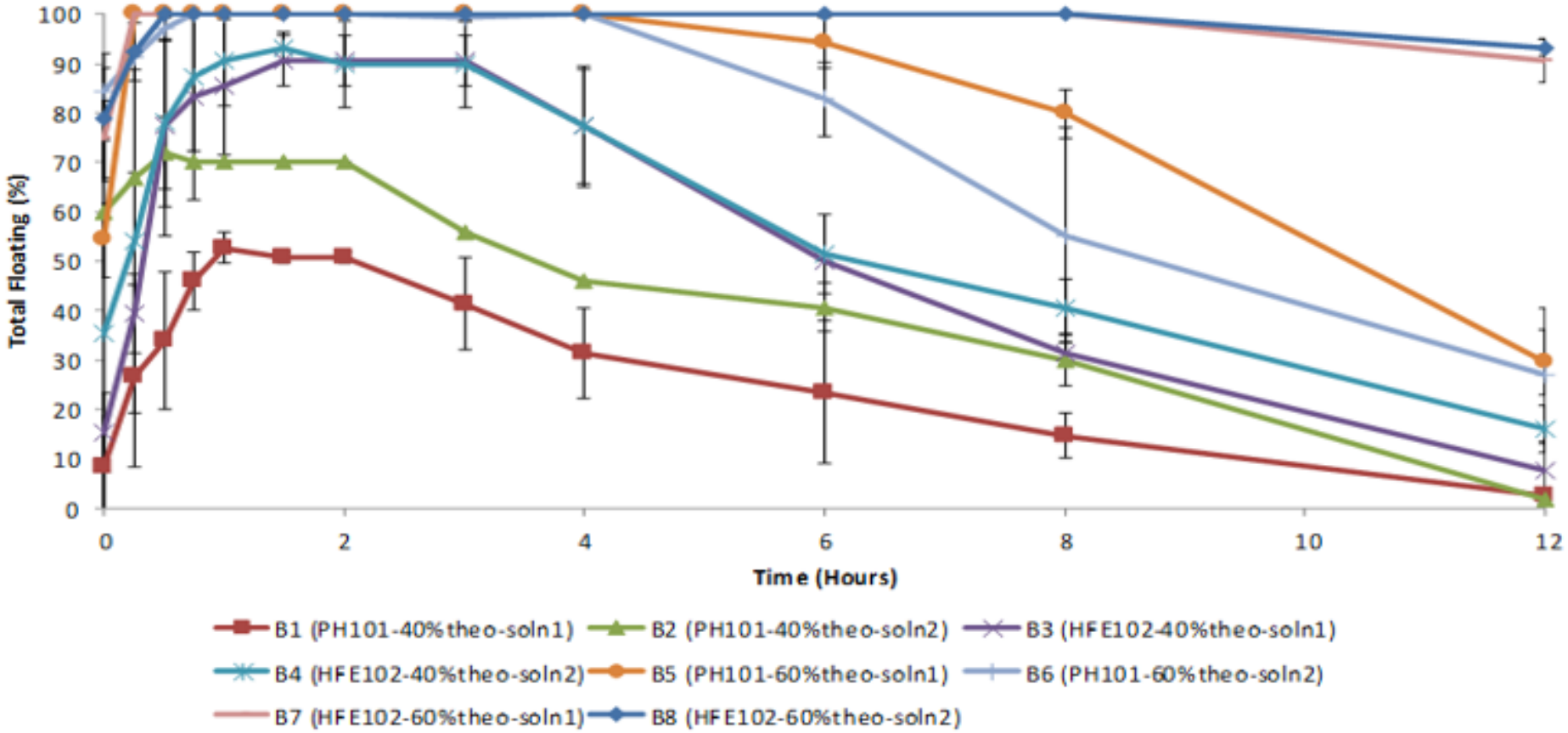


Figure 3.5: The total floating percentages of the double coated pellets. **S1** stands for the film made of the sub-coating dispersion: 6.66: 3.33 w/w% $NaHCO_3$: HPMC, while **S2** stands for the film made of the dispersion of the latter opposite ratio, **S3** is the retard coating film made of the Eudragit NE15D dispersion without the use of ethanol. S3 was applied to all formulations. (mean ±SD, n=3).

3.5.2. Quantification of the drug powder, theophylline

This section is relevant to the drug release profiles obtained in all results chapters, regarding the calculation of drug release. For convenience, it was placed before the drug release profiles of the double-coated floating pellets. To enable the quantification of the drug theophylline, a calibration curve was made from the UV absorbance of diluted concentrations of the drug theophylline in the 0.1N HCl. The readings were graphed, and a linear line was obtained with a high regression value (R^2=0.9999). That is, the regression equation will be used to quantify the theophylline concentration for the drug formulations. The regression line equation (y=mx+b) is also shown in Figure 3.6. The y is the value in the y-axis, the m is the slope of the line, the x is the value in the x axis, and b is the intercept of the line in the y-axis. From the regression line equation here, the x represents the concentration of the drug at a specific absorbance value (y). This is based on the given values of the slope (m) and the intercept (b).

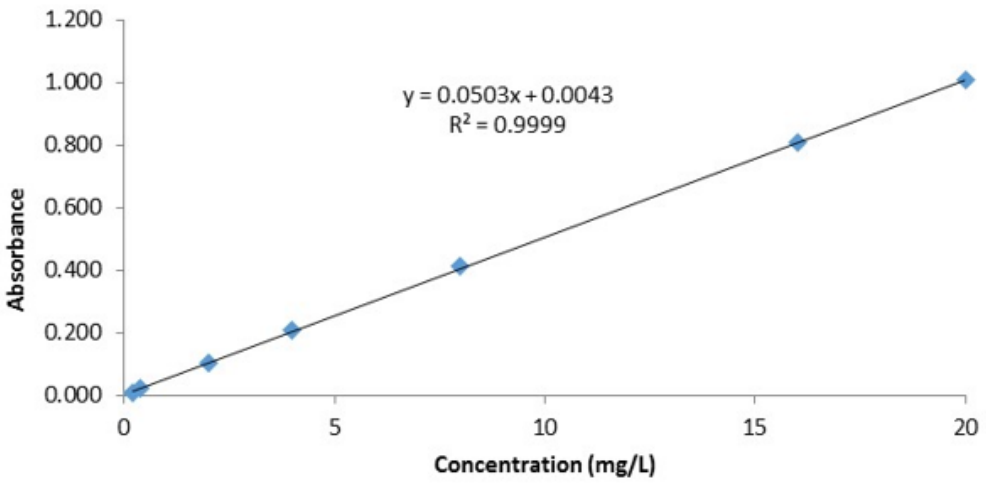


Figure 3.6: Calibration Curve of Theophylline using UV spectrophotometer at 268 nm (mean±SD, n=3). The error bars aren't seen as the results of the triplicate were identical.

3.5.3. Dissolution study

The double coated pellets were tested for their sustained drug release characteristics via the dissolution study, as shown in Figure 3.7. Batches were all in triplicate. The drug release profiles of all formulations nether showed sufficient sustained drug release for the 12 hours' period, nor for the 4 hours' period.

The sustained drug release performance requires a zero-order drug release, where the slope in the regression line equation can be considered as the rate constant if the regression line coefficient (R^2) is high (usually accepted if >0.9). Hence, the regression line equation also considered a form of the integrated rate law for the zero-order reaction: $[A]_t=-kt+[A]_0$. Where the rate constant (k) equal to the slope value (m). For all formulations, the regression line equations were not linear, even for the first four hours of the drug release (R^2 = 0.2341-0.5094). Hence, there was no zero-order drug release obtained for all formulations. Hence, this confirms that the drug release profiles did not sufficiently show a sustained drug release.

Although that, increasing the coating weight gain may improve the sustained drug release profiles. This appears to be discouraged here as the floating profiles can be further compromised when the retard coating gain increases further. Forward to this point, further screening was attempted to enhance the retard coating layer of the batch B7D-HFE,60,6 (which showed the best floating), and examine the feasibility of tabletting this batch of the double-coated pellets, to understand the compression complications of the double-coated pellets.

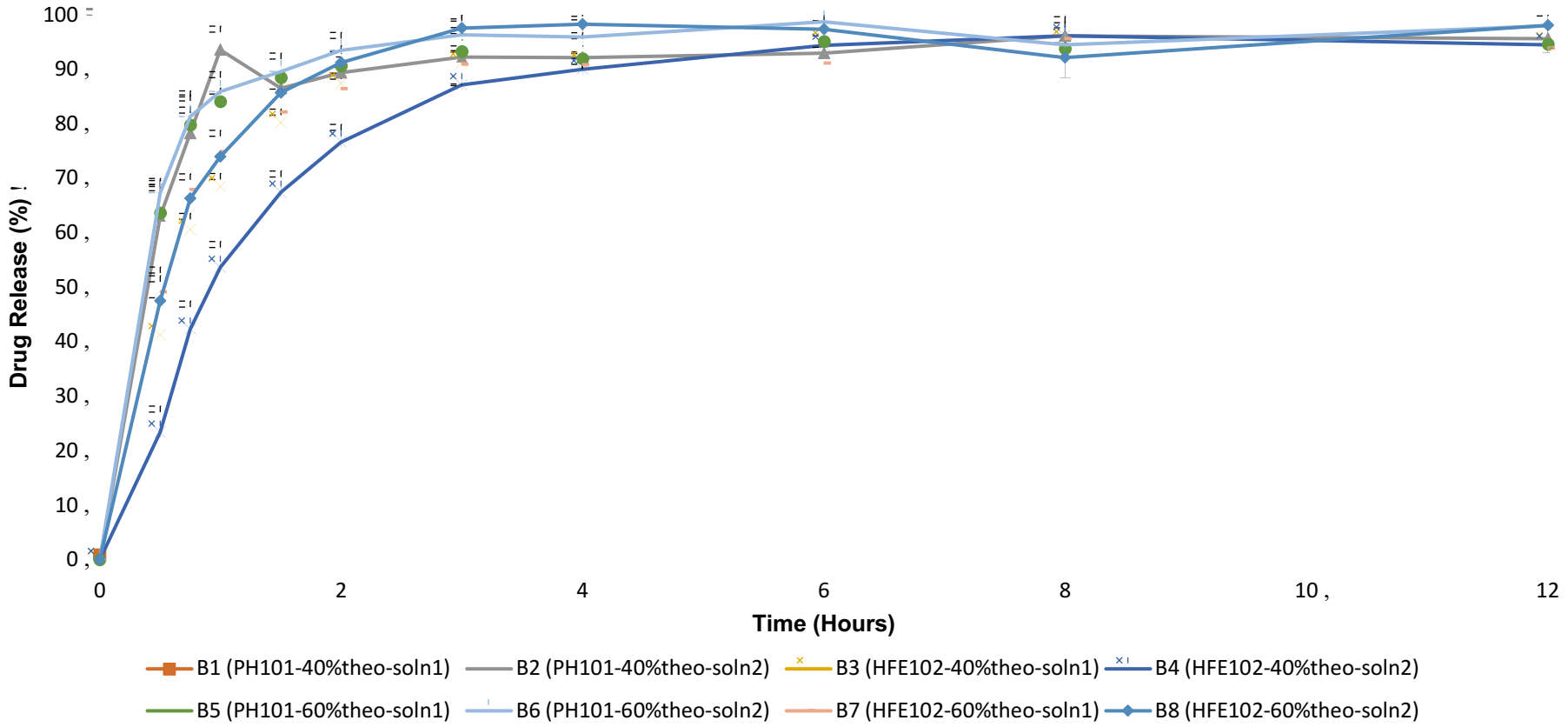


Figure 3.7: Dissolution of the double coated pellets formulations. **S1** stands for the film made of the sub-coating dispersion: 6.66: 3.33 w/w% $NaHCO_3$: HPMC, while **S2** stands for the film made of the dispersion of the latter opposite ratio, **S3** is the retard coating film made of the Eudragit NE15D dispersion without the use of ethanol. S3 was applied to all formulations. (mean ±SD, n=3).

3.6. Characterisation of the Double-Coated Pellets, Further Screening and Tabletting Feasibility

Further screening was attempted to optimise the retard coating layer of the batch B7D-HFE,60,6 (which showed the best floating) and examine the feasibility for tabletting this batch of the double-coated pellets, to understand the compression complications of the double-coated pellets.

3.6.1. The coating weight gain for the pellets

The coating parameters depicted in the chapter 2. The coating process worksheet and the weight gains are recorded in Tables 3.8-9. The core pellets of a 1-1.18 mm size where sub-coated by the 6.66: 3.33 w/w% $NaHCO_3$: HPMC dispersion. The latter dispersion has a lower tendency for blockages in seen in the lab for the previous screening work, and because of its higher spraying efficiency, owing to the lower surface tension (39.13±0.66 instead of 48.34±2.00 mN/m) for the opposite strength). For more details about the surface tension study of liquids, results are listed in Table 5.1. The retard coating layer resulted in an increased weight gain (~11 w/w% sub-coated layer, 15.3 w/w% retard coated layer).

Table 3.8: Shows the coating process worksheet, where the monitoring of the coating weight gain can be seen.

Batch code	Core pellets weight before coating (g)	Weight loss of core pellets after 10 minutes drying at 60 °C (%)*	Weight of core pellets after drying 10 minutes at 60 °C (g)	The final wet weight of the core pellets after coating (g)**	The final dry weight of the core pellets after coating (g)	Coating time (hr)
B7D2-HFE,60,6, 15.6 core pellets	10.00	01.13	09.89	11.26	11.17	2.00
B7D2-HFE,60,6, 15.3 sub-coated pellets	11.17	00.02	11.17	12.89	12.87	1.85
*This refers to the drying equilibrium step, where the weight of the core pellets will be recorded once there is no further decrease in the weight upon further drying or less than 0.1% weight loss was obtained.						
**The wet weight gain was taken twice or trice during the coating process to speculate the remaining time for the targeted dry CWG% to be reached. The ait temperature exposed to the core pellets under coating was at 50 °C.						

Table 3.9: The coating weight gain (CWG) obtained for attempting to optimise the double-coated systems.

Batch code	Targeted dry weight gain on the core pellets (g)*	Targeted dry weight gain on the core pellets (%)	Dry weight gain obtained on the core pellets (g)	Dry weight gain obtained on the core pellets (%)**
B7D2-HFE,60,6, 15.6 core pellets	01.10	11.00	01.17	11.68
B7D2-HFE,60,6, 15.3 sub-coated pellets	01.78	16.00	01.70	15.31
* The targeted CWG solids (g)= (batch size in mass*targeted CWG%)/100.				
** The CWG% obtained= [(CWG solids*targeted CWG in a fraction%)/targeted CWG solids] *100.				

3.6.2. The tabletting studies

A feasibility study was conducted to develop tablets that contains the double-coated pellets. Effects were studied of using different cushioning forms on the tablets' thickness, diameter, hardness, disintegration, friability, dissolution, and floatability parameters. These outcomes will provide some information for the quality control regarding the tablets made from the double coated pellets. It is desired that the double-coated pellets show similar drug release and floating profiles to the tabletted double-coated pellets.

i. The composition of tablets

The B7D batch (has the higher $NaHCO_3$ content in the sub-coating layer) was selected, because the higher $NaHCO_3$ will cause less blockages in the coating tube and the nozzle of the coater. The latter observation was also supported by the lower surface tension obtained by this coating dispersion (39.13±0.66 mN/m), when compared to the lower $NaHCO_3$ content dispersion (48.34±2.00 mN/m). More details about the surface tension results of other coating dispersion not used in this chapter, the reader is kindly advised to see Table 5.1. And also because it showed good floating.

The tablet weight was 400 mg, the maximum weight available for the die tooling in the tabletting machine. Hence, the tablet weight was limited to 400 mg. The total coating weight gain of the two layers was 27% while the drug loading for the core pellets of B7 was 60%. For the tablets' compositions, see Table 3.10. During the compression of double-coated pellets, it is important to allow for a sufficient cushioning and binding. Therefore, the cushioning excipient was used, and it was at >29% of the tablet weight to fill the voids between the coated pellets as possible (Chen, et al., 2017). Thus, a strong and non-friable/indurate tablets and protected coated pellets can be obtained.

Moreover, the cushioning should protect the films of the coated pellets from crushing during compression. The Avicel HFE102 was used as the cushioning excipient in the form of pellets (1-1.18 mm) or powder. The

two different forms were assessed to determine which cushioning form is the most effective in the pellets tabletting. From the above information, at least two tablets were needed to accommodate for the one dose of 200 mg theophylline. That is, 50% of the dose is in one tablet, and the drug: excipient ratio is 1:4 in one tablet, as seen in Table 3.10. For the future scale up manufacturing, a study for the tablet's weight change from 400 mg to 800 mg is needed, to allow for one full dose in one tablet to be tested.

Table 3.10: Shows the summary of the tablets compositions

Batch code	Double coated pellets weight per tablet (mg)*	Cushioning excipient weight per tablet (mg)	The number of tablets per batch**
B7D2CPowder	210.83 (52.7%)	189.17 (47.3%)	61
B7D2CPellets	210.83 (52.7%)	189.17 (47.3%)	61
*The amount was calculated based on the 60% drug loading (DL) and 27% coating weight gain (CWG), and based on the cushioning amount.			
**The batch outcome is 12.8683g coated pellets, considering that 60% DL and 27% CWG were applied, then the dose is 421.66 mg, half of the dose was 210.83 mg that comprise one tablet, and that half of the dose was available for the 61 tablets to make.			

ii. Falling on the floor friability study

This test is an early indication for the friability of the tablet. The compression force was set to 21.5 kN, based on trial and error (data not shown). To pass the test, the falling of a tablet on the ceramic floor from a meter-high distance should show no visual loss, like tablet's chipping or breakage. Based on the preliminary observations obtained, the compression force for tabletting should provide a minimum strength of 5 in kilograms-force (KgF) or 49 N for the tablet of 400mg weight (1KgF=9.80665N), to avoid a friable tablet upon falling. The desired maximum strength was set to be around 10 KgF or 98.05 N, to minimise the film's rupture and/or film's fusion upon compression. The film's rupture and/or film's fusion may negatively or positively affect the dissolution and the floating profiles, and at worse, that may cause a complete failure to the film.

When the die depth of 5 rounds was set, the tablets containing the cushioning pellets showed cracking and detachment of pellets upon

falling, which were largely weak with a crushing strength of 3 KgF (29.42 N). However, when the die depth decreased to 5.5 rounds, these tablets were demonstrated an intact form upon falling without visual losses. Hence, the effect of the same compression force increase when the die depth decrease. The tablets containing the cushioning powder were strong and intact at the die depth of 5 rounds. Therefore, based on this preliminary test for the tablets strength, when the powder cushioning was used (at 21.5 kN compression force), the tablets are shown to be non-friable, without the need to decrease the die depth to 5.5 rounds. Hence, the latter parameters' values were set for making the tablets for the quality control testing.

iii. Hardness study

Complying with the findings above, tablets containing the cushioning pellets result in hardness strength of 7.13±0.9 KgF (69.92 N). On the other hand, the tablets containing the cushioning powder showed higher hardness strength of 10.14±0.59 KgF (99.44 N) without decreasing the die depth, as seen in Table 3.11.

Table 3.11: Shows the tablets properties (thickness, diameter and hardness)

Batch code*	Weight of tablets' compositions before tabletting (mg)	Weight of tablets' compositions after tabletting (mg)	Tablets' thickness and diameter (mm)	Tablets' hardness (KgF)	Tablets' hardness after drum friability test (KgF)
B7D2CPowder	400.37±0.69	398.75±4.46	4.65±00 and 9.6±00	10.14±0.59	10.28±1.33
B7D2CPellets **	400.71±0.32	398.92±0.83	4.65±00 and 9.6±00	7.13±0.9	6.76±1.53
*20 tablets were used as per the (British-Pharmacopoeia., 2017).					
**The cushioning pellets will be capable of accommodating in a less die depth, owing to their higher poured packing properties that result in a lower poured volume. It was capable of accommodating in 5.5 rounds die depth instead of 5 rounds die depth.					

iv. Drum friability study

The drum friability study of the tablets was conducted to assess the strength of the tablets, to confirm whether the tablets can tolerate the subsequent stresses of coating, shipping, and handling. As complied with the hardness testing and the with the falling on the floor friability,

the cushioning powder containing tablets showed strong and intact tablets at the die depth of 5 rounds. An acceptable loss of materials was obtained (<1%), see Table 3.12. Although that the cushioning pellets at a die depth of 5.5 rounds produced intact tablets upon falling, the tablets failed in the drum friability test (~9% weight loss). The cushioning pellets showed weaker binding with the double coated pellets resulting in friable tablets, due to that the surface area available for pellets is smaller than that of the powder.

Table 3.12: Shows the tablets firability results**.**

Batch code	Wight of the tablets before friability*	Wight of the tablets after friability	Weight loss
B7D2CPowder	6.5g	6.47g	0.3%
B7D2CPellets	6.55g	5.92g	9.6%
*16 tablets were used as per the (British-Pharmacopoeia, 2017), which is based on the weight of the tablet.			

v. Disintegration study

Tablet disintegration or the disassembling of the coated pellets from the ensemble pellets was studied. Regardless of the cushioning form used in the tablet, the disintegration time needed to disassemble all pellets was only one minute, as shown in Table 3.13. This is a fast disintegration time, which means the complete contact with the surrounding liquids will be quick for double coated pellets. Hence, the initiation of the floating mechanism will be quick as well. These tablets can be named as disintegrating tablets.

Table 3.13: Shows the tablets disintegration results.

Batch code	Time when the first breakage occurred*	Time when all pellets disassembled	Disintegration time
B7D2CPowder	10 sec	1 min	1 min
B7D2CPellets	10 sec	1 min	1 min
*6 tablets were used as per the (British-Pharmacopoeia, 2017).			

vi. Dissolution study

Interestingly, the tabletted pellets showed similar drug release profiles to the non-compressed ones, regardless of the cushioning form used. This similarity indicates that the outer film of the double coated pellets

was highly protected upon compression as seen in Figure 3.8. However, all drug release profiles showed complete drug release within 4 hours.

Although that the other quality control tests for tablets were promising regarding the use of the powder cushion, the sustained drug release function is not sufficient for the double coated systems to succeed. The latter was even after the coating weight gain increased from ~11 w/w% (in the previous screening work) to 15.3 w/w%. Even the ~4 w/w% increase in the coating weight gain did not sufficiently slow down and streamline the drug release profiles (the regression coefficients; R^2=0.8-0.9). Further excessive increase in the coating weight gain was not encouraged, because that would highly compromise the acceptable yet not optimum floating profiles seen in Figure 3.9.

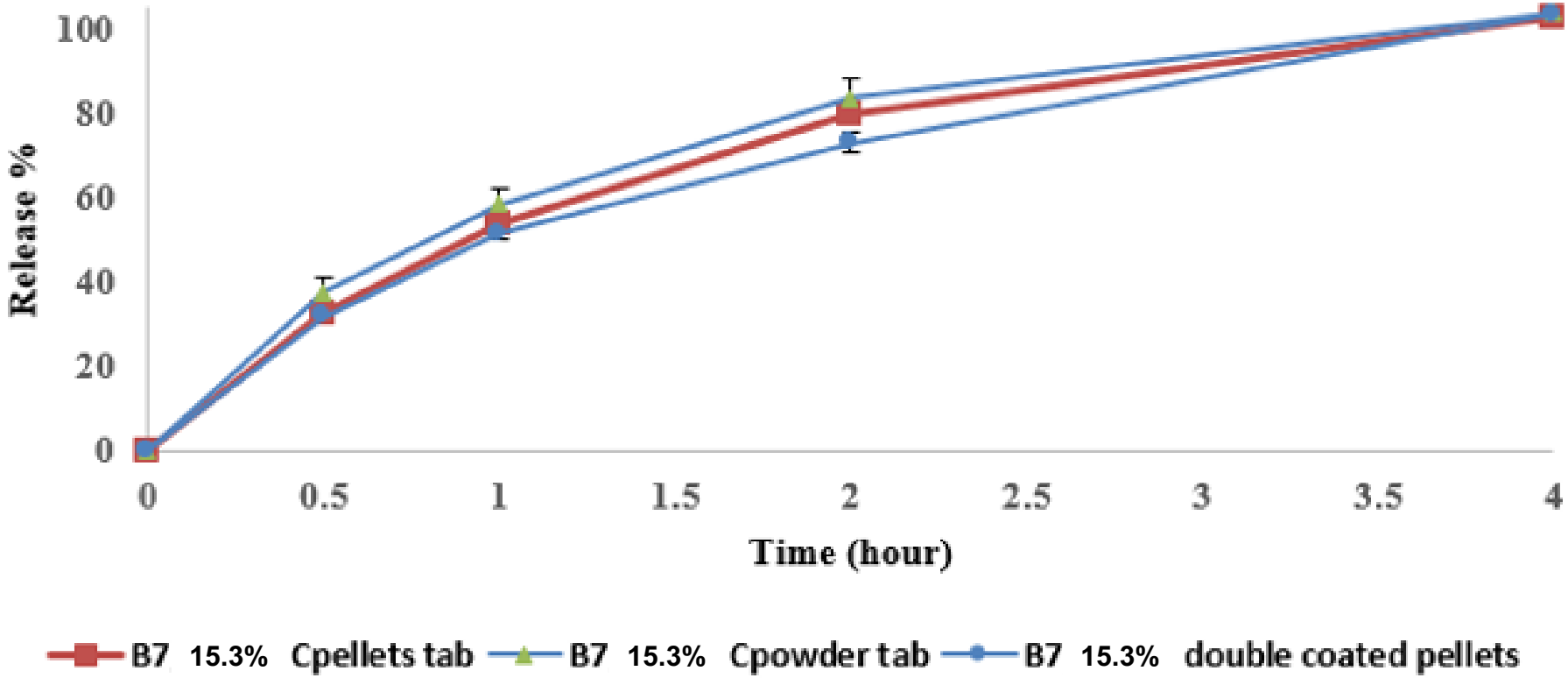


Figure 3.8: The drug release profiles, as an attempt to optimise the double-coated systems, using ~11% weight gain of the 3.33: 6.66% HPMC: $NaHCO_3$ and 15.3% weight gain of the fully aqueous Eudragit NE15D. Cpellets tab stands for the cushioning pellets containing tablets. Cpowder stands for the cushioning powder containing tablets.

vii. Floating study

Regardless of the cushioning form used, the floating profiles were comparable to those of the non-compressed pellets and maintained at least a 70% floatation for 10 hours. Afterward, the non-compressed pellets remained floating for more than 24 hours, but the percentage dropped to around 40% for the tabletted pellets, see Figure 3.9. The drop in the floating percentage is due to the effect of compression on the integrity of the retarding film and the sub-coating film, where some pellets may have ruptured during compression. Therefore, an acceptable but not optimum value of floating (>50%) for 10 hours can be obtained when double coated pellets are compressed.

Moreover, the tablets prepared from the cushioning powder required shorter lag times to reach the surface and become buoyant/floated (9.75±0.35 minutes) while the tablets prepared from the cushioning pellets took longer and displayed heterogeneous lag times (20.5±9.9 minutes). Hence, a fusion for the retard film might result upon the compression with cushioning pellets, making the film less permeable to the dissolution medium. Therefore, the surrounding liquid intended to reach the sub-coat film will be delayed or slowed.

The compression with the cushioning powder is providing tabletted pellets with a desired but not optimum floating lag time (i.e. <15 minutes, but >3 minutes). The latter finding complied with the non-compressed pellets, where a lag time of 7.5±3.54 minutes was needed to reach the surface. When compared to B7 from the previous screening work of the double coated systems, the non-compressed batch here showed ~20% decrease in floating. The latter decrease in floating is expected as the hydrophobic coating weight gain was increased from ~11% to 15.3%.

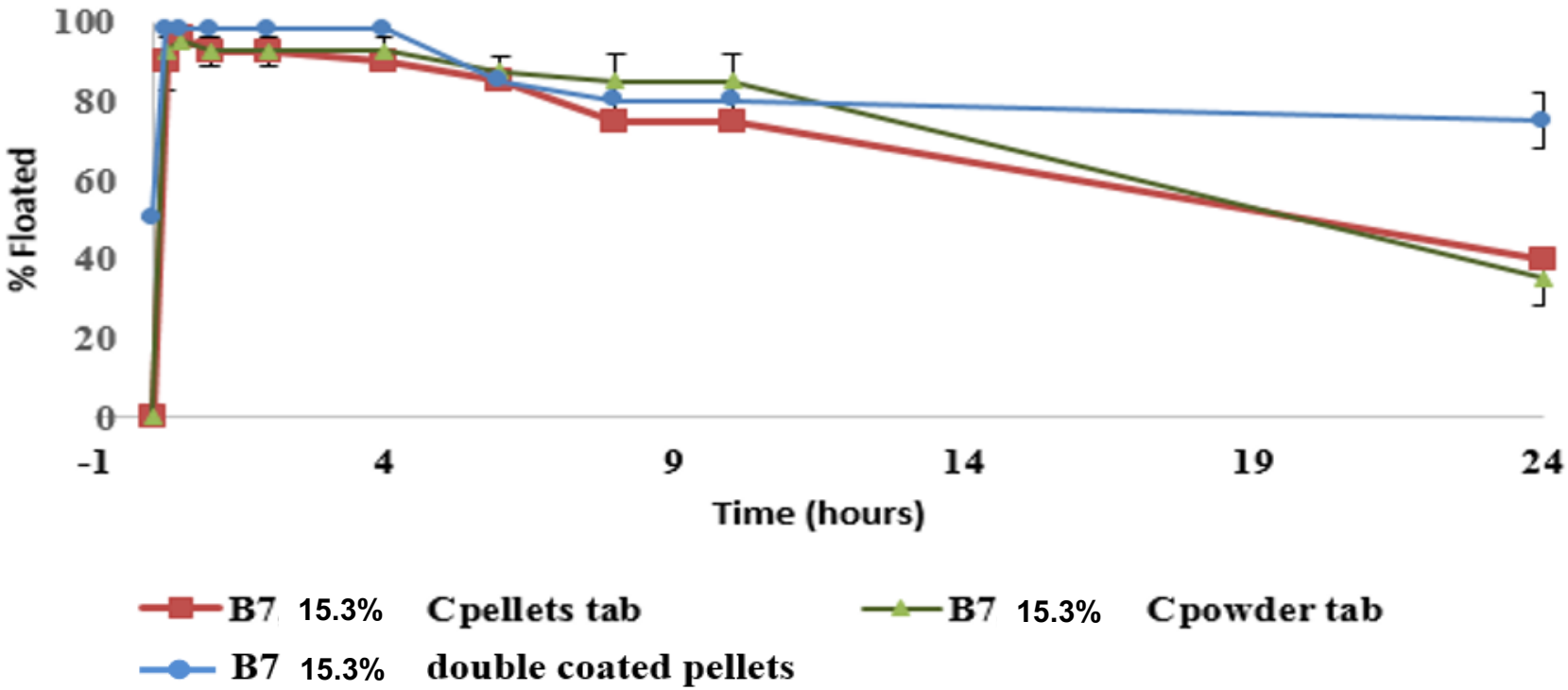


Figure 3.9: The floating profiles of the double-coated system, using 11% weight gain of the 3.33: 6.66% HPMC: $NaHCO_3$ and 15.3±0.7% weight gain of the fully aqueous Eudragit NE15D. Cpellets tab stands for the cushioning pellets containing tablets. Cpowder stands for the cushioning powder containing tablets.

3.7. Conclusion

For the first time, a new functionality was discovered for the mannitol-containing Avicel HFE102 grade (as a spheronisation aid), which was successfully applied to make pellets using the extrusion and the spheronisation processes. Results revealed that the Avicel HFE102 grade can be at least as efficient as the Avicel PH101 grade. The Avicel HFE102 consistently provide higher spheronisation yield and higher narrowed size range (1-1.18 mm sieve yield) that reached up to 100%, and 44%, respectively.

For the floating of the double coated pellets, nearly 80% of the double coated pellets showed immediate floating without a lag time to float. The latter finding is due to the immediate gas/air generation and entrapment upon pouring to the dissolution medium. This immediate gas generation is owing to the nearby sub-coating layer that is concentrated with the gas-generating agent. Another explanation for the immediate floating can be attributed to the coating process. The sprayed dispersion that contains the gas generating agent ($NaHCO_3$) may had interacted through a neutralisation reaction with some of the slightly acidic drug molecules on the surface and in the inside of the core pellets. This possible salt-acid interaction or neutralisation reaction will generate some entrapped gas that induced the low-density of coated pellets. Successful floating profiles for the coated pellets were achieved when the Avicel HFE102 was used. Where most of the coated pellets (>85%) maintained the floating on the liquid surface for a minimum of four hours. The floating profiles preferred the high-level drug loading of 60% (p-values<0.01), then to the lesser extent, for the presence of the mannitol-containing Avicel grade (Avicel HFE102) (p-values>0.05). Therefore, the use of Avicel HFE102 along with the higher drug loading, supplemented with a double coating system is an efficient design for the floating to occur. However, the dissolution results were not sufficient as most of the coated pellets showed a complete drug release in four hours. Therefore, further investigations were conducted to lengthen or to

sustain that period for longer hours. The chosen formulation for further investigation (B7) has the core pellets containing the Avicel HFE102, with 60% drug loading. The higher ratio of the $NaHCO_3$: HPMC dispersion was selected for the sub-coat layer. Also, a higher coating weight gain (~15.3%) was used instead of (~11%) of the Eudragit NE15 dispersion, to ensure the increase of the retarding layer effect. The latter attempt was to enhance the sustained drug release profile of the double coated systems. However, the drug release profiles did not improve, even after tabletting of these coated pellets. More studies were done on the B7 to assess the feasibility for the tableted double-coated pellets. Two types of the cushioning excipients were used, the Avicel HFE102 powder and the Avicel HFE102 pellets. The cushioning powder of the Avicel HFE102 showed the optimum results regarding the tablet's strength and friability. However, regardless of the cushioning form used, similar floating profiles were obtained for 10 hours and similar drug release profiles were obtained as well.

To sum it up, it was feasible to successfully attain the core pellets by a new spheronisation aid (Avicel HFE102). It was encouraged in literature to find alternative spheronisation aids that are co-processed with other materials (Jain, et al., 2010). This alternative and new spheronisation aid may help in addressing the drawbacks of the MCC, which encourages more studies to be made in this grade of Avicel. The drawbacks of MCC claimed in the literature are the absorption/adsorption of drugs, deactivation of drugs like ranitidine, and inducing long dissolution time due to the non-disintegration of pellets (Jain, et al., 2010). Also, the understanding of the double-coated floating pellets design was important before reducing the system into the single-coated floating pellets design. The latter is more intricate yet more cost effective design. This intricacy is owing to the eliminating of the sub-coated layer, and using only one layer to achieve both the sustained drug release and the floating by a controlled swelling mechanism with or without the foaming mechanism.

Chapter Four:

Screening Study for the Single-Coated Floating Pellets

4.1. Introduction

The gastro-retentive drug delivery systems (GRDDSs) were described in the introduction of the previous chapter and described in detail in the introduction chapter. The chapter aim is to screen for the feasibility of making the single coated pellets, where the core pellets are intended to swell under the control of the Eudragit NE15 retard layer. The objectives are to apply a single coating layer of the Eudragit NE15 dispersion, to produce the floating and the sustained drug release properties. Also, to obtain the drug-loaded pellets with an acceptable sphericity, and with a large usable yield. And to understand the complications in the development of such system. The targeted outcome is to make an effervescent type and non- effervescent type of such system, to improve design efficiency. This chapter will provide the bases for further enhancement work in the single-coated floating systems. These coated pellets are expected to reduce a coating step in the floating pellets design. Because the pellets are to be floated with or without an effervescent agent, and aimed for less preparation time and less materials to be used, owing to the single coating stage. Hence, the floating layer in the double coated floating pellets could be removed with a maintained floating profile, with a pH-independent manner, and in an easier and more cost-effective manufacturing procedure. The used tools of risk assessment allowed for more process understanding and allowed for a subsequent improvement in the drug product development. In the making of core pellets intended to be single-coated, the addition of polyvinylpyrrolidone (PVP) and $NaHCO_{3,}$ make the liquid binder optimisation becomes more challenging. That is, only the non-PVP containing core pellets were made successfully (AR<1.2). The floating and the sustained drug release properties were variable for all coated pellets. Therefore, an enhancement work is needed to streamline the results.

4.2. Characterisation of the Core Pellets

4.2.1. Considerations for drying and curing

The long drying of both core pellets and coated pellets was to provide <5% moisture in the coated pellets. Hence, that can increase protection to the coated pellets from the microbiological, chemical and physical instabilities. Also, the long drying time ensures that curing occurred. The curing during storage will not be expected to happen, as the remaining water is <5 % in the coated pellets.

