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Insights into the effects of calcium carbonate versus sodium carbonate as gassing agents on cefalexin monohydrate effervescent floating tablets

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Abstract

Gastroretentive drug delivery systems might enhance bioavailability of some drugs formulated in sustained release dosage forms by providing a longer residence time in the stomach. The aim of this study was to develop and evaluate a swellable floatable gastroretentive drug delivery system applying an effervescent mechanism using two gassing agents: calcium carbonate and sodium carbonate. Cefalexin monohydrate was used as a model drug since it has a short half-life of approximately 1 h and is instable at intestinal pH; its narrow absorption window at the upper gastrointestinal tract (GIT) made it ideal model drug for the gastroretentive delivery systems. **Methods:** a binary (1:1) mixture of hydroxyethyl cellulose and sodium alginate containing the drug at 250mg dose, with either 10% or 20% w/w calcium carbonate or sodium carbonate, was used to prepare floating tablets from either powder admixtures or granulated powders. The possible interactions between the drug and excipients were analysed using differential scanning calorimetry and Fourier transform infrared spectroscopy. The drug release characteristics, floating capacity and swelling behaviours of drug-loaded matrix tablets were evaluated in 0.1 M HCl (pH 1.2) at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Release data were analysed by fitting the power law model of Korsmeyer–Peppas, which describes the drug release from polymeric systems. The stability of all tablets (stored at $40 \pm 2^{\circ}\text{C}$ and $80 \pm 5\%$ RH for 3 months) prepared from a granular origin was evaluated for drug release rate, and floating capacity. **Results:** tablets floated on the surface of the dissolution medium, and drug release was sustained over 10 hours. Tablets produced from granules with 10%(w/w) calcium carbonate were promising with respect to their floating lag time, floating duration, swelling ability, sustained drug release rate, and stability results. Accordingly, calcium carbonate revealed promising results not only with cefalexin monohydrate at high dose but also with pentoxifylline at low dose in our previous research; hence to **conclude** this study shows that a binary mixture of hydroxyethyl cellulose and sodium alginate, together with calcium carbonate as a better choice of gassing agents is feasible to be applied with other drugs intend for gastroretentive delivery systems.

Key words: Gastroretentive drug delivery systems, effervescent floating tablets, calcium carbonate, hydroxyethyl cellulose, sodium alginate

Introduction

Floating tablets are gastroretentive drug delivery system designed to produce an upward motion of the dosage form, maintain its buoyancy the gastric fluid, remain far from the pylorus, and to reduce chances of being emptied from the stomach (1). Increasing gastric residence time can improve the bioavailability of drugs having either narrow absorption window or lower solubility within the more alkaline environment of the intestine or are degraded by the colonic enzymes (2). Floating can be achieved either by effervescent or non-effervescent systems. Non-effervescent systems are constructed with gel-forming or highly swellable matrix forming polymers (3). Effervescent systems are designed to generate carbon dioxide gas upon contact with acidic gastric fluid (acid such as citric acid can be added also to the tablet formulation) which are entrapped in a gel layer formed by hydrocolloids (4). Sodium bicarbonate (5) and calcium carbonate (6,7) are the mainly gassing agents that have been used to enhance tablets floating behavior. Although sodium carbonate decomposes upon contact with acids in the presence of water to produce carbon dioxide and effervescence (8), there are limited studies about its usage in this field of research. Hence, it was used in this current research.

Gastroretentive floating drug delivery systems have been widely investigated by drug delivery researchers within the last four decades. Many of them have been reported to show promising *in vitro* / *in vivo* results. Yet, only a few of them have been evidenced with clinical trials and proved to be marketed commercially such as Cefaclor LP (Galenix, France), Cytotec (Pharmacia/Pfizer, USA), Madopar HBS (Hoffmann-LaRoche, Switzerland), Metformin Hcl LP (Galenix, France), Prazopress XL (Sun Pharma, Japan), SoctecTM (Vectura Group, UK), Tramadol LP (Galenix, France), and Valrelease (Hoffmann-LaRoche, Switzerland) (9).

Cefalexin monohydrate is a lipophilic weak acid, highly water soluble (120 mg/ml at pH 2.3 at 37 °C), and has a short half-life of approximately 1 h (10,11). It is stable in gastric conditions but degrades in intestinal or alkaline conditions (12) with narrow absorption window at the upper gastrointestinal tract (GIT) (13–15). Researchers developed cefalexin extended release matrix tablets (16), sustained release nanocomposites (17), and controlled release beads (18). Yin et al. (2013) prepared cefalexin gastroretentive floating tablets using hydroxypropylmethyl cellulose K100M as a matrix and sodium bicarbonate as a gassing agent. The *in vitro* studies showed floating lag time within 15 seconds and floating duration > 12 h with a satisfactory sustained drug release rate for 12 h. An *in vivo* study was conducted in fed and fasted beagle dogs comparing floating tablets with conventional cefalexin capsules and sustained release tablets. The gastroretentive formulation enhanced cefalexin bioavailability. The relative bioavailability of floating tablets was 99.4% ($AUC_{0-\infty} = 162.35 \pm 34.70 \mu\text{g h/mL}$) compared with the conventional capsules ($AUC_{0-\infty} = 158.02 \pm 24.82 \mu\text{g h/mL}$), whereas sustained release tablets showed only 39.3% ($AUC_{0-\infty} = 63.71 \pm 11.71 \mu\text{g h/mL}$) (12).

The aim of this work was to design and evaluate effervescent floating tablets loaded with cefalexin monohydrate based on calcium carbonate or sodium carbonate gas generating agents, using a binary mixture of hydroxyethyl cellulose and sodium alginate gel-forming polymers.

Effects of different variables such as wet granulation, and ratio of sodium bicarbonate gas-forming agents that may affect drug release and floating properties were investigated during the study.

Experimental

Materials

Calcium carbonate, cefalexin monohydrate, sodium carbonate, and medium viscosity sodium alginate (15-20 cP at 1% at 25°C) were supplied by Sigma-Aldrich (UK), silicified microcrystalline cellulose (Prosolv® 90) was obtained from JRS Pharma (Germany), magnesium stearate was supplied by MEDEX (UK), and hydroxyethyl cellulose (Natrosol™ 250-HHX, 3400-5000 cP at 1% at 25°C) was generously provided by Ashland (USA).

