Influence of calcium carbonate and sodium carbonate gassing agents on pentoxifylline floating tablets properties

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Abstract

Purpose: this study was to design and evaluate effervescent floating tablets with sustained release behaviour. Pentoxifylline is a water-soluble model drug with a short half-life, consequently developing sustained release preparations would be beneficial. **Methods**: a binary (1:1) mixture of sodium alginate and hydroxyethyl cellulose containing pentoxifylline, with either 10% or 20% calcium carbonate or sodium carbonate, was used to prepare floating tablets. **Results**: tablets floated on the surface of the dissolution medium, showed an adequate floating lag time, and floated for more than 12 hours. Tablets manufactured from granules with 20%(w/w) calcium carbonate were promising with respect to their floating lag time (~7min), floating duration (>24 hours), sustained drug release rate, and swelling ability. An *in vivo* study of these promising tablets and a reference solution of pentoxifylline were investigated following oral administration of 5.75±0.15mg in rats. Compared with the reference solution, the pharmacokinetic parameters changed significantly (p<0.05); the C_{max} of the tablets was decreased (945.32ng/ml versus 2552.30ng/ml for the solution), while the T_{max} and $t_{1/2}$ were prolonged. **Conclusion**: the study shows that a binary mixture of hydroxyethyl cellulose and sodium alginate, together with 20%(w/w) calcium carbonate, offers an exciting opportunity to develop sustained release pentoxifylline preparations.

Key words:

Pentoxifylline, floating tablets, hydroxyethyl cellulose, sodium alginate, calcium carbonate

Introduction

Gastroretentive drug delivery systems provide dosage forms with prolonged residence time in the stomach and sustained release behaviour, which can improve bioavailability and acting locally on the stomach.[1,2] Increasing gastric residence time can be achieved either by floating,[3] high density,[4] bioadhesive,[5] or expandable systems.[6] Floating drug delivery systems are designed to have a density lower than that of the gastric fluid, hence they can float for a prolonged period of time without affecting the gastric emptying rate.[7,8] Floating drug delivery systems are classified as either effervescent systems or non-effervescent systems. Non-effervescent floating drug delivery systems are based mainly on gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers, such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.[9] However, effervescent floating drug delivery systems are based on effervescent components that generate carbon dioxide gas due to the presence of acidic gastric fluid. The generated gas bubbles are entrapped in a gel layer formed by hydrocolloids that produce an upward motion of the dosage form and maintains its buoyancy.[10]

Effervescent floating drug delivery systems have been successfully prepared as multi-particulate dosage forms, such as beads,[11] microballoons,[12] and microspheres,[13] or as single unit dosage forms, like tablets and capsules. Floating tablets can be prepared as single or double layered dosage forms. In single layer tablets, carbon dioxide generating agents are mixed within the tablet matrix;[14-16] however, double layered floating tablets can be prepared whereby gassing agents are mixed with hydrocolloid and pressed in a separate layer compared to that controlling drug release.[9] Floating capsules have been shown to float as a result of the generation of carbon dioxide that is trapped in the hydrating gel network upon contact with the acidic medium.[17,18] Inclusion of carbonate gassing agents can provide an alkaline microenvironment for a polymer to initiate gel formation[6]. In addition, liberation of carbon dioxide can accelerate hydration of a polymer, which is essential for formation of a bioadhesive hydrogel that can assist the remaining of the dosage form inside the stomach.[19]

Carbonate gassing agents have been previously used to enhance tablets floating behaviour, such as sodium bicarbonate[20] (mainly used in floating tablet formulations) and calcium carbonate.[21] Although sodium carbonate decomposes upon contact with acids in the presence

of water to produce carbon dioxide and effervescence,[22] there is a lack of information about its usage in this field of research.

The aim of this study was to develop and evaluate a swellable, floatable, gastroretentive drug delivery system utilising an effervesce mechanism. Tablets were based on a binary (1:1) gel-forming polymer mixture of hydroxyethyl cellulose and sodium alginate, and calcium carbonate or sodium carbonate gas generating agents. Pentoxifylline was used as a model drug since it has a short half-life of 1–2 hours,[23] high density,[24] and is highly soluble in water (191 mg/mL at 37°C).[25] The variables that may affect drug release and floating properties were investigated, such as wet granulation (to compare effects of powders versus those of granules), type and the ratio of gas-forming agent.

Materials and Methods

Materials

Calcium carbonate, sodium carbonate, sodium alginate (15–20 cP), and pentoxifylline were supplied by Sigma-Aldrich (UK), silicified microcrystalline cellulose (Prosolv® 90) was obtained from JRS Pharma (Germany), and magnesium stearate was supplied by MEDEX (UK). Emitrecitabine, ammonia, formic acid, methanol, and ACE 5 C18 columns were supplied by the Jordan Centre for Pharmaceutical Research (Jordan). Hydroxyethyl cellulose (Natrosol 250-HHX) was generously provided by Ashland (USA).

Powders and granules containing the pentoxifylline preparation

Powder mixture compositions for the preparation of tablets are shown in Table 1. Powder blends were prepared using a binary (1:1) mixture of hydroxyethyl cellulose and sodium alginate gel forming agents. Prosolv® 90 was used as a filler to enhance the compression process, calcium carbonate or sodium carbonate was added as a gas-forming agent at 0%, 10% or 20% (w/w) concentration, and pentoxifylline was used as a model drug. All ingredients were passed through 180 µm sieve before mixing; sodium alginate was passed through a 350 µm sieve, a size suitable for tablet compression. Pentoxifylline was formulated as floating tablets in a previous research by same authors[20], however a different gassing agent (sodium bicarbonate) was used in the previous study[20].

Table 1 Composition of prepared tablets

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

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

A turbula mixer (Glen Creston Ltd, UK) set at 60 rpm, with a stainless steel mixing vessel, was used to mix the powders for 10 minute. A wet granulation process was used to modify powder flowability and to facilitate automatic compression of the powder; powder mixtures were wetted with 0.5% w/w of water and mixed for 10 minutes using a Kenwood ChefKneader (Thorn Domestic Appliances Ltd, UK) before being manually passed via a 1,000 µm sieve. Prepared granules were dried at 60°C overnight using a drying oven (SciQuio Ltd, UK),[26] and then dried granules ≤853 µm were used.

Preparation of floating tablets

To evaluate the effect of gassing agent concentrations on tablet porosity, floating capacity, swelling, erosion and dissolution behaviours, pentoxifylline tablets were automatically pressed (for granulated powders) using a single-punch tableting machine (Type 3, Manesty Machines Ltd, UK) equipped with flat-faced punches (9.60 mm), and the compression speed was 85 RPM. The compaction pressure (Table 3) was adjusted by decreasing the distance between punches to produce tablets with a hardness level of 49–54 N, as measured using a hardness tester (Model 2E/205, Schleuniger & Co., Switzerland). All the tablets resulting from the F1, F2, F4, and F5 formulations were successfully pressed automatically. However, the F3 formulation could not be pressed automatically at the required hardness level (49–54 N), hence these were pressed manually; the required granule weight was fed directly from the hopper into the die of the single-punch tableting machine and compacted manually.

In order to compare between tablets before and after granulation, in other words to investigate the possible effect of the wet granulation process on tablet porosity, floating capacity and dissolution behaviour, a group of manually pressed tablets were prepared from

powder blends before granulation, where the required powder mixture was weighed and fed manually into the die of the single-punch tableting machine to produce the desired tablets.