During a preliminary study, the additional drying and curing times did not affect the drug release and the floating profiles when compared to the non-cured batches (data not shown). Therefore, from this chapter and beyond, the 24 hours drying time for the core pellets and 24 hours curing time for the coated pellets, will be anticipated here and in the next chapter.

4.2.2. Physical examination of the wet mass, the extrudates, the core pellets, and the spheronisation yields

The compositions of floating pellets are succinctly outlined in the codes table of pellets batches (Table 2.2) and detailed in Table 2.4. A scoping study was conducted to select the feasible distilled water levels. The wet mass consistency was examined using the hand squeeze method. The PVP containing batches (B1S, B3S, and B6-8S) favoured less distilled water. When compared to the non-PVP containing batches, the PVP-containing batches showed large and sticky granules and extrudates. Also, the PVP-containing batches showed spheronisation product of rod or dumbbell shape, as seen in Table 4.1. The latter outcomes persist even after the scoping study of the distilled water level, as seen in the next section. Although the PVP is considered as a water-soluble polyamide (Chemical-Book, 2017), it showed poor wetting with the distilled water, resulting in a poor rheology in the wet mass. This is because the PVP showed high stickiness, resulting in an excessive

cohesion and adhesion. The latter was evident during processing and as complies with (Holman, 2013), where only 2.6% increase of PVP from 3% to 5.6% caused a 205% increase in the work needed for granulation in a twin-screw granulator. It is also in agreement with (Yu, et al., 2016), where the povidone (PVP) has less effective binder spreading in the bed and potentially showing less inter-particle bonding than the copovidone (PVP/VA). For more details regarding the scoping study, see section 4.2.3.

4.2.3. Scoping study for selecting the liquid binder amount

The wet mass consistency showed a significant change with regard to small addition in liquid binder. E.g. 3 ml of liquid per 1 kg of powder will affect the overall performance of the wet mass in the extrusion and the spheronisation processes. Issues like stickiness and powdering were common, resulting in a failure for making the core pellets. The water level needed was decided based on the “eye and hand” method (Caleva, 2017). The right wet powder consistency is achieved when the capillary phase is reached between the solid-liquid molecules, where a complete liquid saturation is expected (Caleva, 2017). The capillary phase can be seen in chapter 1 (Figure 1.11). Using SPSS, a cubic curvilinear (non-linear) regression model was chosen for the scoping study, as it showed the best data fit (R^2>0.95). The relationship between the enhanced water level and the floating agents’ levels showed cubic regressions. The liquid binder interactions with powders is evident in the non-linear regression fitting, which prove significant effects occurred during the wet massing process. Less liquid binder was needed with increasing PVP fraction (p-value=0.001, R^2=0.986), and the reversed was seen with increasing $NaHCO_3$ fraction (p-value=0.013, R^2=0.957), see Figure 4.1. The targeted MCC: drug ratios were around the range of 1:1, to ensure efficient drug loading and spheronisation.

Table 4.1: Shows the visual properties of products during the core pellets preparation and the spheronisation yields %.

Batch code	Wet mass appearance	Extrudates appearance	Spheronisation product appearance	Spheronisation Yield (%)*
B1S-25P	Medium large granules 	Long, smooth and too sticky  	Rods	55.38
B2S-25N	Wet sand-like 	Short, dry, rough and very porous  	Round/ spheres	69.1
B3S-20P	Medium large granules	Long, smooth and too sticky	Dumbbells	57.23
B4S-20N	Wet sand-like	Very dry and short	Round/ spheres	70
B5S-22.5N	Wet sand-like	Very dry and short	Round/ spheres	64.56
B6S-22.5P	Medium large granules	Long, fragile and slightly sticky	Mostly dumbbells and some ellipsoids	54.34
B7S-12P,12N	Large granules	Long, very fragile and sticky	Rounded	72.6
B8S-11P,11N	Some large granules	Long, smooth and some pores	Rounded and some irregular	63.88
*% the core pellets yield= (weight of the dried core pellets/ weight of initial powder materials used)*100.				

Therefore, the MCC: drug was not expected to have an effect on the relationships above, that is, due to the tight range of operability of this ratio in the constructed DoE model. Another important finding is that in the same formulation, when both PVP and $NaHCO_3$ have almost the same concentration (about 11-12% for each component), the water level needed was at about 44%.

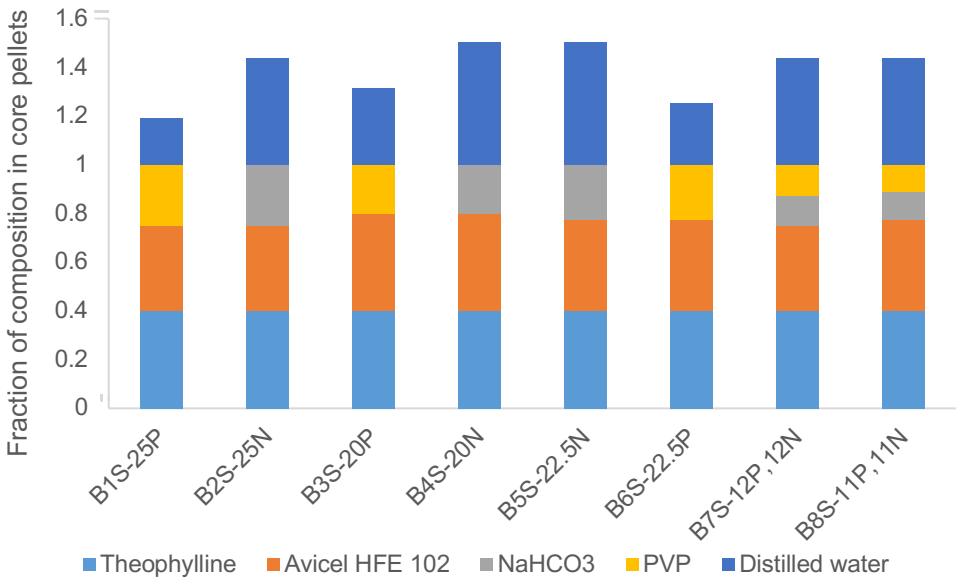


Figure 4.1: Fraction of composition on core pellets*.
*The fraction of the applicable water amount was calculated based on the 80g powder batch size. It was not assumed that the added water is an addition to the formulation batch weight, as a negligible amount of distilled water of less than 5% will remain in the core pellets after drying for 24 hours.

4.2.4. Sieve analysis

The cumulative undersize percentages of the core pellets are shown in Figure 4.2. Non-PVP containing batches showed steep curves that indicates narrow size distribution, also, they showed acceptable sphericity (AR<1.2). Other curves tend to have high skewness toward the coarse pellets. The skewness issue was also seen by (Slavkova, et al., 2016), where the core pellets made of the semi-synthetic hard fat, which were of a coarse size and in a wide size distribution (~1.2-3 mm). Hence, the skewness is not favorable, as the size distribution of the core pellets become wide and more distant from the useable size range (0.71-1.4 mm).

The sieve analysis data is summarised in Table 4.2. Most batches showed >60% spheronisation yields, and >40% 0.72-1.4 mm fraction yields (except that core pellets continuing 11.25% PVP and 11.25% $NaHCO_3$). Regardless of the PVP presence, variations for the size distribution were evident, as the inter-quartile range (IQR) values were 0.17-0.35 mm. These variations are owing to the difficulties of obtaining a highly consistent wet mass when the PVP was used.

4.2.5. Image analysis

The shape diameters of the images were obtained, as seen Table 4.3. The aspect ratio (AR) values were 1.09-1.8, while Feret ratio (FR) values were 0.58-0.91, and circularity values were 0.78-0.93. Moreover, only the non-PVP containing batches (B2S, B4S and B5S) were successfully forming spherical cores with an average ARs of 1.09-1.1 (<1.2), with <5% relative standard deviation (RSD%), and where the Feret ratios and circularities are >0.9. These values are desired for optimum spheres as complied with (Chu & Chaw, 2014). The aspect ratio values comply with the finding in the physical examination above.

4.2.6. Floating study

The core pellets (n=10) did not float when introduced into a beaker contains 0.1N HCl medium. Therefore, a gas retard layer, namely, the Eudragit NE15 layer was needed, to slow water uptake/permeability. The latter is needed to reach an equilibrium swelling and/or to slow the gas release for lowering the pellets density. Also, this layer of coating is needed to sustain the drug release.

4.2.7. Friability study

The friability results are presented in Table 4.4, where all batches were shown to have an acceptable mechanical strength index values (>99% MSI), as complied with (Abdel Rahim, et al., 2015). Hence, the core pellets are expected to withhold the coating and the tabletting stresses and expected to maintain integrity without fractures.

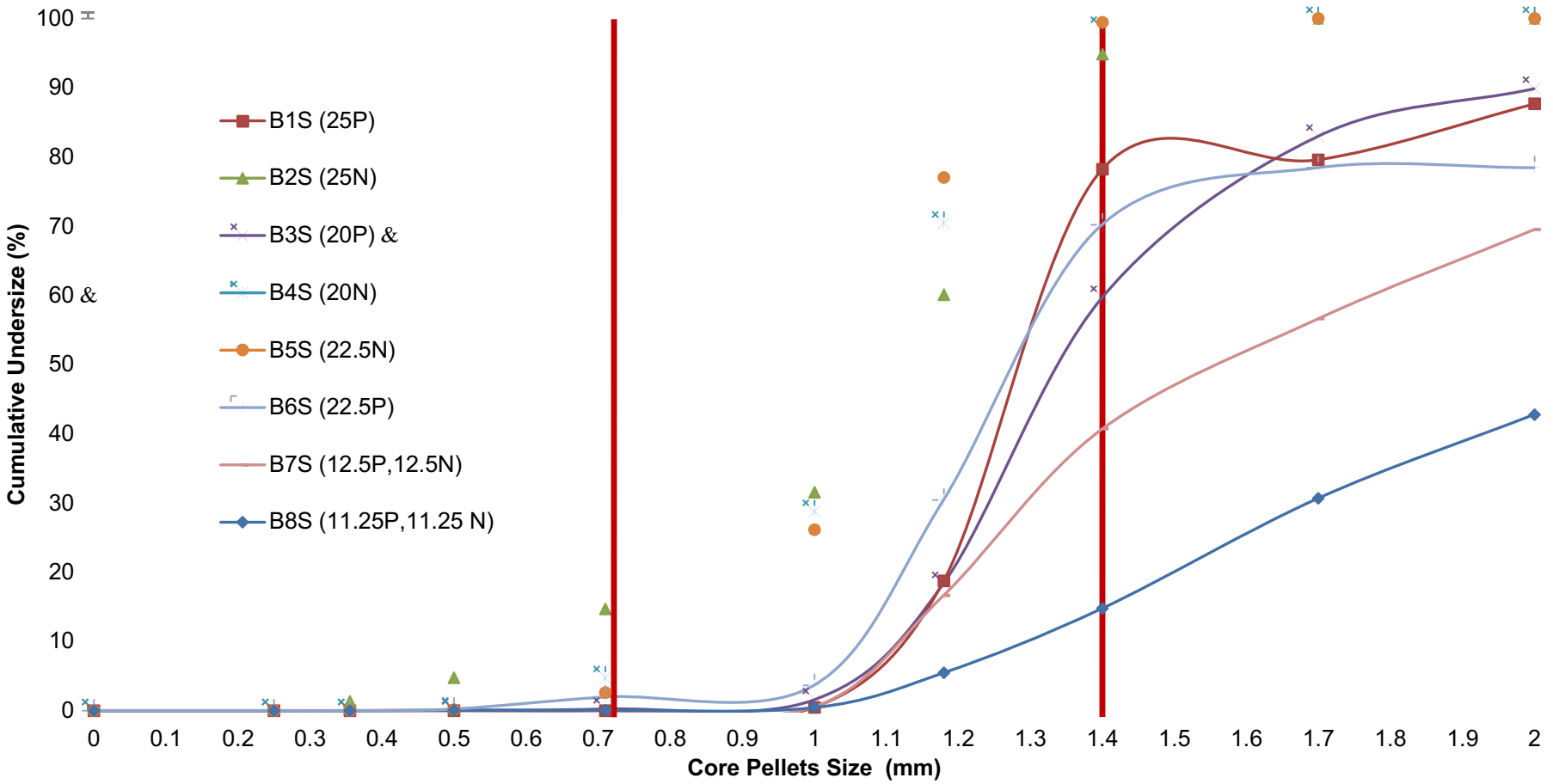


Figure 4.2: Shows the particle size distribution based on the cumulative undersize (%) of the sieved core pellets (n=1) intended for a feasibility of single-coating. The red vertical lines represent the range of the usable size fraction that suitable for the subsequent processes of coating and tabletting

Table 4.2: Shows the size distribution values of the core pellets.

Batch code	Spheronisation Yield (%)	Usable yield of 0.71-1.4 mm (%)	Narrowed yield of 1-1.18 mm (%)	Fine fraction; 0-0.71 mm (%)	Coarse fraction; 1.4-2 mm (%)	IQR (mm)	Median class (mm)
B1S-25P	55.38	78.19	18.27	0	21.81	0.17	1.18-1.4
B2S-25N	69.1	80.14	28.58	14.71	5.16	0.35	1.18-1.4
B3S-20P	57.23	59.41	16.82	0.24	40.35	0.35	1.18-1.4
B4S-20N	70	93.76	41.69	4.78	1.47	0.24	1-1.18
B5S-22.5N	64.56	96.79	50.87	2.63	0.59	0.18	1-1.18
B6S-22.5P	54.34	68.24	26.80	1.98	29.78	0.33	1.18-1.4
B7S-12P,12N	72.6	40.65	16.10	0.03	59.32	0.98*	2
B8S-11P,11N	63.88	14.72	5.03	0.06	85.22	1.05*	2
*Due to the poor size distribution, an estimated value is based on an approximate extrapolation. However, the extrapolation can suffer inaccuracy.							

Table 4.3: Core pellets were analysed using light microscope images*.

Batch code	Feret-Min (mm)	Feret-Max (mm)	Feret Ratio	Perimeter (mm)	F-Circle (Circularity)	Aspect Ratio
B1S-25P**	1.27 ± 0.11	2.31 ± 0.57	0.58 ± 0.12	6.57 ± 1.35	0.78 ± 0.10	1.80 ± 0.36
B2S-25N	1.14 ± 0.06	1.24 ± 0.07	0.91 ± 0.03	4.05 ± 0.25	0.92 ± 0.03	1.09 ± 0.04
B3S-20P	1.17 ± 0.08	1.63 ± 0.33	0.74 ± 0.11	4.90 ± 0.83	0.89 ± 0.06	1.38 ± 0.22
B4S-20N	1.09 ± 0.07	1.20 ± 0.08	0.91 ± 0.02	3.87 ± 0.26	0.93 ± 0.02	1.10 ± 0.03
B5S-22.5N	1.08 ± 0.07	1.18 ± 0.08	0.91 ± 0.02	3.85 ± 0.026	0.90 ± 0.03	1.09 ± 0.03
B6S-22.5P	1.22 ± 0.09	1.90 ± 0.34	0.66 ± 0.10	5.76 ± 1.09	0.80 ± 0.12	1.55 ± 0.26
B7S-12P,12N	1.18 ± 0.06	1.56 ± 0.24	0.77 ± 0.10	4.78 ± 0.59	0.89 ± 0.05	1.32 ± 0.19
B8S-11P,11N	1.17 ± 0.09	1.47 ± 0.20	0.81 ± 0.09	4.50 ± 0.48	0.92 ± 0.06	1.25 ± 0.16
*The values were entered in the following format: (Mean±SD), n=30.						
**This batch was showing rod shapes, resulting in largely skewed values.						

Table 4.4: Shows the mechanical strength index (MSI) values for the core pellets after the friability test.

Batch code	Weight of core pellets before test (g)*	Weight of core pellets after test (g)	MSI* (%)
B1S-25P	2.99	2.98	99.67
B2S-25N	9.99	9.98	99.90
B3S-20P	2.77	2.75	99.28
B4S-20N	10.01	9.95	99.40
B5S-22.5N	10.03	10	99.70
B6S-22.5P	10.01	9.97	99.60
B7S-12P,12N	9.31	9.31	100.00
B8S-11P,11N	1.88	1.87	99.47
*The amount to be tested was 10g. However, some batches were having a low spheronisation yield of 1-1.18 mm core pellets, noticeably, for B1, B2 and B8. Smaller samples were tested for these batches to give some indication about their weight loss.			

4.3. Characterisation of the Single-Coated Pellets

4.3.1. Coating weight gain yields

The coating time to reach the target weight gain and the coating efficiency will be affected by various factors, namely, the size and the shape of the core pellets, coating batch size, the coating process and the coating formulation variables. The coating weight gain values were 15.6±1%, as seen in Table 4.5. Blockages in the nozzle and the tube were observed, which resulted in the frequent poor spraying of the coating dispersion and poor fluidizability of the pellets under coating. Consequently, the coating time was variable (1-1.5 hours), as well as the coating thickness as seen shortly in the section 4.3.5. The poor fluidizability was sourced to be mainly induced by the small size of the coater machine and the poor properties of the aqueous coating dispersion. The shape of the core pellets will affect the coating uniformity. The spherical core pellets were more likely to have the near perfect coating than any other shape. However, the obtained core pellets did not have a uniform coating thickness (51±21 μm). The latter can also be affected by the effects of coating dispersion compositions and the coating process factors.

Table 4.5: Shows the coating yields after drying and coating*.

Batch code	Weight before coating (g)	Time of coating (min)	Weight gain before drying (g)	Weight gain before drying* (%)	Weight gain after drying and curing* (g)	Weight gain after drying and curing (%)
B1S-25P	5.01	68	0.87	17.40	0.82	16.40
B2S-25N	5.00	95	0.81	16.20	0.78	15.60
B3S-20P	5.00	35	0.89	17.80	0.83	16.60
B4S-20N	5.00	73	0.89	17.80	0.83	16.60
B5S-22.5N	5.01	65	0.80	16.00	0.73	14.60
B6S-22.5P	5.00	50	0.87	17.40	0.76	15.20
B7S-12P,12N	5.00	55	0.86	17.20	0.73	14.60
B8S-11P,11N	1.83	115	0.31	16.91	0.27	14.70
Average	-	69.50	-	-	-	15.54

It is calculated as follows: (coating solids obtained before drying% of the target weight gain)/ target coating solids. Drying was maintained for 2 hours at 55 °C to ensure curing.

Coated B2 pellets: Coated B3 dumbbells:

4.3.2. Surface hardness study

The deformation force values were presented in Table 4.6. For most batches, the coated pellets showed sufficient strength of an average force of 0.77-1.21 KgF with SD <0.35 KgF (7.55-11.87 N with SD <3.43 N). Hence, the coated pellets will be expected to withstand the compression stress without fractures. However, during tabletting, a cushioning excipient, like the MCC, will be needed, to ensure that the film on the core pellets will be sufficiently protected and with sufficient binding after tableting.

Table 4.6: Coated pellets compression force values, upon surface hardness study*.

Batch code	Force (KgF)	Batch code	Force (KgF)
B1S-25P	2.25 ± 0.95**	**B5S-22.5N**	0.77 ± 0.14
B2S-25N	0.77 ± 0.14	**B6S-22.5P**	0.77 ± 0.14
B3S-20P	0.95 ± 0.32	**B7S-12P,12N**	1.21 ± 0.34
B4S-20N	0.81 ± 0.16	**B8S-11P,11N**	1.08 ± 0.19

*The values were entered in the following format: (Mean±%SD), n=30.

**This high force value was due to the rod shape of B1 coated product.

4.3.3. Dissolution study

The single coated pellets were tested for their sustained drug release profiles and exhibited drug release variably for 24 hours, as shown in Figure 4.3. Batches were in triplicate.

When either the 25% PVP or 25% $NaHCO_3$ containing batch was used (B1S and B2S, respectively), a significant difference in the drug release profiles were obtained when compared with other batches ($p<0.05$). Unlike the PVP containing batches, the non-PVP containing batches showed significant differences in their drug release profiles ($p<0.05$). The differences were attributed to the differences in the amount of the CO_2 formation and liberation, which affected the facilitation of the drug solubility and diffusion of the dissolved solute (from the core pellets matrix to the surrounding media). That is, the core composition in the coated pellets play a significant role in influencing the drug release. The latter finding was consistent with (Fahier., 2017). For all batches (except B1-3), the mechanism of the drug and gas release was mainly by the diffusion through a membrane, because the layer of the Eudragit NE provided a zero-order rate ($R^2>0.95$) of drug release. The latter information is needed to ensure that the sustained drug release profiles are streamlined. Interestingly, when compared to the double-coated pellets of ~16 % coating weight gain, the 15.3 % coating weight gain (obtained by the Eudragit NE15 dispersion diluted with distilled water only) caused highly prolonged drug release regardless of the core pellets compositions. The reason is because the sub-coating layer in the double-coated design has the sub-coated layer that has the entrapped gas, where the gas can be released, which enhances the drug release as well. Hence, it is expected here that the sub-coating layer will impair the retard coat layer to a great extent for several reasons: (1) the increase in the film's water solubility due to the nearby concentrated salt of the $NaHCO_3$. (2) The increased retard film elongation from the swelled sub-coating film (hydrocolloid film of the HPMC). And (3) the increased film rupture from the excessive pressure of the generated gas.

4.3.4. Floating study

After the screening for the attributes of sphericity and yields, the screening for the floating attribute is the next major concern. The single-coated floating pellets showed that they exhibited >50% floated variably on surface for at least 2 hours, with a lag time of <15 minutes, as shown in Table 4.7 and Figure 4.4. Batches were all in triplicate. Only three batches were successfully floated for at least 4 hours. The successful floating batches were the B2S that contained 25% $NaHCO_3$ (AR=1.09), the B6S that contained 22.5% PVP (AR=1.55), and the B8S that contained 11.25% $NaHCO_3$ and 11.25% PVP (AR=1.25). The former batch (B2S) is the only one to be passable for both aspect ratio and floating. However, more improvement is needed to have reasonably longer floating hours, to ensure a sufficient floating strength in the stomach. B6S was the most successful in floating, though its drug release is not sustained sufficiently. This floating success of the 22.5% PVP containing batch might be an artefact, as higher PVP% (25%) containing batch showed significantly less floating ($p=0.01$).

The 22.5% PVP containing batch (B6S) showed significantly better floating profile ($p<0.05$) than the 22.5% $NaHCO_3$ containing batch (B5S). As expected, the 25% $NaHCO_3$ containing batch (B2S) showed significantly better floating profile ($p=0.01$) than both 20% and 12.5% $NaHCO_3$ containing batches (B4S and B7S). That is because the increased sodium bicarbonate causes an increased gas generation and entrapment, resulting in a further density lowering of the floating pellets.

It is reasonable that the floating percentage was dependent on the $NaHCO_3$ amount. Because when the amount of the $NaHCO_3$ increased to a certain level (25%), the generated gas and the gas entrapment increased. The latter allows for an enhanced and prolonged lowering of the coated pellets' density. Consequently, the floating profile was improved. According to (Treesinchai, et al., 2016), the HPMC K100LV (LV; Low Viscosity) + >10% foam powder of the polypropylene will allow the tablet to float immediately upon contact with the liquid surface and

for a duration of >12 hours. The latter in that study was achieved without the addition of a retarding polymer and without applying any coating layer on the tablets.

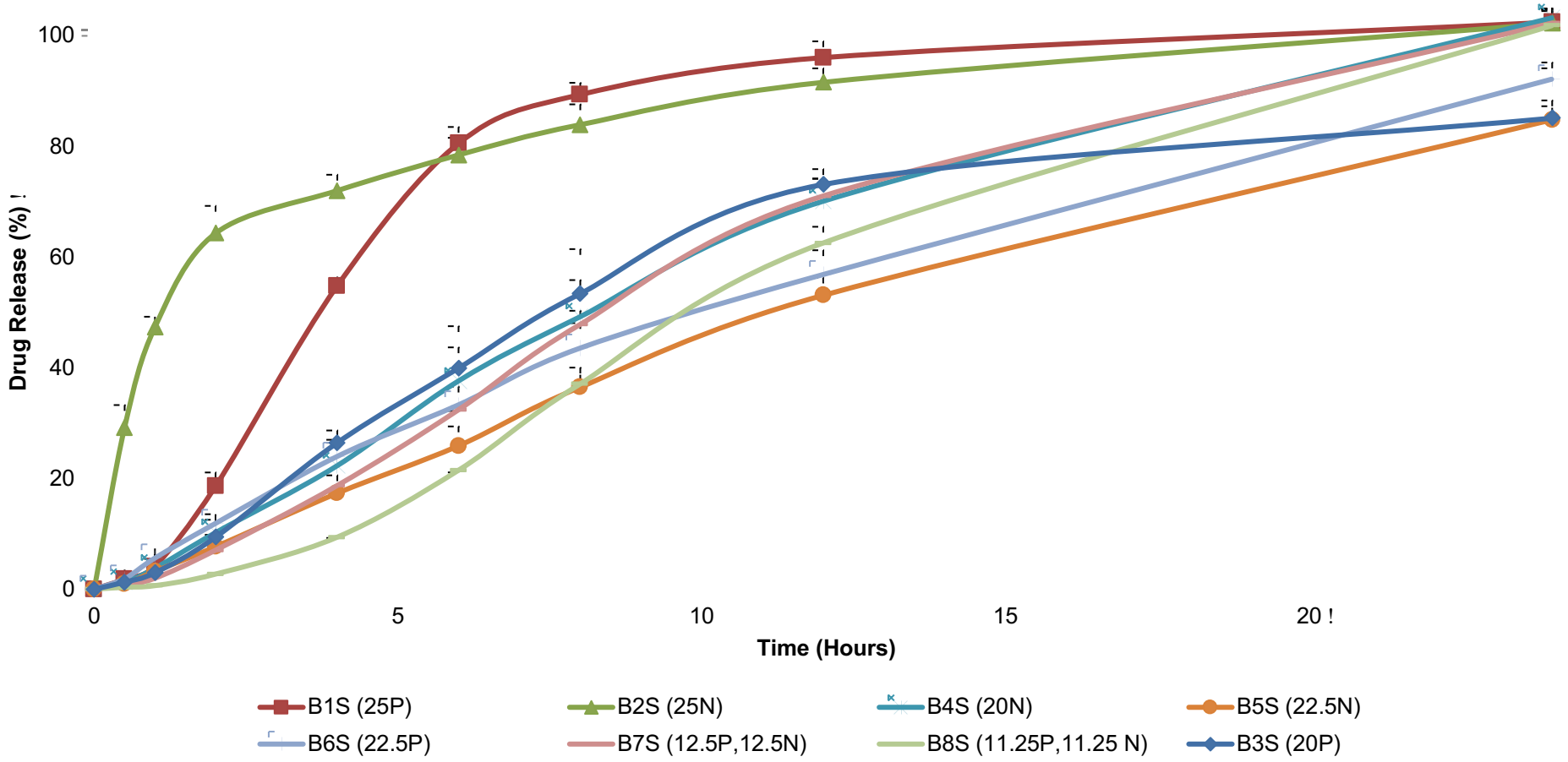


Figure 4.3: The sustained drug release percentages of the single coated pellets.

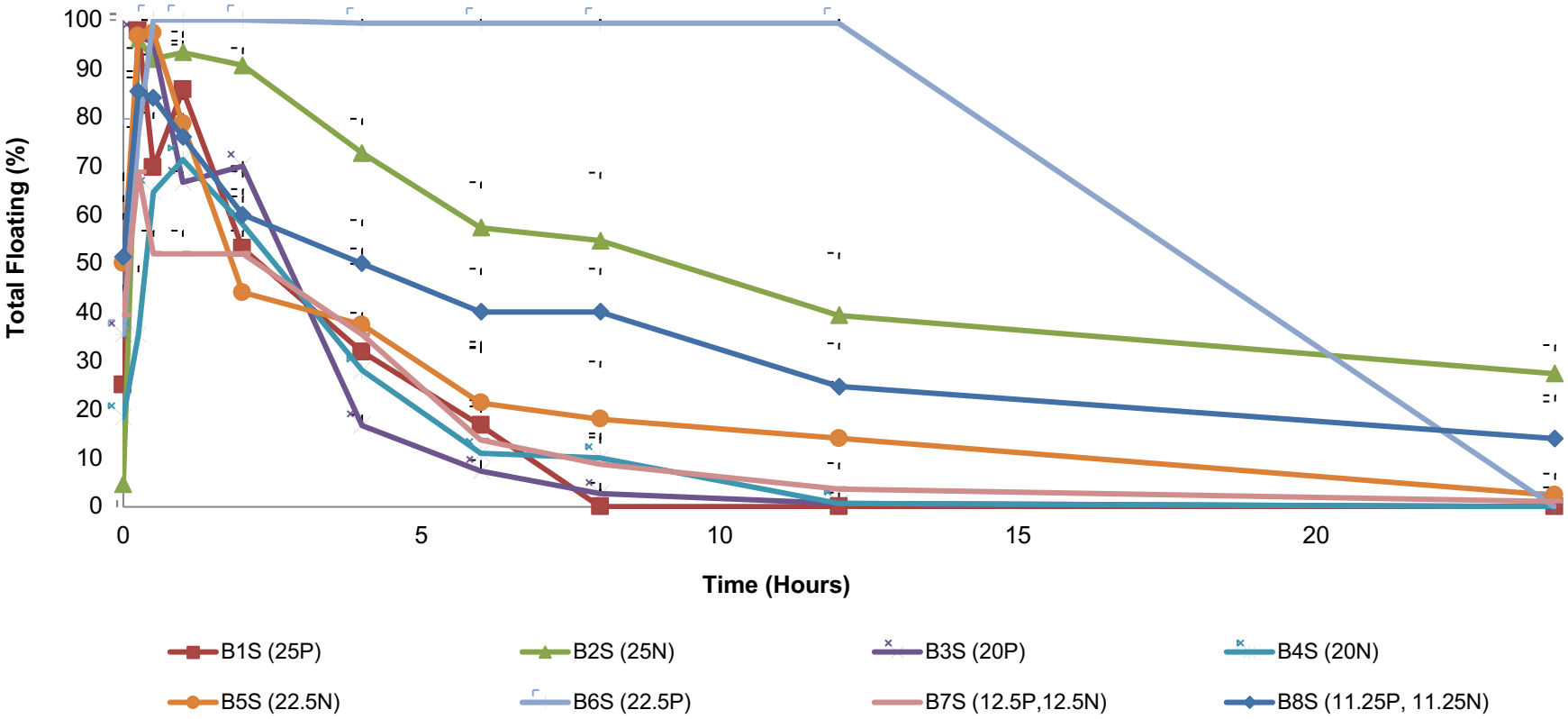


Figure 4.4: The total floating percentages for the single coated pellets.

Table 4.7: Shows the floating study for the single coated pellets.

Batch code	Floating duration (hours)*	Floating lag time onset (minutes)	Suspended Pellets (%)	On Surface Floating (%)**	Total Floating (%)***
B1S-25P	2	10	~18	50 ± 28	68 ± 26
B2S-25N	8	8	~05	84 ± 10	89 ± 09
B3S-20P	2	8-10	~18	51 ± 29	69 ± 32
B4S-20N	2	8-12	~18	33 ± 13	51 ± 19
B5S-22.5N	1	12	~08	63 ± 30	71 ± 29
B6S-22.5P	12	12	~07	88 ± 25	95 ± 10
B7S-12P,12N	2	8-10	~16	36 ± 13	52 ± 12
B8S-11P,11N	4	10	~07	64 ± 12	71 ± 16
Percentages values were entered in the following format: (Mean of 0.25-4hr+-%SD), n~220 for B1 (due to its elongated or rod shape) and n~500 (for all other batches), the number of coated pellets tested was calculated based on the 200mg dose.					
*Values were selected based on the period that maintains at least 50% total floating, which reach up to 100%.					
**Percentages were averaged between 15min-4hrs.					
***The total floating values include both on-surface floated pellets and suspended pellets.					

4.3.5. Scanning electron microscopy (SEM) study

The respectively coated pellets of the successfully spheronised core pellets were tested for their exterior and interior morphologies. Hence, the core pellets were of Feret ratio and circularity approaching unity, while their aspect ratio is below 1.2.

i. SEM images of the intact and the bisected coated pellets before dissolution

Some pores and protrusions were observed on the surface of the intact coated pellets, as seen in Figures 4.5. The protrusions may be mainly because of the poor fluidizability during coating. While in the coated area of the bisected coated pellets, the coating film is shown some variable thickness, see Figures 4.6.

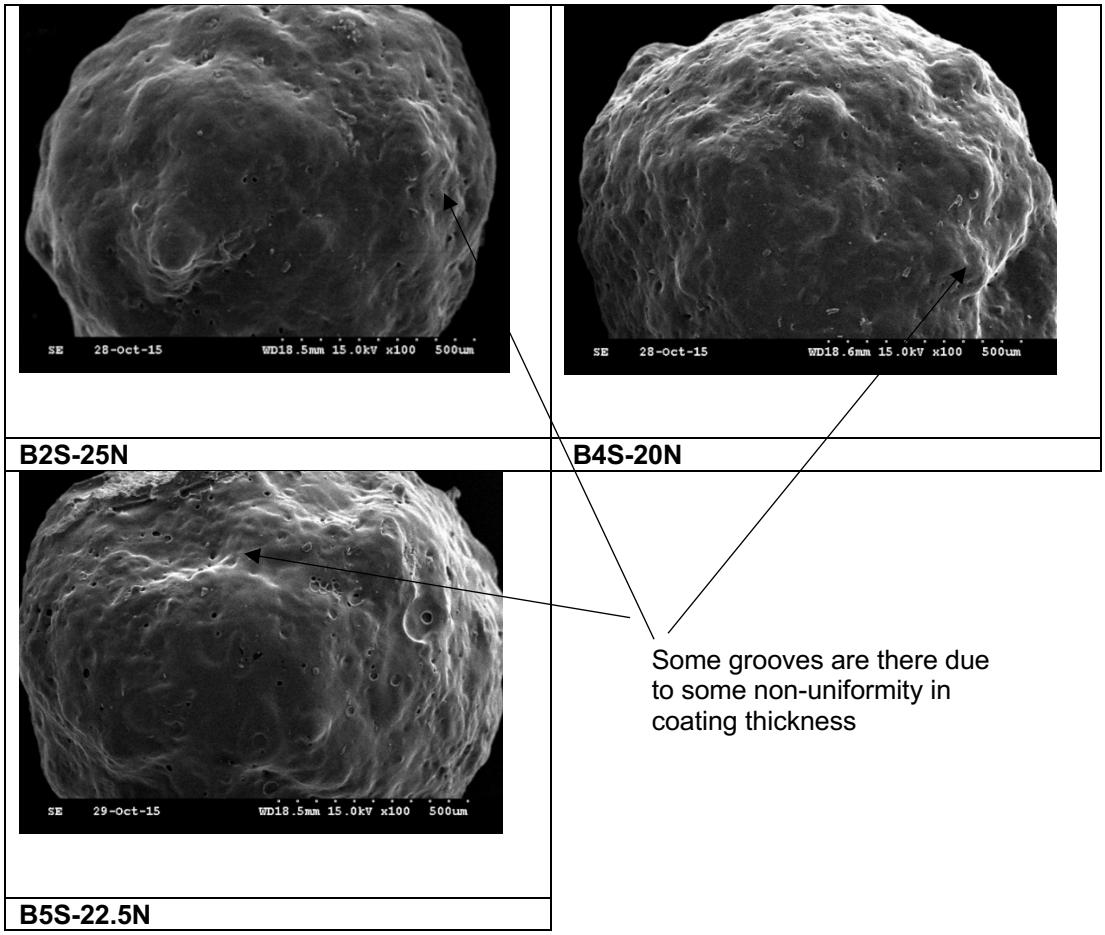


Figure 4.5: SEM images of the intact coated pellets before dissolution.