Formulation development outline

A formulation development aim, for the cefalexin gastroretentive floating tablets, was to get formulations based on binary mixture of hydroxyethyl cellulose and sodium alginate (gel forming polymers); calcium carbonate, or sodium carbonate (gassing agent); and magnesium stearate (lubricant). The formulations should be suitable for the wet granulation process and for compression/pressing. The influence of gassing agent concentration was also considered during the formulation development. Several excipient levels were tried to facilitate manufacturing of the required floating tablets at suitable crushing strength using a single-punch tableting machine (Type 3, Manesty Machines Ltd, UK) equipped with flat-faced punches (9.60 mm), and the compression force was adjusted by decreasing the distance between punches to produce tablets with the required crushing strength level which was measured using the crushing strength tester (Model 2E/205, Schleuniger & Co., Switzerland). A turbula mixer (Glen Creston Ltd, UK) with a glass bottle, 250 ml, mixing vessel, was used to mix the powders.

Preparation of powder mixtures and granules

Powder blends were prepared using a (1:1) binary mixture of hydroxyethyl cellulose and sodium alginate gel forming agents. Calcium carbonate or sodium carbonate was added as a gas forming agent at 0%, 10% or 20% (w/w) concentration of the total tablet weight. All ingredients were passed through a 180 µm sieve before mixing; sodium alginate was passed through a 350 µm sieve, size suitable for tablet compression. A turbula mixer (Glen Creston Ltd, UK) set at 60 rpm, with a glass bottle, 250 ml, mixing vessel, was used to mix the powders for 10 min. The wet granulation process was used to modify powder flowability to facilitate automatic compaction of the powder. Powder mixtures were wetted with a sufficient quantity of water and mixed for 10 min using a Kenwood Chef Kneader (Thorn Domestic Appliances Ltd, UK) before being manually passed through a 1,000 µm sieve. The prepared granules were dried using a drying oven (SciQuio

Ltd, UK) at 60°C overnight (~12 h), and then dried granules passed through 853 μm sieve and granules $\leq 853 \mu\text{m}$ were used.

Preparation of floating cefalexin monohydrate tablets

To evaluate the effect of the gassing agent concentration on tablet porosity, floating capacity, swelling, erosion and dissolution behaviours, cefalexin monohydrate tablets were automatically pressed (from granulated powders) using a single-punch tableting machine (Type 3, Manesty Machines Ltd, UK) equipped with flat-faced punches (9.60 mm), and the compression speed was 85 rpm. The compression force was adjusted by decreasing the distance between punches to produce tablets with crushing strength level of 59-64 N, as measured using the crushing strength tester (Model 2E/205, Schleuniger & Co., Switzerland). Tablets were successfully pressed automatically. Granulated powders were compacted automatically but un-granulated powder mixtures were pressed manually to compare their data with those after granulation. The formulations F1-F5 compositions are presented in Table 1.

Table 1: Composition of prepared F1-F5 tablets.

Ingredients/Formulation	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
Cefalexin monohydrate	250	250	250	250	250
Hydroxyethyl cellulose	68.8	68.8	68.8	68.8	68.8
Sodium alginate	68.8	68.8	68.8	68.8	68.8
Calcium carbonate	42.6	96.8			
Sodium carbonate			42.6	96.8	
Magnesium stearate (0.5%)	2.2	2.4	2.2	2.4	1.9
Total weight	432.4 ^a	486.8 ^a	432.6 ^a	486.8 ^a	389.5

Notes: Sufficient water was added to prepare the wet mass before granulation. Number of moles of the gassing agents used in the formulations is 4.3×10^{-4} (F1), 9.7×10^{-4} (F2), 4.0×10^{-4} (F3), and 9.1×10^{-4} (F4). ^aDifference in weight was due to raising gassing agent content from 10% to 20% (w/w).

Evaluation of the prepared powder admixtures and granules

Flowability test

Bulk and tapped volumes of 50 g samples of the prepared powder mixture and granules were measured by the tapping apparatus (Copley JV1000, UK). Bulk and tapped densities were calculated as the ratio of the powder weights to the related powder volumes. Carr's compressibility index (CI) was calculated using equation (1) (19):

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

Measurements were performed in triplicate and the mean values $\pm$ SD are presented.

Differential scanning calorimetry (DSC) and Fourier-transform infrared (FTIR) spectroscopy

To study compatibility of the drug with excipients of floating tablets before and after granulation process, DSC and FTIR were used. DSC spectra of the model drug, excipients, and all the formulations (prepared from powder mixture and granules) were obtained using a DSC Refrigerated Cooling System (Model Q1000, TA Instruments, UK). Samples of pure materials (2–6 mg) were weighed and transferred into the equipment for analysis in sealed standard aluminum pans, and the calorimetric enthalpy readings were calculated using Q1000, TA software (20). The thermal behaviour of the samples was investigated at a scanning rate of 10°C / min, from 0 to 250°C. Regarding infrared, spectra of the drug and all the formulations (prepared from powder mixture or granules) were obtained using a Perkin Elmer FT-IR system Spectrum BX series (Beaconsfield, Buckinghamshire, UK) in the frequency range of 4000–620 cm⁻¹ at 4 cm⁻¹ resolution. A few milligrams of each sample were placed in the middle of the sample stage using a micro-spatula, before being compressed by twisting the top of the arm of the sample stage clockwise (20). The data were obtained by Spectrum BX series software version 5.3.1.

Evaluation of floating cefalexin monohydrate tablets

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

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

To establish tablet crushing strength, ten tablets were randomly selected, their crushing strength examined using a tablet crushing strength tester, and mean values $\pm$ SD are presented. For friability, twenty tablets were randomly selected and tested at 100 revolutions using friability test apparatus (Copley FRV 1000, UK). The percentage of weight loss (F) was calculated by equation (2) (21):

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

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

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

Drug content was calculated using the generated calibration data of the model drug; the percentages of individual drug content were calculated against the average drug content according to the British Pharmacopoeia (BP) specifications (19).