Evaluation of the formulated powders and granules:

Flowability test

The tapping apparatus (Copley JV1000, UK) was used. Bulk and tapped densities were calculated as the ratio of the powder weight to the related powder volume, and Carr's compressibility index (CI) was calculated using equation (1):[27]

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

Characterisation of floating tablets

Tablets originally prepared from granules were evaluated for tablet friability, hardness, weight uniformity, porosity, drug content uniformity, floating capacity, swelling and erosion, and dissolution. Tablets prepared from powder mixtures were evaluated only for porosity, floating capacity, and dissolution, as these tablets had been compacted manually. Tablet quality control tests were conducted in accordance with the British Pharmacopoeia (BP) specifications.[28]

Tablet apparent density, tensile fracture strength and porosity

Tablet thickness (t) and diameter (D) were recorded using a calliper scale (Moore and Wright Sheffield England Metric, UK). Tablet hardness (P), weight (w), and the circular constant (π) were used to calculate the apparent density (A_d) of the tablets by equation (2)[18] and Tablet tensile fracture strength (σ_t) by equation (3)[29]

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

$$\sigma_t = \frac{2P}{\pi D t} \qquad \text{(Eq. 3)}$$

Mean values ± SD are presented.

Tablet porosity ε, was calculated using equation (4):[30]

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

Where ρ_{tablet} is the tablet's apparent density and ρ_{true} is the true density of the powder mixture or granule sample measured using a multipycnometer (MVP-D160-E, Quantachrome Instruments, USA). A sample of 1.8 g was used, the helium pressure was set to 17 psi, and the difference in helium pressure before and after sample loading was recorded to determine the true volume of the samples. Mean of five replicates ± SD was presented.

In vitro drug release test

Drug release was performed using USP dissolution apparatus II (Erweka GmbH, Germany) at 37°C±0.5°C, and a paddle speed of 50 rpm.[28] Tablets were inserted into 900 mL 0.1 M HCl (pH 1.2) as a simulated gastric fluid without the presence of gastric enzymes. The test was accomplished in triplicate and mean values ± SD are presented.

Tablet floating capacity

Floating capacity was investigated under the same conditions and using the same apparatus as for the *in vitro* studies. The time taken for tablets to show up and remain on the dissolution medium surface (floating lag time) and the period of time that the tablets constantly floated on the dissolution medium surface (floating duration) were determined visually throughout the drug release studies,[15] and mean ± SD values are presented.

Swelling and erosion studies

The initial weights of three randomly chosen tablets were recorded. Dissolution medium uptake (DMU) and mass loss (ML) percentage of the tablets were determined using USP Dissolution Apparatus II (Erweka GmbH, Germany) under similar conditions to the drug release study. Tablets were withdrawn using a spoon spatula from the medium at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours. Excess liquid present on the surface of tablets was carefully removed using a filter paper and the tablets were weighed and then dried at 60°C in a drying oven until a constant dry weight was achieved. Swelling rate and mass loss rate were calculated by equations (5) and (6):[31]

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

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

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

In vivo pharmacokinetic study

Twelve male albino rats weighing 180 ± 20 g were provided by Applied Science Private University. The animals were kept in the animal house at an ambient temperature (25 ± 1 °C) with a 12 h dark and 12 h light cycle. The animals were fed a pellet diet and had access to water *ad libitum*. The experimental protocol was approved by the Research Ethics Committee (Sunderland University), and all methods were conducted according to the University of Applied Science Private University guidelines.

Pentoxifylline tablets (weighing 30±1 mg) of F2 formulation were pressed manually (for granulated powders) using a single-punch tableting machine (Type 3, Manesty Machines Ltd, UK) equipped with flat-faced punches (4.00 mm), and the compression force was adjusted to produce tablets with a hardness level of 20 ± 1 N. An aqueous solution of pentoxifylline (2.88 mg/ml) was prepared as a reference.

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

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

In this pharmacokinetic study, the maximum plasma concentration (C_{max}) and time to reach this concentration (T_{max}) were obtained by actual observations of the plasma concentration-time data. The elimination rate constant (k_e) was calculated from the slope of the linear terminal line of the logarithmic plasma concentration-time data, and the half-life ($t_{1/2}$) was calculated by equation (7):[32]

$$t_{1/2} = \frac{0.693}{k_e} \quad \text{(Eq. 7)}$$

The area under the curve (AUC_{0-t}) was calculated by using the trapezoidal rule from 0 to 24 h, and the area under the curve from zero to infinity ($AUC_{0-\infty}$) was calculated from (AUC_{0-t}) plus the extrapolated portion C_p/k_e by equation (8): [1]

$$AUC_{0-\infty} = AUC_{0-t} + \frac{Cp_t}{k_e} \quad \text{(Eq. 8)}$$

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

The relative bioavailability values (F) were calculated by equation (9):[32]

$$F = \frac{AUC_{tablet}}{AUC_{solution}} \times \frac{Dose_{solution}}{Dose_{tablet}} \quad \text{(Eq. 9)}$$

Statistical analysis

The statistical software package, SPSS 22 (SPSS Inc., Chicago, USA) was used to perform the statistical analyses by applying the paired-sample *t*-test and one-way analysis of variance, depending on the type of data. A *P*-value of <0.05 was considered significant.

Results and Discussion

Flowability for powders and granules

Table 2 shows the results for the CI values for all the formulations before and after granulation. The CI values decreased significantly (p<0.05) following granulation for all the prepared formulations (F1-F5, Table 2), revealing better flow properties of the granules compared to the powder mixtures.[33]

Table 2 Properties of powder mixtures and granules of F1-F5 formulations.

Formulation	Origin of prepared tablets							
	powder mixtures				Granules			
	Bulk density (g/cm³)[a]	Tapped density (g/cm³)[a]	True density (g/cm³)[b]	Carr's Index[a]	Bulk density (g/cm³)[a]	Tapped density (g/cm³)[a]	True density (g/cm³)[b]	Carr's Index[a]
F1	0.502±0.02	0.683±0.00	1.35±0.02	26.57±2.53	0.531±0.01	0.637±0.01	1.43±0.02	16.63±1.69
F2	0.475±0.02	0.677±0.00	1.46±0.01	29.81±3.09	0.539±0.01	0.644±0.01	1.54±0.01	16.33±0.43
F3	0.501±0.01	0.727±0.00	1.47±0.02	31.06±1.58	0.526±0.00	0.621±0.01	1.47±0.01	15.26±1.85
F4	0.541±0.00	0.741±0.01	1.40±0.03	27.02±1.32	0.486±0.01	0.585±0.01	1.49±0.02	16.83±2.05
F5	0.492±0.01	0.700±0.02	1.46±0.02	29.67±1.60	0.455±0.01	0.537±0.01	1.40±0.03	15.29±1.67

[a] The data represent mean ± SD of three determinations.
[b] The data represent mean ± SD of five determinations.
For formulations composition refer to Table 1.

Evaluation of floating tablets

Tablet apparent density and porosity

For floating drug delivery systems it is important that density is <1.00 g/cm^3 in order to initiate buoyancy on the release medium.[8] Upon water uptake, chains of hydrophilic polymers move apart from each other, resulting in both weight and volume increases. Although, this will reduce the density of the swelled matrix, the rate of release medium uptake depends upon the matrix porosity level. The apparent density and porosity results of the tablets were used to evaluate the magnitude of the different formulation factors (wet granulation, type and ratio of gas forming agents) on the prepared tablets.