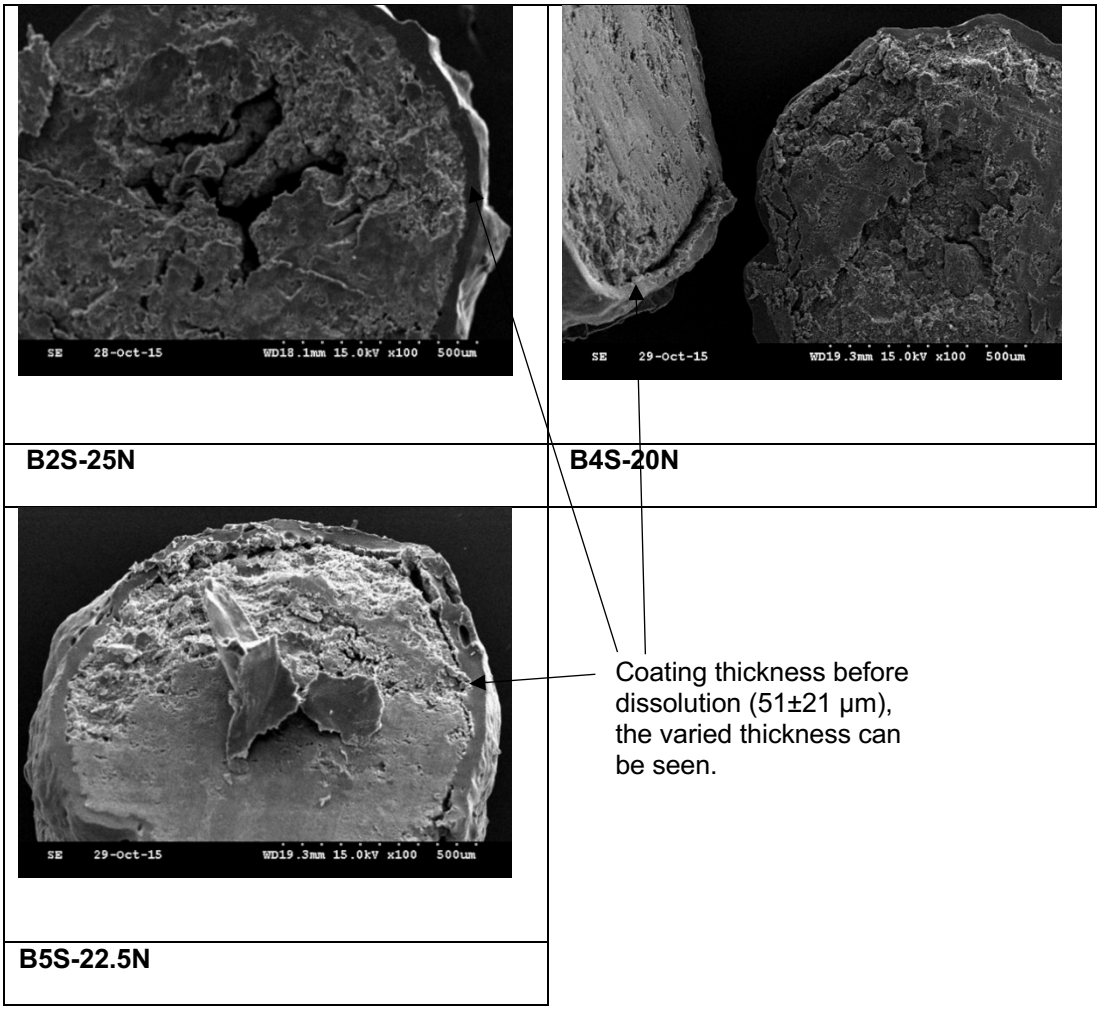


Figure 4.6: SEM images of the bisected coated pellets before dissolution.

iii. SEM images of the intact and the bisected coated pellets after dissolution

Due to the effect of dissolution, fewer pores but large protrusions were observed on the exterior surface of the coated pellets, as seen in Figure 4.7-8. In overall, the external surface of the coated pellets maintained its integrity, and no breakages were observed. Hence, the film layer of the aqueous Eudragit NE15 dispersion will withstand the dissolution process for 24 hours at least.

The internal surface showed voids as a result of the entrapped carbon dioxide (CO_2) and the released drug, as seen in Figure 4.8. The CO_2 was formed upon the neutralisation reaction of the acidic media with the sodium bicarbonate. The air entrapment/ impediment can confer buoyancy, because the entrapped air decreased the bulk density,

resulting in floating. The latter finding complied with other work like (Li, et al., 2014). Moreover, the pressure of the generated gas in the core pellets did not affect the integrity of the coated layer, which is desired for maintaining the floating and the sustained drug release profiles.

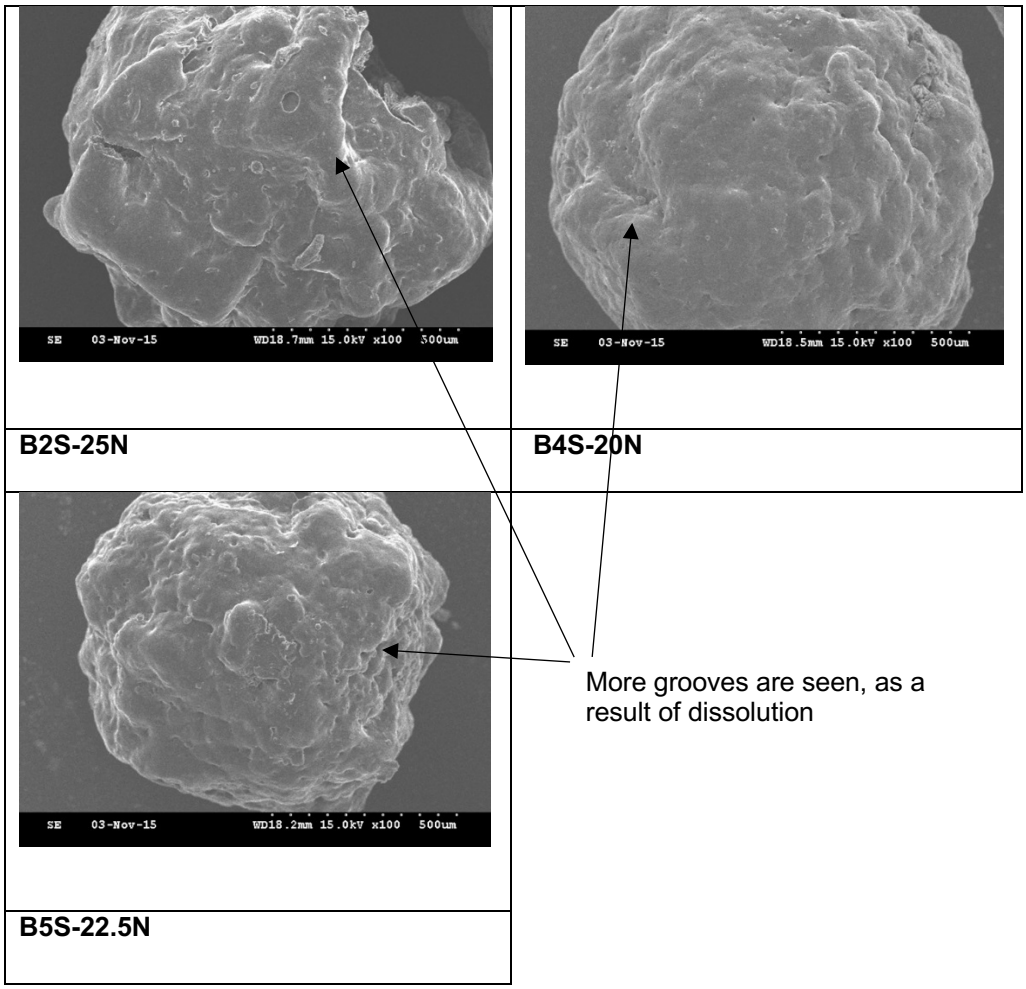


Figure 4.7: SEM images of the intact coated pellets after 24 hours dissolution.

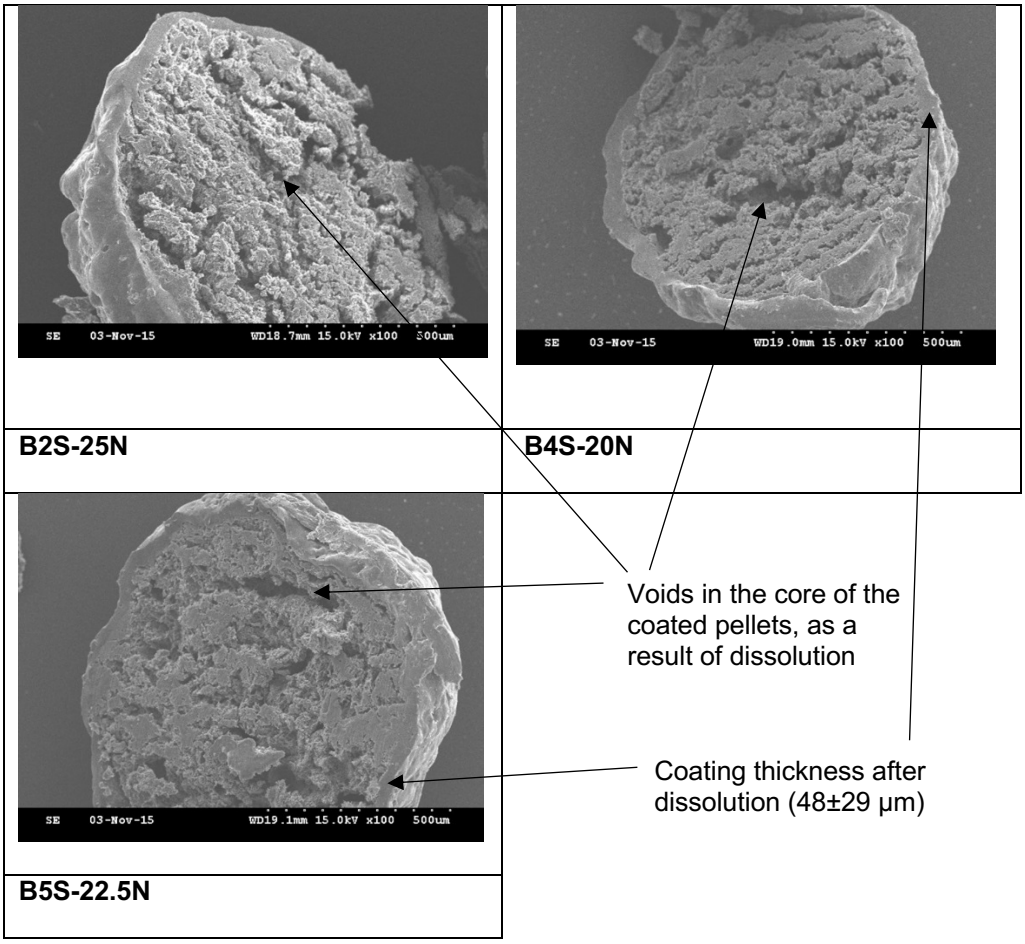


Figure 4.8: SEM images of the bisected coated pellets after 24 hours dissolution.

iii. Coating layer thickness study of the bisected coated pellets, before and after dissolution

The coating thickness values were recorded approximately for the smallest and the largest regions of the coating film, and for before and after dissolution. The pellets after dissolution showed negligible decrease in the coating thickness values when compared to those before dissolution. The average values of the coating thickness before dissolution is 51.31±20.95, and after dissolution is 48.25±28.99 µm. The standard deviation is considered high for the coating thickness, regardless of the dissolution effect, which may explain the variability in the floating and the drug release profiles. Three pellets were tested for each batch, and the respective values between all batches were averaged together.

4.4. Conclusion

The chapter aim is to screen for the single coated floating pellets, where the core pellets are intended to swell under the control of the Eudragit NE15 retard layer. This chapter will provide the bases for further enhancement work in the single-coated floating pellets. These coated pellets are expected to reduce the complexity of the floating pellets design. Because the pellets are to be floated with or without an effervescent agent, and aimed for less preparation time and less materials to be used, owing to the single coating stage. Hence, the floating layer in the double coated floating pellets could be removed with a maintained floating profile, with a pH-independent manner, and in an easier and more cost-effective manufacturing procedure.

In the core pellets making that intended to be single-coated, the addition of the polyvinylpyrrolidone (PVP) and the $NaHCO_3$, makes the liquid binder optimisation becomes more challenging. The distilled water showed significant interaction effects with the PVP and the $NaHCO_3$ (p-values<0.05). The PVP favours a small amount of water in the wet mass, while the $NaHCO_3$ was vice versa. The PVP containing core pellets exhibited poor quality, and the $NaHCO_3$ was easier to process into the desirable core pellets than the PVP, and the $NaHCO_3$ can better meet the desired outcomes than the PVP. The floating was proportionally dependent on the PVP and the $NaHCO_3$ amounts. As their amounts increase to 25%, the extent of the swelling and the CO_2 entrapment increase, respective to these excipients. The sustained drug release was dis-proportionally dependent on the $NaHCO_3$ amount, as the increase in the $NaHCO_3$ will increase the liquid uptake process, by a salting-out process, resulting in a faster drug release in the highly concentrated $NaHCO_3$ containing batch (25%; B2S). It was recommended to increase the MCC amount over the PVP amount in the core pellets, to improve the aspect ratio and to ease processing of the PVP containing batches (B1S, B3S, and B6S-B8S). It was decided to do further modifications to obtain the optimum formulation, by the use of the 10% ethanol liquid binder, and by the use of the smaller extrusion screen

size of 1 mm. Moreover, the ethanol is also recommended to be used in the coating liquid, to enhance the coating efficiency and to provide a uniform coating thickness. Additionally, the coating weight gain is recommended to be decreased to <14%, to streamline the sustained drug release profiles for 12 hours only. The latter attempts are expected to improve the coating uniformity and the film quality and to ease processing, to meet the desired outcomes of the floating and the drug release of the single-coated floating pellets.

To sum it up, the attainment of the single-coated floating pellets design through a screening study was feasible. Specifically, the attainment of the core pellets where the effervescent and hydrating polymers are incorporated into the matrix (core pellets). However, when these pellets were coated, the floating and the sustained drug release properties for all formulations were variable. Therefore, an enhancement work is needed to streamline the results.

Chapter Five:

Enhancement Study for the Single-Coated Floating Pellets

5.1. Introduction

The enhancement is concerned with choosing inputs that allows for obtaining an improved outcome. Hence, previous knowledge in the studied formulation design is requested, as seen in the previous chapter. Based on the latter, some recommendations were stated to improve the formulation design. It was recommended that the wet mass and the coating dispersion compositions need to be changed, to improve the ease of manufacturing, usable size distribution, sphericity, floating, and drug release outcomes. As it was noted before, the prolonging of gastric retention can improve the drug bioavailability for some drugs, such as theophylline.

The enhancement work had some limitations, namely, the liquid binder effect may not be easily isolated on the quality of the final product. It may have an effect in obtaining different spheronisation yields. However, the main outcomes mentioned above showed no statistical differences (p-values>0.05) for the different amounts of liquid binder used in all formulations. Moreover, the coating process and the film formation mechanisms require further understanding, and how that understanding reflects to the quality of the final product (Felton, 2013).

The aim in this work was to enhance the core pellets and the coated layer in the single-coated floating pellets. The first objective is to use 10 w/w% ethanol as the liquid binder in the wet massing process. Also, a higher MCC amount will be used, and a smaller pore size of the extruder screen was used (1 mm instead of 1.2 mm). These modifications were made to improve the extrusion and spheronisation process and the core pellets quality. In particular, it was expected that these modifications can potential reduce the sticking ability of the PVP-containing extrudates will be expected. The second objective was to apply a single coating layer from the Eudragit NE15 dispersion, out of which is 25 w/w% ethanol (15Eud25Eth dispersion). The ethanol was used to improve the coating process and the resulted film quality. The pellets can expand in the volume with the aid of a hydrating polymer, including povidone (PVP)

and crospovidone (cros-PVP) polymers, and with or without the need for a gas forming agent. The extent of swelling to be controlled by the coating layer, which made from the 15Eud25Eth dispersion. The controlled swelling -as determined shortly- will improve the floating and the sustained drug release properties. Hence, in this work, the single-coated floating pellets system designs of the effervescent type and the non-effervescent type are expected to be feasible and show optimum efficiency.

Although more intricate to make, the single-coated floating pellets have reduced the number of coating layers into one layer only, reducing the cost of manufacturing. The enhanced core pellets are suitable for being applied to further processing, like coating and tabletting. The enhanced retard coating layer was made from the 15Eud25Eth dispersion.

5.2. Characterisation of Coating Liquids and Liquid Binders; Surface Tension

A force tensiometric study was conducted for the coating liquids and the liquid binders, to examine their physical properties regarding the surface tension of liquid. A summary of the results is shown in Table 5.1. The coating process efficiency will be affected by the coating liquid formulation variables and the coating process variables. The effect of dilution by an aqueous liquid and a non-aqueous liquid was assessed.

For the 15 w/w% Eudragit NE dispersion with 10 w/w% ethanol (15NE10eth), the surface tension was 45.65±0.05 mN/m, while the Eudragit NE15 dispersion, of which 25 w/w% ethanol (15Eud25Eth) showed a surface tension of 34.07±0.03 mN/m. This decrease in surface tension is related to the increase in the ethanol content, that is owing to the ability of ethanol to make less hydrogen bonding than water, resulting in a weaker liquid surface. The latter is a desired property for consistent spraying, uniform liquid spreading, and uniform film formation (Cole, et al., 2002). The high-HPMC containing dispersion has relatively a larger standard deviation in the surface tension (48.34±2.00 mN/m)

when compared to the other dispersions shown in the Table 5.1. This variation in the surface tension measurements of the latter could be owing to the HPMC presence, as the HPMC was visually observed to be more viscous (the exact viscosity values not determined). Resulting in a potential variation between the dynamics readings of the same sample. The reading frequency was set every ~15 seconds, that rate of measurements may be fast enough to make a redundant reading of viscous liquid.

Table 5.1: Shows the surface tension results for the coating liquids and liquid binders*,

Coating liquid batch	**Average surface tension (mN/m)****
Eudragit NE30D (30Eud0Eth)	47.70±0.01
Eudragit NE15D (15Eud0Eth)	48.00±0.06
10% ethanol Eudragit NE15D (15Eud10Eth)	43.65±0.05
25% ethanol Eudragit NE15D (15Eud25Eth)	34.07±0.03
HPMC:$NaHCO_3$:PEG6000 3.33:6.66:0.5%	39.13±0.66
HPMC:$NaHCO_3$:PEG6000 6.66:3.33:1%	48.34±2.00
10 w/w% ethanol	46.70±0.04
Distilled water	70.90±0.80
* All results were measured at ambient room temperature (~22 °C).	
** The surface tension measurements were 10 dynamic measurements for the same sample.	

There are common failures in a coating process, which result in the coating in-efficiency. The coating failures are likely to be sequential, like an increased sedimentation of the coating liquid can result in blockage of the coating tubes and spraying nozzle, poor spraying pattern and rate consistency, uneven spreading of the sprayed droplet, and poor fluidisability of pellets under coating. The tendency of failure can increase when a fully aqueous coating liquid is used (Cole, et al., 2002). The Eudragit NE30D dispersion has 30% solids. Based on Evonik guidelines of the Eudragit NE grade, it is recommended to use a diluted concentration during coating, which is 20% or less, to reduce the likelihood of the coating failure, such as blockages in tube and nozzle (Evonik, 2016).

Since, the use of non-aqueous solvent incurs safety concerns, it is desirable to focus first on the use of an aqueous solvent, which is safe for coating.

5.3. Characterisation of the Core Pellets

The compositions of floating pellets are succinctly outlined in the codes table of pellets batches (Table 2.2) and detailed in Table 2.4

5.3.1. Physical examination of the wet mass, the extrudates, the core pellets, and the spheronisation yields

The physical examinations during the core pellets making were recorded in Table 5.2. The wet mass of most batches appeared as a wet sand, which is a desired appearance that usually indicates a consistent wet mass. The extrudates of all batches appeared as non-sticky and either as smooth or perforated with a length diameter of 1-1.5 cm. The non-stickiness and short diameter of extrudates can indicate their ease of spheronisation. The core pellets of all batches appeared as round.

The ethanol usage and the high MCC: PVP ratio were needed, to decrease the stickiness of the PVP. The decreased stickiness will improve the processing and the usable yield as well as the sphericity of the core pellets. Moreover, when compared to the PVP, the cros-PVP was showed a large water uptake to reach the consistent wet mass, because the cros-PVP is considered as a water-insoluble polyamide polymer (Chemical-Book, 2017).

The decrease in surface tension of a liquid binder can decrease the viscosity and maximum torque of that liquid, resulting in an increased binder spreading and distribution (Sakr, et al., 2012). The latter outcome is desirable for obtaining a consistent wet mass prior extrusion and spheronisation processes. Also, the decrease in surface tension also decrease the work of cohesion and adhesion (Ebnesajjad, 2011). Hence, it will decrease the sticking of PVP.

The cros-PVP polymer is water-insoluble, owing to its cros-linking nature, which also impart high retention of liquid. The cros-PVP ease the extrusion and spheronisation processes, due to its effect on producing a high consistent wet mass, owing to low sticking (low adhesion) that was visually checked during processing. A 1:1 ratio of liquid binder: powder was needed for the powder mix that contained the cros-PVP. That is owing to the crosslinking of the cros-PVP polymer, which allows for high swelling capacity. Rowe, et al., 2009 confirms that the cros-PVP will rapidly exhibits high capillary activity and hydration capacity. The spheronisation aid of the cros-PVP was explained by (Jain, et al., 2010). The core pellets containing the cros-PVP (B11S) were easily made with a superior yield (>80%) when compared to other batches, owing to the high swelling of cros-PVP. It had a comparable sphericity to that of the other batches.

The low surface tension of the 10 w/w% ethanol solution (46.7±0.035 mN/m) compared to distilled water only (70.9±0.8 mN/m) explains the improved wet mass consistency when ethanol is used. Resulting with core pellets of improved spheronisation yields (70.4-81.2%) and sphericity (Aspect ratio; AR<1.2) in all batches when compared to the core pellets made with distilled water only (chapter 4; 54.3-72.6% and AR of 1.05-2.16 respectively). Hence, the addition of the organic solvent decreased the preferential liquid migration toward the PVP. This allowed the PVP to decrease its sticking propensity to the equipment tooling and to the adjacent pellets during spheronisation (Ebnesajjad, 2011).

On the other hand, the ethanol may excessively weaken the integrity of the extrudates, due to the potential induction of the excessive channelling in their internal structure as the ethanol evaporates increasing the agglomerates porosity (Nordström, et al., 2013). That weakness can de-agglomerate the extrudates into powder upon the first contact by the high-speed effect of the rotating disc spheroniser. Hence, the powdering of the extrudates can be avoided using a small ratio of ethanol: water in the liquid binder, i.e. 10: 90.

Table 5.2: Shows the visual observations of the intermediate products during the core pellets preparation, and the total yields of the core pellets after spheronisation and drying.

Batch code	Wet mass appearance	Extrudates appearance	Core pellets appearance*
B9S-8P,3N,10E	Wet sand-like	Medium and perforated (~1 cm)	Round/ Spheres
B10S-12P,47HF,10E	Wet sand-like	Fragile, smooth no stickiness, medium length (~1 cm)	Round/ Spheres
B11S-12CP,47HF, 10E	Large granules and sticky	Medium, perforated and liable to break easily; fragile (~1 cm)	Round/ Spheres
B12S-12P,47PH,10E	Wet sand-like	Smooth no stickiness and medium to large size (~1.5 cm)	Majority rounded and some are coarse in size
B13S-60DL,10E	Wet sand-like	Perforated, and small (~1 cm)	Round/ Spheres
B14S-2P,17N,10E	Wet sand-like	Smooth no stickiness, small (~1 cm)	Round/ Spheres
B15-Cushioning Pellets	Wet sand-like	Smooth no stickiness, medium length (~1 cm)	Round/ Spheres
*If the core pellets appearance is round/sphere, then the expected AR will be <1.2.			

5.3.2. Sieve analysis

The cumulative undersize distribution of the core pellets graph is shown in Figure 5.1. Most batches exhibit steep curves that indicates narrow size distribution, while B12S demonstrates the widest distribution. The narrow size distribution is favourable as it indicates that the yield of the core pellets is mostly within the usable size fraction yield (0.71-1.4 mm). The size distribution values of the core pellets were summarised in Table 5.3. The cumulative undersize curves showed usable size range of >80.30% for all batches of the core pellets, except B12S. Also, all batches showed a narrowed size range (1-1.18 mm) of >24% yield, while B11S and B13S showed <11% yield. Despite the high amount of MCC in the latter batches, they did not relatively show highly narrowed size distribution. That could be due to the liquid binder amount, but that potential cause cannot be isolated in this work. The narrowed yield of 1-1.18 mm of all batches (7.4-44.6%) was narrower when compared with those in chapter 4 (5-51%). The usable yield of 0.71-1.4 mm (62-99.6%)

was also narrower when compared to those in chapter 4 (14-97%). Hence, the narrowing of the yields was relatively improved.

The IQR values of all batches were ranging from 0.15 to 0.62 mm, where some batches (B12S and B14S) were positively skewed, due to some avalanching during spheronisation. It could be due to the use of Avicel PH101 and the high $NaHCO_3$ amount, respectively, that made the wet mass to be not as consistent as those of other batches. The median diameter values of all batches were 0.88-1.12 mm. The use of the Avicel PH101 resulted in the lowest usable yield (62%). The presence of cros-PVP required a double increase of the liquid binder amount, to achieve a consistent wet mass that is applicable for extrusion and spheronisation. The resulted wet mass was extruded with negligible losses, resulting in the highest usable yield (99.65%) with the lowest scattering from the mean (IQR=0.15 mm). That can be attributed to the high swelling ability of the cros-PVP.

The core pellets yield after drying for all batches ranges from 70-81%. Interestingly, although B11S showed a wet mass of sticky and large granules, it resulted with the highest spheronisation yield of 81%. And although its narrowed size yield of 1-1.18 mm was only 10%, it showed up to 90.6% usable size yield of 0.71-1.4 mm. Hence, it resulted with negligible coarse and fine yields.

5.3.3. Sphericity testing by the image analysis

The core pellets were analysed using the images of the light microscope, where the shape diameters were calculated using the Ziess software, data shown in Table 5.4. Like the screening experiments of the non-PVP containing batches (B2S, B4S and B5S), the core pellets have successful sphericity with aspect ratio (AR) values of 1.09-1.17 with SD of less than 0.1, the circularity values approaching unity with SD of less than 0.03. The spheronisation yields were all above 70%. The obtained values were as desired for good quality of the core pellets. Hence, the core pellets are enhanced, which is beneficial for a uniform coating process (Kumari, et al., 2013).

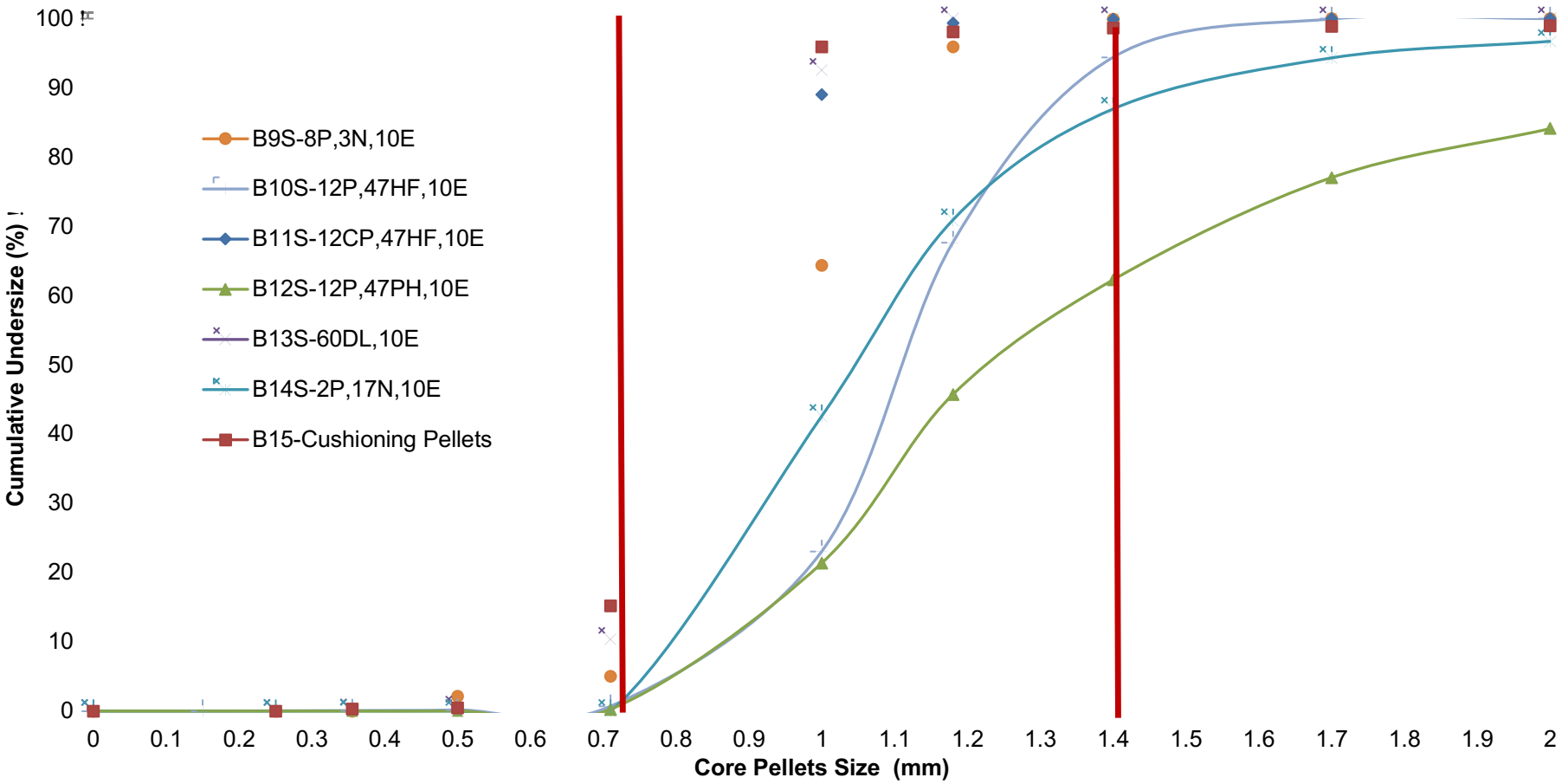


Figure 5.1: Shows the particle size distribution based on the cumulative undersize (%) of the sieved core pellets (n=1) intended for applying an enhanced single-coating. The red vertical lines represent the range of the usable size fraction that suitable for the subsequent processes of coating and tabletting.

Table 5.3: Shows the size distribution values of the core pellets.

Batch code	Spheronisation yield (%)*	Narrowed yield of 1-1.18 mm (%)	Usable yield of 0.71-1.4 mm (%)	Fine fraction; 0-71mm (%)	Coarse fraction; 1.4-2 mm (%)	IQR (mm)	Median class (mm)
B9S-8P,3N,10E	71.42	31.30	94.88	05.01	00.10	0.23	0.71-1
B10S-12P,47HF,10E	71.18	44.59	93.71	00.68	05.61	0.35	1-1.18
B11S-12CP,47HF,10E	81.22	10.32	99.65	00.23	00.12	0.15	0.71-1
B12S-12P,47PH,10E	70.37	24.33	61.99	00.27	37.75	0.62	1-1.18
B13S-60DL,10E	76.61	07.46	89.60	10.40	00.00	0.16	0.71-1
B14S-2P,17N,10E	76.12	28.33	86.93	00.00	13.07	0.33	0.71-1
B15-Cushioning Pellets**	56.00	57.25	90.58	09.15	00.27	0.23	1-1.18

*% of the dried core pellets yield 2= (weight of the dried core pellets after spheronisation/ weight of the initial powder materials used)*100.

**Although that the cushioning pellets will not be used in the upcoming chapter (as proved less efficient than the cushioning powder in chapter 3), it will be studied here for the comparison with the other single-coated pellets. Hence, to compare with the non-drug loaded and the drug-loaded pellets.

Table 5.4 Shows the shape parameters for the core pellets*. !

Batch code	Feret-Min (mm)	Feret-Max (mm)	Feret Ratio	Perimeter (mm)	F-Circle (Circularity)	Aspect Ratio
B9S-8P,3N,10E	1.09±0.06	1.23±0.10	0.86±0.05	4.05±0.26	0.95± 0.02	1.12± 0.06
B10S-12P,47HF,10E	1.14±0.06	1.24±0.07	0.91±0.03	4.05±0.25	0.92± 0.03	1.09± 0.04
B11S-12CP,47HF,10E	1.06±0.06	1.20±0.07	0.87±0.04	3.85±0.21	0.93± 0.02	1.13± 0.04
B12S-12P,47PH,10E	1.14±0.06	1.29±0.08	0.84±0.06	4.16±0.03	0.93±0.03	1.13±0.05
B13S-60DL,10E	0.83±0.06	0.91±.07	0.91±0.03	2.83±0.21	0.97±0.01	1.10±0.08
B14S-2P,17N,10E	1.05±0.08	1.18±0.08	0.88±0.04	3.75±0.30	0.94±0.02	1.12±0.05
*Values were in the following format: (Mean±SD), n=30.						

5.3.4. Friability study, using the abrasion drum

The friability results of the core pellets were summarised for all batches in Table 5.6. Similar to the previous chapter, the weight loss values were within the acceptable limits (<1% weight loss; MSI>99%) as agreed by (Sungthongjeen, et al., 2006). Hence, the core pellets were mechanically strong and showed sufficient integrity to withhold subsequent processes of coating, tabletting, packaging, and shipping.

Table 5.6: Shows the mechanical strength index values of the core pellets upon the friability study.

Batch code	Weight before test (g)	Weight after test (g)	Weight loss (%)	MSI (%)
B9S-8P,3N,10E	10.0273	10.0258	0.015	99.98
B10S-12P,47HF,10E	10.0113	10.0078	0.035	99.97
B11S-12CP,47HF,10E	10.0238	10.0102	0.408	99.59
B12S-12P,47PH,10E	10.0420	10.0110	0.310	99.69
B13S-60DL,10E	06.7091	06.7085	0.009	99.99
B14S-2P,17N,10E	10.0390	10.0220	0.017	99.83
B15-Cushioning Pellets	10.0390	10.0220	0.017	99.83

5.3.5. Floating study, using the beaker method

Expectedly, the core pellets did not float, which is similar to the core pellets made in the previous chapter. All the core pellets sank to the bottom of the beaker after few seconds of pouring in either distilled water or 0.1N HCl media, due to the excessive wetting of the core pellets. Hence, for floating to be achieved, a layer of a polymeric membrane was needed for the gas entrapment and/or to control the matrix swelling.

5.4. Characterisation of the Coated Pellets

5.4.1. Coating weight gain yields

After 24 hours of drying and curing, the coating weight gain was 6±1%, as seen in Table 5.7. Hence, fewer materials were needed for the coating. The coating time was short, which was completed in 30 minutes to reach 6±1% weight gain by the 15Eud25Eth dispersion. Applying a layer of a pH-independent and swellable retard coat is essential for the pellets to float, and the same layer is expected to exhibit a sustained release property.

Table 5.7: Shows the coating yields after coating and after drying.

Batch code	Weight before coating (g)	Time of coating (min)	Weight gain before drying (g)	Weight gain before drying (%)*	Weight gain after drying and curing (g)	Weight gain after drying and curing (%)**
B9S-8P,3N,10E	6.70	45	0.3305	4.72	0.35	5.00
B10S-12P,47HF,10E	6.70	45	0.3494	4.99	0.37	5.23
B11S-12CP,47HF,10E	6.70	45	0.5406	7.72	0.46	6.60
B12S-12P,47PH,10E	7.00	55	0.5600	8.00	0.48	6.93
B13S-60DL,10E	4.54	47	0.3300	7.27	0.26	5.73
B14S-2P,17N,10E	7.00	50	0.4200	6.00	0.42	6.00
B15-Cushioning Pellets	7.00	55	0.4800	6.86	0.46	6.57
Average	-	48.86±4.56	0.43±0.1	6.51±1.3	0.39±0.08	6±0.73***
*The wet and the dry weight will be used to calculate the wet and the dry weight gain percentages, respectively, which are based on the weight before the coating. Then, based on previous trial and error, a speculation of the remaining time for the coating will be estimated.						
** The % of the CWG obtained= [(CWG solids*targeted % CWG in a fraction)/targeted CWG solids]*100. The targeted CWG solids= (batch size in mass*% of targeted CWG)/100.						
***This average value is within the targeted coating gain range of 6±1% (0.42±0.07g solids).						

5.4.2. Surface hardness study

The compression force values applied on the coated pellets were summarised in Table 5.8. The hardness of floating pellets of all batches was 0.9-1.01 KgF, SD <0.23 KgF (8.82-9.9 N, SD <2.25 N), such a range of values considered more narrowed when compared to those batches in chapter 4 (0.77-1.21 KgF, SD <0.35 KgF; 7.55-11.86 N, SD <3.43 N). That was because the former batches coating thickness was 10±2 µm, while the latter batches coating thickness was more varied 51±21 µm. Hence, the less varied coating thickness ensures less varied surface hardness of coated pellets. The latter implied that the coated pellets can withstand the tableting force upon compression without breakage. However, cushioning excipients such as MCC or waxy materials may still be needed to ensure complete protection from film deformation and/or fractures (Dwibhashyam and Ratna, 2008).