Tablet apparent density and porosity

Tablet height (h) and diameter (m) were measured using Vernier caliper (Moore and Wright Sheffield England Metric, UK). Tablet weight (w) and the circular constant (π) were also used to calculate the apparent density (D) of the tablets by equation (3) (22):

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

Mean values $\pm$ SD are presented.

Tablet porosity (ε), was calculated using equation (4) (23):

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

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). Five replicate measurements of almost 1.3 g samples of cefalexin monohydrate were used. The helium pressure was set to 17 psi, and the difference in helium pressure before and after sample loading was reported to determine the true volume of the samples. Mean values $\pm$ SD are presented.

Tablet floating capacity

Floating capacity was determined under the same conditions and using the same apparatus as for the *in vitro* drug release studies. The time taken for tablets to appear and remain on the dissolution medium surface (floating lag time) and the period of time that the tablets constantly floated on the dissolution medium surface (floating duration) were determined visually throughout the drug release studies (12), and mean values $\pm$ SD are presented.

Swelling and erosion studies

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

Swelling rate and mass loss rate were calculated by equations (5) and (6) (24):

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

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

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 $\pm$ SD are presented.

In vitro drug release studies

Drug release studies of the prepared tablets were carried out using USP dissolution apparatus II (Erweka GmbH, Germany) at 37°C $\pm$ 0.5°C, and a paddle speed of 100 rpm. For cefalexin, no official monograph is available for sustained release tablets; thus the paddle rotation speed was adapted from the literature (12,18). Tablets were placed into 900 ml of 0.1 M HCl (pH 1.2) as a simulated gastric fluid without the presence of gastric enzymes (6,12,25,26). Samples (10 ml) were withdrawn from the dissolution at 0.5, 1, 2, 4, 6, 8, 10 and 12 h. Withdrawn samples were

replaced with fresh medium, and drug content was determined and the cumulative drug release percentage was calculated. The test was performed in triplicate and mean values $\pm$ SD are presented. The pH of the dissolution medium at each sampling time interval was measured by pH-meter (Hanna Instruments HI 8424N Digital, Portable pH Meter, USA). Sink conditions were met as the concentration of the active substance in the saturated medium will be greater than the used concentrations.

Release data modeling and analysis

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

Moreover, Higuchi kinetic model equation (10) represents the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion (27).

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

$$\log(100 - Q) = \log Q_0 - \frac{k_1 t}{2.303} \quad \text{Eq. (8)}$$

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

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

Where Q is the amount of drug released at time t , Q_0 is the initial amount of the drug in tablet, k_0 is the zero order release rate constant, k_1 is the first order release rate constant, k_{HC} is the Hixson-Crowell release rate constant, and k_H is the Higuchi release rate constant.

In order to characterise the model drug release mechanism (release data modeling and analysis), the power law model of Korsmeyer–Peppas equation (11) was fitted to the first 60% release data (28).

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

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

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

Stability studies

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

In this work, the stability studies were conducted for 3 months which met those of other gastroretentive dosage form stability studies (6,29), however the stability chambers were maintained at higher relative humidity level ($80\% \pm 5\%$) instead of ICH requirements ($75\% \pm 5\%$) to apply further stressful conditions. Furthermore, storage in closed containers is reflective to the storage conditions of the packed pharmaceutical products; however, storage in open containers will raise the stress as the product will be in direct contact with the elevated temperature and humidity. Accordingly, granules and tablets prepared from the granules for all the formulations were packed in open or closed polyethylene (high density type) containers and stored in a stability chamber. Granules were withdrawn after 3 months and analysed by DSC and FTIR spectroscopy. Also, after 3 months, tablets were withdrawn and evaluated for their apparent density, floating capacity, and drug release rate.

Statistical analysis

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

Results and Discussion

Evaluation of powder admixtures and granules

All the prepared powder mixtures and granules of the formulations F1-F5 were evaluated for flowability CI index, DSC, and FTIR.

Regarding flowability for powders and granules, the granulation process caused the flowability testing as per Carr's index (CI) decreased following the granulation in all the formulations (F1-F5), as shown in Fig. 1, which reveal better flow properties of the granules compared to the powder mixture (30). The effect was significant ($P < 0.05$) in the formulations based on sodium carbonate (F3 and F4) as gassing agents, but not significant ($P > 0.05$) in all the other formulations (F1, F2, and F5).

The water solubility of sodium carbonate could enhance formation of a homogenous mass with the hydrophilic polymeric binary mixture of hydroxyethyl cellulose and sodium alginate during the wet massing process. This could assist agglomeration techniques of the granulation process where fine solid particles are converted into larger ones by mixing them in the presence of water binding liquid. Accordingly, there was a significant ($P < 0.05$) decrease in CI results of F3 and F4 based on sodium carbonate as a gassing agent. Additionally, this may explain the non-significant ($P > 0.05$) effect of the granulation process on the formulations F1 and F2 based on calcium carbonate which is less water soluble. Hamed et al. (2005) proposed that changing proportions of water soluble excipients in formulations could significantly modify granules' properties which may explain the absence of significant effect of the granulation on the CI results of cefalexin monohydrate control formulation (F5) (31).

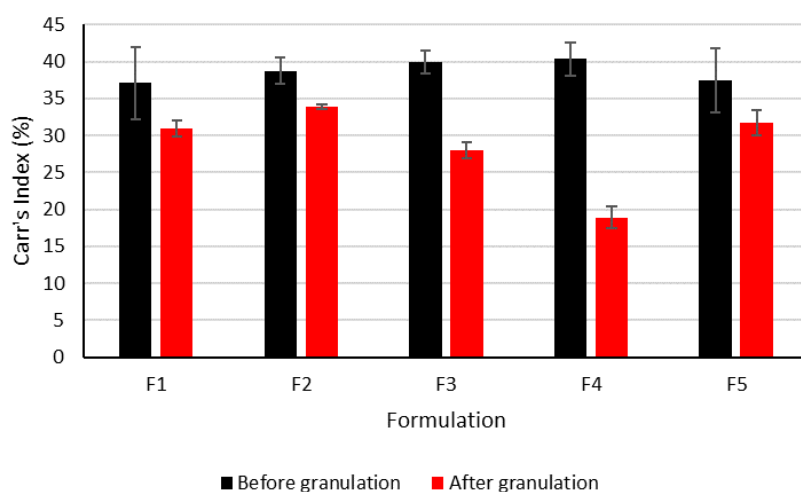


Fig. 1: Carr's Index percentage of the formulations F1-F5 before and after granulation. The compression force of the prepared tablets was adjusted to give 59-64 N crushing strength level. For formulation composition, refer to Table 1.