The apparent densities of all the prepared tablets before and after granulation are shown in Figure 1. The granulation process caused a significant (P<0.05) increase in tablet apparent density for F1, F2, and F3 formulations, which was not observed for F4 and F5 formulations. The granulation process might enhance the elastic recovery of alginate molecules after compression, which justifies the results for the F5 (0% w/w gassing agent) formulation, where tablet thicknesses after granulation increased (Table 3) whilst the apparent density decreased (Figure 1). It has been reported that the chemical composition of alginates affects their compression behaviour, where alginates with low guluronic acid content behave more elastically than alginates with low mannuronic acid content. In this study the ratio of mannuronic acid to guluronic acid is 1.56. Furthermore, the plasticity of potassium alginates is higher than that of sodium alginates, though, alginates deform elastically.[34] This is in agreement with the apparent density result for F4 (20% w/w sodium carbonate) and complies with the sodium bicarbonate floating tablet results published in our previous study.[20]

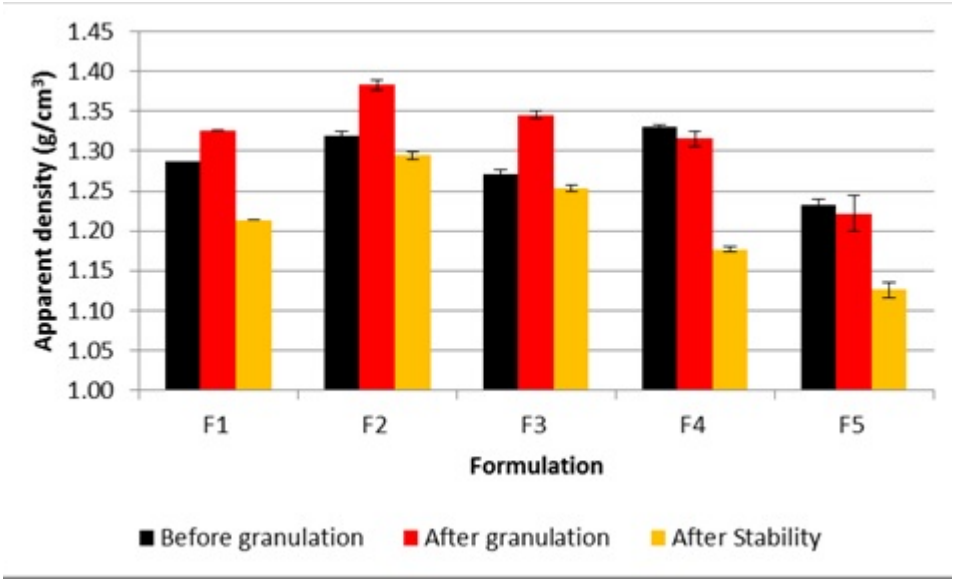


Figure 1: Apparent density of F1, F2, F3, F4, and F5 tablets before granulation and after granulation. The data represents the mean ± SD of six determinations. For formulation composition, refer to Table 1.

The apparent density of the F3 (10% w/w sodium carbonate) tablets increased after granulation. This formulation was pressed manually, and the longer contact time between powder/granules and punches of the tableting machine might overcome the alginate elastic recovery following compression. Additionally, it has been reported that the amount of stress developed at the points of local deformation depend upon several factors, such as physical properties of the material, force magnitude, rate of application, and contact time.[35]

The tablet thicknesses of F1 (10% w/w) and F2 (20% w/w) calcium carbonate based tablets, decreased after granulation (Table 3). This may be explained by the good compressibility of calcium carbonate that might overcome the effect of sodium alginate elastic recovery following compression due to the granulation process; this also explains the benefits of using calcium carbonate in effervescent floating tablets. As shown in Table 3, lower compaction pressure were applied to prepare calcium carbonate based tablets (F1 and F2) with higher tablet tensile fracture strength (Table 5) and lower porosity percentages (Figure 2) in comparison with the other tablets.

Moreover, changing the calcium carbonate concentration from 10% to 20% (w/w) significantly increased (P<0.05) the apparent density of all the tablets prepared from powder mixtures or granules. However, raising the sodium carbonate concentration to 20% (w/w) significantly increased (P<0.05) the apparent density of only those tablets prepared from powder mixtures.

This might be justified by the high specific gravities of calcium carbonate and sodium carbonate, which are 2.70[36] and 2.53,[22] respectively, which is in agreement with the results for sodium bicarbonate published in our previous study.[20]

A non-significant (P>0.05) decrease in the apparent density of tablets prepared from granules due to changing the sodium carbonate concentration from 10% to 20% (w/w) was noted. As mentioned above, the manual pressing of the F3 (10% w/w sodium carbonate) formulation may enhance a reduction in the tablet thickness, with a higher ratio than that of F4 (20% w/w sodium carbonate) tablets, which could justify this reduction in density.

Table 3 Properties of F1-F5 formulation tablets before granulation and after granulation.

Formulation	Origin of prepared tablets					
	Before granulation			After granulation		
	Compaction pressure (kN)	Tablet weight (g)[a]	Tablet thickness (cm)[a]	Compaction pressure (kN)	Tablet weight (g)[a]	Tablet thickness (cm)[a]
F1	25.00	0.277±0.00	0.299±0.01	30.10	0.272±0.00	0.285±0.02
F2	26.00	0.310±0.00	0.326±0.01	31.20	0.309±0.00	0.311±0.01
F3	26.50	0.278±0.00	0.298±0.00	28.50	0.279±0.00	0.286±0.01
F4	26.25	0.312±0.00	0.326±0.01	28.25	0.315±0.00	0.329±0.08
F5	28.00	0.275±0.00	0.305±0.01	31.00	0.280±0.00	0.318±0.02

[a] The data represent mean ± SD of six determinations. For formulations composition refer to Table 1.

The tablet porosity percentages of F1, F2, F3, F4, and F5 formulations are presented in Figure 2. The granulation process significantly increased (P<0.05) the porosity of the F1 and F4 tablets, and non-significantly (P>0.05) the porosity of the F2 tablets. In contrast, the porosity significantly decreased (P<0.05) in the F3 and F5 tablets due to the granulation process.