The MCC only cushioning pellets (B15 core pellets) were weak (0.57 ± 0.17). When coated, this weakness was significantly reduced (0.76 ± 0.13) by the added strength from the polymeric film (p-value=0.05). That complied with the density study in section 5.4.4, where the coated and uncoated cushioning pellets (of only Avicel HFE102) had a low density of ~0.5 g/cm^3, implying large voids in the pellets' structure. That is when compared to the coated and uncoated medicated pellets density of 1.45-1.49 g/cm^3.

Table 5.8: Shows the compression force values for the coated pellets.

Batch code	**Average Force (KgF)**	**Average Force (N)**	**Batch code**	**Force (KgF)**	**Average Force (N)**
B9S-8P,3N,10E	0.85 ± 0.21	8.34 ± 2.06	**B13S-60DL,10E**	0.89 ± 0.22	8.69 ± 2.12
B10S-12P,47HF, 10E	0.90 ± 0.22	8.83 ± 2.16	**B14S-2P,17N,10E**	0.91 ± 0.19	8.95 ± 1.82
B11S-12CP,47HF ,10E	1.01 ± 0.20	9.91 ± 1.96	**B15-Cushioning Pellets**	0.76 ± 0.13	7.43 ± 1.32
B12S-12P,47PH, 10E	1.00 ± 0.20	9.78 ± 1.99	**B15-Cushioning Pellets (not coated)**	0.57 ± 0.17	5.59 ± 1.70

5.4.3. Dissolution study

Figures 5.2-3 show drug release profiles from 0-24 hours. The sustained drug release is achieved were all batches being streamlined and enhanced for 24 hours in both media of 0.1N HCl and distilled water. There was no significant difference in the drug release profiles (p-values>0.05). The dissolution profiles for the coated pellets of some batches (B9S-B11S) showed a complete drug release in duration of 24 hours in both the 0.1N HCl and the distilled water media. Other batches had ~90% drug release after 24 hours of dissolution, that for some batches (B9S and B10S) could be due to their lower coating gain (5 and 5.23%, respectively), when compared to B12S and B13S (6.73 and 6.93%). The drug release results for all batches may fit for the zero-order model (R^2>0.8) during the 24 hours dissolution, indicating a diffusion-based mechanism predominating the drug release mechanism, which is an outcome that is comparable to (Sungthongjeen, et al., 2006) and (Katakam, et al., 2013). All batches of the coated pellets that placed in the 0.1N HCl medium showed a complete drug release in the range of the 100±5%, while those placed in the distilled water showed a complete drug release in the range of the 98.5±3.5%. Regardless of the core pellets composition and the medium of dissolution, all of the drug release profiles were not significantly different (p-values<0.05).

The ethanol uses in the coating dispersion resulted in a film that increased and streamlined the sustained drug release profile from the coated pellets. The study done by (Nokhodchi, et al., 2010) has suggested that the non-volatile cosolvent is vital in the sustained drug release property of some of the liquisolid tablets. Although, tablets can be usually different from pellets in size and shape, the volatile solvent like ethanol, was found in the work here to have a vital effect on the drug release as well.

There could be two patterns of drug release in your curves, from 0-6 hrs and from 6-24 hrs. The former (6 hours period) is a bit faster where 40-60% of the drug released, and the latter period (18 hours period; three

times longer) is a bit slower where also 40-60% of the drug released. Hence, approximately half of drug release was seen in the initial 6 hours, where the other approximate half of the dose was released at a longer time (18 hours). A zero-order rate can be more accurately obtained in each of these time ranges separately (R^2>0.95 and R^2>0.99, respectively).

As discussed earlier in section 1.5.3.ii, it was assumed that the drug theophylline may show more ionization (dissociation) at a medium pH of 1.2 instead of 5.8, and perhaps more streamlined dissolution profiles. However, the less ionization of the drug at a medium pH of 5.8 (distilled water) still showing a comparable dissolution profile when compared to that of a medium pH of 1.2 (0.1N HCl), as seen in Figure 5.2-3.

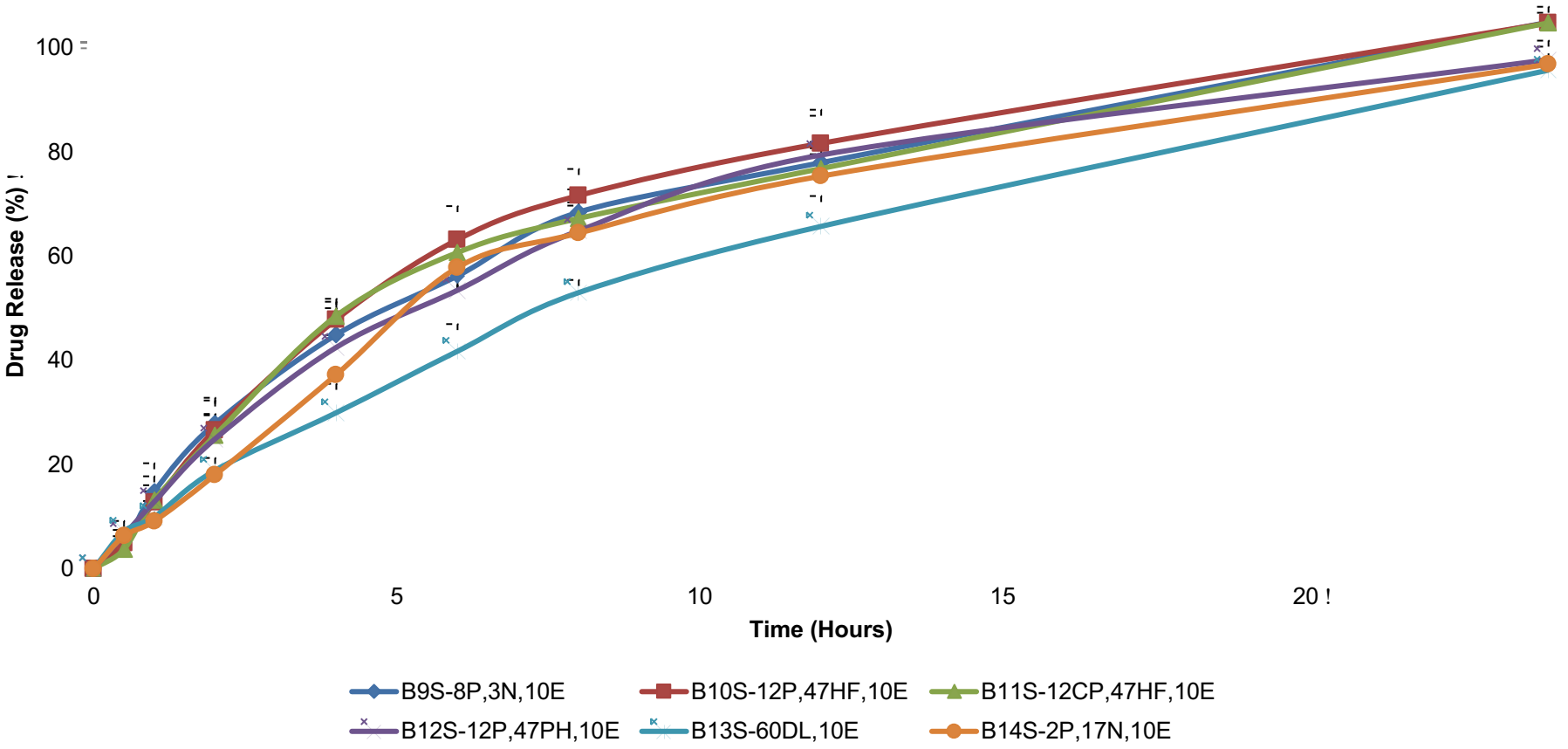


Figure 5.2: The sustained drug release curves of the single-coated pellets in the 0.1N HCl medium (pH ~1.2) (n=3). This figure shows the streamlined drug release curves in a period of 24 hours

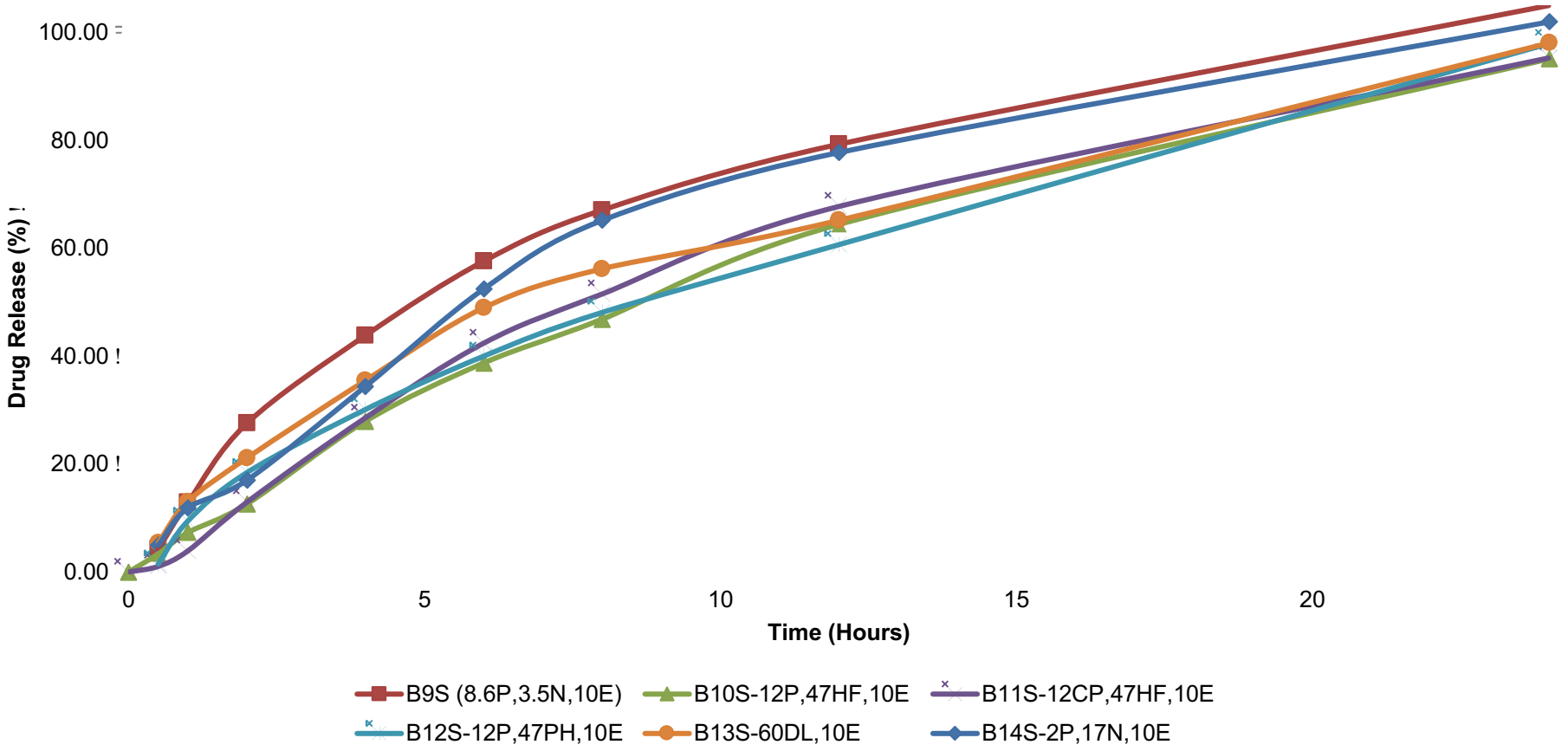


Figure 5.3: The sustained drug release curves of the single-coated pellets in the distilled water medium (pH ~5.8) (n=1). This figure shows the streamlined drug release curves in a period of 24 hours.

5.4.4. Floating study and the related studies for the anticipated floating mechanisms

i. Floating study

The floating profiles were summarised in Tables 5.9-10, and graphed in Figures 5.4-5, for 0.1N HCl and distilled water media, respectively. There was no significant difference in the floating profiles (p-values >0.05). The lag time to float was 10 minutes. The floating was maintained for at least 24 hours in 0.1N HCl and 12-24 hours in distilled water. The percentage of floating was at least 90% for a minimum of 12 hours. B10S was showing less floating after 8 hours of dissolution in 0.1N HCl medium, however, that was not a significant change (p-value<0.05). Unlike the previous chapter, the results here showed shorter lag time, longer duration, and complete floating. Some of the pellets immediately floated upon pouring into the medium, owing to their initial low density. After then, the pellets initiated swelling within 10 minutes, to maintain the floating. Hence, they initiated the swelling during the floating lag time.

The critical quality attribute of the floating duration response is to be from 6-12 hours, favorably for 12 hours. Therefore, the results obtained using the distilled water medium for floating are also considered optimum, regardless of the drop occurred somewhere between 12-24 hours in all batches, except the cros-PVP containing batch (B11S), as shown in Figure 5.5. The latter batch may improve floating in the distilled water medium, however, that would to be determined in future work by making replicates. The results indicate that the floating performance of floating pellets are likely to withstand the pH increase in the stomach at the fed state. Hence, the floating of the floating pellets is not dependent on the gas generating agent to occur. The latter will lower the risk of failure in floating.

The coating layer that was made from the 15Eud25Eth dispersion can control the liquid permeation into and out from the core pellets, resulting

in a controlled swelling. The expected mechanisms are (1) gradual increase in the pellets' volume, as the coating layer (made from 15Eud25Eth dispersion, where the emulsifier concentration was 1.5% nonoxynol) can help in allowing and controlling the extent of this expansion in the film layer. And (2) increased pores by the swelled polymer and/or by the generated gas from the $NaHCO_3$ (Singh & Kim, 2000). Based on (Popova, et al., 2016), they needed to increase the concentration of ethanol -as a liquid binder- from 40% to 80% to induce a sustained drug release from the ethyl cellulose (EC) containing matrix pellets. Relating to the latter finding, the work here showed, upon the addition of 25% ethanol to the coating liquid, an increased and enhanced sustained drug release profiles as well as floating profiles were obtained for the single-coated pellets. However, in the floating profiles, the enhanced water-retarding layer made from the 15Eud25Eth dispersion will have the prominent effect over the hydrating polymers' swelling. Hence, this outer layer will control the swelling of the hydrating polymers, like cros-PVP, in the core pellets. That is, the prominent control of the resulting coating layer will shrivel the high swelling capacity of the cros-PVP polymer. Therefore, the PVP-containing coated pellets will have no significant difference in the swelling when compared to the cros-PVP-containing coated pellets. Additionally, the microcrystalline cellulose (MCC) polymer is expected to contribute in the core pellets' swelling of the coated pellets.

Table 5.9: Shows the floating study for the single coated pellets in 0.1N HCl medium*.

Batch code	Floating duration** (hr)	Floating lag time onset (min)	Time at Maximum Floating (min)	Maximum floating %	On surface floating %***
B9S-8P,3N,10E	>24	10	15	100 ± 0	99 ± 1
B10S-12P,47HF,10E	>24	10	15	100 ± 0	98 ± 2
B11S-12CP,47HF,10E	>24	10	15	100 ± 0	99 ± 1
B12S-12P,47PH,10E	>24	10	15	100 ± 0	100 ± 0
B13S-60DL,10E	>24	10	15	100 ± 0	100 ± 0
B14S-2P,17N,10E	>24	10	15	100 ± 0	100 ± 0
B15-Cushioning Pellets	>24	15	25	100 ± 0	100 ± 0
B15-Cushioning Pellets (not coated)	0	NA	NA	0	0
*The percentages values were entered in the following format: (Mean of 0.25-4hr ±%SD), n~500 for all batches (except for B13; n~350), the number of the coated pellets tested was calculated based on the 200mg dose. All results were based on "the on-surface" floating only.					
** The values were selected based on the period that maintains at least 90% on-surface floating.					
*** Floating % values were averaged for the values in the period between the end of the lag time to the 12 hours of floating					

Table 5.10: Shows the floating study for the single coated pellets in a distilled water medium*.

Batch code	Floating duration (hr)	Floating lag time onset (min)	Time at Maximum Floating (min)	Maximum floating %	On surface floating %
B9S-8P,3N,10E	12-24	15	15	100 ± 0	98 ± 2
B10S-12P,47HF,10E	12-24	15	15	100 ± 0	100 ± 0
B11S-12CP,47HF,10E	>24	15	15	100 ± 0	100 ± 0
B12S-12P,47PH,10E	12-24	15	15	100 ± 0	100 ± 0
B13S-60DL,10E	>24	15	15	100 ± 0	100 ± 0
B14S-2P,17N,10E	>24	15	15	100 ± 0	100 ± 0
B15-Cushioning Pellets	12-24	20	35	100 ± 0	100 ± 0
B15-Cushioning Pellets (not coated)	0	NA	NA	0	0
*Notes are as similar with the previous table.					

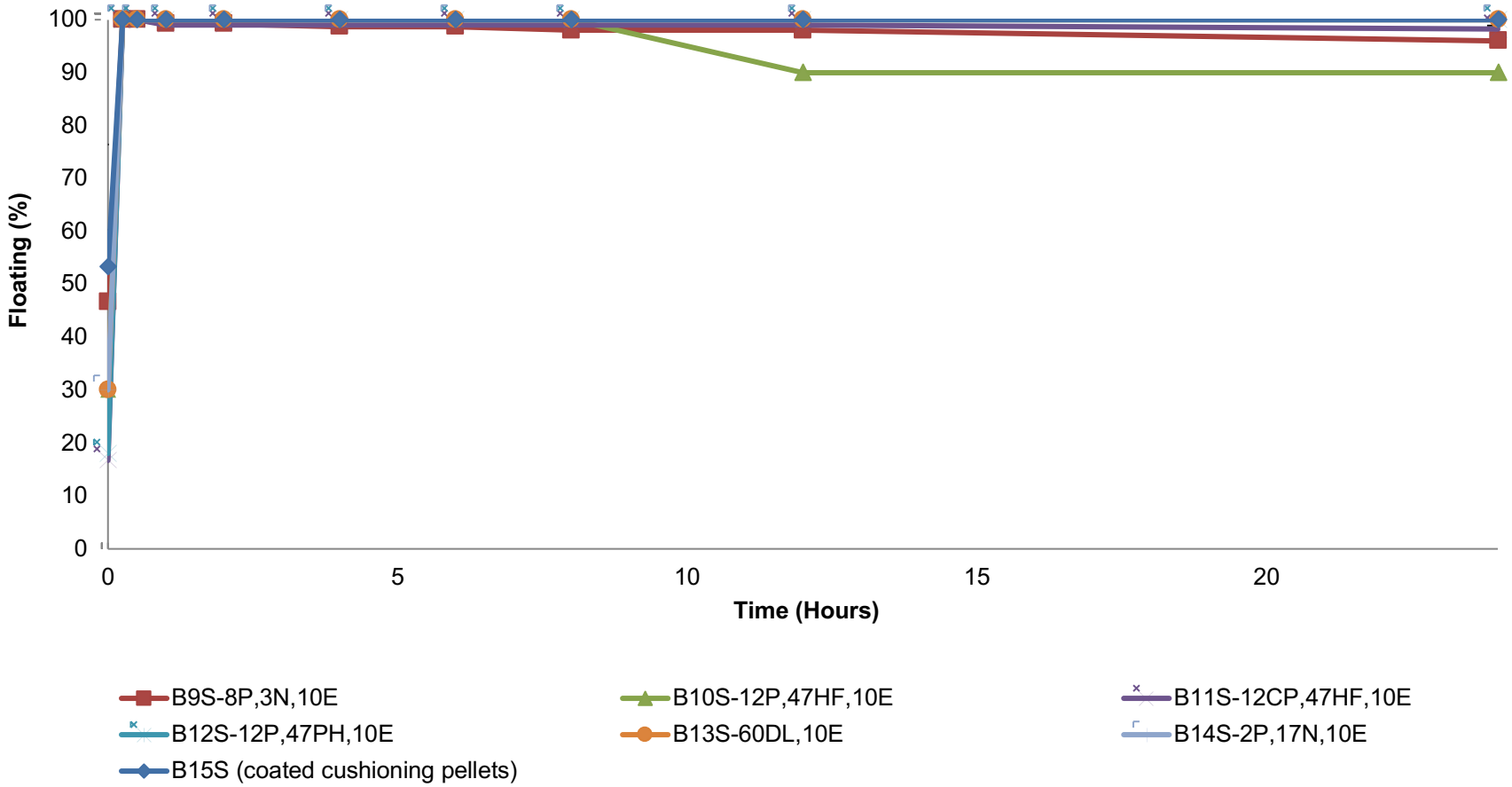


Figure 5.4: Shows the floating profiles of the single-coated pellets in a 0.1N HCl medium (n=3). This figure shows the floating curves in a period of 24 hours.

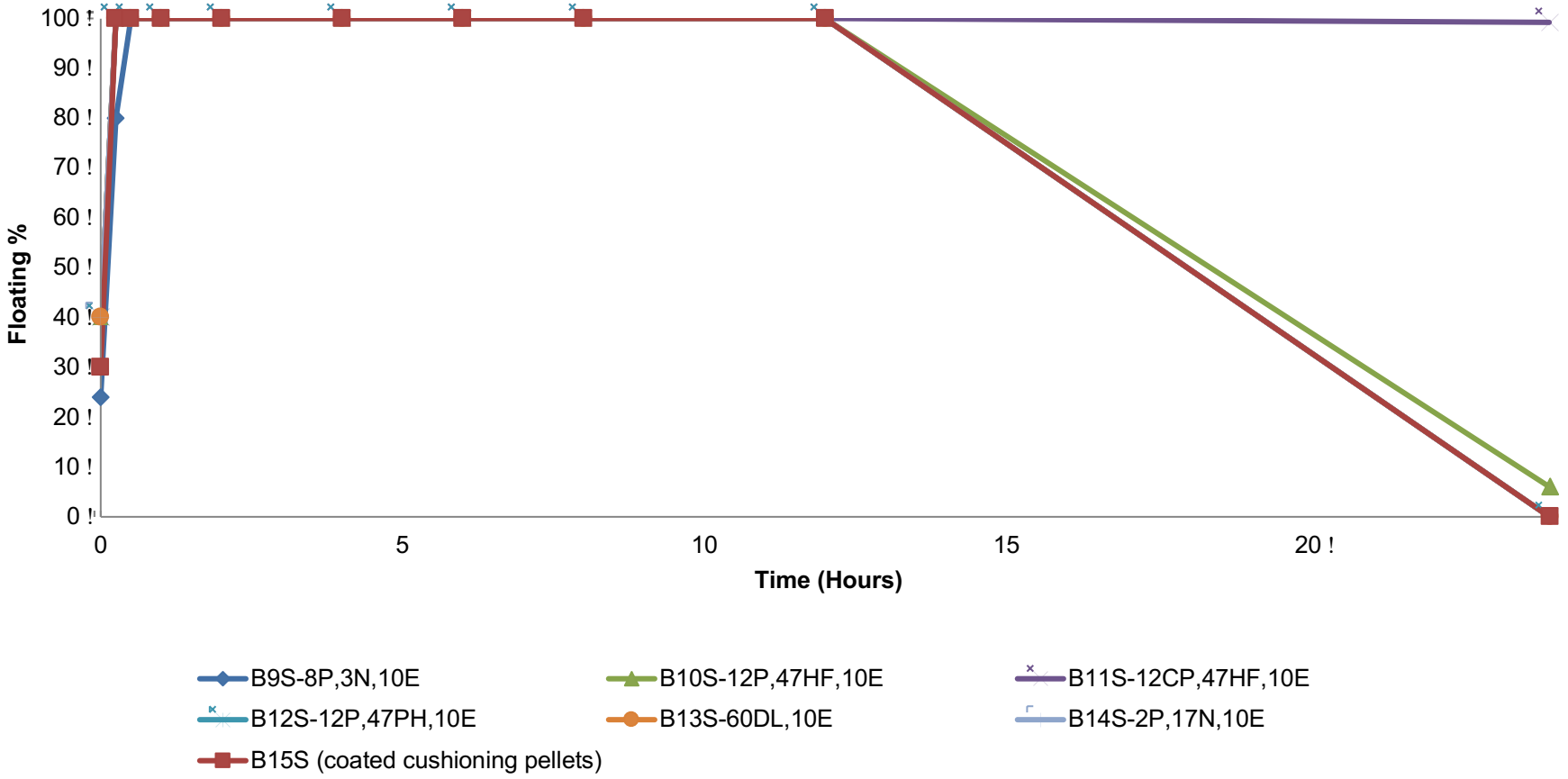


Figure 5.5: Shows the floating profiles of the single-coated pellets in a distilled water medium (n=3, error bars were not seen because 100% reproducibility was obtained). This figure shows the floating curves in a period of 24 hours.

ii. Swelling study per weight, using the beaker method

The coated pellets were immersed in a beaker of either the distilled water or the 0.1N HCl media. After 30-60 minutes of immersion, all of the coated pellets re-weighed and possessed 20-30% liquid *mass* uptake regardless of the medium used (n=1). These percentages were maintained for at least 4 hours. These fluid uptake percentages were deemed desired for the floating to occur. The cros-PVP-containing batch (B11S) was showing the high end in the values range (30%). The latter is due to the high swelling capacity of the cros-PVP. All of the fluid uptake percentages were not significantly different from each other (p-value >0.05), confirming that the small variation in the coating levels (6±1 w/w %) is not significant. The swelling of the coated pellets was also examined through the increase in diameters of coated pellets, as seen in the following paragraph.

iii. Swelling study per diameter, using the image analysis method

The diameter increase and mass increase of the single coated pellets were seen in Figures 5.6-7. The restricted permeability or diffusion of the liquid in to and out from the coated pellets will allow for the required swelling to occur, which is needed for the floating as well as the sustained drug release to take place. Also, this restriction is needed to ensure that the floating is sustained over time with a reduced variability. This floating enhancement was due to that the liquid uptake percentages were enhanced for initiating and maintaining the low density in the coated pellets that is below the media density, i.e. below 1 mg/cm^3, which render the pellets to float on surface. The optimum fluid uptake percentages were 20-30% in the previous paragraph. In this study, the optimum fluid uptake (20-25%) is comparable to the latter.

An increase of 8-16% in the diameter of the coated pellets was obtained at 30 minutes of dipping, and their diameters remained high during four hours of measurements. The mass increase was of 20-25% in the coated pellets after 30 minutes of immersion. The most desired fluid uptake threshold was determined in this study to be averaged for 22.5%, where the coated pellets can achieve and sustain the floating.

After 0.5 hour of immersion into distilled water, the volume increase was 51.56-82.36% for the coated pellets. Where also the surface area increase was 32.93-49.33% for the coated pellets. While the surface area to volume (SA:V) ratio decreases by 13.15-17.98% for the coated pellets. It is known that the decrease in size of spheres can increase the SA:V ratio, providing a decreased diffusion path and faster drug release (Rizvia & Saleh, 2018). Here, the SA:V ratio decreased to some extent, which indicates an increase in the diffusion path in the coated pellets, owing to the increase in swelling to some extent. However, the drug release was constant since the beginning of the dissolution, where it was also constant before the swelling became in a steady state.

The SA:V ratio did not exceed the 20% decrease. The latter is critical to ensure an enhanced floating and sustained drug release profiles. It implies an enhanced controlled swelling. At this SA:V ratio, a swelling threshold and equilibrium is obtained where it is assumed that the density of the coated pellets would be lowered to <1g/cm^3. It is where the floating phenomena can be initiated, completed and sustained until an imbalance in this threshold start to occur after 12-24 hours of pouring the coated pellets into the medium. Hence, after the latter period elapse, further swelling may occur, resulting in a further decrease in the SA:V ratio. The latter can result in an increase of the coated pellets mass that exceed the increase in volume, allowing the coated floated pellets to increase in density and subsequently sink to the bottom of the vessel after 12 hours of floating, as seen in Figure 5.5. Moreover, excessive swelling can cause film rupture and fast drug release.

The coating layer made from the 15Eud25Eth dispersion controls the fluid in-flux and the fluid out-flux, and avoids the over-increase in mass and ensures the attainment and the maintenance of the optimum SA:V ratio. Moreover, this behavior will protect the film and the core pellets from over-swelling and rupture, and avoid the subsequent unfavorable events of sinking and the immediate drug release.

After 0.5 hour of immersion into distilled water, the volume increase was 185.56% for the cushioning core pellets. Where also the surface area increase was 100.88% for the coated pellets. While the surface area to volume (SA:V) ratio decreases by 29.65% for the cushioning core pellets. After 1 hour of pouring, a sudden drop in the weight and diameter that is comparable to the original weight prior pouring. Hence, the SA:V ratio increased by ~30%.

The excessive increase in volume and surface area of the core pellets is owing to the lack of the retard coating layer, resulted in a non-restricted liquid permeation followed by an over-swelling, where a potential excessive mass increase could have occurred, rendering the core pellets to be heavy and unable to float. After which, a sudden shrinking occurred where excessive decrease in volume and surface area of the core pellets occurred. The latter resulted in a complete drug release in 1 hour time (drug release data not shown for the cushioning pellets). Hence, the latter resulting in an uncontrolled swelling, which will not provide the insufficient time for the uncoated pellets to reduce in density and to maintain that reduction. Therefore, the uncoated pellets will not initiate nor maintain the floating as well.

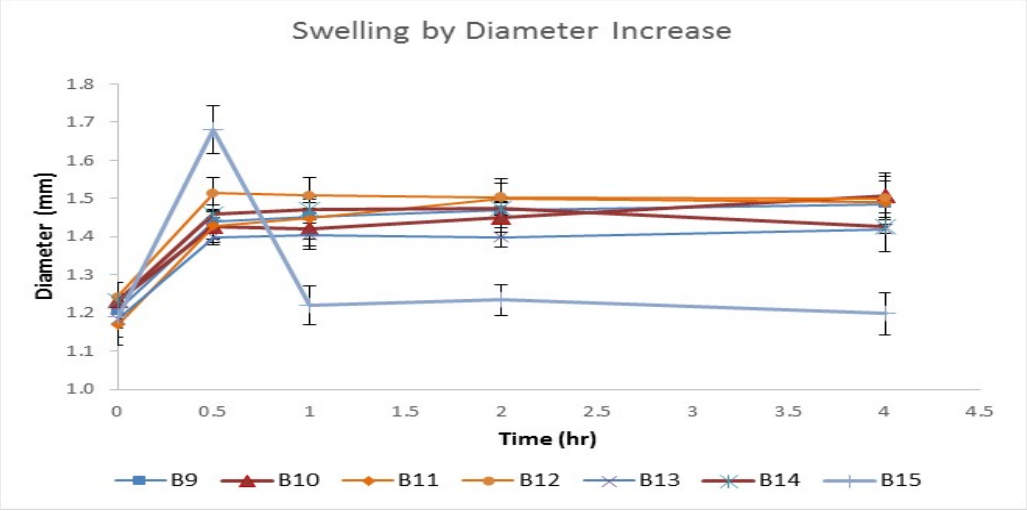


Figure 5.6: The changes in diameter over time in the distilled water for the single-coated pellets. Refer to Table 2.4 for the compositions of these formulations. B15 is the cushioning pellets not coated.

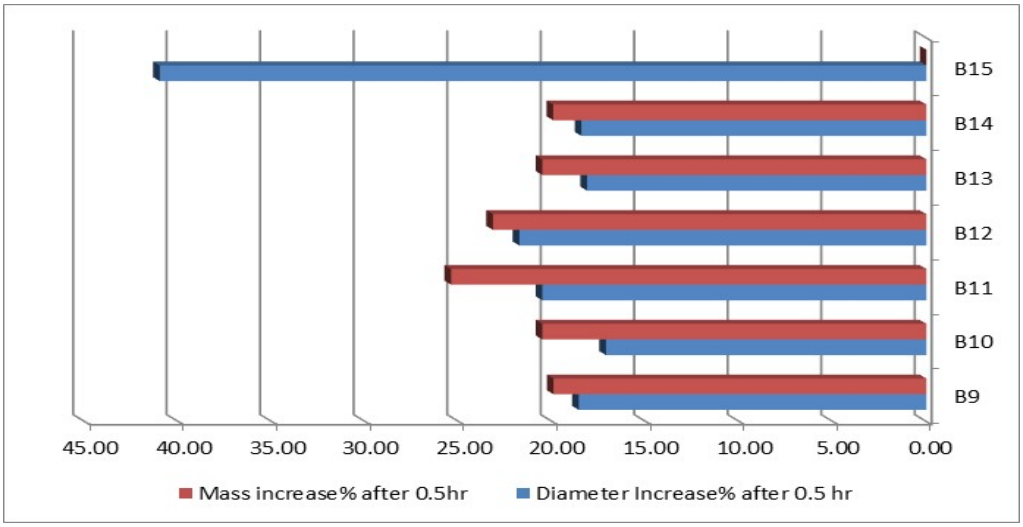


Figure 5.7: The changes in diameter and mass after 30 minutes of immersion in the distilled water for the single-coated pellets. Refer to Table 2.4 for the compositions of these formulations. B15 is the cushioning pellets not coated, where the mass increase measurement was not feasible, as the wet uncoated pellets will squash upon handling.

iv. Density study

The mean density values of theophylline, Avicel HFE102, PVP, cros-PVP and $NaHCO_3$ were 1.59, 1.76, 1.38, 1.1 and 2.22 g/cm^3, respectively. Noticeably, the density of the $NaHCO_3$ was the highest amongst all other raw materials, see Figure 5.8. On the other hand, the cros-PVP density showed a low value, owing to its micronised size, where a large inter-particulate void is expected. Based on (Abdel Rahim, et al., 2015), the relationship between density and porosity can be manifested as follows; porosity=1-(density/1.4), where porosity can increase when the density decrease. However, that did not lower the density of the core pellets as well, owing to the compaction mechanism of the extrusion/spheronisation method. Notably, the coated and the uncoated cushion pellets showed significantly smaller density values (~0.5 g/cm^3) when compared to the medicated pellets. The density of the core and the coated pellets were highly similar (1.45-1.49 g/cm^3). The similar density was due to that the thin coat did not contribute much to the density of the core pellets. Also, the high density $NaHCO_3$ was not used in high proportions. Interestingly the coated pellets tend to possess lower density than the core pellets. This lowered density could be partly due to the air entrapment during the coating process. Although the cros-PVP density is very low, the final pellets density of a cros-PVP

containing batch (B11S) was not different when compared to other batches. That because the extrusion and spheronisation will densify the agglomerates of powders. Therefore, the relatively low amount of cros-PVP used was not affecting the total pellets density. The latter argument is also applicable to the $NaHCO_3$ in the opposite direction.

At the first instance, the high density of $NaHCO_3$ may increase the overall density of the core pellets containing the $NaHCO_3$. However, there were no significant differences in the density values of the core pellets of all batches, including the non-$NaHCO_3$ containing core pellets. The reason for this indifference in the density of the core pellets is that the extrusion and the spheronisation processes will densify the agglomerates of powders, where a uniform decrease in voids will be obtained.

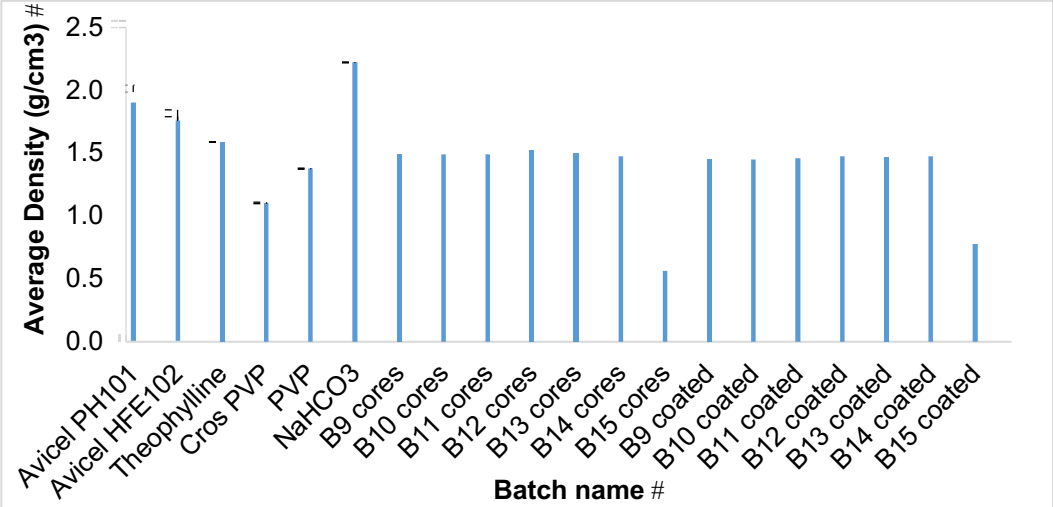


Figure 5.8: The density of the powder, the core pellets, and the single-coated pellets. Refer to Table 2.4 for the compositions of these formulations.