There was compatibility of cefalexin monohydrate with excipients within the formulations F1-F5 before and after the granulation as confirmed by both DSC and FTIR results (Supplementary file, Fig. S1-S6 and Fig. S12-S16). However, the results of DSC and FTIR suggest dependency of cefalexin monohydrate physical stability (in open containers for 3 months at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $80\% \pm 5\%$ RH) on the gassing agent water solubility and the resulted matrix microenvironment pH. Thus, better physical stability of cefalexin monohydrate loaded in sodium carbonate floating tablets for 3 months at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $80\% \pm 5\%$ RH in closed containers than in open ones was noted (Supplementary file, Fig. S7-S11 and Fig. S17-S21). This suggests that all cefalexin monohydrate floating systems, if taken forward for translational research, based on such gas forming agents should be packaged by pharmaceutical companies in tightly closed containers with an eye-catching label to direct patients for good practice.

Evaluation of floating tablets

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

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

All the prepared tablets' results of crushing strength (N), friability (%), average weight (g), and average drug content (mg) are presented in Table 2. All the tablets of the formulations F1-F5 were successfully pressed automatically at 59-64 N of crushing strength.

For the friability test, although there were no signs of cracked, split, or broken tablets at the end of the test, results were 1.10% (F1), 1.67% (F2), and 1.23% (F5) which almost fit the (BP) limit, as the friability values were slightly more than 1% (21). The results of both F3 and F4 formulations fit the BP limit of friability (Table 2). In this study, the compression force of all prepared tablets was adjusted to give 59-64 N crushing strength level. However, utilizing a higher compression force may reduce tablet friability to turn into the BP limit ($< 1\%$). All the prepared tablets of the formulations F1-F5 (Table 2) complied with BP specifications (21) with respect to weight uniformity test. With regards to content uniformity test, Table 2, results were in the acceptable range, indicating that all matrix tablets fitted the (BP) criteria in which each tablet drug content was between 85% and 115% of related average content (21).

Table 2: Properties of cefalexin monohydrate floating tablets of the formulations F1-F5.

Formulation	Crushing strength (N) ^a	Friability (%)	Tablet weight (g) ^b	Drug content (mg) ^a
F1	63.74 ± 0.81	1.10	0.457 ± 0.01	280.61 ± 5.91
F2	62.76 ± 0.69	1.67	0.523 ± 0.01	273.55 ± 6.39
F3	63.74 ± 0.28	0.69	0.464 ± 0.01	283.40 ± 8.21
F4	60.80 ± 0.25	0.85	0.520 ± 0.01	284.18 ± 8.02
F5	63.74 ± 0.30	1.23	0.417 ± 0.00	269.32 ± 8.44

Notes: ^aThe data represents the mean ± SD of 10 determinations. ^bThe data represents the mean ± SD of 20 determinations. For formulation composition, refer to Table 1.

Tablet porosity

The tablet porosity percentages of the formulations F1-F5 are presented in Fig. 2. The granulation process increased the porosity levels of the formulations F1, F4, and F5, and decreased the porosity of F2, and F3 tablets (Fig. 2). Their porosity percentages decreased following the granulation process because increasing the water binder volume decreases porosity during the wet massing stage (32).

Nevertheless, Gokhale et al. (2005) proposed that the drug loading and the amount of excipients could affect the rate and the final degree of densification of the resulted granules (33). For the tablets based on calcium carbonate (F1 and F2), the porosity percentages increased after the granulation for F1 (10% (w/w)) (Fig. 2). This may be related to calcium carbonate water insolubility that enhanced voids formation between adjacent molecules during the wet massing stage. In contrast, the porosity level decreased after the granulation in F2 (20% (w/w) calcium carbonate) tablets. The good bonding capacity under compression of calcium carbonate and its role as a filler in the pharmaceutical formulations in addition to the granulation process improvement role on tablets mechanical properties (34) explain the decrease in the porosity level of F2 formulation.

Regarding the porosity results (after granulation) of the tablets based on sodium carbonate as a gassing agent (F3 and F4), water solubility of sodium carbonate especially at the lower concentration (F3) assisted a homogeneous mixture formation with the hydrophilic polymers during the wet massing stage of the granulation that reduced the final porosity percentages. However, at 20% (w/w) concentration (F4), the hygroscopicity of sodium carbonate may support more water molecules loss through the granulation drying step which increased their porosity percentages (Fig. 2).

Increasing calcium carbonate concentration from 10% (w/w) (F1) to 20% (w/w) (F2) increased significantly ($P < 0.001$) the porosity percentages of the tablets prepared either from the

powder mixtures or the granules (Fig. 2). It has been reported that calcium carbonate mainly undergoes fragmentation when compressed (35); fragmentation establishes a large number of bonding points between calcium carbonate molecules during volume reduction, which will maintain the porosity of such tablets relatively high (36). In contrast, a significant ($P<0.05$) decrease in the porosity levels was noted when sodium carbonate concentration raised from 10% (w/w) (F3) to 20% (w/w) (F4) in the tablets prepared from the powder mixtures or the granules.

The results of F3 and F4 tablets prepared from the powder mixtures with ability of sodium carbonate to fill voids between molecules after compression clarifies the reduction in the tablets porosity due to increasing its concentration. For the tablets prepared from the granules, raising sodium carbonate concentration from 10% (F3) to 20% (F4) (w/w) decreased the porosity of cefalexin monohydrate tablets (Fig. 2).