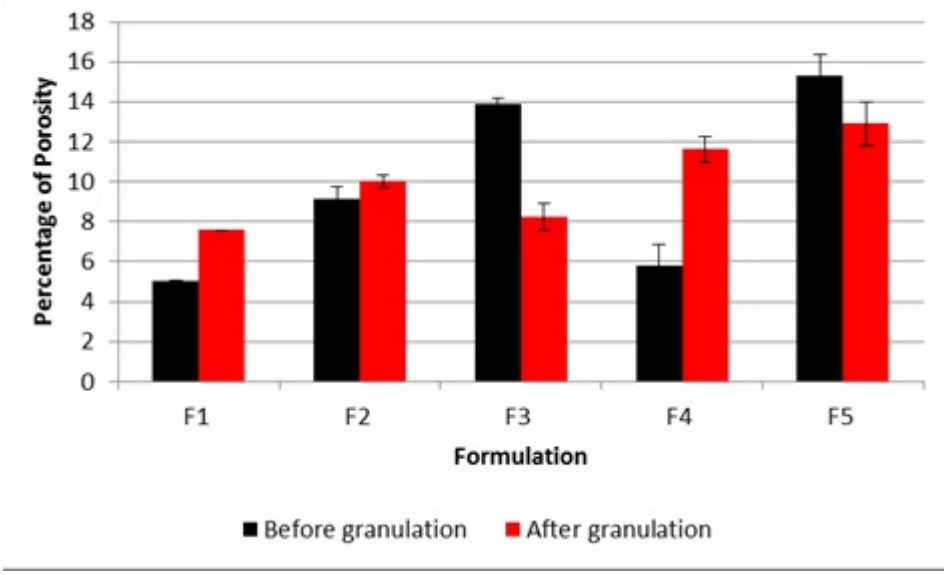


Figure 2: Porosity percentage of F1, F2, F3, F4 and F5 tablets before and after granulation. The data represents the mean ± SD of five determinations. For formulation composition, refer to Table 1.

It has been demonstrated in a previous study of cross-linked drug alginate granules that increasing the water binder volume decreases porosity during the wet massing stage.[37] This supports the results for the F5 (0% w/w gassing agent) formulation, where the granulation process reduced the tablet porosity in comparison to tablets with no gassing agents. However, tablet porosities of calcium carbonate based formulations (F1 and F2) increased following granulation, which may be related to the insolubility of calcium carbonate in water[36] that could enhance the formation of voids between adjacent molecules during the wet massing stage with water. In contrast, sodium carbonate as a gassing agent is a water-soluble material,[22] which might form a homogenous mass with the hydrophilic polymeric binary mixture during the wet massing process. This probably accounts for the tablet porosity reduction at 10% (w/w) in the F3 formulation after the granulation process. Moreover, this is in agreement with the results of our previous study of sodium bicarbonate[20] which is also water-soluble.[38] However, the significant (P<0.05) elevation in porosity observed for the F4 tablets could be explained by the hygroscopic properties of sodium carbonate, whereby one mole of sodium carbonate can gradually absorb one mole of water on exposure to air.[22] Raising the sodium carbonate concentration means that more water molecules may be absorbed and evaporated through the granulation process, and the total porosity will be increased.

Increasing the calcium carbonate concentration from 10% (w/w) (F1) to 20% (w/w) (F2) significantly increased (P<0.05) the porosity percentage of tablets prepared from both powder mixtures and granules. A significant (P<0.05) increase in porosity was noted when the sodium carbonate concentration was raised from 10% (w/w) (F3) to 20% (w/w) (F4) in tablets prepared from granules; however, the porosity significantly decreased (P<0.05) for tablets prepared originally from powder mixtures. It has been reported that calcium carbonate mainly undergoes fragmentation when compressed;[39] which will produce high porosity tablets at comparable compaction pressure due to its high yield pressure.[40] This may explain the increase in tablet porosity due to the change in calcium carbonate concentration in tablets prepared from either powder mixtures or granules.

For tablets prepared originally from powder mixtures, raising the sodium carbonate concentration from 10% (w/w) (F3) to 20% (w/w) (F4) could enhance more voids between molecules being filled after compression, which might reduce porosity. This also is in

agreement with the results of our previous study of sodium bicarbonate as a gassing agent.[20] However, the significant (P<0.05) increase in the porosity value of tablets prepared originally from granules could be explained by the hygroscopic properties of sodium carbonate, as mentioned earlier.

Tablet floating capacity

Floating drug delivery systems aim to keep floating for a long period of time on the release medium of the stomach without affecting the gastric emptying time. Normally, in humans the average gastric emptying time takes 2-3 hours during fasting and a longer time in fed conditions. Moreover, all undigested materials are normally emptied out of the stomach and down the small intestine at the end of the gastric emptying process.[41] However, it is important for floating tablets to avoid premature sweeping from their major absorption zone of the stomach and upper intestine, which can be managed by achieving the least possible lag time, and longer floating duration.

Table 4 presents the floating capacities of all the formulations before and after granulation. All the tablets (F1-F5) were tested for floating capacity under the same conditions and using the same apparatus for the *in vitro* studies. The F5 tablets had no floating capacity, as they do not contain any gassing agent. Both calcium carbonate and sodium carbonate as gassing agents enhance the floating behaviour of the formulated tablets; carbon dioxide is generated by reaction with the acidic dissolution medium (0.1M HCl) and entrapped in the formed gel layer around the swollen tablets.

Table 4: Floating capacity of F1-F5 formulations before granulation and after granulation.

Formulation	Floating lag time (min)		Total floating duration (h)	
	Origin of tablet		Origin of tablets	
	Before granulation[a]	After granulation[a]	Before granulation	After granulation
F1	0.32±0.07	21.81±4.00	Complete disintegration	> 5
F2	0.21±0.04	6.93±1.03	Complete disintegration	> 24
F3	1.88±0.65	6.95±0.91	> 12	> 12
F4	4.20±0.73	8.27±1.25	> 24	> 24
F5	Complete disintegration	No floating	Complete disintegration	No floating

[a]The data represent mean ± SD of three determinations. For formulations composition refer to Table 1

The granulation process caused a significant increase (P<0.05) in the lag time for all the floating tablets (F1-F4) compared to tablets prepared from powder mixtures before granulation (Table

4). A complete disintegration effect was seen in tablets prepared from powder mixtures based on calcium carbonate as the gassing agent (F1 and F2), whereby tablets rapidly moved in an upward motion and disintegrated on the surface of the dissolution medium. All the tablets based on sodium carbonate as the gassing agent (F3 and F4), either prepared originally from powder mixtures or granules, did not show any disintegration behaviour. This disintegration behaviour might be justified by the stronger effervescence activity of calcium carbonate compared to sodium carbonate, which ruptured the tablet structure of F1 and F2 formulations prepared from powder mixture (Table 4). During the granulation process, liquid bridges of adhesives, like hydroxyethyl cellulose, are formed between particles during the wet massing step and these harden due to the drying step.[42] This could make the internal structure of the tablets much more resistant to the disintegration effect of the calcium carbonate effervescence reaction, and provide sufficient time for swelling and gel layer formation. However, the absence of the disintegration behaviour in F3 and F4 tablets prepared from powder mixtures could be explained by the better ability of sodium carbonate compared to calcium carbonate to provide an alkaline microenvironment for the polymer to initiate gel formation.[6] It has been recorded that a 1% (w/v) aqueous solution of sodium carbonate generates a pH of 11.4 at 25°C[22], while a 10% (w/v) aqueous dispersion of calcium carbonate produces a pH of 9.0.[36]

The increase in lag time results for F3 (10% (w/w) sodium carbonate) tablets after granulation might be due to the reduction in porosity. Although the porosity level of the F4 (20% (w/w) sodium carbonate) tablets increased due to the granulation process, as mentioned earlier, the floating lag time also increased. The increase in the porosity level might enhance rapid contact between the gassing agent and the acidic medium, but it also accelerates the escape of liberated gas bubbles from the matrix structure before the formation of a coherent gel layer around the tablet, which might delay the floating process.