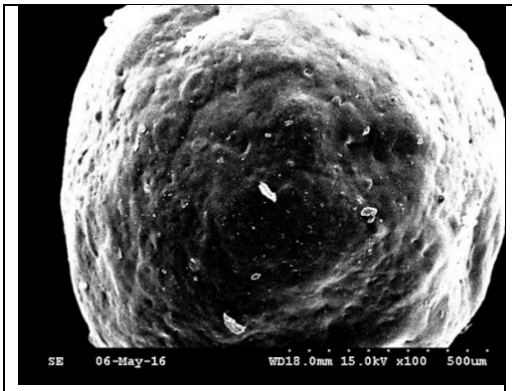
Also, the used amount of the cros-PVP and the $NaHCO_3$ were relatively low, as the maximum amount used was 25%. Therefore, for these two reasons, the overall density of the core pellets was not affected. Moreover, the density of the core pellets and the coated pellets were similar (1.45-1.49 g/cm^3), where the core pellets being slightly less in density (~1.45).

5.4.5. Scanning electron microscopy (SEM) study

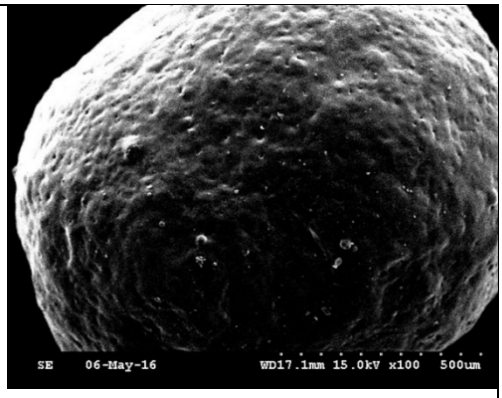
The SEM images were shown for the intact and the bisected coated pellets in Figure 5.9-12. The film membrane formed was thin, typically 10±2 μm, as observed in Figure 5.12.

After dissolution, the coat of the coated pellets was intact without a reduction in the coating thickness. Hence, the coating thickness remained with a diameter of 10±2 μm. This observation showed that the film of the coating layer made from the 15Eud25Eth dispersion was very flexible, as agreed with (Chen, et al., 2012). It can withstand the expansion in the coated pellet's dimension, which induced by the physical changes, like swelling in the core pellets and in the coat of the coated pellets. The coat tolerability of swelling correlate to the success in floating and the sustained drug release profiles.

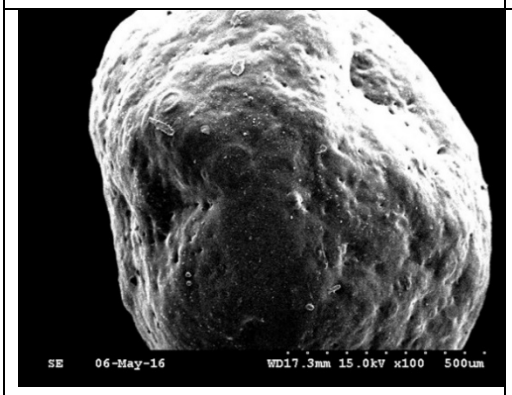
i. The SEM study for the intact and the bisected coated pellets before dissolution



B9S
(8.6P,3.5N,10E)



B10S
(12.5P,0N,10E)



B11S (12.5CP,0N,47.5PH,10E)

Figure 5.9: The SEM images of the intact coated pellets before dissolution.

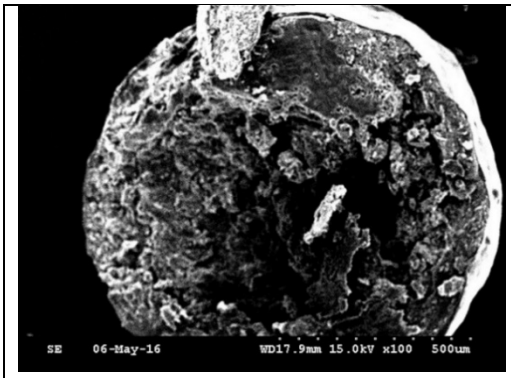
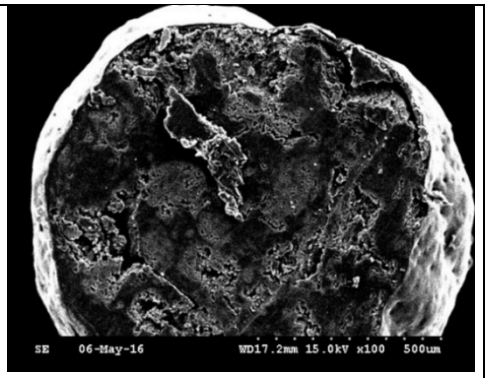
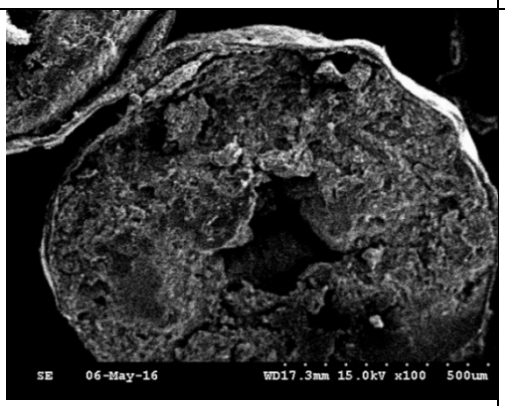
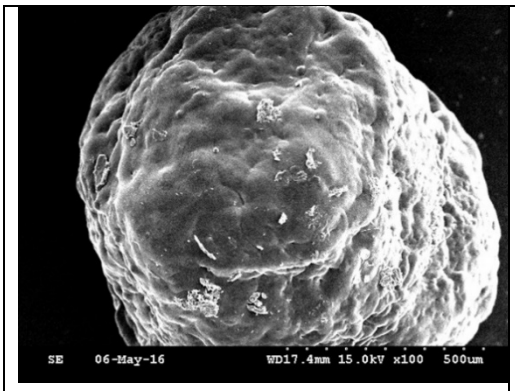
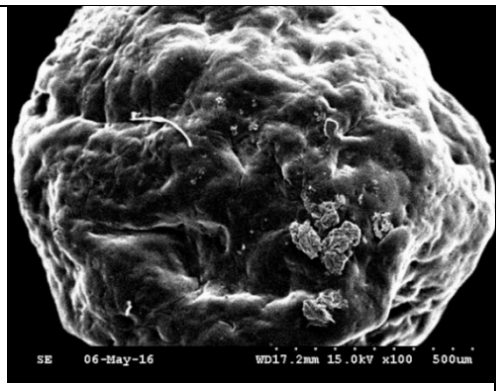
	
B9S (8.6P,3.5N,10E)	**B10S (12.5P,0N,10E)**
	
B11S (12.5CP,0N,47.5PH,10E)	

Figure 5.10: The SEM images of the bisected coated pellets before dissolution.

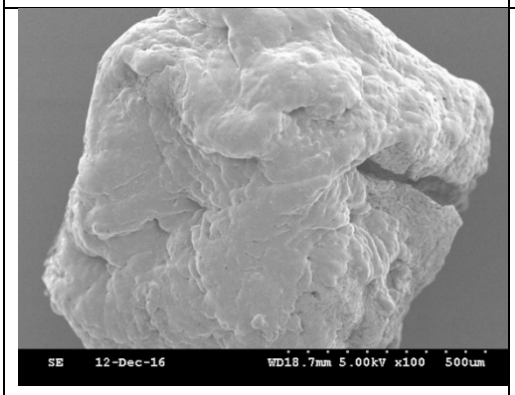
ii. The SEM study for the intact and the bisected coated pellets after dissolution



B9S
(8.6P,3.5N,10E)



B10S
(12.5P,0N,10E)



B11S (12.5CP,0N,47.5PH,10E)

Figure 5.11: The SEM images of the intact coated pellets after dissolution.

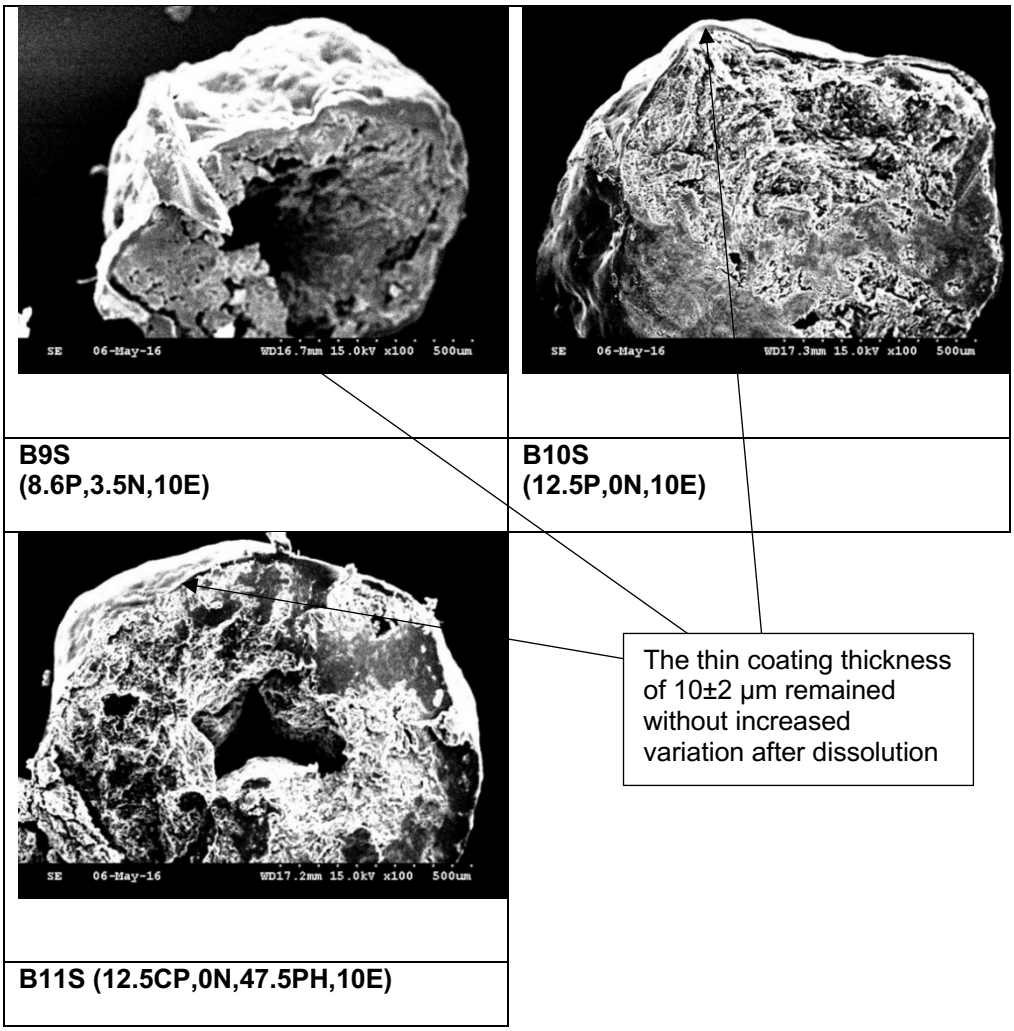


Figure 5.12: The SEM images of the bisected coated pellets after dissolution.

5.4.6. Differential scanning calorimetry (DSC) study

The free films -made from the coating liquids- that comprise the coated layers were thermally studied. The DSC study can be used for further correlation to the performance of the enhanced floating pellets. The DSC can measure the melting point (MP) and glass transition (Tg) of a sample upon melting and softening, respectively. The MP indicates crystal melting, while Tg indicates amorphous softening. The free film of 6.66% HPMC: 3.33% $NaHCO_3$ solutions showed melting points at 119.25 °C and 151.85 °C, respectively. The peaks intensity/size and shape change when the ratio of the film's components change, as noticed in Figures 5.13-18, which is owing to the varying strength in some of the coating

liquids, a potential polymorphic change was occurred prior the film formation, as explained shortly.

In Figure 5.15, the thermogram of the Eudragit containing film (where no dilution made for the dispersion where the film was made), at nearly 54 °C, a relatively decent intensity melting point of the crystal regions of the polymethacrylates (PMA) polymer was seen. This melting point intensity may indicate a decent number of crystal regions in the polymethacrylates (PMA) polymer.

In Figure 5.16, the thermogram of the Eudragit containing film (where only distilled water was used for diluting the dispersion where the film was made), at nearly 53 °C, a low intensity melting point of the crystal regions of the PMA polymer was seen. This low melting point intensity may indicate a reduced number of crystal regions in the PMA polymer. The dilution of Eudragit dispersion is expected to result in a reduced number of crystal regions in the polymer.

In Figure 5.17-18, the thermograms of the Eudragit containing films (where ethanol was used for diluting the dispersions where the films made from), at nearly 50 °C, a step change may be seen from the baseline that may indicate a softening of a predominantly amorphous polymethacrylates (PMA) polymer, where no distinctive crystal melting point can be seen. Also, the emulsifier concentration will be diluted as well, resulting in less stability for the PMA polymer, causing it to have an increased precipitation. These precipitated crystals may affect the quality of the crystal regions in the polymer upon drying, and may undergone a polymorphic change into a higher amorphous content in the polymer, as a step change of glass transition (Tg) was likely occurred. However, the precipitated crystals may maintain their order after precipitation, because the water evaporation is slower when compared to the ethanol evaporation.

The increased amorphousity is expected to occur upon diluting the Eudragit dispersion with ethanol, prior and during the drying the dispersion. Upon the Eudragit dilution with ethanol, the ethanol will

cause a preferential solvation that causes amourphosisation. During drying, the ethanol causes a rapid process, owing to its rapid evaporation. The rapid drying can cause amporphosisation as well. The obtained amorphous polymer of PMA is expected to incur high toughness, as it showed an enhanced sustained drug release and floating profiles for the enhanced floating pellets with a small coating gain. As complies with the latter, the (Taylor & Shamblin, 2009) stated that the amorphous ionic polymer, like the PMAs, can favorably precipitates in the aqueous ant-solvent. Hence, adding a solvent like ethanol, which can provide a preferential solvation. That may render the distilled water to act as aqueous ant-solvent. Along, with the relatively quicker evaporation of ethanol, an increased amorphosisation of PMA will be induced, and a favorable precipitation of the PMAs amorphous material were obtained upon cooling. In (Donnelly & Evans, 1991), a stating that an increased toughness can be due to amorphosisation. In (Aulton, 2018), a stated that some “tougher materials can undergo plastic flow, which allows strain energy relaxation without crack propagation”. Hence, the increased toughness allows for the swelling to take place without rupturing the coating film, the latter enhanced the sustained drug release and the floating profiles of the single-coated floating pellets.

Upon administering the coated floating pellets to the patients, the increased toughness of the amorphous PMA polymer may not soften at a temperature below 50 °C, like the dissolution temperature of 37 °C. Thus, a glassy state is maintained, where a sufficiently hard film is maintained. However, if softening occurred to the film during dissolution, the polymer is expected to maintain the control regarding the liquid permeation, because no melting is expected to occur.

Therefore, in the Eudragit NE dispersion, upon liquid dilution with the ethanol content and upon drying, physical changes are expected to occur for the dried film. This change is dependent on the ethanol concentration as observed in the thermograms. For future remarks,

more DSC studies need to be done to quantify the amount of the amorphous regions in the PMA polymer, and elongation at break study is needed for the free film to quantify the toughness of the enhanced film. This increased polymer amorphosity would be needed to simultaneously enhance the sustained drug release and the floating profiles of the coated floating pellets.

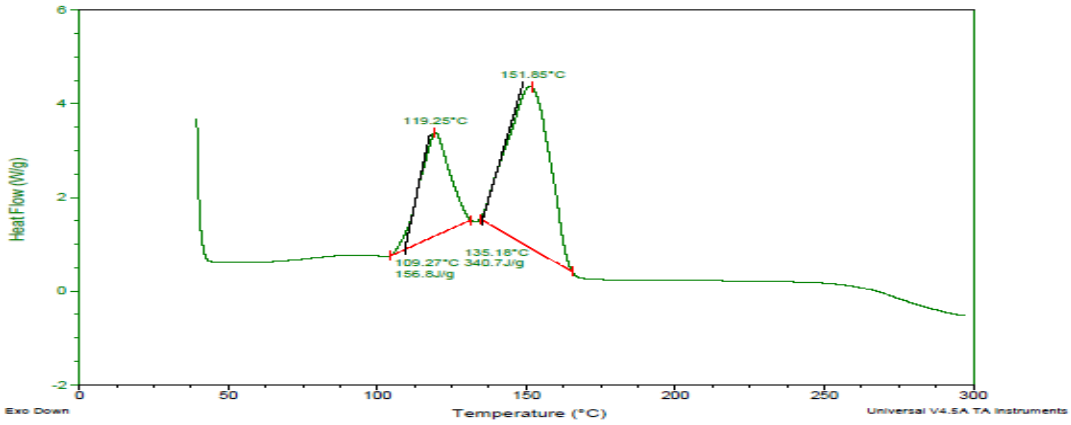


Figure 5.13: DSC thermogram made by the 6.66: 3.33% HPMC: $NaHCO_3$ solution.

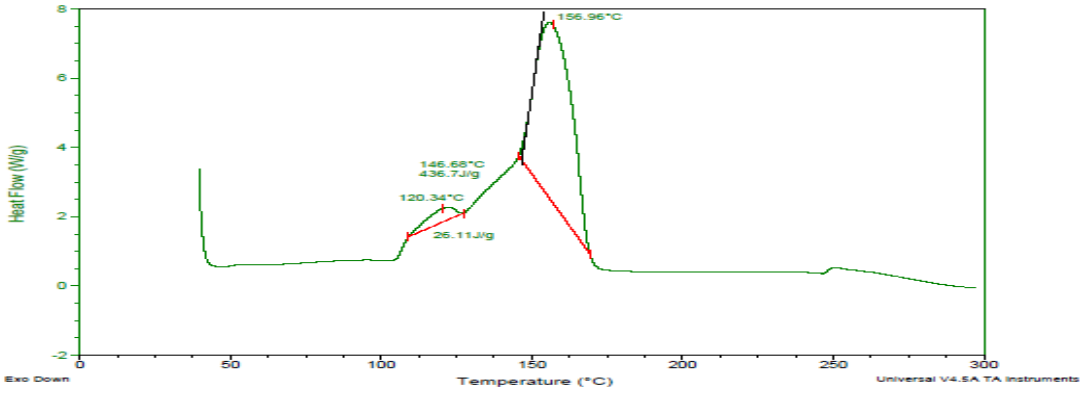


Figure 5.14: DSC thermogram for the film made by the 3.33: 6.66% HPMC: $NaHCO_3$ solution.

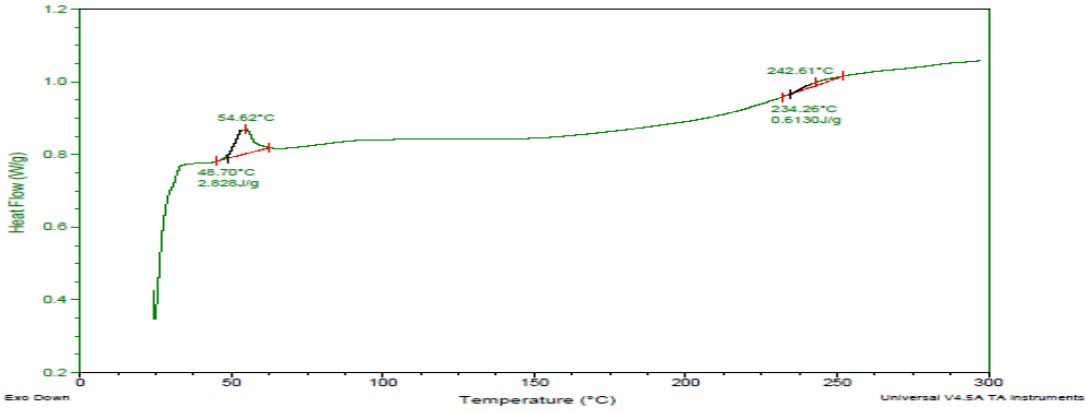


Figure 5.15: DSC thermogram for the film made by the Eudragit NE30D dispersion.

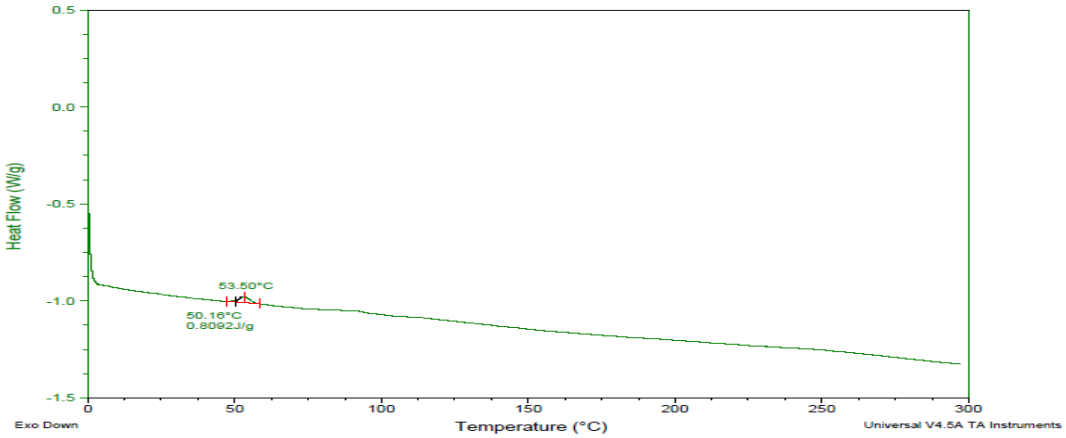


Figure 5.16: DSC thermogram for the film made by the Eudragit NE15D dispersion. $

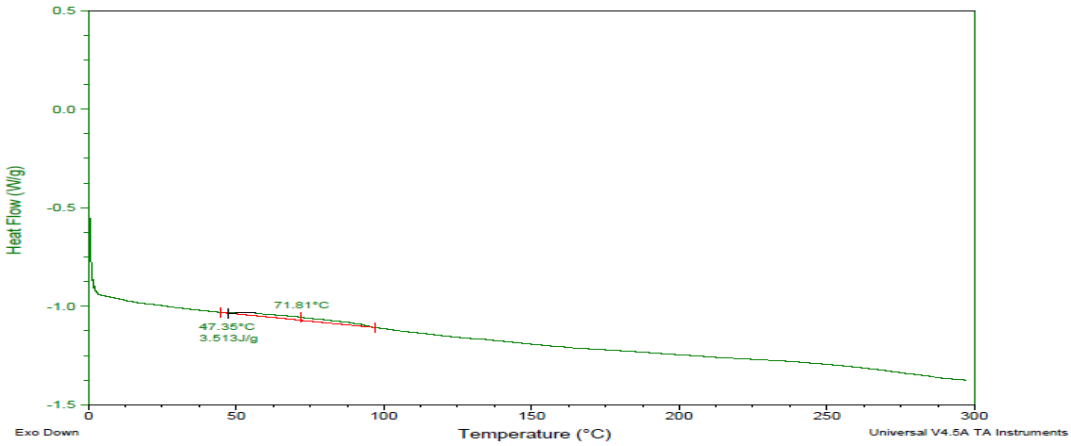


Figure 5.17: DSC thermogram for the film made by the Eudragit NE15D dispersion, out of which 25 w/w% ethanol.

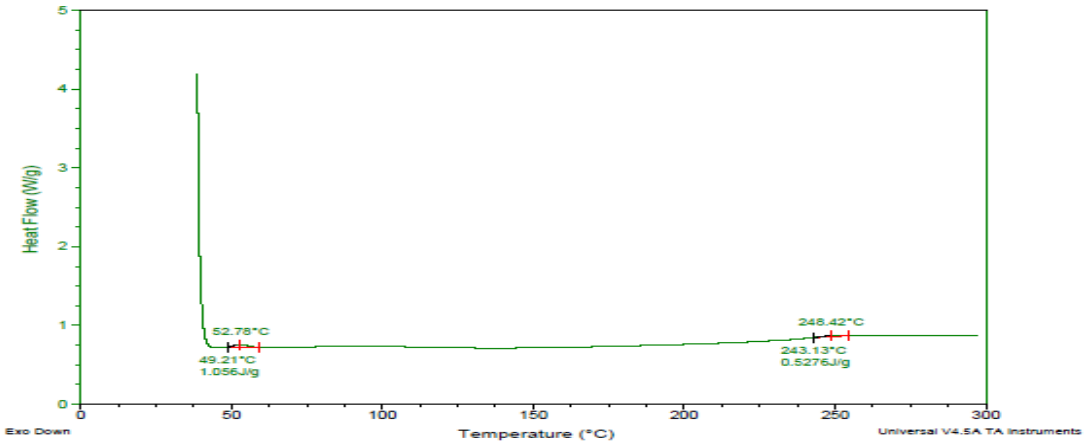


Figure 5.18: DSC thermogram for the film made by the Eudragit NE15D dispersion, out of which 10 w/w% ethanol.

5.5. Conclusion

As a sequential continuation from the screening studies, the single coated floating pellets were enhanced. During the pelletisation, the core pellets were enhanced mainly for the shape and the ease of the extrusion and spheronisation processes. The enhanced core pellets are suitable for being applied to further processing, like coating and tabletting. Successful floating and drug release profiles were obtained as stated shortly. The single-coated floating pellets are intricate to make due to demanding two main functions from a single layer. Although these pellets were more intricate to function successfully, these pellets of single-coating reduced the cost of making floating pellets. The enhanced retard coating layer was made from the 15Eud25Eth dispersion, which was applied to the enhanced core pellets. The efficiency of coating process takes into account of several features such as consistent spraying, adequate wetting of the core surface by the coating liquid, the film drying rate, the pattern of pellets movement (fluidizability), and the liquid flow property in tube and nozzle. It is governed by multiple factors including the operation of the coating process, that is owing to the ability of ethanol to make less hydrogen bonding than water, resulting in a weaker liquid surface. The latter is a desired the property of coating formulations and the nature of cores to be coated such as their sizes, shapes and integrity (Srivastava & Mishra, 2010). An aqueous based coating liquid is usually the preferred approach for coating, because it is less hazardous. However, the presence of organic solvent in the coating liquid tends to lower the surface tension, property for efficient spraying and film formation. Owing to the decreased surface tension, the coating efficiency was shown by the reduced sedimentation in the tubes and nozzle (observed visually), increased uniformity in the spraying pattern and droplet spreading, increased uniformity and speed of the solvent evaporation, and the continued fluidisation of the pellets bed. The uniform spraying pattern and the higher droplet spreadability on the core pellets surface is because of the lowered surface tension. This will allow for an easier breakage in the solid-liquid linkages of the sprayed droplet,

resulting in an increased wettability of the liquid (Cole, et al., 2002). Consequently, this results in an even coating thickness (Cole, et al., 2002), as seen by SEM images in this chapter. On the other hand, as seen in chapter 4, the SEM images of the pellets that have a coat made from the 15Eud0Eth dispersion showed uneven coating thickness, and fluctuated floating and drug release profiles were resulted. The enhanced layer achieved successful floating and sustained drug release profiles for up to 24 hours or more. The coating layer consists of 6% solids only, where the coating thickness was relatively small and relatively uniform (10±2 μm), obtaining a thin film. The surface area to volume (SA:V) ratio decreases by 13.15-17.98% for the coated pellets. The latter is critical to ensure an enhanced floating and sustained drug release profiles. This specific range of SA:V ratio reduction implies an enhanced controlled swelling. The successful floating and the sustained drug release profiles in the acidic and neutral media may allow for more predictable and consistent floating behaviours in the stomach. The latter will lower the risk of failure in floating, because the coated pellets will be independent on the pH variation in the stomach. This reduced design of the enhanced single-coated floating system offers several advantages as stated in the abstract of this chapter. The attainment of an enhanced single-coated floating pellets through an enhancement study was achieved. Specifically, a successful attainment of the core pellets as well as the coated layer were obtained for achieving the enhanced floating and the sustained drug release properties. The successful pH-independent floating may allow for more predictable and consistent floating behaviours in the stomach. The reduced and enhanced design of the single-coated floating pellets offers several advantages, include, (1) reduced processing time, (2) reduced scale-up optimisation workload, hence, reduced time to market, (3) reduced cost of operation and materials use, (4) increased flexibility in the timing of the dosage administration, regardless whether the stomach in the fasted state or in the fed state, (5) offer a once daily administration, hence, increased patient compliance, and (6) increase the bioavailability of the drug theophylline in a consistent manner.

Chapter Six:

Tabletting Feasibility Study for the Enhanced Single-Coated Floating Pellets

6.1. Introduction

The tableted pellets dosage form is considered highly advantageous when compared to other oral solids, primarily because of its cost-effectiveness, divisibility, reduced counterfeit, scoring tolerance, high patentability, and high drug loading capability. Hence, the multiple units of pellets system (MUPS) tablet is more advantageous than the MUPS capsule (Abdul, et al., 2010). Therefore, it is highly encouraged to do a feasibility study on the compression of the enhanced coated pellets that results in the ensemble pellets. The ensemble pellets consisted of the enhanced single-coated pellets and the cushioning powder. The cushioning powder inside the tablets was in different ratios, to screen for the cushioning effects for the protection of the film structure and the film function. The aim in the work of this chapter is to screen the feasibility of making tablets made from the enhanced single-coated floating pellets. Although that the enhanced coated pellets may be filled into hard gelatine capsule as the final dosage form. The objective in this chapter is to introduce the tablet as a final dosage form for those pellets. The gelatine capsule need few minutes to dissolve, hence, the capsule-filling of those pellets will expectedly show few minutes of lag time for both floating and drug release. However, the compression of the coated pellet can unexpectedly affect those profiles, hence, investigating that at this point is more needed and it is important to understand the compression effects on those pellets. The enhanced single-coated pellets will be mixed with the cushioning powder and compacted by a specific compression force. This is needed to protect the film on the pellets and to ensure a sufficient binding that form strong and non-friable tablets. Favourably, the sustained drug release as well as the floating profiles of those tablets should be maintained as possible when compared to the non-compressed coated pellets.

6.2. Characterisation of the Ensemble Pellets

The compositions of floating pellets are succinctly outlined in the codes table of pellets batches (Table 2.2) and detailed in Table 2.4. The Avicel

HFE102 here was used as a novel cushioning agent in the form of powder, to protect the film structure, and subsequently, the film function from an excessive deformation by the compression force applied. Also, the coated pellets fusion with other pellets is an issue as stated by (Dwibhashyam & Ratna, 2008). It is usually recommended that the cushioning agent need to be of the same size and shape to the coated pellets. The MCC material is the most protective as a cushioning agent, owing to the MCC high elasticity.

6.2.1 Preliminary Findings

The tabletting parameters were set to obtain minimum hardness as possible to have the minimum impact of the compression force on the coating layers of pellets. Based on the preliminary study (data not shown), 21.5-22.5 kN compression force would be appropriate to obtain tablets with strength of 5.5-9.0 KgF (53.94-88.26 N). However, other factors will affect this relationship, as seen later in this chapter. To obtain sufficient binding ability, good hardness, and non-friable tablets, the applied enhanced compression force was 21.5 kN, the die depth was of 5 rounds from the bottom (the die volume capacity will vary in different dies and machines), and the cushioning powder was of 33.33-90%. It is good to mention here that 21 kN compression force is used in literature for making tablets of 250 mg each that result in <100 N crushing force (IMA, 2019). Hence, a 21.5 kN force would be a reasonable amount of force for compressing a tablet of 400 mg that contain coated pellets. A lower force than that was not giving a sufficient strength and integrity to the tablets made in this project.

6.2.2. The falling-to-floor friability test

The compression force was initially enhanced by this test, for the ensemble pellets to be made with the sufficient strength. Different compression forces were applied. The ensemble pellets were left to fall at a distance of ~1 meter height from a marble floor. In order to initially accept their integrity and to pass to the next strength test, the ensemble pellets should not crack or get friabilated into individual pellets. The dye

depth of five cycles from the bottom was fixed, where 400mg weight of pellets was filled to the dye hole. The compression force of 21.5 kN was fixed, as it found to be the least acceptable compression force for the pellets to be ensembled into a tablet of a sufficient strength. The compression force is expected to show the least damage of the film surface and structure.

6.2.3. The hardness test

Before hardness testing and subsequent testing, the tablets were stored for 24 hours to allow for a post-compression relaxation in the tablets. As explained by (Zhang, et al., 2017), though the post-compression was expected to be at high rate at the first hour after ejection, the first 8 hours after ejection were also considered.

Table 6.1 summarises the physical analysis of ensemble pellets. A threshold of 5 KgF was set, tablets that have less than that force value will get rejected. The average crushing forces for the ensemble pellets were recorded. It is quite difficult to aim for a targeted crushing force in this study. The targeted force is usually based mainly on the friability test outcome and the tablets' weight. Also, the tablet's size and shape can have an effect. Although it can be different for each formulation, usually the higher the weight of the tablet, the higher the crushing force is aimed to -up to a certain threshold-. This is because the risk of the friability is suspected to be increased with the increasing weight of the tablets, and a higher crushing force will be required to compensate for that.

Here, to lesser extent, the crushing force can affect other quality attributes in tablets, like the floating and the sustained drug release profiles. Although cushioning powder are used to minimise that effect, the crushing force here has to be as minimum as possible to protect the coating layer on the pellets surface. The latter mitigations for film protection upon the compression of pellets are important to minimise the variations in the film's quality.

Unlike the hardness of the tablets containing the double-coated floating pellets in chapter 3 (99 N), the hardness of the tablets containing the enhanced single-coated floating pellets showed lower strength (51-72 N). The latter finding was when the tabletting process variables and the cushioning agent variables were kept the same. The relatively lower strength could be due to the less thickness of the polymeric layers on the single-coated pellets (10±2 μm), which may require a weaker force to break upon crushing.

Table 6.1: Shows the properties of the coated pellets and the ensemble pellets.

Batch code*	Weight (mg)**	Crushing force (N)	Tensile strength (MPa)	Friability (MSI) (%)	Disintegration time (min)
B9SLow	399.40±0.85	50.68±2.37	0.75±0.034	0.44	2
B10SLow	400.00±0.79	51.01±3.1	0.75±0.046	0.39	2
B11SLow	401.86±2.13	56.244± 2.27	0.83± 0.03	0.46	2
B12SLow	398.94±1.05	55.59± 5.66	0.82±0.08	0.53	1
B12SHigh	399.44±0.88	59.514± 10.8	0.88± 0.16	0.52	2
B13SLow	399.81± 0.25	57.55± 10.07	0.85± 0.15	0.67	1
B13SHigh	400.02± 0.15	72.27± 12.42	1.07± 0.18	0.48	2
B14SLow	400.09± 0.09	58.2± 4.94	0.86±0.07	0.45	1
B14SHigh	399.72± 0.39	63.44± 4.53	0.94±0.06	0.56	2
* Mean values ± SD were presented where applicable. Batches with LC abbreviation relates to the use of "low amount of cushioning powder" based on the stated ratio in chapter 2, where those of HC batches are vice versa. N=16 for weight measurements and friability test, N=3 for density measurements, N=6 for hardness and for the disintegration test. Exception is for B14 (HC), where N=20 for both the friability and the hardness tests.					
** The weight uniformity results were not determined based on the batch mix poured into a hopper prior feeding into the die. The results were based on a pre-weight tablet mix poured into the die directly. These results are to ensure the filling was reproducible within the scope of the study here, but can neither reflect the actual hopper filling mechanism nor the automatic filling mechanism. Hence, this limitation need optimisation work during the manufacture scale up of the formulation.					
Apparent density values of the tablets mixtures were all equal to 1.24±0.00.					

6.2.4. The friability test, using the sliding drum

Regardless of the cushioning powder amount used, the tablets showed sufficient mechanical strength (weight loss<1%). This strength is owing to the MCC powder that increased the binding strength with the coated pellets, see Table 6.1.

6.2.5. The tensile strength test

The average thickness and diameter of the ensemble pellets were measured using the caliper. Then the tensile strength values were measured for all batches, see Figure 6.1, and Table 6.1. The tablet tensile strength values were ranging from 0.75-1.05 MPa.