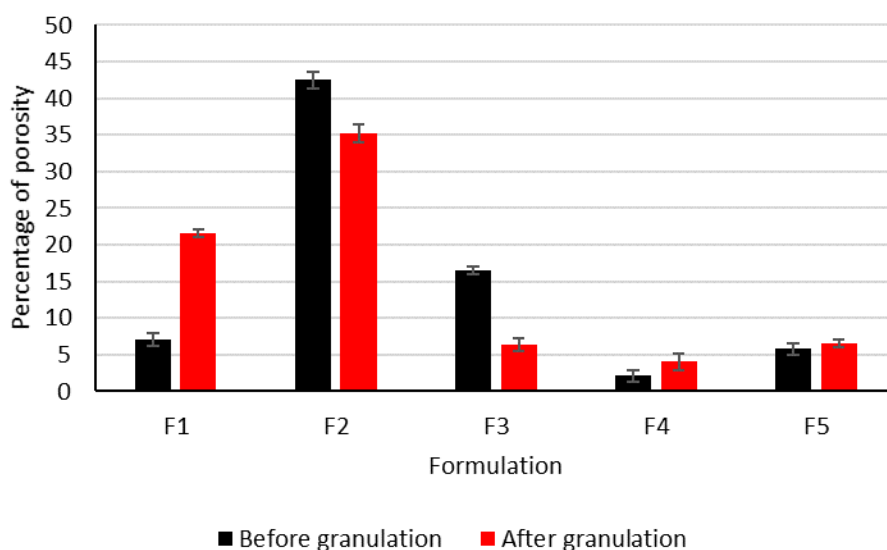


Fig. 2: Porosity percentage of the formulations F1-F5 before and after granulation.

The compression force of the prepared tablets was adjusted to give 59-64 N crushing strength level. For formulation composition, refer to Table 1.

Tablet floating capacity

It is vital for floating tablets to avoid premature evacuation from their major absorption area of the stomach and upper intestine, which could be accomplished by achieving the least possible lag time, and longer floating duration. Gassing agents such as calcium carbonate and sodium carbonate enhanced the floating behaviour of tablets due to the release of carbon dioxide gas, which entrapped in the formed gel layer around the tablets and results in reducing tablet density to facilitate the floating process. Tables 3 and 4 represent floating lag time and floating duration results of all prepared tablets respectively. All the formulations (F1-F5) were tested for

floating capacity under the same conditions and using the same apparatus for the *in vitro* drug release studies.

The granulation process increased the floating lag time results of all the tablets F1-F4 compared to that of the tablets prepared from the powder mixture before the granulation (Table 3). The effect of the granulation process was significant ($P < 0.05$) for F1, F2 and F3 tablets and non-significant ($P > 0.05$) for F4 tablets.

Table 3: Floating lag-time of the formulations F1-F5 before granulation, after granulation, and after stability (tablets prepared from granules stored at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $80\% \pm 5\%$ RH for 3 months in closed or open container).

Formulation	Floating lag time (min)			
	Origin of prepared tablet			
	Before granulation	After granulation	After stability (closed container)	After stability (open container)
F1	0.15 ± 0.08	2.28 ± 0.59	0.38 ± 0.08	0.18 ± 0.01
F2	0.13 ± 0.04	1.17 ± 0.22	0.35 ± 0.09	0.18 ± 0.01
F3	1.87 ± 0.16	10.92 ± 1.80	No floating	No floating
F4	4.83 ± 0.14	7.22 ± 1.41	No floating	No floating
F5	Complete disintegration within 30 min	17.57 ± 1.96	No floating	No floating

Notes: The data represents the mean $\pm$ SD of three determinations. For formulation composition, refer to Table 1

Table 4: Floating duration of the formulations F1-F5 before granulation, after granulation, and after stability (tablets prepared from granules stored at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $80\% \pm 5\%$ RH for 3 months in closed or open container).

Formulation	Total floating duration (h)			
	Origin of prepared tablet			
	Before granulation	After granulation	After stability (closed container)	After stability (open container)
F1	Complete disintegration within 30 min	> 8	Partial disintegration	Partial disintegration
F2	Complete disintegration within 30 min	> 12	Complete disintegration within 30 min	Complete disintegration within 30 min

F3	> 8	> 10	Complete disintegration within 30 min	No floating
F4	> 8	> 12	Complete disintegration within 30 min	Complete disintegration within 30 min
F5	Complete disintegration within 30 min	> 12	Complete disintegration within 30 min	Complete disintegration within 30 min

For formulation composition, refer to Table 1

The results of F1 (10% (w/w)) and F2 (20% (w/w)) tablets based on calcium carbonate as a gassing agent display that the absence of the disintegration behaviour due to strengthening the tablets internal structure after the granulation delayed the entrapment of the acidic medium and increased their lag time results (Table 3).

Moreover, the increase in the lag time values of the tablets based on sodium carbonate as a gassing agent (F3 (10% (w/w)) and F4 (20% (w/w))) complies with the relevant pentoxifylline tablets prepared in our previous study (37). Although, the decrease in F3 porosity percentages following the granulation (Fig. 2) hindered the initiation of the effervescent process, the increase in F4 porosity percentages (after the granulation) reduced their matrices ability to retain the liberated gas bubbles and delayed their floating process.

Changing the concentration of calcium carbonate from 10% (F1) to 20% (w/w) (F2) decreased the lag time results significantly ($P < 0.05$) for the tablets prepared from the granules, nonetheless, the effect was not significant ($P > 0.05$) for the tablets prepared from the powder mixtures (Table 3). Increasing the gassing agent content available for the acidic medium enhanced the rate as well as the efficiency of the effervescent reaction, which was represented by the shorter floating lag time values.

Regarding sodium carbonate gassing agent, changing its concentration from 10% (F3) to 20% (w/w) (F4), the lag time values changed but non-significantly ($P > 0.05$) in the tablets prepared from the powder mixtures and granules (Table 3).