Increasing the calcium carbonate concentration from 10% (w/w) (F1) to 20% (w/w) (F2) in tablets prepared originally from powder mixtures decreased the lag time non-significantly ($P>0.05$), which may be due to the disintegration behaviour of these tablets. Moreover, a significant ($P<0.05$) reduction in the floating lag time was noted in tablets prepared originally from granules when the calcium carbonate level was increased from 10% to 20% (w/w). This in agreement with the results of our previous study of sodium bicarbonate where increasing

the gassing agent content available for an acidic medium enhances the efficiency of the effervescence reaction, which will be represented by a shorter floating lag time[20]. Changing the sodium carbonate concentration from 10% (F3) to 20% (w/w) (F4) increased the measured lag time non-significantly (P>0.05) in all the tablets. The ability of sodium carbonate to generate an alkaline microenvironment to accelerate swelling and gel formation may reduce the dissolution medium entrapment rate and the quantity of acidic medium available for the effervescence reaction. This means that raising the sodium carbonate level to 20% (w/w) will increase tablets density, as mentioned earlier, and more time will be taken to move the tablets upward.

Table 4 shows the floating duration results for all the tablets. As mentioned above, tablets based on calcium carbonate as the gassing agent, F1 and F2 tablets, originally prepared from powder mixtures showed complete disintegration behaviour. However, due to the granulation process, F1 (10% w/w) tablets floated for >5 hours, while F2 (20% w/w) tablets floated >24 hours due to the high gassing agent reservoir available for the floating process. The granulation process did not cause any difference in floating duration for F3 and F4 tablets based on sodium carbonate as the gassing agent, where >12 hours and >24 hours were recorded, respectively. This could be related to the absence of the disintegration effect due to the ability of sodium carbonate to generate an alkaline microenvironment to accelerate gel formation; however, the longer floating duration may be related to the high gassing agent reservoir during the test. This complies with the results of our previous study of sodium bicarbonate, where a 20% (w/w) gassing agent concentration was found to be more effective than a 10% (w/w) concentration in keeping tablets on the surface of the dissolution medium for a longer duration of time.[20]

Tablet friability, hardness, weight uniformity and drug content uniformity

The good flow properties of the granules which facilitate their automatic pressing made them more suitable to benefit the pharmaceutical industry, therefore, only the tablets prepared from the granules were subjected to friability, hardness weight uniformity and drug content uniformity tests. Results for hardness (N), tablet tensile fracture strength (MPa), friability (%), average weight (g), and average drug content (mg) of all prepared tablets are presented in Table 5. All tablets for the F1, F2, F4, and F5 formulations were successfully pressed automatically, while those for the F3 formulation were pressed manually.

Table 5 Properties of pentoxifylline tablets prepared from granules of F1- F5 formulations.

Formulation	Hardness (N)[a]	Tablet tensile fracture strength (MPa)	Friability (%)	Tablet weight (g)[b]	Drug content (mg)[a]
F1	51.98±0.16	1.21	0.96	0.305±0.00	61.22±0.57
F2	53.94±0.40	1.15	1.34	0.343±0.00	61.78±1.28
F3	50.03±0.27	1.16	1.16	0.299±0.00	58.34±1.81
F4	52.96±0.75	1.06	0.89	0.315±0.00	56.91±2.12
F5	49.03±0.52	1.02	0.79	0.296±0.00	69.15±0.80

[a] The data represent mean ± SD of 10 determinations.

[b] The data represent mean ± SD of 20 determinations. For formulations compositions refer to Table 1.

It has been reported in some studies that the hardness of tablets prepared from a mixture of two materials can be predicted from the hardness of tablets prepared from each of these materials, as a linear relationship can be drawn for the composition of the mixture.[43,44] Tablet hardness has been shown to exceed the hardness of tablets prepared from individual materials,[45,46] whilst in other studies it has been lowered compared to that of the individual components.[47,44]

F1 and F2 formulations using calcium carbonate were pressed successfully, and the good bonding capacity under compression of calcium carbonate[40] and its role as a filler in pharmaceutical formulations[36] probably justifies this. However, although pressing sodium carbonate alone shows good bonding capacity,[48] tablets containing sodium carbonate at 10% (w/w) (F3) could not be pressed automatically, although increasing the concentration to 20% (w/w) (F4) overcame this issue, and tablets were successfully pressed. Generally, this suggests that compressibility of these floating formulations (F3 and F4) is dependent by the concentration of sodium carbonate. F5 tablets without any gassing agent were successfully pressed at the required level of hardness (49–54 N). However, the granulation process might enhance the elastic recovery of alginate molecules following compression, which could explain the inability to prepare tablets based on sodium bicarbonate as the gassing agent even at a higher level (59–64 N) of hardness following granulation as shown in our previous study.[20] In addition, it has been reported that sodium bicarbonate has a lower bonding capacity than sodium carbonate[48] and calcium carbonate.[40] Hence, it is worth testing sodium carbonate and calcium carbonate as gassing agents, as per this study, especially as the available information in the literature on using them in floating tablets is inadequate.

All the prepared tablet results (Table V) comply with BP specifications[28] with respect to weight and drug content uniformity tests. For the friability test, there were no signs of cracked, split, or broken tablets throughout the test. Additionally, the results of the F1, F4, and F5 formulations fit the BP limits, as the tablets had friability values less than 1%;[28] however, the results for the F2 and F3 formulations exceeded the BP limit of friability at 1.34% and 1.16%, respectively. Drug content was found to be in the range of 85%-115%.

In vitro drug release studies

Dissolution profiles of all the tablets are shown in Figures 3 and 4. Figure 3 relates to tablets prepared from powder mixtures, and F1, F2 and F5 tablets showed only a small difference between their drug release results due to their complete disintegration behaviour. However, F3 and F4 tablets, which contain sodium carbonate, did not show any disintegration behaviour.

As mentioned earlier, calcium carbonate may show higher effervescence behaviour than sodium carbonate, but the ability of sodium carbonate to generate an alkaline microenvironment to accelerate swelling and gel formation is better than that of calcium carbonate. Consequently, an insufficient gel layer might lead to partial or complete tablet disintegration.

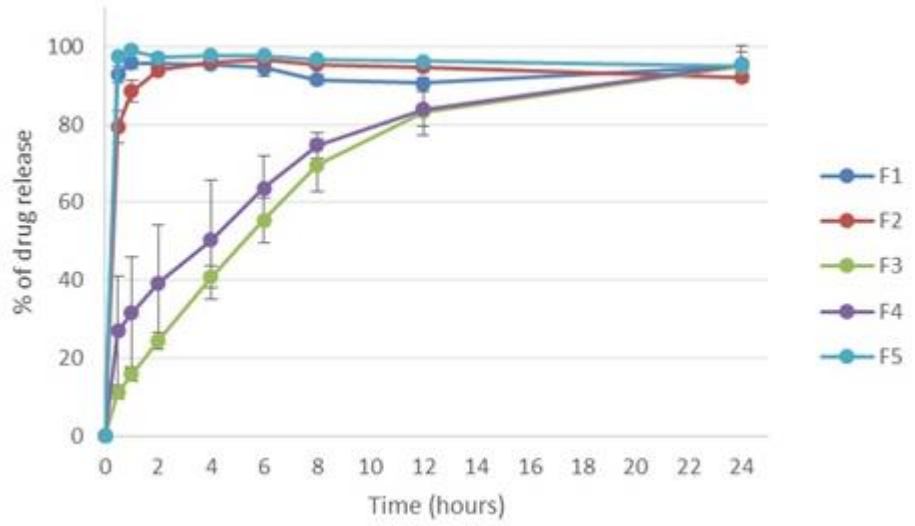


Figure 3: Percentage drug release for F1, F2, F3, F4, and F5 tablets prepared originally from powder mixtures in 0.1 M HCl medium. The data represents the mean ± SD of three determinations. For formulation compositions, refer to Table 1.