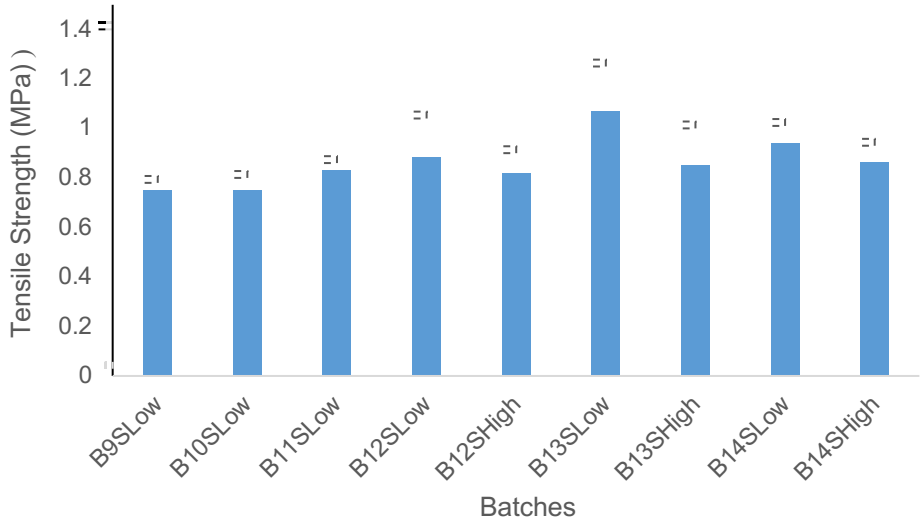


Figure 6.1: Shows the tensile strength values of the ensemble enhanced single-coated pellets. Refer to Table 2.4 for the compositions.

6.2.6. The disintegration test

The tablets should disintegrate into dis-assembled coated pellets, to allow for the coated pellets to initiate and maintain floating. The tablets were placed in a beaker filled with a dissolution medium, of either a distilled water or 0.1 N HCl. Results showed that all batches required 1-2 minutes for disintegration to be completed, see Table 6.1. The findings implied that the ensemble pellets were weak enough to dis-assemble into separate pellets in a short time. Which is a desired quality, as it allows for a quick initiation of both floating and drug release

mechanisms. Therefore, the coated pellets will have a similar chance to complete their floating lag time before the start of the housekeeping wave, assuming the floating lag time was less than 15 minutes.

It is good to be reminded here, that this housekeeping wave occur in a fasted stomach and it is initiated every 1-2 hour/s. To avoid being at the bottom of the stomach when this wave occurs, the formulations should be able to reach the floating state as soon as possible after the oral administration. Hence, a very quick disintegration time is highly desirable for the ensemble pellets system (Qi, et al., 2015). For more details regarding the physiological challenges faces the floating dosage form, the reader is advised to consult section 1.6 in the introduction chapter. Although that all the ensemble pellets were disintegrated in a fast time, the tablets of the low amount of the cushioning powder were mostly disintegrated relatively faster (1 minute instead of 2 minutes). Expectedly, the crushing force was relatively lower for the most batches with faster disintegration, see Table 6.1.

6.2.7. The apparent density test

The apparent density values of the ensemble pellets mixtures were 1.24 g/cm^3, regardless of the amount of cushions used, see Table 6.1. This value was higher than the liquid medium density (~1g/cm^3), which means the tablets will inevitably sink when poured into the liquid medium.

6.2.8. The apparent porosity test

The calculated apparent porosity was based on the density values of the tablets' mixtures of the enhanced single-coated pellets and the cushioning powder. The latter was important to understand the porosity of the tablet’s mixture pre-compression. The mixture was intended to be compressed into ensemble pellets. The porosity values ranged between 7-9 % for all of the mixtures, see Figure 6.2. The low porosity values of pellets mixtures were expected due to several reasons (Ghebre-Sellassie, 1989), namely:

1) Unlike the porous granules, the pellets were considered dense agglomerates, resulting in less intra-particulate pores,

2) Unlike the irregularly shaped granules, the pellets used were highly spherical in shape (ARs<1.2) and dense, resulting in fewer surface pores channels,

3) The pellets used had a narrow size distribution (1-1.18 mm), which may result in small pores and less potential variability in the pore sizes (Ghebre-Sellassie, 1989).

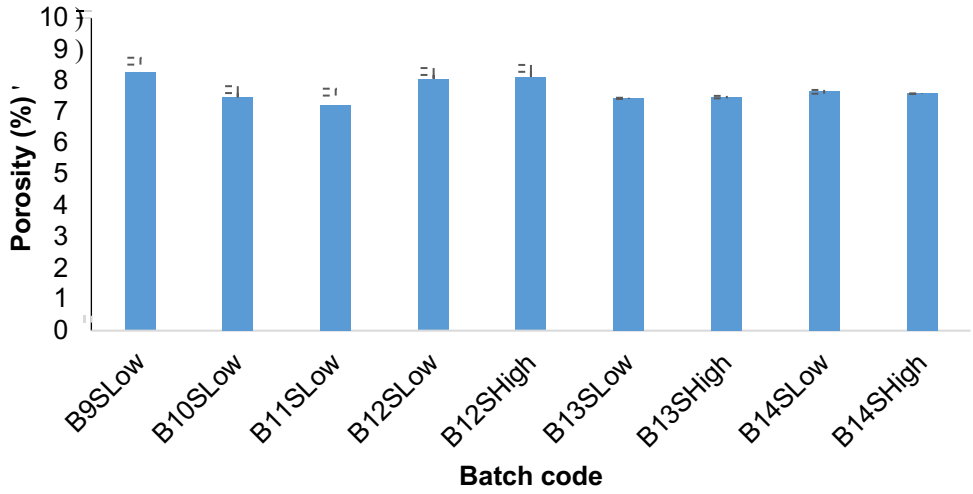


Figure 6.2: Porosity percentages of the ensemble enhanced single-coated pellets. Refer to Table 2.4 for the compositions.

6.2.9. The drug release study

Regardless of the cushions amount used, the drug release profiles showed zero-order drug release for 8 hours (R^2 values range from 0.885 to 0.964), see Figure 6.3. A larger amount of drug was released per unit time when compared to the non-ensemble pellets (as compared to chapter 5 results). This increased drug release upon tableting was also observed by (Qi et al., 2014). Some potential reasons for the faster dissolution profiles, namely, (1) the insufficient amount of the cushioning powder added, and (2) the thin coating film applied that susceptible to rupture by compression. Thus, the ratio of the drug to the cushioning powder needs to be adjusted.

According to (Dwibhashyam and Ratna, 2008), using typically more than 50% of the cushioning material is needed to have a minimum protection to the films upon compression. There was no significant increase in the drug release when compared to the pellets with high cushions, which confirmed that the factor of cushioning level could be less significant from the factor of compression force level. The latter still cannot be confirmed in this study whether the presence of cushions at all can make a significant increase in drug release or not. Despite using a low compression force to maintain sufficient strength of the tablets and to avoid films rupture or fusion, the film integrity became weaker, where the drug release profiles of the ensemble pellets were relatively faster as they were sustained for up to 8 hours only (as compared to chapter 5 results).

The film is holding highly critical roles in the formulation function, namely, the drug release and the floating control. However, when ensemble pellets compared to the non-ensemble pellets, the changes in the film quality is likely -in either a negative or a positive way-, as proven in various literature studies (Li, et al., 2016). However, some literature also claims that the use of cushioning excipient can fully protect the film on the coated pellets upon compression (Zeeshan & Bukhari, 2010).

Regardless of the core pellets size used, the core pellets did not float. Noticeably, the smaller size of the core pellets (0.71 mm) fastens the drug release. This is due to that the diffusion path for these core pellets is shorter than the bigger core pellets. Unexpectedly, the coated pellets of smaller size (0.71 mm) showed poorer floating than larger size ranges. These risk mitigation efforts concluded the avoidance of using the lower usable size range (0.71mm) of the core pellets in the subsequent coating and tabletting development (data is not shown).

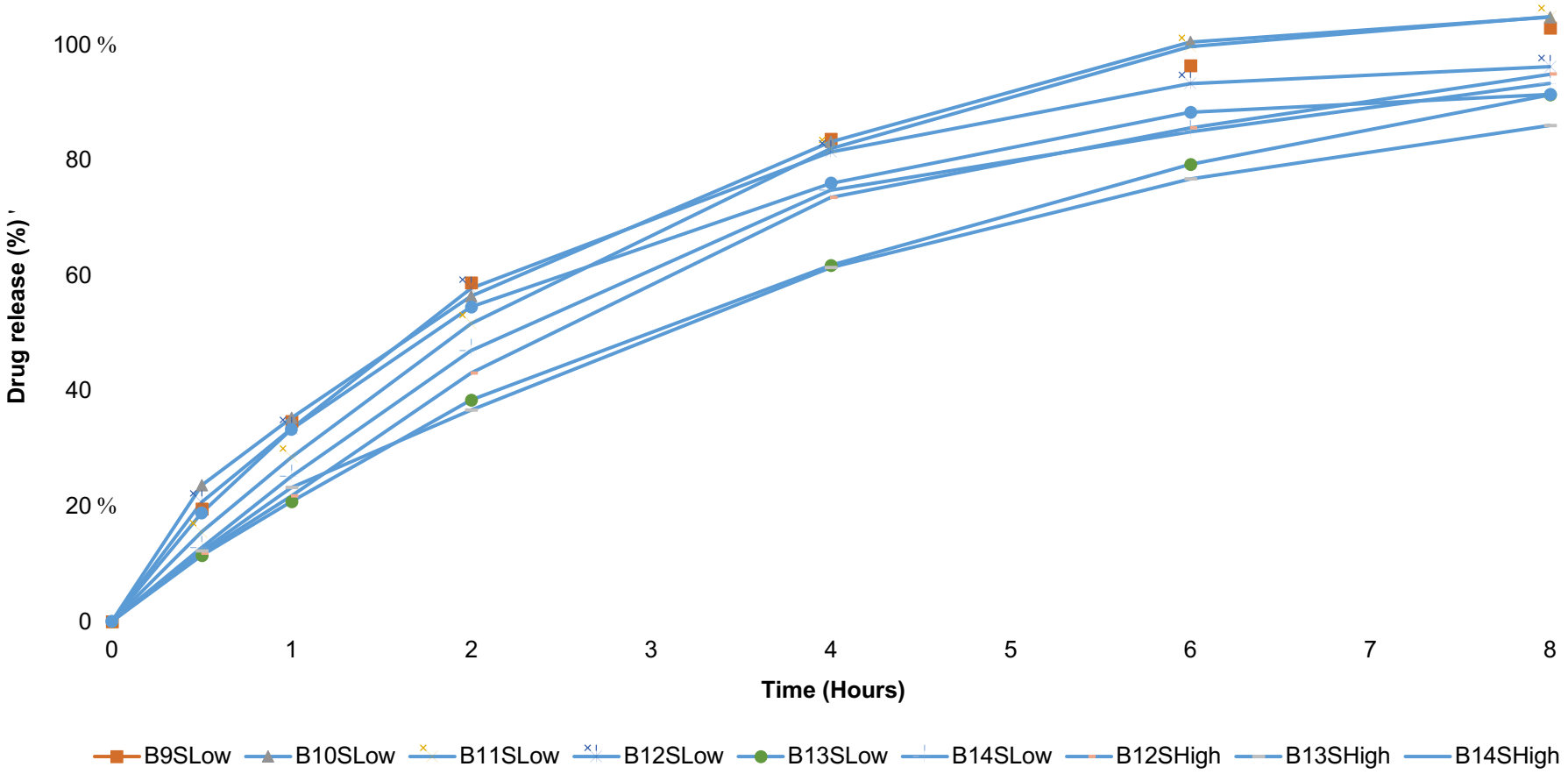


Figure 6.3: Drug release profiles for the ensemble enhanced single-coated pellets in 0.1N HCl medium. Refer to Table 2.4 for the compositions (n=1).

6.2.10. The floating study

The ensemble pellets floated successfully, where more than 90% of the pellets maintained floating for 24 hours in the 0.1 N HCl medium. The latter findings were comparable to the non-ensemble pellets in chapter 5, except that the floating lag time for the coated pellets to float was within 15 minutes. This relatively small increase in the floating lag time was expected, due to two reasons, (1) the need for the two minutes disintegration time, and (2) the compression force effects on the film quality, as potential rupture might occur. However, the floating was still under the passable limits of the critical quality attribute of the floating lag time (floating onset) of less than 30 minutes, see Figure 6.4.

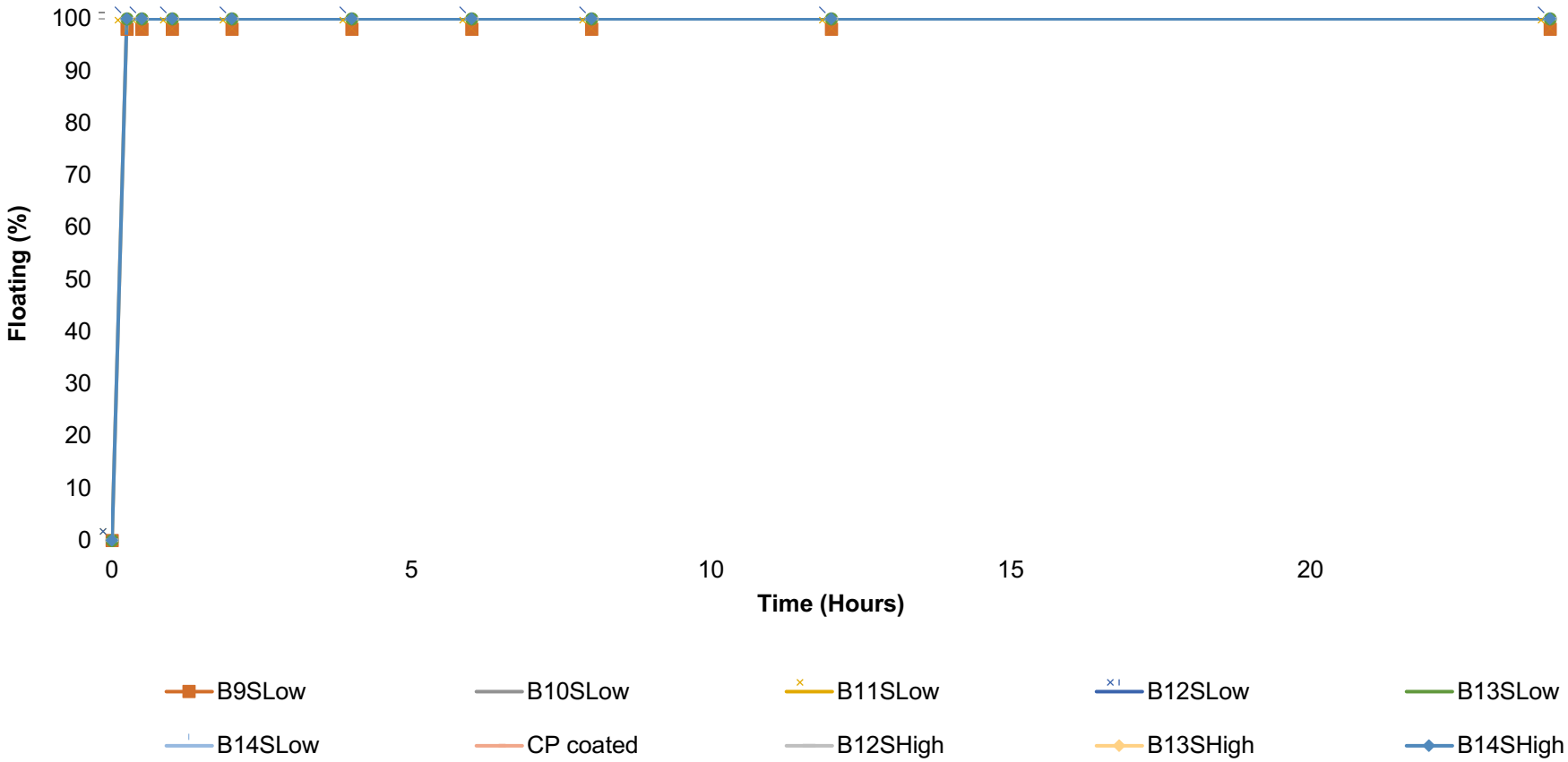


Figure 6.4: Floating profiles for the ensemble enhanced single-coated pellets in 0.1N HCl medium. (n=1). Refer to Table 2.4 for the compositions.

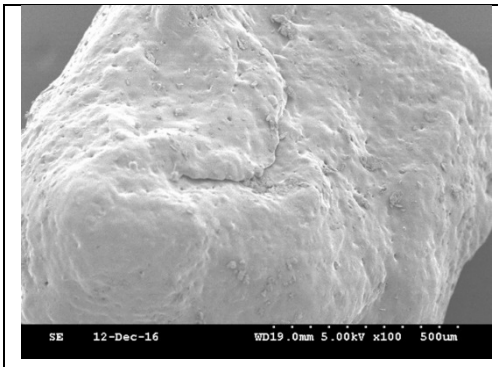
6.2.11. The scanning electron microscopy (SEM) study

The SEM images revealed important amount of information that can be used to further characterise the obtained ensemble pellets. The evidence of the dissolution effect and potentially the cushioning effect and can be drawn.

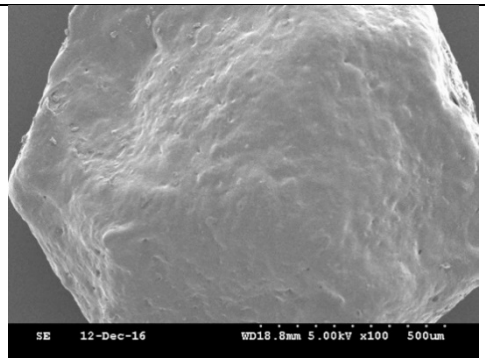
i. The SEM study of the intact coated pellets of the crushed tablets, before dissolution

The coated pellet where taken from the ensemble pellets after crushing. That is, the coated pellets were taken from the dis-assembled ensemble pellets via the hardness tester. The tested pellets here were exposed to two forces, the compression force and the crushing force. Regardless of the latter forces combined effects, the coated pellets maintained their intactness.

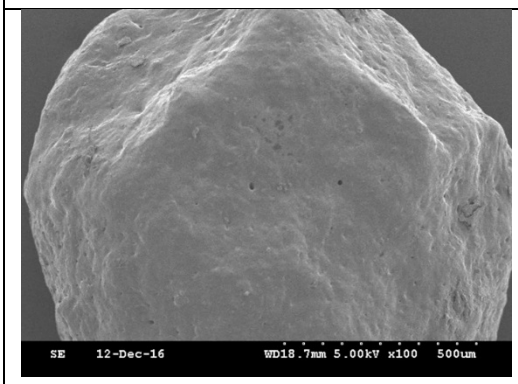
The deformation of the coated pellets before dissolution is due to two confounding factors, the compression force and the crushing force. Regardless of the amount of cushions, the images showed some deformation from the optimal spherical shape with some protrusions. Although more than 50% cushions were recommended by the literature to obtain a sufficient film protection, the 66.66-90% cushion powder was not enough to fully protect the coating film, which showed rupture, see Figures 6.5-6. These ruptures resulted in faster drug release profiles, though the drug was sufficiently sustained for 8 hours at least, as seen in Figure 6.3.



B12SHigh



B13SHigh



B14SHigh

Figure 6.5: The SEM images of the intact coated pellets before dissolution. The images taken from crushed tablets that were compacts of the coated pellets (i.e. ensemble pellets) with **high** amount (66.66%, but it is 90% for B13) of non-medicated cushion powder.

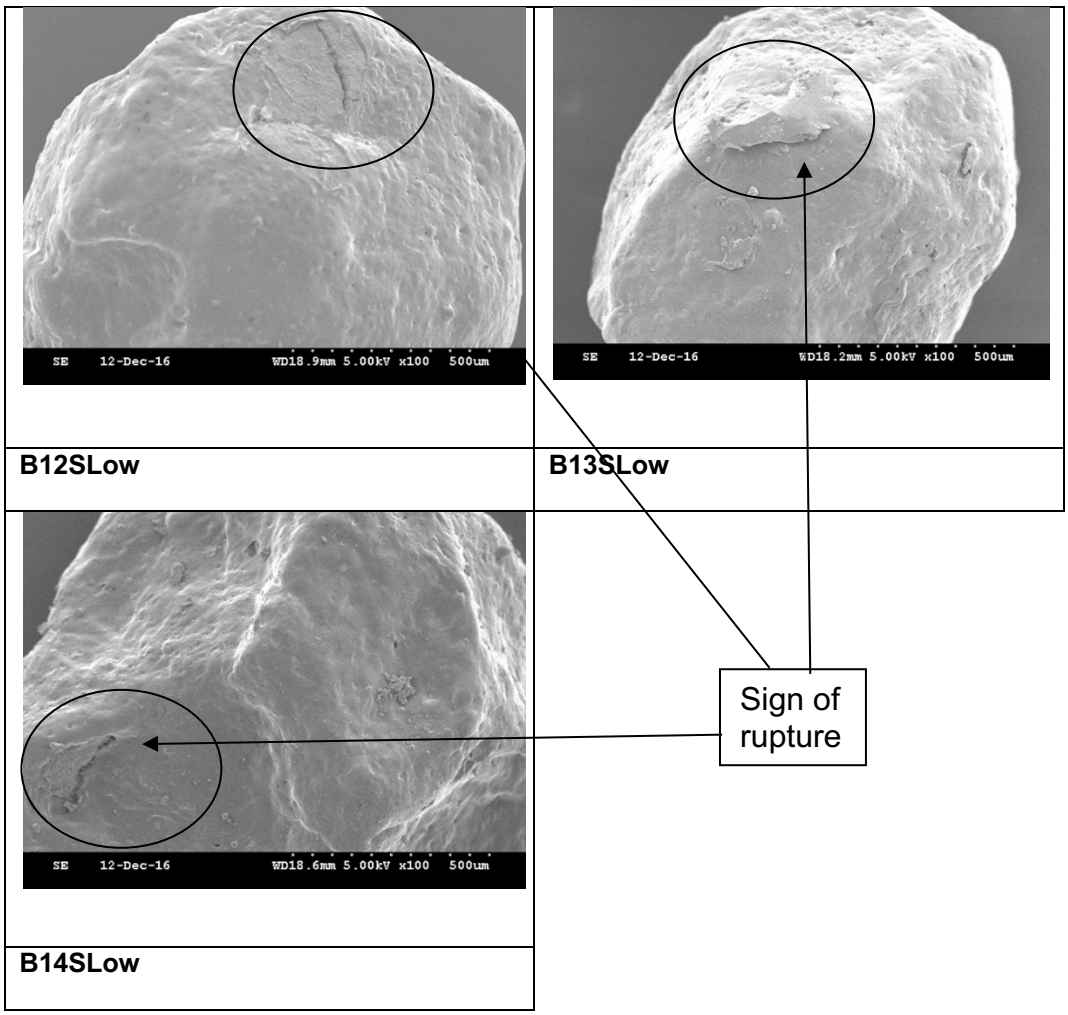


Figure 6.6: SEM image of intact coated pellets, before dissolution, where taken from crushed tablets that were compacts of the coated pellets (i.e. ensemble pellets) with **low** amount (33.33%, but it is 10% for B13) of non-medicated cushion powder.

ii. SEM study for "bisected" coated pellets of the crushed tablets, before dissolution

The coated pellet where taken from a crushed tablet contained compacted coated pellets, i.e from the dis-assembled ensemble pellets via the hardness tester. Some of the bisected pellets with a low amount of cushions (33&10%) in Figure 6.7 shows some cracks in the film. However, it can be a crack resulted due to the crushing force exerted to break the ensemble pellets into individual pellets, or due to the blade effect upon bisecting the pellets into two halves. The images showed the thickness of the enhanced thin film (10±2 μm), and illustrated the integrity and the uniformity of the film thickness throughout the pellets' surface, also see Figure 6.8.

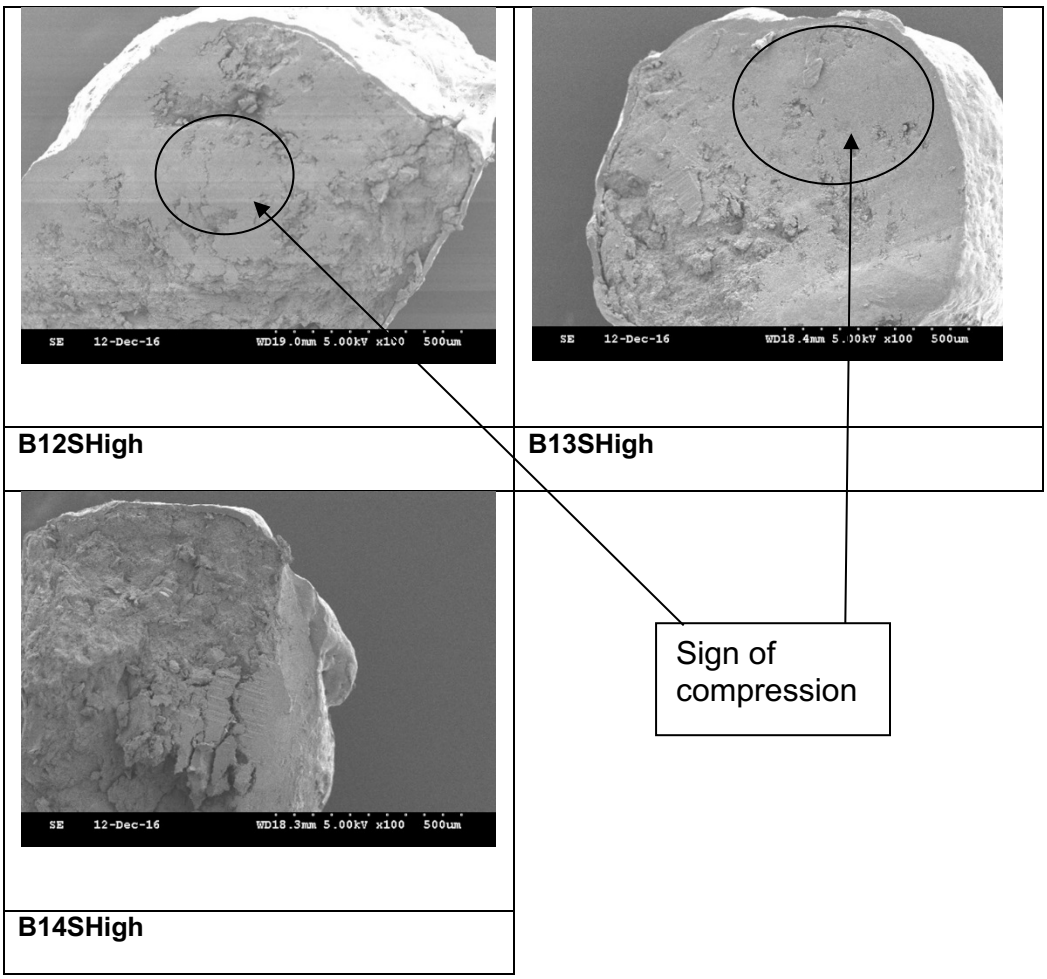


Figure 6.7: SEM image of *bisected* coated pellets, before dissolution, where taken from crushed tablets that were compacts of the coated pellets (i.e. ensemble pellets) with **high** amount (66.66%, but it is 90% for B13) of non-medicated cushion powder.

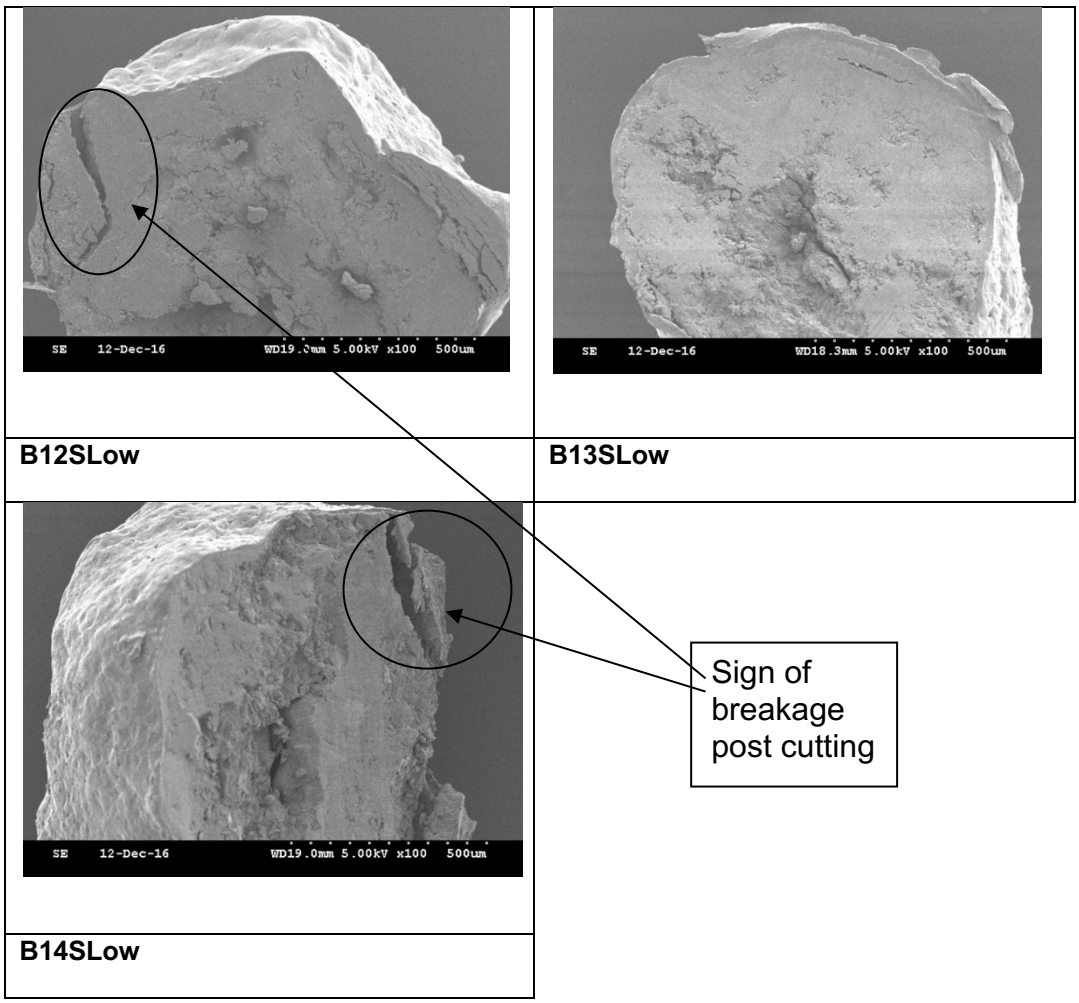
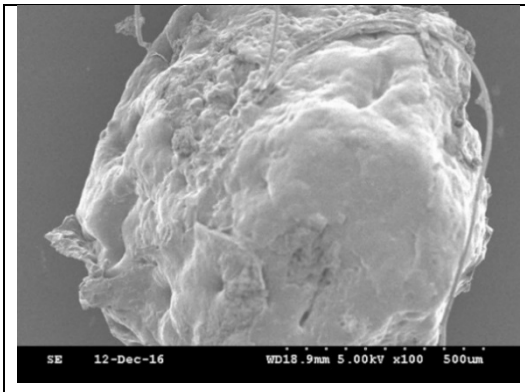


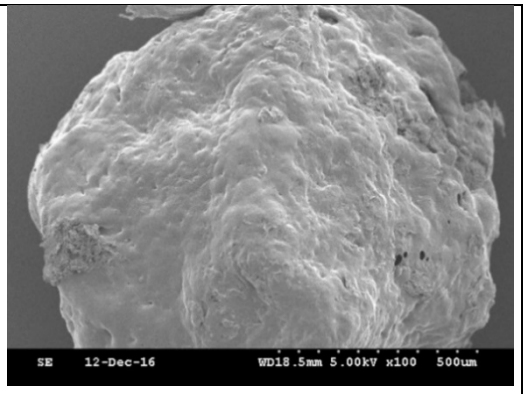
Figure 6.8: SEM image of *bisected* coated pellets, before dissolution, where taken from crushed tablets that were compacts of the coated pellets (i.e. ensemble pellets) with **low** amount (33.33%, but it is 10% for B13) of non-medicated cushion powder.

iii. SEM study for "intact" coated pellets of the dis-assembled pellets, after 24 hours dissolution

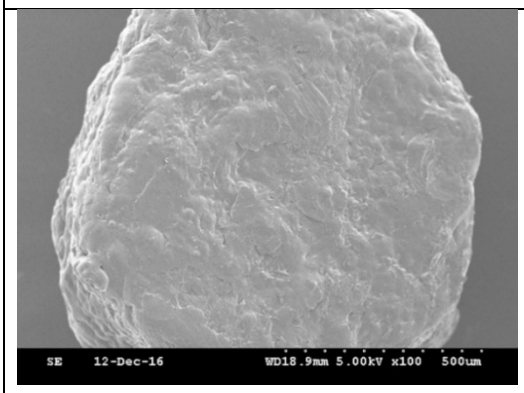
The tested coated pellets were taken from the dried coated pellets after they undergone disintegration and 24 hours dissolution, i.e. they were dis-assembled by the dissolution hydrodynamics from the ensemble pellets. The images in Figures 6.9-10 revealed potential evidence of small ruptures in the film structure That is, the cracked film integrity allowed for a faster drug release. After 24 hours of dissolution, the pellets images remained intact. This confirms that the coated film showed high integrity, regardless of the compression force, the dissolution hydrodynamic, and the drying stresses. However, the latter stresses were evident, because the grooves become bigger and numerous on the surface of the coated pellets (Qi, et al., 2015).



B12SHigh

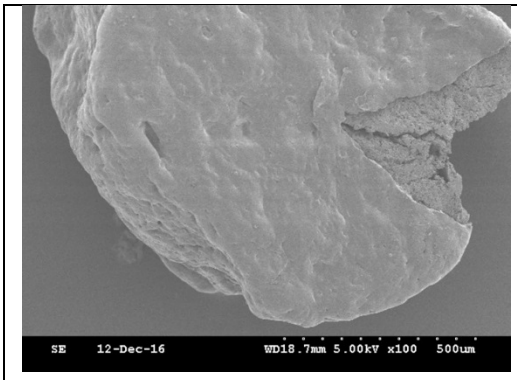


B13SHigh

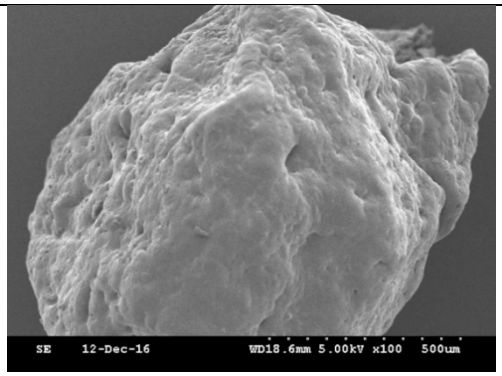


B14SHigh

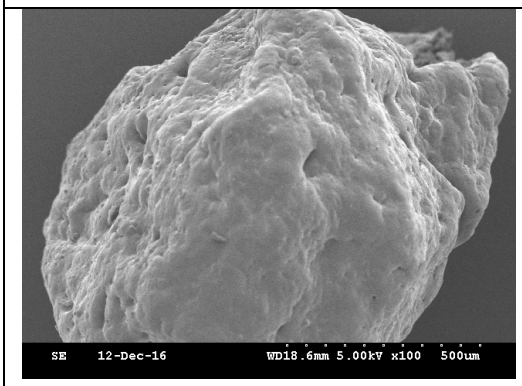
Figure 6.9: SEM image of *intact* coated pellets, after dissolution, where taken from disintegrated tablets contained compacted coated pellets (i.e. ensemble pellets) with **high** amount (66.66%, but it is 90% for B13) of non-medicated cushion powder.