Sodium carbonate has better ability compared to calcium carbonate to provide a suitable microenvironment for the polymer to start gelling. It has been reported that 1% (w/v) aqueous solution of sodium carbonate generates a pH of 11.4 at 25°C (8) while 10% (w/v) aqueous dispersion of calcium carbonate produces a pH of 9.0 (38). The alkalinity of sodium carbonate enhanced the swelling rate (at 20% w/w) and delayed the effervescent process due to the reduction in the dissolution medium entrapment rate. More time was taken for the floating process due to sodium carbonate alkalinity effect on the dissolution medium entrapment rate and due to the

increase in the tablet apparent density at the higher concentration level (20% (w/w)) of sodium carbonate.

The polymeric content is relatively low due to the high dose of cefalexin monohydrate (250mg/tablet weight) compared to that used with pentoxifylline (37), consequently, more sodium carbonate molecules became available alongside the hydrophilic polymeric mixture to accelerate the swelling process, and also to generate better effervescent process efficiency for cefalexin formulations. Upon quicker water uptake, chains of the polymeric mixture moved apart from each other resulted in both weight and volume growth which rapidly reduced the density of the swollen matrix and decreased their floating lag time values.

The tablets based on calcium carbonate as a gassing agent of the formulations F1 and F2 prepared from the powder mixtures showed complete disintegration behaviour within short time (30 min) after the floating process. Following the granulation process, F1 (10% (w/w)) tablets floated for > 8 h and the tablets of F2 (20% (w/w)) floated for > 12 h (Table 4). The higher calcium carbonate reservoir available for the floating process increased the floating duration.

For the tablets based on sodium carbonate as a gassing agent, the granulation process increased the floating duration results for F3 (10% (w/w)) from > 8 to > 10 h and for F4 (20% (w/w)) from > 8 to > 12 h (Table 4). Raising sodium carbonate concentration increased the floating duration from > 10 h (F3) to > 12 h (F4) for the tablets prepared from the granules and kept the floating duration without change (> 8 h) for the tablets prepared from the powder mixtures.

As shown in Table 4, the control tablets of cefalexin monohydrate (F5) prepared from the powder mixture did not show any floating behaviour. Moreover, the complete disintegration of F5 tablets was noted within short time (30 min) after immersion into the dissolution medium.

The reported elastic behaviour of cefalexin under compression with elevated pressure (39) may justify the disintegration behaviour of F5 tablets pressed at 59-64 N of crushing strength. Although cefalexin monohydrate control tablets (F5) prepared from the granules had 0% (w/w) content of gassing agents, those compacted tablets floated at 17.57 min. (Table 3) and kept floating for > 12 h on the surface of the dissolution medium (Table 4). The granulation process improved F5 tablets internal structure, and increased their porosity percentages (Fig. 2). This may entrap more dissolution medium and consequently enhanced rapid swelling rate behaviour which further reduced their tablets density to initiate and to maintain the floating process.

Regarding stability studies, the effect of storage at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $80\% \pm 5\%$ RH for 3 months on the tablets floating lag time and the floating duration was evaluated and presented in Tables 3 and 4, respectively. Concerning the tablets based on calcium carbonate as a gassing agent (F1 and F2), storage in closed or open containers decreased their floating lag time results significantly ($P < 0.05$) for F1 (10% (w/w)) and for F2 (20% (w/w)) (Table 3). Moreover, both F1 and F2 tablets could not maintain the floating on the surface of the dissolution medium as both formulations showed partial and complete disintegration behaviour respectively after short time

(30 min) of their floating process (Table 4) due to a rapid contact between the gassing agent and the acidic medium to start the effervescent and the floating processes rapidly. The low polymeric content of cefalexin monohydrate formulations (F1 and F2) in addition to the high effervescent activity of calcium carbonate caused the partial or complete rupture of the aged relaxed tablets according to calcium carbonate concentration. However, calcium carbonate is still the most effective gassing agent to keep floating integrity compared to the other gassing agent (sodium carbonate).

A complete loss of the floating ability was noted in sodium carbonate based formulations (F3 and F4) after storage at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $80\% \pm 5\%$ RH for 3 months in either closed or open containers (Table 3). This was accompanied with a complete disintegration behaviour in all the tablets except those of F3 (10% (w/w)) formulation stored in the open containers (Table 4) which sank till the end of the experiment. Storage under the stressful humidity conditions may decrease the available sodium carbonate molecules (due to hygroscopicity) for the effervescent process and consequently delayed the floating process.

This also clarifies the absence of the floating behaviour in the closed container stability samples of F3 (10% (w/w) sodium carbonate and F4 (20% (w/w) sodium carbonate tablets which could not float, and their relaxed aged structure completely ruptured within a short time (30 min) of immersion in the dissolution medium. Moreover, the aged matrices of the formulations F3 and F4 were weak. The loss in the floating ability of F3 tablets complies with its open container DSC stability thermogram (Supplementary file, Fig. S9) which indicates absence of sodium carbonate crystals and its role in the effervescent reaction. Although the open container DSC stability thermogram of F4 formulation (Supplementary file, Fig. S10) also indicates absence of the crystallinity of sodium carbonate, F4 tablets completely disintegrated while F3 tablets did not. This may be explained by the noticed morphological changes in F4 tablets after storage under stressful conditions which suggests a concentration dependent interaction of sodium carbonate.

Results of the control tablets (F5) stored either in closed or open containers presented complete disintegration behaviour within a short period of time (30 min) of starting the test (Table 4).

Swelling and erosion studies

Swelling and erosion studies were carried out to make a correlation with the drug release rate and the release mechanisms (40). The percentage of dissolution medium uptake and the percentage of mass loss of all the tablets prepared from the granules (F1-F5) in 0.1 M HCl medium are presented in Fig. 2 and 3, respectively.

Raising the level of calcium carbonate from 10% (w/w) (F1) to 20% (w/w) (F2) caused a significant ($P<0.05$) decrease in the tablet swelling rate at most of the time points (Fig. 3) and a significant ($P<0.05$) increase in the mass loss percentages at bulk of the time points (Fig. 4). The

high effervescent activity of calcium carbonate explains the higher erosional behaviour in 20% (w/w) tablets in comparison with that in 10% (w/w) concentration.