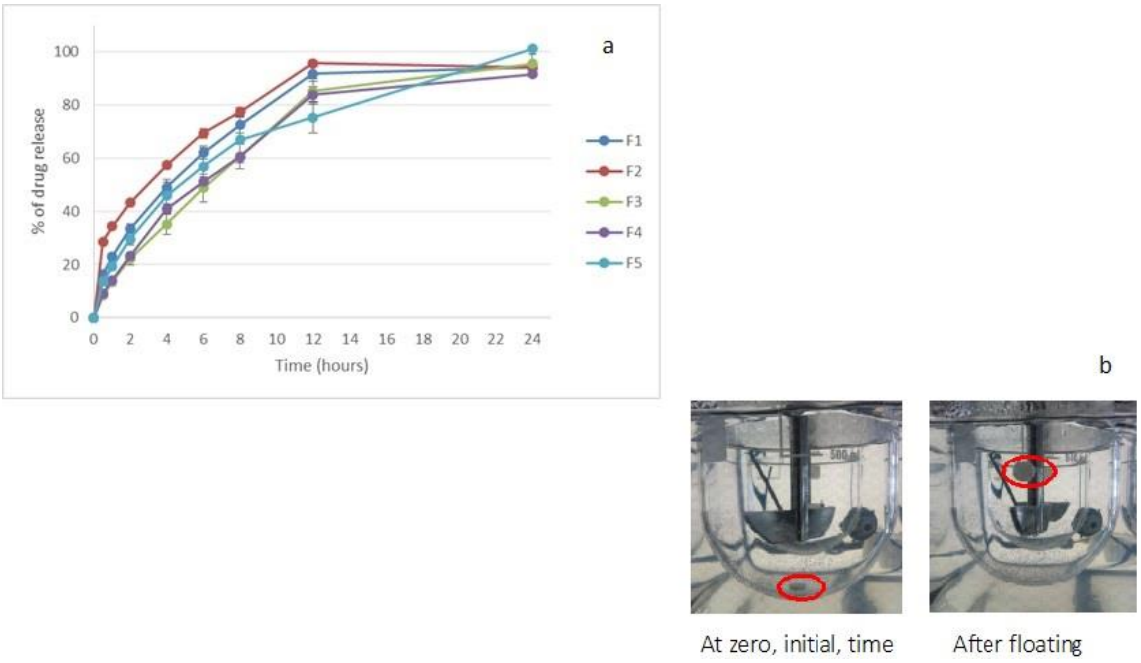


Figure 4: **a** Percentage drug release for F1, F2, F3, F4, and F5 tablets prepared originally from granules in 0.1 M HCl medium. The data represents the mean ± SD of three determinations. For formulation compositions, refer to Table 1.**b**: Floating process of a F2 tablet (marked with a circle) during drug release.

Figure 4a shows the drug release rate of tablets prepared from granules and Figure 4b reveals the floating of F2 tablets, as an example, a floating lag time was ~ 7 minutes and tablets kept floating for > 24 hours. The effect of the granulation process on drug release rate from F1-F5 tablets reveals that the granulation process extended the drug release rate for all the prepared tablets; this effect was significant (P<0.05) at all the time points in F1, F2, and F5 formulations except at the time point 12 hours in F1 and F2 where the effect was not significant (P>0.05). For F3 and F4 formulations, the granulation process did not cause a significant (P>0.05) decrease in the drug release rate except at the initial time points (0.5-2 hours) in F4 formulation where P<0.05.

The granulation process makes F1 and F2 tablets more resistant to rupture due to calcium carbonate effervescence behaviour and provides sufficient time for swelling and gel layer formation to control the drug release process. The F5 formulation results comply with those of Mukhopadhyay et al.,[37] where increasing the water binder volume decreased the porosity during the wet massing stage, and this reduction delayed the dissolution media entrapment through the matrix at an early stage of the dissolution test, which decreased the drug release

process. Generally, the insignificance (P>0.05) effect of the granulation process on of F3 and F4 tablets could be explained by the high alkalinity of sodium carbonate as the gassing agent, which may justify the ability of the tablets either before or after granulation to swell at a similar rate. Although the porosity of the F4 tablets increased after granulation, as mentioned earlier, it has been proposed that dissolution medium can pass through tablet surface pores to initiate gel layer formation through the swelling process.[49] The formed gel will block the liquid filled pores in less than 15 minutes, after which water will be primarily transported through the created coherent gel layer.[50] This swelling rate could control the drug release rate and might justify the insignificant (P>0.05) effect of granulation.

There was a non-significant (P>0.05) effect of raising the concentration of calcium carbonate as the gassing agent on the rate of drug release for tablets prepared originally from powder mixtures except at 0.5 hour time point where P<0.05, as shown in Figure 3, which might be due to the complete disintegration behaviour of the tablets; however, the effect was significant (P<0.05) at the initial time points (0.5-2 hours) in tablets prepared originally from granules (Figure 4a). Increasing the calcium carbonate concentration from 10% to 20% (w/w) increases pore formation in the formed gel layer around tablets due to the entrapped gas bubbles, and this leads to higher drug release rate. In contrast, increasing the sodium carbonate concentration caused a non-significant (P>0.05) increase at all the time points in the rate of drug release from tablets prepared originally from powder mixtures (Figure 3) as well as from granules (Figure 4a) except at time points 1 and 2 hours in tablets prepared originally from powder mixtures where P<0.05. This is in agreement with the previous justification of the effect of sodium carbonate alkalinity on the swelling behaviour of tablets.

The effect of adding a gassing agent on the drug release rate of the tablets prepared originally from powder mixtures or granules was evaluated by comparing the results for F5 (0% w/w gassing agent) tablets with other formulations. Adding calcium carbonate at both concentrations caused high drug release rate due to the liberation of carbon dioxide bubbles. Generally, the effect was not significant (P>0.05) at all the time points for tablets prepared originally from powder mixtures due to the disintegration behaviour in the F1, F2, and F5 tablets. However, for tablets prepared originally from granules, the increase in the drug release rate was not significant (P>0.05) at 10% (w/w) calcium carbonate, and significant (P<0.05) at 20% (w/w) calcium carbonate at all the time points except at 12 hours at 10% (w/w) calcium

carbonate where *P*<0.05. In contrast, adding sodium carbonate as the gassing agent at 10% (F3) and 20% (F4) (w/w) decreased the drug release rate compared to that for the non-floating (F5) tablets of both powder mixtures and granules origin. Generally, the effect at all the time points was not significant (*P*>0.05) except for tablets prepared from powder mixtures, where the F5 tablets showed complete disintegration behaviour.

As mentioned earlier, although F3 and F4 tablets floated >12 and >24 hours, respectively (Table 4), however, their DMU results were almost the same due to the alkalinity of sodium carbonate, which may justify the non-significant difference in their drug release rate.