B12SLow



B13SLow

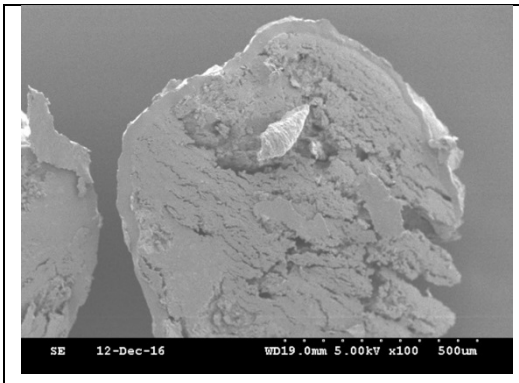


B14SLow

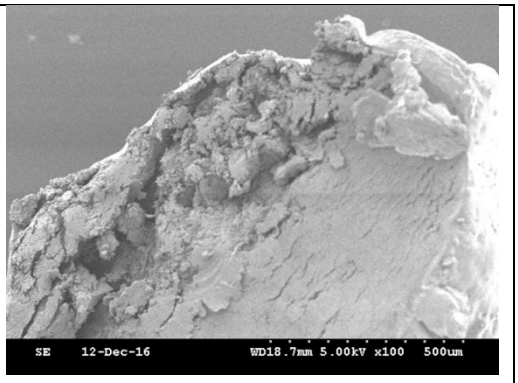
Figure 6.10: SEM image of *intact* coated pellets, after dissolution, where taken from disintegrated tablets contained compacted coated pellets (i.e. ensemble pellets) with **low** amount (33.33%, but it is 10% for B13) of non-medicated cushion powder.

iv. SEM study for "bisected" coated pellets of the dis-assembled pellets, after 24 hours dissolution

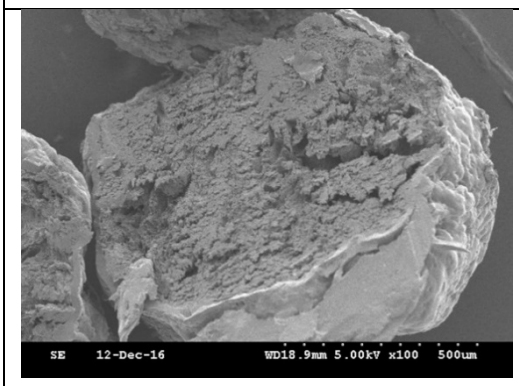
After 24 hours dissolution, the coated pellets were dried and bisected, and studied under the SEM, see Figures 6.11-12. Although the compression force, dissolution and the drying stresses on the coated pellets were considered harsh, the intactness of coated pellets structure remained high and with high reservation in the film size, shape and integrity. Consistently with the images in the previous sub-sections, the high cushions containing ensemble pellets showed no difference in shapes when compared to the low cushions ones. Because the deformation and the ruptures of the films were primarily controlled by the compression force of the tabletting machine and the crushing force, regardless of the cushions amount used (Al-Hashimi, et al., 2018).



B12SHigh

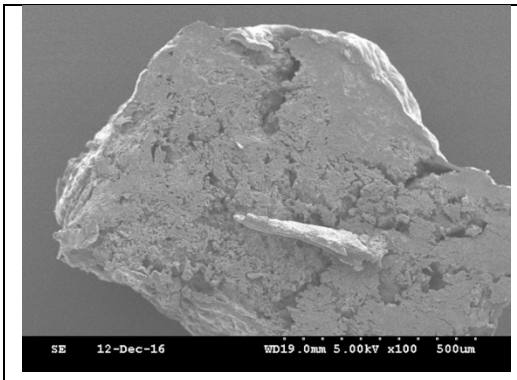


B13SHigh

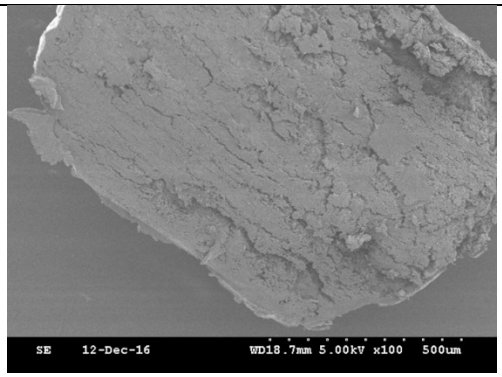


B14SHigh

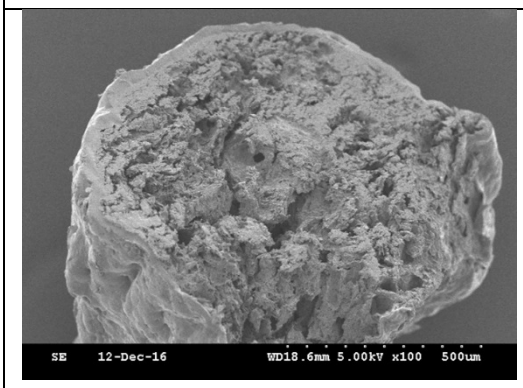
Figure 6.11: SEM image of *bisected* coated pellets, after dissolution, where taken from disintegrated tablets contained compacted coated pellets with **high** amount (66.66%, but it is 90% for B13) of the cushioning powder.



B12SLow



B13SLow



B14SLow

Figure 6.12: SEM image of *bisected* coated pellets, after dissolution, where taken from disintegrated tablets contained compacted coated pellets with **low** amount (33.33%, but it is 10% for B13) of the cushioning powder.

6.3. Conclusion

The tableted pellets dosage form is considered highly advantageous as stated in the introduction of this chapter. The ensemble pellets consisted of the enhanced single-coated pellets and the cushioning powder. The cushioning powder inside the tablets was in different ratios, to screen for the cushioning effects for the protection of the film structure and the film function. When the cushioning powder amounts were lower (33.33&10 %). the crushing force values ranged from ~50-58 N with standard deviation (SD) values of 2-10 N. However, when the cushioning powder amounts were higher (66.66&90 %), the force needed to crush the tablet increased by about 15 %, i.e. ranged from ~59-72 N with SD values of 4-13 N. Hence, a proportional relationship can be seen between the amount of the cushioning powder and the crushing force. In other words, as the cushioning amount increase in the tablet, the crushing force of tablet increase, indicating an increased binding forces. The tablets were placed into a beaker filled with either dissolution medium of the distilled water or with the 0.1N HCl media. The disintegration of the ensemble pellets into the disassembled single-coated pellets will take 1-2 minutes for all tablets. Also, all of the tablets' mixtures showed similar apparent density values (1.24±0.00 g/cm^3). Though it is acceptable, the ensemble pellets showed drug release profiles that only sustained for up to 8 hours. The compression of the single-coated pellets has reduced the functionality of the sustained drug release from 12 hours to 8 hours. That implied that the coat on pellets had some fractures induced by the compression force, which caused an increase in the drug release over time. It is where an acceptable zero-order drug release (R^2>0.9) can be obtained in 8 hours instead of 12 hours. The drug release rate was ~12.5%/hour, instead of ~8.33%/hour. The MUPS tablet review of (Al-Hashimi, et al., 2018) stated that some studied showed an increase of drug release from coated pellets upon compression, while other studies showed a decrease of drug release from coated pellets upon compression, due to film rupture or fusion, respectively. The latter review also stated that a low porosity in the core pellets can affect the drug release of the coated pellets upon compression. Hence, in this work, the porosity of the coated pellets may need to be higher than 7-9% of tablets mixtures pre-compression, to allow for higher film protection upon compression.

After the disassembly from the intact tablet, the single-coated pellets were showing successful floating. The coated layers on the disassembled single-coated pellets provide controlled fluid diffusion in to and out of the pellets. The controlled diffusion will induce the controlled swelling, which will initiate and maintain the floating mechanism, the same applied to the sustained drug release mechanism. But, unlike the drug release profiles, the floating profiles for all of the ensemble pellets batches remained optimum, as they were not affected by the compression force. The scanning electron microscopy (SEM) images revealed important morphological information that can be used to elaborate on the results of the ensemble pellets. For example, it was founded that regardless of the amount of the cushioning powder, the SEM images of the single-coated pellets showed some protrusions and deformation from the optimal spherical shape, which is expected, due to the impact of the combined forces of compression force and crushing. Regardless of the amount of the cushioning powder, the increased drug release is due to the deformation and the rupture of the films, which were primarily controlled by the compression force of the tabletting machine. After 24 hours of dissolution, the single-coated pellets remained intact, as seen in the SEM images. The latter confirms that the coated films on the pellets showed high integrity. The latter finding was regardless of the compression force, the dissolution hydrodynamics, and regardless of the subsequent drying stress after dissolution. This intactness here is desirable to allow the single-coated pellets to remain functional and to withstand the harsh environment of the GIT. Hence, the ensemble pellets dosage form is expected to have a desirable biopharmaceutics performance. The work in this chapter attained the tablets of an enhanced single-coated floating pellets. Specifically, it sufficiently maintained the functions of the coated layer, which is simultaneously responsible for the floating and sustained drug release properties.

Chapter Seven:

General Conclusion

7.1. General Conclusion

Pharmaceutics is a voyage of multi-disciplinary collections of theories and technologies that mainly focus on the physical chemistry and the design of the dosage forms of the drug products, and the accompanying methods of preparation and testing. In this project, the dosage form design of interest is the pellets-containing dosage form. The specific designs of interest are the double-coated and the single-coated floating pellets designs, which could potentially be compressed into tablets. Pellets can be defined as oral solid intermediate formulations, spherical in shape, relatively small in size, and made by a pelletisation technique, usually by extrusion and spheronisation method with a spheronisation aid to obtain dense agglomerates of pellets. Floating pellets achieve floating as they contain floating agents and retard polymeric agents, usually through the application of coating layer/s. The pellets can be made to be as a gastro-retentive drug delivery system (GRDDS). The gastro-retentive term, as the name implied, is derived from its ability to achieve retention of the dosage form in the stomach. Unlike the other GRDDS, floating systems are established in the marketed products, and they will avoid the irritation to the epithelium of the gastro-intestinal tract (GIT). The latter is especially advantageous when the floating system is a floating pellets system, owing to the high distribution of the dose in the pellets, which further reduce the dose localisation. The additional advantage of floating pellets is that pellets will avoid the “all or none” risk of emptying. Therefore, the floating pellets system is said to be one of the most preferred approaches in the GRDDS. The floating pellets system is of a particular interest for specific situations in specific drug substances, like the situation of the drugs with erratic absorption, like theophylline. The erratic absorption means non-uniformity drug absorption in the GIT, resulting in a variable drug bioavailability. The factors that affect the drug absorption are numerous including the drug product and the physiological factors, which subsequently affect the drug bioavailability. All of these factors may cause a variable absorption in the gastro-intestinal tract (GIT) for certain drugs, like theophylline. That can result in unfavourable fluctuated plasma drug levels. However, the risk of attaining a toxic dose or not attaining the efficacious dose becomes more pronounced when such drugs also have a narrow therapeutic window, like theophylline. Hence, that drives the

formulators to think of more reliable means for the delivery of such drugs. The floating pellets are expected to ensure the consistency of the bioavailability of the drug theophylline, by the gastro-retention and the sustained drug release properties. Numerous preparation processes, in-vitro characterisation processes, and methodological tools, and materials were used throughout the work in this thesis. Thesis structure is seen in Figure 7.1.

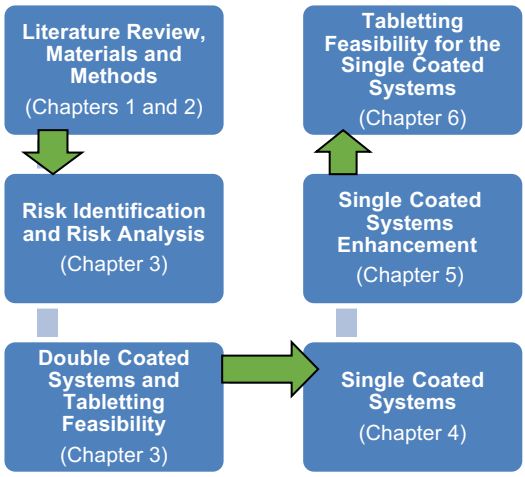


Figure 7.1: It shows the thesis structure showing the workflow/the risk assessment during the PhD research program.

It was feasible to successfully attain the core pellets by a new spheronisation aid (Avicel HFE102) for up to 60% drug loading. It was encouraged in literature to find alternative spheronisation aids that are co-processed with other materials (Jain, et al., 2010). This alternative and new spheronisation aid may help in addressing the drawbacks of the MCC, like drug deactivation, which encourages more studies to be made in this grade of Avicel. The double-coated floating pellets showed insufficient sustained drug release for <4 hours, and where only 34-72% floated on surface (except B5D-B8D, which were >95% floated for 8 to >12 hours). However, the understanding of the double-coated floating pellets design was important before reducing the system into the single-coated floating pellets design. The latter is more intricate yet more cost-effective design. This intricacy is owing to the eliminating of the sub-coated layer, and using only one layer to achieve both the sustained drug release and the floating by a controlled swelling mechanism with or without the foaming mechanism.

For the non-PVP containing core pellets (B2S, B4S, and B5S), the attainment of the core pellets was successful (AR<1.2), where the effervescent and the hydrating polymers are incorporated. However, when these pellets were coated, the floating and the sustained drug release properties for all formulations were variable. Therefore, an enhancement work was needed to streamline the results.

As a sequential continuation from the screening studies, the single coated floating pellets were enhanced. All of the core pellets of B9S-B14S (these are the core pellets made by from the 10% ethanol containing-wet mass) were successful. During the pelletisation, the core pellets were enhanced mainly for the shape and the ease of the extrusion and spheronisation processes (all batches have AR<1.2). The enhanced core pellets are suitable for being applied to further processing, like coating and tabletting. Successful floating and drug release profiles were obtained. The best formulations of the coated pellets were of the B9S-B14S (these are the coated pellets made by from the 25 w/w% ethanol containing-Eudragit NE dispersion). All of the single-coated floating pellets showed sustained drug release for 24 hours or more in 0.1N HCl medium, and the floating was at least for 24 hours in 0.1N HCl medium and 12 hours in the distilled water medium. The single-coated floating pellets are intricate to make due to the demanding two main functions from a single layer. Although these pellets were more intricate to function successfully, these pellets of single-coating reduced the cost of making floating pellets. The enhanced retard coating layer was made from the 15Eud25Eth dispersion, which was applied to the enhanced core pellets. The coating layer consists of 6% solids only, where the coating thickness was relatively small and relatively uniform (10±2 μm), obtaining a thin film. The surface area to volume (SA:V) ratio of the coated pellets decreases by 13.15-17.98%. The latter ratio range is critical to ensure an enhanced floating and sustained drug release profiles. This specific range of SA:V ratio reduction implies an enhanced controlled swelling, hence, where the swelling is in the desired equilibrium position. The successful floating and the sustained drug release profiles in the acidic and neutral media may allow for more predictable and consistent floating behaviours in the stomach. The latter will lower the risk of failure in floating, because the coated pellets will be independent on the pH variation in the

stomach. This reduced design of the enhanced single-coated floating system offers several advantages regarding cost reduction and drug bioavailability improvement. The attainment of an enhanced and novel single-coated floating pellets through an enhancement study was achieved. Specifically, a successful attainment of the core pellets as well as the coated layer were obtained for achieving the enhanced floating and the sustained drug release properties.

Upon disintegration, all of the compressed or tabletted single-coated floating pellets showed sustained drug release for up to 8 hours or more in 0.1N HCl medium, and the floating was at least for 24 hours in 0.1N distilled water medium (where all batches showed complete floating for 24 hours). Hence, all of the single-coated floating pellets sufficiently sustained the drug release (for 8 hours) and maintained floating for at least 24 hours. That is, the best formulations still produced useful performance. The tabletting of these best formulations were superior over the literature findings obtained (Qi, et al., 2015). The tableted floating pellets were floated immediately for more than 12 hours for non-compressed and compressed coated pellets (% of floating not stated) and SR for up to 6-8 hours, though DR reach 80% in 4 hours (for both non-compressed and compressed coated pellets and comparable to PK data of absorbed drug in animals). The medium used for drug release is not stated.

The significance of this work is that these best floating pellets formulations (containing the drug theophylline) encourages further testing in animals, to obtain bioequivalence prior manufacturing. These best floating pellets formulations will also reduce the cost during manufacturing, because only single and thin coating layer will be needed on the core pellets made by the extrusion and spheronisation method. The latter is unlike the respective literature (Qi, et al., 2015), (Hung, et al., 2014), (Chen, et al., 2012), where all failed to consistently obtain more than 8 hours of drug release, though all of them had batches floated for >12 hours. In particular, the researchers of (Qi, et al., 2015) were the most successful (respective to similar literature) in using one layer of coating with a non-effervescent system, where the core pellets made by the extrusion and spheronisation. Their developed formulations were noticeably different from the formulations made in this project by five means; (1) They used a combination of Eudragit RL30D and RS30D, to achieve the

dual functionality in one coating layer, while in this project, only one retard polymer was used, the Eudragit NE30D. (2) They used only distilled water for diluting the Eudragit coating dispersion, while in this project ethanol was used for dilution. (3) They used larger coating weight gains (10, 20, and 25%), while in this project it is only 6%. And, (4) They used the alcoholic PVP K30 as a liquid binder (PVP solubilised in the liquid), to obtain a consistent wet mass, while in this project, an ethanol liquid binder was used and the PVP powder was used, where it is more likely for the PVP to be wetted without soaking in the powder bed, owing to the rapid evaporation of ethanol. That is, the core pellets were made with the wetted PVP (PVP is not solubilised in the liquid), which will have a low risk of not restoring the swellability function of PVP. And, (5) also, in their work, regardless of the tableting and the compression force used, the tableted pellets as well as the non-compressed ones showed 80% or more of drug release after 4 hours, though it floated sufficiently for 9 hours. The maximum concentration of the drug in the rat blood plasma reached at 3 hours. Hence, the drug is not sufficiently sustained, which render the floating pellets to be not successful, hence that requires enhancement. While in this project, even after tableting, the floating and the sustained drug release were better improved. Regardless of tableting, the floating was at least for 12 hours and the sustained drug release was at least for 8 hours. To sum it up, in this work, the core originality is in successfully making a cost effective single-coated floating pellets, using the extrusion/spheronisation method of preparing the spherical and narrowed size core pellets, and using a one polymer grade in the top-spray fluidised bed coater for making the dual functional and thin coating film. The dual functional film was made from a modified Eudragit NE dispersion. When the dispersion was applied to the spherical and the narrowed size core pellets, the floating can be successfully produced without the need for an effervescent. The feasibility to compact such pellets into dispersible tablets was also found to be promising and encouraged further tabletting development. My contribution to the field was by providing a successful floating and sustained drug release using a single-coated design, which improve cost effectiveness. The latter was owing to (1) a reduced coating weight gain and coating process runtime, due to the decreased material used and the increased efficiency in coating. And (2) a reduced number of coating batches to one coating per batch instead of two coatings per batch, which reduced the

preparation time. Hence, this work can encourage further work on this formulation design during pre-clinical and clinical development, as it may facilitate the manufacturing of floating pellets.

7.2. Future Work

The major difficulties in this project, where in obtaining consistent wet mass to be used for extrusion and spheronisation. Moreover, the coating liquid formulation was the most difficult and the most critical in the performance of the coating process and of the coated pellets. Hence, it is recommended, especially during scale up, that to focus on conducting intensive studies for optimising the wet mass properties (using e.g. mixer torque rheometer) and the coating process and the coated product properties (using a laser technique for size analysis in-process, to measure the sprayed droplet properties). Moreover, transmission electron microscope (TEM) is also recommended, to visualise the internal morphology of the coated pellets without bisecting them into two halves. The latter will remove the bias of the cutting blade effect on rupturing the film. Also, a familiarity (f_2) test between the dissolution profiles also need to be considered, to further investigate the differences between the dissolution profiles. The latter will allow the increased understanding of whether a certain change in excipients is acceptable in the drug formulation. The work in this thesis was focused mainly on the various in-vitro testing of the enhanced floating pellets. However, more studies in-vitro (like the short term and long term stability studies), and in-vivo (animal studies, to obtain supra-bioavailability with a marketed theophylline product that is also a sustained drug release system), in-silico (statistical and mechanistic modelling, to simulate formulation scale up) can be made, to further develop these obtained formulations. Hence, the work in this thesis can serve as the bases for further development in the enhanced single-coated floating pellets, in order to fasten their time to market. The work in this thesis and the future work will indeed help to complement the efforts for supra-bioavailability, and the subsequent scaling up of the enhanced single-coated floating pellets all the way from the lab-scale to the production-scale production. Perhaps, the scaling up can be made through the pilot-scaling in a continuous manufacturing mode, for instance. Hence, the latter can be controlled and reviewed through the risk control and the risk review categories of the QbD, respectively.

8. References

Abdel Rahim, S., Carter, P. A. & Elkordy, A., 2015. Design and evaluation of effervescent floating tablets based on hydroxyethyl cellulose and sodium alginate using pentoxifylline as a model drug. *Drug Des, Dev and Therapy,* 9, pp. 1843-1857.

Abdul, S., Chandewar, A. & Jaiswal, S., 2010. A flexible technology for modified-release drugs: multiple-unit pellet system (MUPS). *J Cont Rel,* 147(1), pp. 2-16.

Al-Hashimi, N., Begg, N., Alany, RG., Hassanin, H., Elshaer A., 2018. Review: Oral modified release multiple-unit particulate systems: compressed pellets, microparticles and nanoparticles. *Pharmaceutics,* 10, pp. 176.

Al-Khattawi, A., Iyire, A., Dennison, T., Dahmash, E., Bailey, CJ., Smith, J., Rue, P., Mohammed, AR., 2014. Systematic screening of compressed ODT excipients: cellulosic versus non-cellulosic. *Current Drug Delivery,* 11(4), pp. 486-500.

Alderborn, G., 2013. Tablets and Compaction. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, The Design and Manufacture of Medicines.* 4th ed. London: Churchill Livingstone Elsevier, pp. 505-506.

Allen, L. V., Popovich, N. G. & Ansel, H. C., 2005. Dosage Form Design: Biopharmaceutical and Pharmacokinetic Considerations. In: *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems.* 8th ed. Baltimore, USA: Lippincott Williams & Wilkins, pp. 171.

Allen, L. V., Popovich, N. G. & Ansel, H. C., 2005. Dosage Form Design: Pharmaceutical and Formulation Considerations. In: *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems.* 8th ed. Baltimore, USA,: Lippincott Williams & Wilkins, pp. 107, 124.

Allen, L. V., Popovich, N. G. & Ansel, H. C., 2005. Solid Oral Modified-Release Dosage forms and Drug Delivery Systems. In: *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems.* 8th ed. Baltimore, USA: Lippincott Williams & Wilkins, pp. 260-272.

Amidon, G. L., Lennernas, H., Shah, V. P. & Crison, J. R., 1995. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability. *Pharm Res,* 12(3), pp. 413-420.

Amrutkar, P., Chaudhari, P. & Patil, S., 2012. Design and in vitro evaluation of multiparticulate floating drug delivery system of zolpidem tartarate. *Colloids Surf B Biointerfaces.,* 89(1), pp. 182-187.

Anuj, G. and Fuloria, N.K. 2012. Short review on quality by design: a new era of pharmaceutical drug development, Int. J. Drug Dev. & Res., 4, pp.19-26.

Bardonnet, P. et al., 2006. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. *Journal of Controlled Release,* 111, pp. 1-18.

Aoki H, Iwao Y, Mizoguchi M, Noguchi S, Itai S, 2015. Clarithromycin highly-loaded gastro-floating fine granules prepared by high-shear melt granulation can enhance the efficacy of Helicobacter pylori eradication. *Europ J Pharm & Biopharm,* 92, pp. 22-27.

Arora S, Ali J, Ahuja A, Khar RK, Baboota S, 2005. Floating Drug Delivery Systems: A Review. *AAPS PharmSciTech,* 6(3), pp. 372-390.

Ashford, M., 2013. Assessment of Biopharmaceutical Properties. In: M. Aulton & K. M. Taylor, eds. Aulton's Pharmaceutics, The Design and Manufacture of Medicines, 4th ed. London: Churchill Livingstone Elsevier, pp. 353.

Ashford, M., 2013. Bioavailability - Physicochemical and Dosage Form Factors. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, The Design and Manufacture of Medicines.* 4th ed. London: Churchill Livingstone Elsevier, pp. 314-333.

Ashford, M., 2013. Gastrointestinal Tract - Physiology and Drug Absorption. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, The Design and Manufacture of Medicines.* 4th ed. London: Churchill Livingstone Elsevier, pp. 301-306.

Atension, 2014. *Sigma700 and 701, Operation Manual of Attention Force Tensiometer, Revision 2.1,* Helsinki, Finland: Atension.

Atkins, P., 1995. Acid and Base. In: *Concepts in Physical Chemistry.* 1st ed. Oxford: Oxford University Press, pp. 1 & 25.

Atkins, P., 2010. The first law: The conservation of energy. Free energy: The availability of work. In: *The Laws of Thermodynamics: A Very Short Introduction.* Oxford: Oxford University Press, pp. 31-35, 63-79.

Atkins, P., 2014. Changing the state of matter. In: *Physical Chemistry, A Very Short Introduction.* 1st ed. Oxford: Oxford University Press, pp. 70-85.

Atyabi, F., Sharma, H. L., Mohammad, H. A. H. & Fell, J. T., 1996. Controlled drug release from coated floating ion exchange resin beads. *J Cont Rel,* 42, pp. 25-28.

Aulton, M. E., 2013. Properties of the Solutions. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, The Design and Manufacture of Medicines.* 4th ed. London: Churchill Livingstone Elsevier, pp. 38-48.

Aulton, M. E., 2013. Dissolution and Solubility. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, The Design and Manufacture of Medicines.* 4th ed. London: Churchill Livingstone Elsevier, pp. 20-37.

Aulton, M., 2018. Particle Size Reduction and Size Seperation. In: 5th, ed. *Aulton's Pharmaceutics, the Design and Manufacture of Medicine.* ME Aulton; KMG Taylor ed. London: Elsevier, pp. 159.

Aulton, M. E. & Summers, M. P., 2013. Powders, granules, and granulation. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, The Design and Manufacture of Medicines.* 4th ed. London: Churchill Livingstone Elsevier, pp. 472-473 and 480-482.

Avinash, K., Abha, D., Praween, K. & Abhinav, G., 2012. Floating Drug Delivery System a Significant Tool for Stomach Specific Release of Cardiovascular Drugs. *InterJ Drug Dev& Res,* 4(4), pp. 116-129.

Awasthi, R. & Kulkarni, G., 2014. Development of novel gastroretentive drug delivery system of gliclazide: hollow beads. *Drug Dev Ind Pharm J,* 40(3), pp. 398-408.

Ayad, M. H., 2014. Rational formulation strategy from drug discovery profiling to human proof of concept. *Drug Deliv,* pp. 1-8.

Baert, L. & Remon, J., 1993. Influence of amount of granulation liquid on the drug release rate from pellets made by extrusion-spheronization. *Int J Pharm,* 95, pp. 135-141.

Barker, S. A., 2013. Suspensions. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, the Design and Manufacture of Medicines.* London: Churchill Livingstone Elsevier, pp. 427.

Barnes, P. J., 2010. Theophylline. *Pharmaceuticals J,* 3(3), p. 725–747.

BASF, 2009. *Technical Information, Anhydrous Theophylline in Ph. Eur., USP and JP,* s.l.: BASF Chemicals, Pharma Ingredients and Services.

Bashaiwoldu, A. B., Podczeck, F. & Newton, J., 2004. A study on the effect of drying techniques on the mechanical properties of pellets and compacted pellets. *Euro J Pharm Sci,* 21(2-3), pp. 119-129.
Bera, H., Kandukuri, S. G., Nayak, A. K. & Boddupalli, S., 2015. Alginate–sterculia gum gel-coated oil-entrapped alginate beads forgastroretentive risperidone delivery. *Carb Polym,* 120, pp. 74-84.
Bhardwaj, L., Sharma, P. K. & Malviya, R., 2011. A Short Review on Gastro Retentive Formulations for Stomach Specific Drug Delivery: Special Emphasis on Floating In situ Gel Systems. *Afri J Basic & Appl Sci,* 3(6), pp. 300-312.
Bhardwaj, V. & Harikumar, N. S. L., 2013. Floating drug delivery systems: a review. *Pharmacophore J,* 4(1), pp. 26-38.
Bhattacharjya, S. & Wurster, D. E., 2008. Investigation of the drug release and surface morphological properties of film coated pellets, and physical, thermal and mechanical properties of free films as a function of variuos curing conditions. *AAPS PharmSciTech,* 9(2), pp. 449-457.
Biswas, S., Paul, S., Chowdhury, A. & Das, J., 2012. Preparation and evaluation of gastroretentive floating pellets of metronidazole using Na-alginate and hydroxyl propyl methyl cellulose polymers. *Pak J Bio Sci,* 15(6), pp. 290-295.
Bodmeier, R. & Paeratakul, O., 1994. Mechanical properties of dry and wet cellulosic and acrylic films prepared from aqueous colloidal polymer dispersions used in the coating of solid dosage forms. *Pharm Res.,* 11(6), pp. 882-888.
British-Pharmacopoeia., 2017. Appendix XII-C. In: *British Pharmacopoeia 2018.* London: British Pharmacopoeia Commition Office, pp. V-A384/5.
British-Pharmacopoeia, 2017. Appendix XII-A. In: *British Pharmacopoeia 2018.* London: British Pharmacopoeia Commition Office, pp. V-A362.
British-Pharmacopoeia, 2017. Appendix XVII-G. In: *British Pharmacopoeia* Caleva, 2015. *Caleva Multi Bowl Spheronizer MBS, all variants, installation and operation manual,* Dorset, UK: Caleva. *2018.* London: British Pharmacopoeia Commition Office, pp. V-A539.
Caleva, 2017. *Determination of moisture requirement to prepare spheroids by extrusion-spheronisation, the hand squeeze test. Is it the right way?.* [Online] Available at:

https://www.caleva.com/Uploads/ApplicationNotes/00/00/00/19/ApplicationNo $
teFile_FILE/Determine-moisture-content-requirement-to-prepare-spheroids-by-extrusion-spheronization.pdf [Accessed 27 09 2018].
Caleva, 2017. *Inconsistent extrusion and spheronisation with a difficult active ingredient? An example of the Caleva MTR-3 in practical use.* [Online]
Available at:
https://www.caleva.com/Uploads/ApplicationNotes/00/00/00/18/ApplicationNo $
teFile_FILE/Solve-problems-with-inconsistent-extrusion-or-spheronization-when-using-a-difficult-active-ingredient.pdf [Accessed 27 09 2018].
Caleva, 2017. *Mini coater/drier 2, technichal specification.* [Online]
Available at:
https://www.caleva.com/Uploads/VariationDescriptions/00/00/00/45/Variation $
DescriptionTechnicalSpec_FILE/Mini-Tablet-Coater-Pellet-Drier-Technical-Specification.pdf [Accessed 27 09 2018].
CapsuleConnection, 2018. *Capsule Sizes.* [Online]
Available at: https://capsuleconnection.com/capsule-sizing-info/
Chemical-Book, 2017. *Polyvinylpyrrolidone and Polyvinylpyrrolidone cross-linked.* [Online] Available at:
http://www.chemicalbook.com/ChemicalProductProperty_EN_CB4209342.ht $
m [Accessed 05 12 2017].
Chandel, A. et al., 2012. Review Article: Floating drug delivery systems: A better approach. *Inter Cur Pharm J,* 1(5), pp. 110-118.
Chaurasia, G., 2016. A review on pharmaceutical preformulation studies in formulation and development of new drug molecules. *International journal of pharmaceutical sciences and research (ijpsr),* 7(6), pp. 2313-2320.
Chawla, G., Gupta, P., Koradia, V. & Bansal, A. K., 2003. Gastroretention: Means to Address Regional Variability in Intestinal Drug Absorption. *J Pharmac Tech,* pp. 50-68.
Chen, YC. Lee, LW. Ho, HO., Sha, C., Sheu MT., 2012. Evaluation of water uptake and mechanical properties of blended polymer films for preparing gas-generated multiple-unit floating drug delivery systems. *J of Pharm Sci,* 101(10), pp. 3811-3822.
Chhetri, H. P. & Thapa, P., 2014. An overview on gastroretentive drug delivery system. *J Sci, Eng, & Tech,* 10(1), pp. 90-103.

Chiu, M. & Prenner, E., 2011. Differential scanning calorimetry: An invaluable tool for a detailed thermodynamic characterization of macromolecules and their interactions. J Pharm Bioallied Sci., 3(1), pp. 39-59.
Cole, G., Hogan, J. & Aulton, M., 2002. The Coating Process. In: G. Cole, ed. *Pharmaceutical Coating Technology.* London: Taylor and Francis, pp. 198-201.
Cole, G., Hogan, J. & Aulton, M., 2002. Introduction. In: G. Cole, ed. *Pharmaceutical Coating Technology.* London: Taylor and Francis, pp. 4-5.
Chopra, R., Podczeck, F., Newton, J. & Alderborn, G., 2002. The influence of pellet shape and film coating on the filling of pellets into hard shell capsules. *Eur J Pharm Biopharm. ,* 53(3), pp. 327-333.
Costa, P. & Lobo, J. M. S., 2001. Review; modeling and comparison of dissolution profiles. *Euro J Pharm Sci,* 13 , pp. 123–133.
Chu, M. & Chaw, C., 2014. Ketoprofen loaded pellets produced by extrusion/spheronization using Avicel CL611 as an alternative spheronization aid. Sunderland.
Das, N. G. & Das, S. K., 2003. Controlled Release of Oral Dosage Forms. *Formul, Fill & Finish J,* pp. 10-16.
Davis, S. S., 2005. Formulation Strategies for Absorption Windows. *Drug Disc Today Rev J,* 10(4), pp. 249-257.
DFE-Pharma, 2011. *Introduction to tableting by wet granulation.*
Donnelly, S. & Evans, J., 1991. *Fundamental Aspects of Inert Gases in Solids.* 1st ed. New York: Plenum Press. pp 153.
Dow, 2002. *Methocel Cellulose Ethers, Technical Handbook, Dow.* [Online] Available at: http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_096d/0901b80$38096d9ff.pdf?filepath=/pdfs/noreg/192-01062.pdf&fromPage=GetDoc [Accessed 02 12 2017].
DrugBank, 2015. *Theophylline.* [Online] Available at: http://www.drugbank.ca/drugs/DB00277 [Accessed 13 04 2015].
Ebnesajjad, S., 2011. Surface Tension and Its Measurement. In: Handbook of Adhesives and Surface Preparation, Technology, Applications and Manufacturing. William Andrew, pp. 21-30.
Dwibhashyam, V. M. & Ratna, J. V., 2008. Key formulation variables in tableting of coated pellets. *Ind J Pharm Sci.,* 70(5), pp. 555-564.

Eriksson, L., 2012. Introduction. In: *User Guide to MODDE 10.1.*:MKS Umetric.
Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wikstrom, C., Wold, S., 2008. D-optimal designs. In: *Design of Experiments, Principles and Apllications.* Umea, Sweden: Umetrics Academy, pp. 217-230.
Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wikstrom, C., Wold, S., 2008. Appendix 2: Statistical Notes. In: *Design of Experiments, Principles and Apllications.* Umea, Sweden: Umetrics Academy, pp. 417-435.
Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wikstrom, C., Wold, S., 2008. DoE in formulation development. In: *Design of Experiments, Principles and Apllications.* Umea, Sweden: Umetrics Academy, pp. 371-372.
Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wikstrom, C., Wold, S., 2008. DoE in PAT. In: *Design of Experiments, Principles and Apllications.* Umea, Sweden: Umetrics Academy, pp. 387-398.
Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wikstrom, C., Wold, S., 2008. Experimental objective: Screening. In: *Design of Experiments, Principles and Apllications.* Umea, Sweden : Umetrics Academy, pp. 107-108.
Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wikstrom, C., Wold, S., 2008. Factorial designs. In: *Design of Experiments, Principles and Apllications.* Umea, Sweden: Umetrics Academy, pp. 53-74.
Eriksson, L. et al., 2008. Preface. In: *Design of Experiments, Principles and Apllications.* Umea, Sweden: Umetrics Academy, pp. 1-6.
Evonik, 2016. *EUDRAGIT Application Guidelines.* 12 ed.
Evonik, 2017. *Eudragit® Setting benchmarks in oral solid dosage forms since 1954.* [Online] Available at: http://healthcare.evonik.com/sites/lists/NC/DocumentsHC/Evonik-Eudragit_brochure.pdf [Accessed 2017].
Fahier., J., 2017. *Polymeric controlled release film coatings.* [Online] Available at: https://tel.archives-ouvertes.fr/tel-01505652/document [Accessed 05 04 2019].
Felton, L. A., 2013. Review: Mechanisms of polymeric film formation. International Journal of Pharmaceutics, 457(2), pp. 423-427.
FDA-CDER, 2015. *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules, Guidance for Industry. CDER; Center for Drug Evaluation and Research,* Silver Spring, Maryland: U.S. Department of

Health and Human Services, Food and Drug Administration/FDA, Pharmaceutical Quality/CMC. [Online] Available at: https://www.fda.gov/downloads/drugs/guidances/ucm377938.pdf [Accessed 27 01 2017].

Field, A., Miles, J. & Field, Z., 2012. Comparing two means, Assumptions of the t-test. In: *Discovering Statistics Using R.* 1st ed. London: SAGE Publications Ltd, pp. 372.