In contrast, changing the concentration of the gassing agent from 10% (w/w) to 20% (w/w) in the formulations based on sodium carbonate (F3 and F4) significantly ($P<0.05$) increased the dissolution medium uptake results at majority of the time points (Fig. 3). Also, the percentage of mass loss significantly increased ($P<0.05$) (Fig. 4).

Regarding the tablets based sodium carbonate gassing agent, alginates have better ability to swell in a higher pH environment (41). Meanwhile, aqueous solution 1% (w/v) of sodium carbonate generates a pH of 11.4 at 25°C (8), hence, the higher sodium carbonate concentration may influence the swelling rate behaviour. Besides, the strength of the hydrated microstructure of the swollen matrix tablets may be altered by the concentration of the gassing agent available. Therefore, the coherent gel layer formed around F4 (20% (w/w) sodium carbonate matrices may assist a higher swelling rate (Fig. 3) and a better resistance to the erosional behaviour due to the effervescent reaction (Fig. 4) in comparison with 10% (w/w) gassing agent based formulations.

Regarding cefalexin monohydrate control tablets (F5), their swelling rate at majority of the time points (Fig. 3) was significantly ($P<0.05$) the highest at bulk of the time points in comparison with all the other formulations except with F4 (20% (w/w) sodium carbonate) tablets where $P>0.05$ at most of the time points. Additionally, their mass loss percentages were almost the lowest (Fig. 4), but the difference was not significant ($P>0.05$) at larger part of the time points in comparison with all the other tablets except with F2 (20% (w/w) calcium carbonate) tablets where $P<0.05$ at most of the time points. Although cefalexin monohydrate control tablets (F5) floated on the surface of the dissolution medium for all the experiment time, they had the highest swelling rate (Fig. 3). The absence of the gassing agents in such tablets may explain their highest swelling rate and lowest mass loss results as it excluded additional accelerated erosional process by the gas bubbles (liberated through the effervescent reaction) and enhanced normal polymeric swelling process.

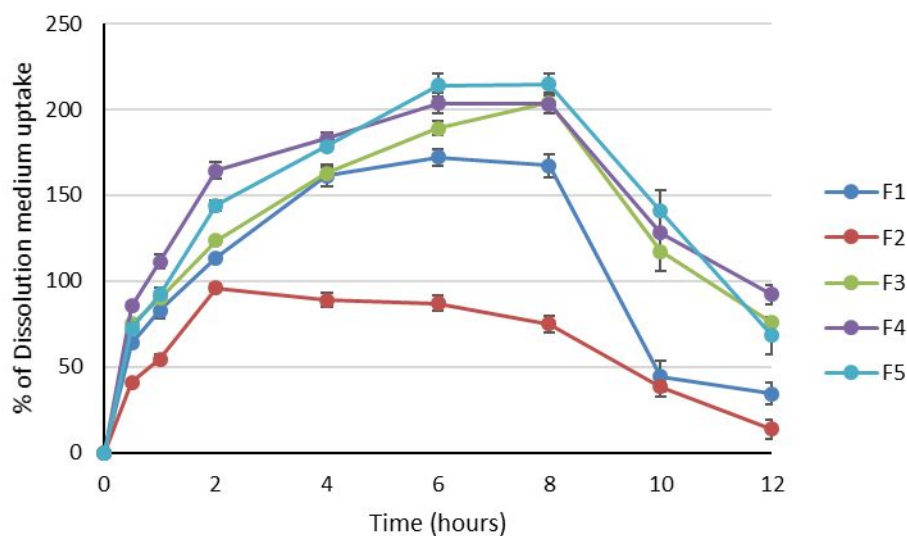


Fig. 3: Percentage of medium uptake for the formulations F1-F5 (prepared from granules) in 0.1 M HCl medium.

Notes: The data represents the mean $\pm$ SD of three determinations. The compression force of the prepared tablets was adjusted to give crushing strength level of 59-64 N. For formulation composition, refer to Table 1.

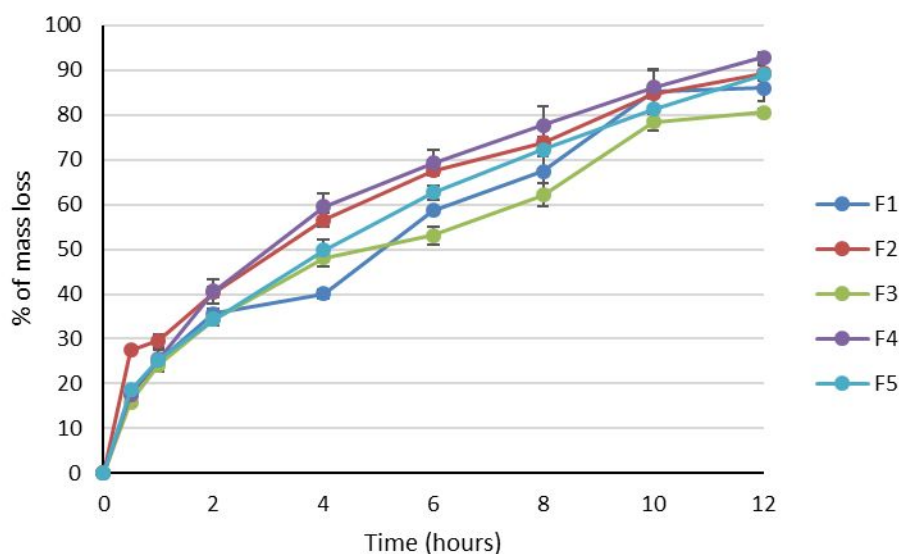


Fig. 4: Percentage of mass loss for the formulations F1-F5 (prepared from granules) in 0.1 M HCl medium. For formulation composition, refer to Table 1.

***In vitro* drug release studies**

The effect of the granulation process on drug release rate from the tablets (F1-F5) revealed that the granulation extended the drug release rate of all the prepared tablets significantly ($P < 0.05$) at most of the time points (Fig. 4 and 5).