The results of drug release rate from F2 and F4 floating tablets (floated for >24 hours) were compared with release profiles of sustained release pentoxifylline market products as reported by Popescu et al.,[51] who investigated the *in vitro* performance of several pentoxifylline commercial products. One of these products was based on hydroxyethyl cellulose while the others were formulated with hydroxypropylmethyl cellulose. The mean *in vitro* dissolution profiles indicated similar release rates of all tested samples; the release rates were not more than 20 % in the first hour, less than 30% at 2 hours, and all products had less than 60% release at 6 hours. Those results were less than that obtained from F2 and more than that from F4 (Figure 4a), meaning that the designed floating tablets from this current study can control the performance of the formulations based on the composition.

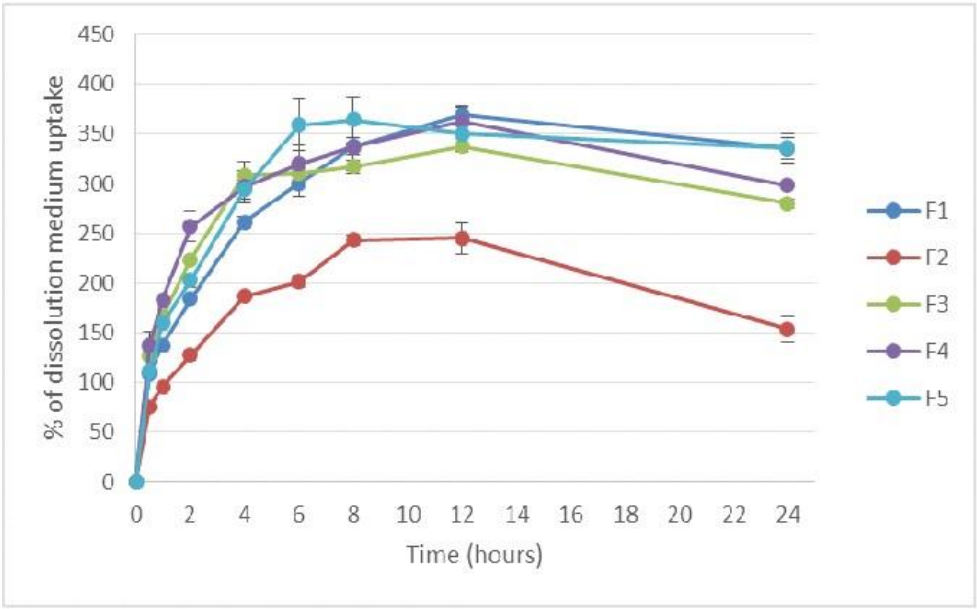
Swelling and erosion studies

Figure 5a shows the % DMU for all the tablets prepared originally from granules, in 0.1 M HCl medium. Increasing the calcium carbonate levels from 10% (w/w) (F1) to 20% (w/w) (F2) caused a significant (*P*<0.05) decrease in tablet swelling at all the time points, however, increasing the sodium carbonate level did not cause a significant (*P*>0.05) effect on the swelling of F3 and F4 tablets. Figure 5b reveals images of F2 and F5 tablets (as examples) during their swelling characterization test for 24 hours.

F2 tablets floated for >24 hours while F1 tablets floated for only >5 hours, causing the upper tablet surface of the F1 tablet to became available for DMU after sinking, and the tablet showed great swelling by the end of the experiment. Although F3 (10% w/w) and F4 (20% w/w) tablets based on the sodium carbonate as the gassing agent floated >12 and >24 hours,

respectively (Table 4), the DMU results were almost the same. The results for the F3 and F4 tablets (Figure 5a) show a continuous increase in swelling rate only up to 12 hours, which could justify the absence of a significant (P>0.05) difference between the F3 and F4 formulations. The non-floating F5 tablets remained under the surface of the dissolution medium for the entire period of the experiment and demonstrated a significantly higher (P<0.05) swelling rate profile at all the time points compared to F1 and F2 tablets based on calcium carbonate as the gassing agent except at the late time points (8-12 hours) of F1 tablets. However, this difference at all the time points was not significant (P>0.05) for F3 and F4 tablets based on sodium carbonate except at 0.5 hour time point. As mentioned earlier, sodium carbonate is a stronger alkaline material than calcium carbonate which might explain the ability of the F3 and F4 tablets to swell at an almost similar rate to the F5 tablets even after the long period of floating.

a



b

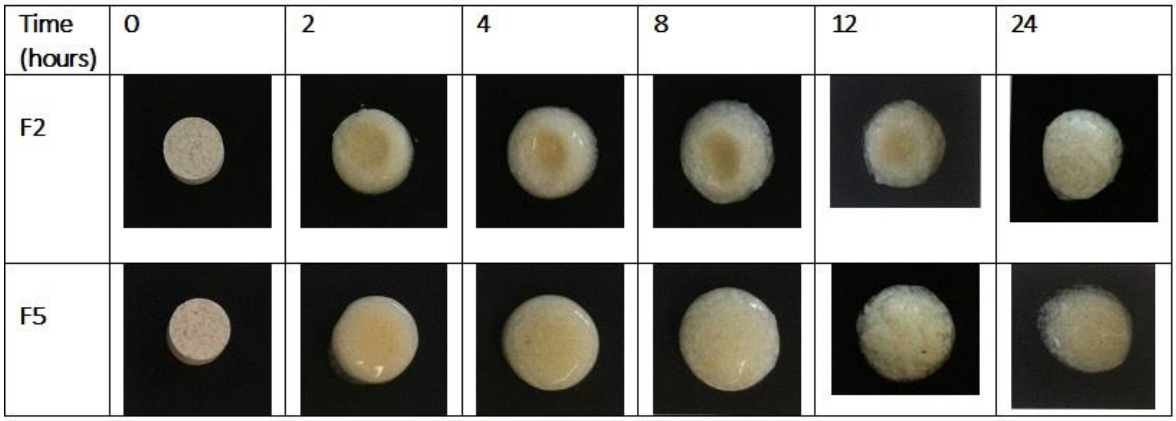


Figure 5: a Percentage of dissolution medium uptake for F1, F2, F3, F4, and F5 tablets (prepared originally from granules) in 0.1 M HCl medium. The data represents the mean ± SD of three determinations. For formulation composition, refer to Table 1. **b**: Images of F2 and F5 tablets during their swelling for 24 hours.