Fell, J. & Newton, J., 1970. Determination of tablet strength by the diametral-compression test. *J Pharm Sci,* 59(5), pp. 688-691.

Foster, K., Sun, H., Fancher. RM., Proszynski, M., Dixon, G., Ford, K., Cornelius, G., Gudmundsson, OS., Hageman, MJ., 2013. Utility of gastric-retained alginate gels to modulate pharmacokinetic profiles in rats. *J Pharm Sci,* 102(8), pp. 2440-2449.

Freire, A. C. & Basit, A. W., 2013. Dissolution testing of solid dosage forms. M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, The Design and Manufacture of Medicines.* 4th Ed. London: Churchill Livingstone Elsevier, pp. 611-622.

Gaisford, S., 2013. Pharmaceutical Preformulation. In: M. E. Aulton & K. M. Taylor, eds. *Aulton's Pharmaceutics: The Design and Manufacture of Medicines.* 4th ed. London: Churchill Livingstone Elsevier, pp. 367.

Garekani, H., Nokhodchi, A., Rayeni, M. & Sadeghi, F., 2013. Preparation and characterization and release properties of Eudragit RS based ibuprofen pellets prepared by extrusion spheronization: effect of binder type and concentration. *Drug Dev & Ind Pharmacy,* 39(8), pp. 1238-1246.

Garg, R. & Gupta, G., 2008. Review Article: Progress in Controlled Gastroretentive Delivery Systems. *Trop J Pharm Res,* 7(3), pp. 1055-1066.

George, M. L., Rowlands, D., Price, M. & Maxey, J., 2005. Identifying and Verifying Causes. In: *The Lean Six Sigma Pocket (6Q) Toolbook.* 1st ed. London: McGraw-Hill, pp. 141-196.

Ghebre-Sellassie, I., 1989. Extrusion and Sheronizing Equipment. In: I. Ghebre-Sellassie, ed. *Pharmaceutical Pelletization Technology.* New York: Marcel Dekker, pp. 71-100.

Ghebre-Sellassie, I., 1989. Pellets: A General Overview. In: *Pharmaceutical Pelletization Technology.* New York: Marcel Dekker, INC, pp. 3.

Hand, D. J., 2008. Collecting Good Data. In: *Statistics, A very Short Introduction.* 1st ed. Oxford: Oxford University Press, pp. 36-54.
Goyal, A. N. K. & Sharma, P. K., 2014. Effervescent Floating Drug Delivery System: A Review. *Glob J Pharmacology,* 8(4), pp. 478-485.
Guguloth, M., Bomma, R. & Veerabrahma, K., 2011. Development of sustained release floating drug delivery system for norfloxacin: in vitro and in vivo evaluation. *PDA J Pharm Sci Technol.,* pp. 198-206.
Gupta, N. V., Gowda, D., Balamuralidhara, V. & Khan, S. M., 2011. Formulation and evaluation of olanzapine matrix pellets for controlled release. *J Daru. ,* 19(4), pp. 249–256.
Gupta, P. & Kothiyal, G. P., 2015. Floating Drug Delivery System: A Review. *Inter J Pharma Res & Rev,* 4(8), pp. 37-44.
Habib, Y. S., Shangraw, R. & Augsburger, L. L., 2002. Production of inert cushioning beads: Effect of excipients on the physicomechanical properties of freeze-dried beads containing microcrystalline cellulose produced by extrusion-spheronization. *Int J Pharm.,* 233(1-2), pp. 67-83.
Hamman, H., Hamman, J. & Steenekamp, J., 2017. Review Article: Multiple-Unit Pellet Systems (MUPS): Production and Applications as Advanced Drug Delivery Systems. 7(3), pp. 201-210.
Hamman, J. H., Demana, P. H. & Olivier, E. I., 2007. Targeting receptors, transporters and site of absorption to improve oral drug delivery. *J Drug Targ Ins,* 2, pp. 71-81.
Hardenia, S. S., Jain, A., Patel, R. & kaushal, A., 2011. Floating Drug Delivery Systems: A Review. *Asian J Pharmacy & Life Sci,* 1(3), pp. 284-293.
He, Y., Li, Y., Yang, D. & Zhu, C., 2017. Preparation and evaluation of gastric adhesive-floating pellets for Bolo leaf phenols. *Zhongguo Zhong Yao Za Zhi,* 42(1), pp. 107-112.
Heinicke, G. & Schwartz, J., 2004. Particle size distributions of inert spheres and pelletized pharmaceutical products by image analysis. *Pharm Dev Technol.,* 9(4), pp. 359-367.
Hendeles, L. & Weinberger, M., 1983. Theophylline. A "state of the art" review. *J Pharmacotherapy,* 3(1), pp. 2-44.
Holman, J., 2013. *Assessing the use of twin screw wet granulation in a multi stage manufacturing process for the continuous production of pharmaceutical*

products. [Online] Available at: https://core.ac.uk/download/pdf/30341523.pdf [Accessed 05 04 2019].

Hossain, A., Nandi, U., Fule, R., Nokhodchi, A., Maniruzzaman, M., 2017. Advanced surface chemical analysis of continuously manufactured drug loaded composite pellets. *J Colloid and Interface Sci,* 492, pp. 157–166.

Hosseini, A., Körber, M. & Bodmeier, R., 2013. Direct compression of cushion-layered ethyl cellulose-coated extended release pellets into rapidly disintegrating tablets without changes in the release profile. *Inter J Pharm,* 457, pp. 503-509.

Hung, S.-F.et al., 2014. Characterizations of plasticized polymeric film coatings for preparing multiple-unit floating drug delivery systems (muFDDSs) with controlled-release characteristics. *PLOS ONE,* 9(6), pp. 1-10.

Hwang, K., Byun, W., Cho, C. & Park, E., 2016 . Preparation and optimization of glyceryl behenate-based highly porous pellets containing cilostazol. *Pharm Dev Technol.,* 3, pp. 1-12.

Iannuccelli, V., Coppi, G., Bernabei, M. & Cameroni, R., 1998. Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. *Inter J Pharm,* 174(1-2), pp. 47–54.

ICH, 2005. *Quality Risk Management (Q9).* [Online] Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf [Accessed 6 2017].

ICH, 2008. *Pharmaceutical Quality Systems (Q10).* [Online] Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf [Accessed 6 2017].

ICH, 2009. *Pharmaceutical Development Q8(R2).* [Online] Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf [Accessed 5 12 2015].

Ichikawa, M., Watanabe, S. & Miyake, Y., 1991. A new multiple-unit oral floating dosage system. I: Preparation and in vitro evaluation of floating and sustained-release characteristics. *J Pharm Sci,* 80(11), pp. 1062-1066.

IMA, 2019. *IMA.* [Online] Available at: https://ima.it/pharma/prexima-300-determination-of-the-effect-of-the-pre-compression-force-on-the-tablet-hardness-obtained-at-constant-value-of-the-main-compression-force/ [Accessed 11 11 2019].

Ishak, R. A. H., 2015. Buoyancy-Generating Agents for Stomach-Specific Drug Delivery: An Overview with Special Emphasis on Floating Behavior. *J Pharm Pharm Sci,* 18(1), pp. 77-100.
Jain, S. P., Singh, P. P. & Amin, P. D., 2010. Alternative extrusion– $ spheronization aids. *Drug Dev & Ind Pharmacy,* 35(11), pp. 1364-1376.
Kadajji, V. G. & Betageri, G. V., 2011. A Review: Water Soluble Polymers for Pharmaceutical Applications. *J Polym,* 3, pp. 1972-2009.
Kallakunta, V., Sarabu, S. & Tiwari, R., 2017. Multiple Unit Particle Systems (MUPS), a Versatile Strategy for Controlled Drug Delivery: Focus on Formulation and Process Concerns. *Journal of Formulation Science & Bioavailability,* 1(1), pp. 1-3.
Kadono, K., Yokoe, JI., Ogawara, KI., Higaki, K., Kimura, T., 2002. Analysis and prediction of absorption behavior for theophylline orally administered as powders based on gastrointestinal-transit-absorption (Gita) model. *J Drug Metab & Pharmacokinetics,* 17(4), pp. 307-315.
Kandwal, M., Gnanarajan, G. & Kothiyal, P., 2014. Floating drug delivery system: A novel approach. *J the Pharma Innov,* 3(3), pp. 57-69.
Katakam, V., Reddy, S., Panakanti, P. & Yamsani, M., 2013. Design and evaluation of a novel gas formation-based multiple-unit gastro-retentive floating drug delivery system for quetiapine fumarate. *Tropical J Pharm Res,* 13(2), pp. 33-46.
Kavanagh, N. & Corrigan, O. I., 2004. Swelling and erosion properties of hydroxypropylmethylcellulose (hypromellose) matrices—influence of agitation rate and dissolution medium composition. *International Journal of Pharmaceutics,* 1-2(279), pp. 141-152.
Kharia AA., Hiremath SN., Singhai AK., Omray, Jain LK., 2010. Design and optimization of floating drug delivery system of acyclovir. *Indian J Pharm Sci.,* 75(11), pp. 599–606.
Klausner, E. A., Lavy, E., Friedman, M. & Hoffman, A., 2003. Review: Expandable gastroretentive dosage forms. *J Cont Rel,* 90, pp. 143-162.
Kaur, B., Sharma, S., Sharma, G., Saini, R., Singh, S., Nagpal, M., Jain, UK., Sharma, M., 2013. A review of floating drug delivery system. *Asian J Biomed & Pharm Sci,* 3(24), pp. 1-6.

Koda-Kimble, M. A. et al., 2007. Theophylline. In: *Handbook of Applied Therapeutics.* 8th ed. s.l.:Lippincott Williams & Wilkins, Sections: 22.5, 23.13, 92.13, and 92.8.

Koester, M. & Thommes, M., 2010. New insights into the pelletization mechanism by extrusion/spheronization. *AAPS PharmSciTech,* 11(4).

Kong, Y. & Hay, J., 2003. The enthalpy of fusion and degree of crystallinity of polymers as measured by DSC. *Euro Polym J,* 39(8), pp. 1721-1727.

Korakianiti, E. S., Rekkas, D. M., Dallas, P. P. & Choulis, N. H., 2000. Optimization of the pelletization process in a fluid-bed rotor granulator using experimental design. *AAPS Pharm Sci Tech,* 1(4), pp. 71-75.

Kozloski, GD., De Vito, JM., Johnson, JB., Holmes, GB., Adams, MA., Hunt, TL., 1992. Bioequivalence of verapamil hydrochloride extended-release pellet-filled capsules when opened and sprinkled on food and when swallowed intact. *Clin Pharm.,* 11(6), pp. 539-542.

Krögel, I. & Bodmeier, R., 1999. Floating or pulsatile drug delivery systems based on coated effervescent cores. *Int J Pharm.,* 187(2), pp. 175-184.

Kumaran, K. S., Manjunath, S. Y. & Wamorkar, V. V., 2010. Development of a floating multiple unit controlled-release system for mosapride. *Asian J Pharmaceutics,* 4(2), pp. 163-167.

Kumaran, K. S., Manjunath, S. Y. & Wamorkar, V. V., 2010. Development of a floating multiple unit controlled-release system for mosapride. *Asian J Pharmaceutics,* 4(2), pp. 163-167.

Kumar, A., Tiwari, B. K. & Kant, R., 2017. A Study on Formulation of Multiparticulate GastroRetentive Drug Delivery System of Curcumin. *Int. J. Life. Sci. Scienti. Res.,* 3(2), pp. 909-913.

Kumari, M. H., Samatha, K., Balaji, A. & Shankar, M. U., 2013. Recent novel advancements in pellet formulation: A review. *Inter J Pharm Sci & Res,* 4(10), pp. 3803-3822.

LFA, 2017. *LFA Tablet Presses.* [Online] Available at:https://www.lfatabletpresses.com/ [Accessed 21 11 2017].

Lightfoot, D., 2000. *Capsule Filling, answers to 10 common questions about capsule filling.* [Online] Available at: http://www.capsugel.com/media/library/answers-to-10-common-questions-about-capsule-filling.pdf [Accessed 18 02 2015].

Lingam, M., Ashok, T., Venkateswarlu, V. & Raw, Y. M., 2008. Design and evaluation of novel matrix type multiple units as biphasic gastroretentive drug delivery systems. *AAPS Pharm Sci Tech,* 9(4), pp. 1253-1261.
Li, Zhao; Xu, Heming; Li, Shujuan; Li, Qijun; Zhang, Wenji; Ye, Tiantian; Yang, Xinggang; Pan, Weisan Lin, A., Muhammad, N. & Pope, D., 2001. Study of crystallization of endogenous surfactant in Eudragit NE30D-free films and its influence on drug-release properties of controlled-release diphenhydramine HCl pellets coated with Eudragit NE30D. *AAPS Pharmsci,* 3(2).
Loftsson, T., 2015. Basic concepts of pharmacokinetics. In: *Essential Pharmacokinetics.* London, pp. 30-76.
Loftsson, T., 2015. Physicochemical properties and pharmacokinetics. In: *Essential Pharmacokinetics.* London, pp. 85-93.
Lopes, CM., Bettencourt, C., Rossi, A., Francesca, B., Barata, P., 2016. Review: Overview on gastroretentive drug delivery systems for improving drug bioavailability. *Inter J Pharm,* 510, pp. 144–158.
Low, C. & Chaw, C., 2012. *Ibuprofen loaded Avicel CL611 pellets: effect of liquid binder.* Sunderland.
Malode, V. N., Paradkar, A. & Devarajan, P. V., 2015. Controlled release floating multiparticulates of metoprolol succinate by hot melt extrusion. *Inter J Pharm,* 491, pp. 345-351.
Mandal, U. K., Chatterjee, B. & Senjoti, F. G., 2016. Review: Gastro-retentive drug delivery systems and their in vivo success: A recent update. *Asian j pharm sci,* 11, pp. 575–584.
Mathur, P., Saroha, K., Syan, N., Verma, S., Nanda, S., 2011. An overview on recent advancements and developments in gastroretentive buoyant drug delivery system. *Der Pharmacia Sinica,* 2(1), pp. 161-169.
Mayur, C., Senthilkumaran & Hemant, G., 2012. Review article: Super porous hydrogels: A recent advancement in gastroretentive drug delivery system. *Indonesian J. Pharm.,* 24(1), pp. 1-13.
Mazurek-Wadołkowska, E., Winnicka, K., Czajkowska-Kośnik, A., Czyzewska, U., Miltyk, W., 2013. Application of differential scanning calorimetry in evaluation of solid state interactions in tablets containing acetaminophen. *Acta Pol Pharm.,* 70(5), pp. 787-93.

McConnell, E. L. & Basit, A. W., 2013. Modified-Release Oral Drug Delivery. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, the Design and Manufacture of Medicine.* 4th ed. London: Churchill Livingstone Elsevier, pp. 550-565.

Meenakshi, B., Santosh, K. & Annapurna, O., 2014. Floating drug delivery system: A review. *J Drug Delev & Therap,* 4(2), pp. 130-134.

Mehta, K. A., Rekhi, G. S. & Parikh, D. M., 2005. Extrusion/Spheronization as a Granulation Technique. In: D. M. Parikh, ed. *Handbook of Pharmaceutical Granulation Technology.* 2nd ed. Research Triangle Park: Taylor and Francis, pp. 330, 340, and 348.

Mettler-Toledo, 2017. *UserCom: Interpreting DSC curves, Part 1: Dynamic Measurements.* [Online] Available at: http://www.masontechnology.ie/x/Usercom_11.pdf [Accessed 19 12 2017].

MedLinePlus, 2017. *Theophylline.* [Online] Available at: https://medlineplus.gov/druginfo/meds/a681006.html [Accessed 6 2017].

Minitab, 2017. *Factorial and fractional factorial designs.* [Online] Available at: https://support.minitab.com/en-us/minitab/18/help-and-how-to/modeling-statistics/doe/supporting-topics/factorial-and-screening-designs/factorial-and-fractional-factorial-designs/ [Accessed 22 11 2017].

Montgomery, D., 2013. Introduction. In: *Design and Analysis.* 8th ed. London: John Wiley & Sons, Inc, pp. 21-22.

Mukesh, K., Shubhendra, J., Kumar, SS., Kumar, MA., Bhagat, S., 2012. Review article: floating drug delivery system: An innovative approach. *J Drug Deliv & Therap,* 2(6), pp. 117-123.

Muley, S., Nandgude, T. & Poddar, S., 2016. Extrusion–spheronization, a promising pelletization technique: In-depth review. *Asian j pharm sci,* 11, pp. 684–699.

Mura, P., Maestrelli, F., Cirri, M., Rodríguez, MLG., Alvarez, AMR., 2003. Development of enteric-coated pectin-based matrix tablets for colonic delivery of theophylline. *J Drug Targ,* 11(6), pp. 365-371.

Murdan, S., 2013. Solutions. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, the Design and Manufacture of Medicines.* London: Churchill Livingstone Elsevier, pp. 24.

Murphy, C., Pillay, V., Choonara, YE., Toit, Lisa CD., Ndesendo, VMK.; Chirwa, N., Kumar, P., 2012. Optimization of a Dual Mechanism

Gastrofloatable and Gastroadhesive Delivery System for Narrow Absorption Window Drugs. *AAPS Pharm Sci Tech,* 13(1), pp. 1-14.
Mustafa, O. & Chaw, C. S., 2016. Silicified microcrystalline cellulose based pellets and their physicochemical properties. *J of Appl Polym Sci,* pp. 1-9.
Nadigoti, J., Dharani, S., Shayeda & Yamsani, M. R., 2011. Formulation and evaluation of floating microparticles of metoprolol succinate. *Asian J of Pharm. & Clin. Res.,* 4.
Narang, N., 2011. An updated review on: Floating drug delivery system (FDDS). *Int J App Pharm,* 3(1), pp. 1-7.
Nokhodchi, A., Aliakbar, R., Desai, S. & Javadzadeh, Y., 2010. Liquisolid compacts: the effect of cosolvent and HPMC on theophylline release. *Colloids and Surfaces B: Biointerfaces,* 79(1), pp. 262-269.
Nordström, J., Lazorova, A. P. L., Frenning, G. & Alderborn, G., 2013. The degree of compression of spherical granular solids controls the evolution of microstructure and bond probability during compaction. International Journal of Pharmaceutics, 442(1-2), pp. 3-12.
Omidian, H. & Park, K., 2010. Oral Targeted Drug Delivery Systems, Gastric Retention Devices. In: *Oral Controlled Release Formulation Design and Drug Delivery, Theory to Practice.* 2 ed. New Jersey, Canada: John Wiley & Sons, pp. 187.
Padfield, J. M., 1989. Assessment of gastrointestinal transit and drug absorption. In: *Novel Drug Delivery and its Therapeutic Applications.* Chichester, England: John Wiley & Sons Ltd, pp. 89-101.
Padfield, J. M., 1989. Therapeutic status of controlled oral drug delivery. In: *Novel Drug Delivery and its Therapeutic Applications.* Chichester, England: John Wiley & Sons Ltd, pp. 177-183.
Pagariya, T. & Patil, S., 2013. Development and optimization of multiparticulate drug delivery system of alfuzosin hydrochloride. *J Colloids Surf B Biointerfaces,* 102(1), pp. 171-177.
Pandey, A., Kumar, G., Kothiyal, P. & Barshiliya, Y., 2012. A Review on current approaches in gastro retentive drug delivery system. *Asian J Pharmacy and Medic Sci,* 2(4), pp. 60-77.
Pant, S., badola, A. & kothiyal, P., 2016. A review on gastroretentive drug delivery system. *Inter J Res & Dev in Pharmacy and Life Sci,* 5(4), pp. 2178-2187.

Patil, J. M., Hirlekar, R. S., Gide, P. S. & Kadam, V. J., 2006. Trends in floating drug delivery systems. *J Sci & Ind Res,* 65, pp. 11-21.
Patil, K. K. & Saptarshi, D., 2013. A Review on Floating Drug Delivery System. *Int J Pharm Sci Rev Res,* 21(1), pp. 276-283.
Pawar, VK., Kansal, S., Garg, G., Awasthi, R., Singodia, D., Kulkarni, GT., 2011. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. *J Drug Deliv,* 18(2), pp. 97-110.
Politis, S. N. & Rekkas, D. M., 2011. Recent patents on drug delivery & formulation. *Pelletization processes for pharmaceutical applications: A patent review,* 5, pp. 61-78.
Pejchal, V., Žagar, G., Charvet, R., Dénéréaz, C., Mortensen, A., 2017. Compression testing spherical particles for strength: Theory of the meridian crack test and implementation for microscopic fused quartz. *J Mechanics and Physics of Solids,* 99, pp. 70-92.
Pooja, S., Shiv, G. & Monika, M., 2015. Recent advancement in floating drug delivery system and current approaches. *World J Pharmacy and Pharm Sci,* 4(3), pp. 317-341.
Popova, T., Dimitrov, M. & Lambov, N., 2016. Short Paper: *Ethanol as potential tool for extending the release rate of theophtlline from ethylcellulose-containing pellets, prepared by extrusion/spheronisation.* Glasgow, The 10th World Meeting on Pharmaceutics, Biopharmaceutics, and Pharmaceutical Technology.
Porter, S. C., 2013. Coating of tablets and multiparticulates. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, The Design and Manufacture of Medicines.* London: Churchill Livingstone Elsevier, pp. 578-581.
Prajapati, V. D., Jani, G. K., Khutliwala, T. A. & Zala, B. S., 2013. Raft forming system—An upcoming approach of gastroretentive drug delivery system. *J Cont Rel,* 168, pp. 151–165.
Prasad, MB., Vidyadhara, S., Sasidhar, RLC., Balakrishna, T., Trilochani, P., 2013. Development and evaluation of diltiazem hydrochloride controlled-release pellets by fluid bed coating process.. *J Adv Pharm Tech Res. ,* 4(2), pp. 101-107.

Prescott, L. F. & Nimmo, W. S., 1979. Important Formulation Factors Influencing Drug Absorption. In: *Drug Absorption, Proceedings of Edinburgh Inernational Conference.* Edinbbugh : MTP Press Ltd, pp. 133-143.

Puah, S. Y., Yap, H. N. & Chaw, C. S., 2013. Production and characterization of pellets using Avicel CL611 as spheronization aid. *J Drug Dev & Ind Pharmacy,* pp. 1-7.

PubChem, 2019. *Theophylline,* PubChem, Open Chemistry Database. .[Online] Available at: https://pubchem.ncbi.nlm.nih.gov/compound/theophylline [Accessed 08 04 2019].

Pugh, W. J., 2013. Kinetics. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, The Design and Manufacture of Medicines.* 4th ed. London: Churchill Livingstone Elsevier, pp. 119 and 115-125.

Qi, X., Jiang, Y., Zhang, H. & Wu, Z., 2015. Tablets compressed with gastric floating pellets coated with acrylic resin for gastro retention and sustained release of famotidine; in-vitro and in-vivo study. *J of Pharm & Pharm,* 67, pp. 493-500.

Reddy, S., Das, P., Das, H. & Ghosh, A., 2011. MUPS (multiple unit pellets systems) tablets- a brief review. *J. pharm. and Biomed. Sci. (JPBMS),* 12(2), pp. 1-5.

Rewar, S. & Shakya, V., 2015. Article review: a novel approach for floating drug delivery system. *J Glob Trends in Pharm Sci,* 6(1), pp. 2417-2422.

Rizvia, S. A. & Saleh, A. M., 2018. Applications of nanoparticle systems in drug delivery technology. *Saudi Pharm J.,* 26(1), pp. 64-70.

Rowe, R., 1985. Spheronization: a novel pill-making process?. *Int J Pharm,* 6, pp. 119-123.

Rowe, R., Sheskey, P. & Quinn, M., 2009. Crospovidone. In: *Handbook of Pharmaceutical Excipients*. 6th ed London: Pharmaceutical Press, pp. 208.

Sakr, W. F., Ibrahim, M. A., Alanazi, F. K. & Sakr, A. A., 2012. Upgrading wet granulation monitoring from hand squeeze test to mixing torque rheometry. *Saudi Pharm J,* 20, pp. 9-19.

Sarawade, A., Ratnaparkhi, M. P. & Chaudhari, S., 2014. Review article: Floating drug delivery system: An overview. *Inter J Res & Dev in Pharmacy and Life Sci,* 3(5), pp. 1106-1115.

Sarkar, S., Wong, T. W. & Liew, C. V., 2013. Importance of wet packability of component particles in pellet formation. *AAPS Pharm Sci Tech,* 14(3), pp. 1267-1277.

Sauer, D., Cerea, M., DiNunzio, J. & McGinity, J., 2013. Dry powder coating of pharmaceuticals: A review. *Inter J Pharm,* 457, pp. 488-502.

Sawicki, W. & Łunio, R., 2005. Note: Compressibility of floating pellets with verapamil hydrochloride coated with dispersion Kollicoat SR 30 D. *Euro J Pharm & Biopharm,* 60, pp. 153–158.

Schlindwein, W. S. & Gibson, M., 2018. *Pharmaceutical Quality by Design, A Practical Approach.* A Preface. 1st ed. Chichester: Wiley and Sons Ltd.

Setthacheewakul, S., Kedjinda, W., Maneenuan, D. & Wiwattanapatapee, R., 2011. Controlled release of oral tetrahydrocurcumin from a novel self-emulsifying floating drug delivery system (SEFDDS). *AAPS Pharm Sci Tech,* 12(1), pp. 152-164.

Shaha, S. H., Patel, J. K., Pundarikakshudu, K. & Patel, N. V., 2009. An overview of a gastro-retentive floating drug delivery system. *Asian J Pharm Sci,* 4(1), pp. 65-80.

Shargel, L., Wu-Pong, S. & Yu, A. B., 2012. Modified-Release Drug Products. In: *Applied Biopharmaceutics and Pharmacokinetics.* 6th ed. London: McGraw Hill, pp. 469-501.

Shargel, L., Wu-Pong, S. & Yu, A. B., 2012. Application of Pharmacokinetics to Clinical Situations, Effect of Food in Drug Disposition. In: *Applied Biopharmaceutics and Pharmacokinetics.* 6th ed. London: McGraw Hill, pp. 597.

Shipway, P. & Hutchings, I., 1993. Attrition of brittle spheres by fracture under compression and impact loading. *J Powder Tech,* 76, pp. 23-30.

Sigma-Aldrich, 2018. (Hydroxypropyl) methyl cellulose. [Online] Available at: https://www.sigmaaldrich.com/catalog/product/sigma/h9262?lang=en&region $ =GB [Accessed 05 06 2018].

Sigma-Aldrich, 2018. Sodium bicarbonate. [Online] Available at: https://www.sigmaaldrich.com/catalog/substance/sodiumbicarbonate8401144 $ 55811?lang=en&region=GB [Accessed 05 06 2018].

Singh, B. & Kim, K., 2000. Review: floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J of Cont. Rel.,* 63(3), pp. 235–259.

Sinko, P. J., 2017. Drug delivery systems and drug product design. In: 7th, ed. *Martin's Physical Pharmacy and Pharmaceutical Sciences.* Wolters Kluwer, pp. 646-647.
Siraj, S., Khurshid, M. & Nazim, S., 2013. Various perspectives of gastroretentive drug delivery system: A review. *Ameri J Adv Drug Deliv,* 1(4), pp. 443-451.
Slavkova, M., Petrovick, G., Breitkreutz, J. & Dimitrov, M., 2016. *Systemic investigation of the shape evaluation results of solid lipid pellets with diverse composition employing two different characterization methods..* [Online] Available at: https://blog.caleva.com/systematic-investigation-of-the-shape-evaluation-results-of-solid-lipid-pellets-with-diverse-composition-employing-two-different-characterization-methods [Accessed 05 04 2019].
Smith, I. et al., 2016. *Aston Particle Technologies.* [Online] Available at: http://www.astonparticletechnologies.com/ [Accessed 2017].
Solanki, D., Patidar, S., Motiwale, M. & Kushwah, L., 2017. Floating Drug Delivery System – Novel Tool for Delivering H2 Antagonist. *Int J Pharmacy and Pharm Res,* 8(2), pp. 118-133.
Srivastava, S. & Mishra, G., 2010. Review article: fluid bed technology: overview and parameters for process selection. *Inter J Pharm Sci & Drug Res,* 2(4), pp. 236-246.
Staib, AH., Loew, D., Harder, S., Graul, EH., Pfab, R., 1986. Measurement of theophylline absorption from different regions of the gastro-intestinal tract using a remote controlled drug delivery device. *Eur J Clin Pharmacol. ,* 30(6), pp. 691-697.
Streubel, A., Siepmann, J. & Bodmeier, R., 2003. Multiple unit gastroretentive drug delivery systems: a new preparation method for low density microparticles. *J Microencapsul.,* 20(3), pp. 329-347.
Streubel, A., Siepmann, J. & Bodmeier, R., 2006. Drug delivery to the upper small intestine window using gastroretentive technologies. *Cur Opin Pharmacol J,* 6, pp. 501-608.
Strübing, S., Metz, H. & Mäder, K., 2008. Characterization of poly(vinyl acetate) based floating matrix tablets. *J Cont Rel,* 126, pp. 149-155.
Sungthongjeen, S., Paeratakul, O., Limmatvapirat, S. & Puttipipatkhachorn, S., 2006. Preparation and in vitro evaluation of a multiple-unit floating drug

delivery system based on gas formation technique. *Int J Pharm. ,* 324(2), pp. 136-143.
Sungthongjeen, S., Sriamornsak, P. & Puttipipatkhachorn, S., 2008. Design and evaluation of floating multi-layer coated tablets based on gas formation. *Euro J Pharm & Biopharm,* 69, pp. 255-263.
TA-Instruments, 2009. *TA Instruments Inc. Indium.* [Online]
Available at: http://www.tainstruments.com/pdf/indium.pdf
[Accessed 16 01 2018]. Wagner, K. G., 2015. *BioPharma., Webinar on MUPS tablets* [Online] Available at: https://biopharma-asia.com/webinars/compression-film-coated-pellets-key-parameters-optimal-tablet-quality/ [Accessed 11 9 2017].
Talukder, R. & Fassihi, R., 2004. Gastroretentive delivery systems: hollow beads. *Drug Dev Ind Pharm.,* 30(4), pp. 405-412.
Tan, X. & Hu, J., 2015. Investigation for the quality factors on the tablets containing medicated pellets review. *Saudi Pharm J,* pp. 1-8.
Taylor, K., 2018. Particle size analysis. In M. E. Aulton, & K. M. Taylor eds., *Aulton's Pharmaceutics, The Design and Manufacture of Medicines*. 5th ed. London: Churchill Livingstone Elsevier, pp. 143.
Taylor, L. S. & Shamblin, S. L., 2009. Polymorphism in Pharmaceutical Solids. In: H. G. Brittain, ed. *Amorphous Solids.* 2nd ed. London: Informa Healthcare, pp. 615.
Thakral, S., Thakral, N. K., & Majumdar, D. K. (2013). Eudragit®: a technology evaluation,. *J of Expert Opinion on Drug Delivery , 10*(1), pp. 131-149.
Thomas, S., Chong, Y. N. & Chaw, C. S., 2012. Preparation and characterization of enteric microparticles by coacervation. *Drug Dev & Ind Pharmacy,* pp. 1-10.
Thummel, K. E., 2007. Gut instincts: CYP3A4 and intestinal drug metabolism Kenneth E. Thummel. *J Clin Invest.,* 117(11), pp. 3173–3176.
Timmermans, J. & Moes, A. J., 1990. How well do floating dosage forms float?. *Int. J. Pharm.,* 62, pp. 207-216.
Tongkai, C., Jian, L., Ting, C., Changquan, CS., Ying, Z., 2017. Tablets of multi-unit pellet system for controlled drug delivery. *J Cont Rel,* 262, pp. 222– $ 231.

Treesinchai, S., Puttipipatkhachorn, S., Pitaksuteepong, T. & Sungthongjeen., S., 2016. *Development of curcumin floating tablets based on low density foam powder..* [Online] Available at: https://www.researchgate.net/profile/Tasana_Pitaksuteepong/publication/284798178_Development_of_curcumin_floating_tablets_based_on_low_density_foam_powder/links/56b17b0408ae56d7b06a1490/Development-of-curcumin-floating-tablets-based-on-low-density-foam-po [Accessed 04 05 2019].

Tripathi, J., Thapa, P., Maharjan, R. & Jeong, S. H., 2019. Review: Current State and Future Perspectives on Gastroretentive Drug Delivery Systems. Pharmaceutics, 193, pp. 11.

USP25, U. S. P., 2002. *Theophylline/ Official Monographs.*

Vidyadhara, S., Sasidhar, RL., Balakrishna, T., Balaji, B., Amrutha, R., 2015. Formulation and Evaluation of Controlled Release Floating Microballoons of Stavudine. *Scientia Pharmaceutica J,* 83, pp. 671-682.

Vladyka, R. S., Erkoboni, D. F. & Sweriduk, C. A., 2005. *microcrystalline cellulose cushioning granules.* US, Patent No. US 6,858,725 B1.

Vo, AQ., Feng, X., Morott, JT., Pimparade, MB., Tiwari, RV., Zhang, F., Repka, MA., 2016. A novel floating controlled release drug delivery system prepared by hot-melt extrusion. *Euro J Pharm & Biopharm,* 98, pp. 108-121.

Vo, AQ., Feng, X., Pimparade, M., Ye, X., Kim, DW., Martin, ST., Repka, MA., 2017. Dual-mechanism gastroretentive drug delivery system loaded with an amorphous solid dispersion prepared by hot-melt extrusion. *Euro J Pharm Sci,* 102, pp. 71–84.

Wang, J., Kan, S., Chen, T. & Liu, J., 2015. Application of quality by design (QbD) to formulation and processing of naproxen pellets by extrusion– spheronization. *J Pharm Dev & Tech,* 20(2), pp. 246-256.

Waterman, K., 2007. A critical review of gastric retentive controlled drug delivery. *J Pharm Dev Technol.,* 12(1), pp. 1-10.

Weiss, M., Kriangkrai, W. & Sungthongjeen, S., 2014. An empirical model for dissolution profile and its application to floating. *Euro J Pharm Sci,* 56, pp. 87-91.

Weston, JS., Jentoft, RE., Grady, BP., Resasco, DE., Harwell, JH., 2015. Silica nanoparticle wettability: Characterization and effects on the emulsion properties. *Ind Eng Chem Res,* 54(16), pp. 4274–4284.

Wu, C. & Benet, L., 2005. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. *Pharm Res.,* 22(1), pp. 11-23.

Xu, M., Liew, C. V. & Heng, P. W., 2015. Evaluation of the coat quality of sustained release pellets by individual pellet dissolution methodology. *Inter J Pharm,* 478, pp. 318-327.

Yang, L., Eshraghi, J. & Fassihi, R., 1990. A new intragastric delivery system for the treatment of Helicobacter pylori associated gastric ulcer: in vitro evaluation. *J Cont Rel,* 57(3), pp. 215-222.

York, P., 2013. Design of Dosage Forms. In: M. E. Aulton & K. M. G. Taylor, eds. *Aulton's Pharmaceutics, The Design and Manufacture of Medicines.* 4th ed. London: Churchill Livingstone Elsevier, pp. 10-11.

Yu, S., Huang, Z., Gabbott, I., El-Saleh, F., Muehlenfeld, C., Warnke, G., Stoyanov, E., de-Matas, M., Salman, AD., 2016. Short Paper: *Experimental study of binder selection using twin screw and batch high-shear wet granulation.* Glasgow, The 10th World Meeting on Pharmaceutics, Biopharmaceutics, and Pharmaceutical Technology**.**

Zeeshan, F. & Bukhari, N., 2010. Development and evaluation of a novel modified-release pellet-based tablet system for the delivery of loratidine and pseudoephedrine hydrochloride as model drugs. *AAPS PharmSciTech,* 11(2), pp. 910-916.

Zhang, C., Xu, M., Tao, X., Tang, J., Liu, Z., Zhang, Y., Lin, X., He, H., Tang, X., 2012. A floating multiparticulate system for ofloxacin based on a multilayer structure: In vitro and in vivo evaluation. 430, pp. 141-150.

Zhang, J., Wu, C.-Y., Pan, X. & Wu, C., 2017. On Identification of Critical Material Attributes for Compression Behaviour of Pharmaceutical Diluent Powders.. *J of Materials ,* 10(7), pp. 1-16.

Zhang, L., Jiang, P. & Liu, J., 2014. Novel sustained-release of propafenone through pellets: preparation and in vitro/ in vivo evaluation. *Int J Mol Sci.,* 15(9), p. 15503–15511.

Zhang, L. & Mao, S., 2017. Review: Application of quality by design in the current drug development. *Asian J pharm sci,* 12, pp. 1-8.