Figure 6 shows the percentage of mass loss for all the tablets prepared originally from granules. Increasing the gassing agent concentration of both calcium carbonate and sodium carbonate from 10% to 20% (w/w) significantly (P<0.05) increased the mass loss at all the time points. The non-floating F5 tablets demonstrated the lowest mass loss percentage profile and their results, at all the time points, were significantly (P<0.05) lower than all other formulations except F3. Our previous study reported a higher effervescence effect due to a higher gassing

agent level, which will liberate more carbon dioxide bubbles that enhance erosion of the matrix.[20]

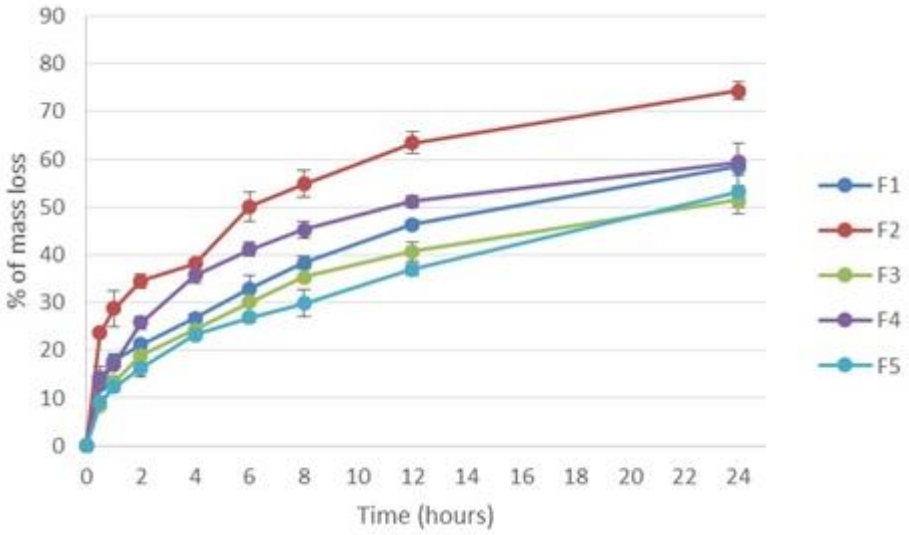


Figure 6: Percentage of mass loss for F1, F2, F3, F4, and F5 tablets (prepared originally from granules) in 0.1 M HCl medium. The data represents the mean ± SD of three determinations. For formulation composition, refer to Table 1.

In vivo pharmacokinetic study

Tablets manufactured from granules with 20% (w/w) calcium carbonate (F2) were selected for further *in vivo* evaluation as these were promising with respect to their floating lag time (~ 7min), floating duration (>24 hours), swelling ability, and sustained drug release rate.

Pentoxifylline is completely absorbed from the gastrointestinal tract when given either in the form of sustained release tablets or immediate release capsules; however, its bioavailability averages only 20% to 30% due to extensive first pass metabolism.[52] No advantage is expected from a comparative *in vivo* evaluation between non-floating sustained release tablets (F5) and the selected floating tablets (F2) (as no tablet images have been taken inside rats), hence F2 floating tablets only were chosen for this *in vivo* study. However, it was a challenge using this highly soluble model drug, pentoxifylline, in the designed floating tablets with sustaining the drug release which is the main aim of this research. Therefore, it was worth preliminary investigating the ability of the designed floating formulation (F2) for improvements to pentoxifylline pharmacokinetic parameters as a controlled release dosage form. Further *in vivo* research is required in the future to confirm this preliminary *in vivo* data explanation.

An *in vivo* study of the F2 floating tablets and a reference solution of pentoxifylline were investigated following oral administration of 5.75±0.15 mg in rats. Drug plasma levels were determined by HPLC-MS/MS, and the regression equation was y = 0.0251x - 0.000893 (r=0.9993) for pentoxifylline with a linear concentration of 4 – 400 ng/mL. The retention time was 0.45 and 0.30 min for pentoxifylline and the internal standard, respectively.

The average plasma concentration-time profiles for the two formulations are shown in Figure 7, and the pharmacokinetic parameters are shown in Table 6. The maximum plasma concentrations for the F2 tablets and the reference solution were 945.32 and 2552.30 ng/mL, respectively, and these were achieved at 1.58 and 0.50 h, respectively. Compared to the reference solution, the C_{max} of the tablets decreased significantly (p<0.05), and the T_{max} was prolonged significantly (p<0.05). Moreover, the half-life ($t_{1/2}$) value increased significantly (p<0.05) from 0.29 to 0.61 h for the tablets in comparison with the solution; thus indicating the sustained-release behaviour of the F2 floating tablets.

The relative bioavailability (F) of the tablets compared to the reference solution was 80.75%. This could be due to the significant (p<0.05) reduction in the $AUC_{0-\infty}$ value of the F2 tablets in comparison with the reference solution, which were 2368.11 and 2932.53 ng h/mL, respectively.

The results of *in vivo* studies demonstrated that the formulation, F2, did show different pharmacokinetics respect to the solution, however, it can not be stated that it is gastroretentive. It can be only hypothesized from the *in vitro* data in a simulated gastric fluid.

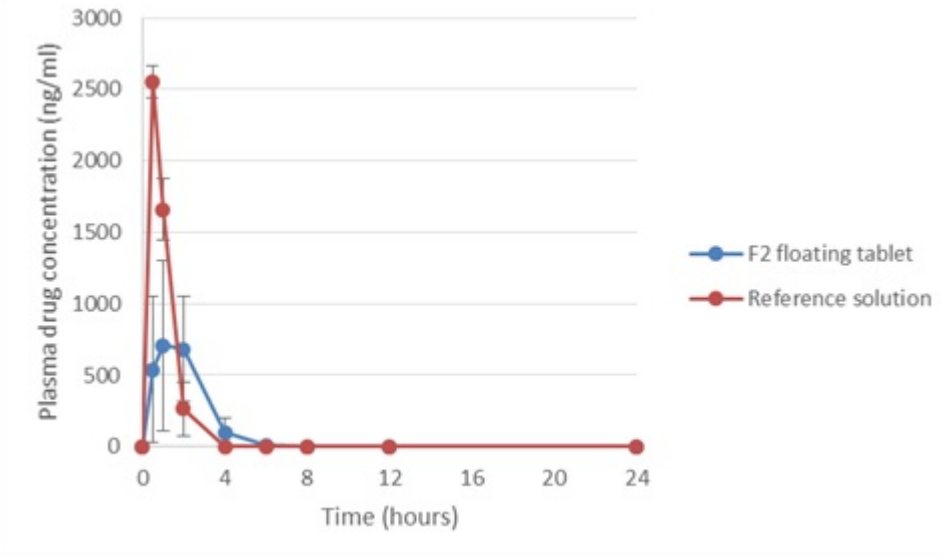


Figure 7: Average pentoxifylline plasma concentration-time curve following oral administration of F2 floating tablets and a reference solution in rats. The data represents the mean ± SD of six determinations.

Table 6: Pharmacokinetic parameters of pentoxifylline F2 tablets and reference solution.

Formulation	K_e (h^{-1})	$t_{1/2}$ (h)	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0-\infty}$(ng h/ml)
F2 floating tablets	1.25±0.48	0.61±0.19	945.32±442.87	1.58±0.66	2368.11±712.59
Reference solution	2.42±0.21	0.29±0.03	2552.30±110.85	0.50±0.00	2932.53±351.23

The data represent mean ± SD of six determinations. For F2 formulation composition refer to Table 1

Conclusions

Effervescent pentoxifylline floating tablets were successfully prepared using a (1:1) binary mixture of hydroxyethyl cellulose and sodium alginate polymeric mixture based on either calcium carbonate or sodium carbonate as the gas-forming agent. All tablets prepared via wet granulation showed acceptable physicochemical properties by metting the BP requirements of friability, weight and drug content uniformity. Increasing the concentration of the gassing agent decreased the floating lag time results for tablets based on calcium carbonate and increased it for those based on sodium carbonate. All the tablets floated on the surface of the dissolution medium and drug release was sustained over 24 hours. Tablets prepared with 20% (w/w) calcium carbonate were promising with respect to their floating lag time, floating duration, swelling ability, sustained drug release rate, and an *in vivo* study of these tablets showed sustained-release behaviour.

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