The granulation process made the formulations F1 (10% (w/w)) and F2 (20% (w/w)) more resistant to rupture due to calcium carbonate effervescent behaviour and gave sufficient time for swelling and gel layer formation to control the drug release process (Fig. 6). This complies as well with DSC thermograms, refer to supplementary file, Fig. S1-S3. For the tablets based on sodium carbonate (F3 and F4), the decrease in their drug release rate following the granulation complies with the reduction in their porosity percentages after the granulation (Fig. 2), where penetration rate of the dissolution medium inside these tablets decreased as well as drug release rate (Fig. 6);

DSC profiles, supplementary file, Fig. S4-S5, confirmed the release data as there was a noticeable changes compared to those of F1 and F2 formulations.

For F5 tablets, after the granulation, their porosity level increased and their internal structure became stronger. This rapidly initiated a gel layer (due to more dissolution medium entrapment rate) that prevented the tablet rupture by the disintegration and reduced the drug release rate (Fig. 6) in comparison with the tablets prepared from the powder mixture.

As shown in Fig. 5, increasing the concentration of calcium carbonate from 10% (w/w) (F1) to 20% (w/w) (F2) in the tablets prepared from the powder mixture did not affect significantly ($P>0.05$) on their drug release rate at most of the time points because of the complete disintegration behavior, their DSC profiles (supplementary file, Fig. S2-S3 for powder mixtures) were similar. Yet, at larger part of the time points for the tablets prepared from the granules, increasing calcium carbonate concentration caused a non-significant ($P>0.05$) increase in the drug release (Fig. 6), also, their DSC profiles (supplementary file, Fig. S2-S3 for granules) were similar. Increasing the concentration of calcium carbonate from 10% (F1) to 20% (w/w) (F2) increased pore formation in the formed gel layer due to the entrapped gas bubbles, and this resulted in the higher drug release rate.

Increasing sodium carbonate concentration from 10% (F3) to 20% (w/w) (F4) caused a non-significant ($P>0.05$) decrease in the drug release rate from the tablets prepared from the powder mixtures at majority of the time points (Fig. 5) and a non-significant ($P>0.05$) increase from the tablets prepared from the granules at larger part of the time points (Fig. 6), where the ability of sodium carbonate to generate an alkaline microenvironment enhanced drug tablets to swell and to release the drug in almost similar rate. Nevertheless, as discussed earlier, a higher swelling rate was noted with cefalexin monohydrate tablets based on 20% (w/w) sodium carbonate (F4) compared to 10% (w/w) (F3). This agrees with the increase in the number of parts of sodium carbonate available for the hydrophilic polymeric mixture in these formulations which enhanced their swelling rate behaviour. This difference in the swelling rate did not cause a difference in the drug release rate of F3 and F4 tablets suggesting that the coherent hydrated gel microstructure that was formed at 10% (w/w) sodium carbonate (F3) reached a point of strength after which no further decrease in the drug release rate can be noted.

The effect of adding a gassing agent on the drug release rate of the tablets prepared from the powder mixture or the granules was evaluated by comparing the control formulation (F5) results with all the other formulations (F1-F4). Regarding the addition of calcium carbonate, a significant ($P<0.05$) lower dissolution rate of cefalexin monohydrate from F5 control tablets prepared from the powder mixture at most of the time points was noted (Fig. 5) compared to the formulation F1 (10% (w/w)). But the effect was not significant ($P>0.05$) at majority of the time points due to the complete disintegration behaviour of the tablets F1, F2, and F5. Nonetheless, for the tablets prepared from the granules, the drug release rate significantly ($P<0.05$) decreased at larger part of the time points on the addition of 10% (w/w) calcium carbonate and non-significantly

($P>0.05$) decreased on the addition of 20% (w/w) of it. For clarity, Table 5 reveals key general differences between the two gassing agents (calcium carbonate and sodium carbonate).

Table 5: Key general differences between the gassing agents (calcium carbonate vs sodium carbonate).

Characteristics (8,38)	Calcium carbonate	Sodium carbonate
Solubility in water	Practically insoluble	Highly soluble
Molecular weight, g/mol	100.0869	105.99
Chemical structure	A single Ca^{2+} ion (divalent), which forms a relatively strong electrostatic bond with the CO_3 group	Two Na cations (monovalent) bonded to a single CO_3 anion, highly dissociable in aqueous media
Effect of pH, reaction with acids	Slow, hence slow CO_2 generation and more sustained floating	Rapid, hence fast CO_2 generation and less buoyancy

Changing the (gassing agent: polymeric mixture) ratio in cefalexin monohydrate tablets facilitated the formation of a more cohesive hydrated gel microstructure. This explains the significant decrease in the drug release rate upon addition of 10% (w/w) calcium carbonate. Still, the absence of the significance effect at the higher level (20 % w/w) suggests that the effervescent activity of calcium carbonate increased the pore formation in the hydrated gel layer which may inverse the effect of the (gassing agent: polymeric mixture) ratio. Adding sodium carbonate as a gassing agent at 10% (w/w) (F3) or at 20% (w/w) (F4) decreased significantly ($P<0.05$), at majority of the time points, the drug release rate from the tablets either prepared from the powder mixture or the granules.

Regarding, the stability studies of the tablets based on calcium carbonate as a gassing agent (F1 and F2) and the control tablets (F5) stored either in the closed or the open containers, results showed a significant ($P<0.05$) increase in their drug release rate at majority of the time points. This complies with earlier discussion about the relaxation behaviour of the tablets during the storage time where a complete disintegration was reported (Table 4). An exception was noted for F1 tablets (10% calcium carbonate) which presented a partial control of the drug release (Fig. 7). This conforms to the *in situ* ability of the anionic alginate molecules to form a gel in the presence of multivalent cations such as calcium ions in aqueous medium, which fit in to the guluronate block structure like eggs in an egg box (42). During the storage process, especially under a relatively high moisture level (80%), this may generate an insoluble gel that could decrease the drug release rate. But, the low polymeric content in cefalexin monohydrate based tablets and the high calcium carbonate level for F2 (20% (w/w)) tablets counteracted the *in situ* cross linking effect and resulted in a complete disintegration behaviour (Fig. 7). This makes this formulation

with calcium carbonate successful and confirms the feasibility of using calcium carbonate as a stability indicating gassing agent within floating drug delivery systems.

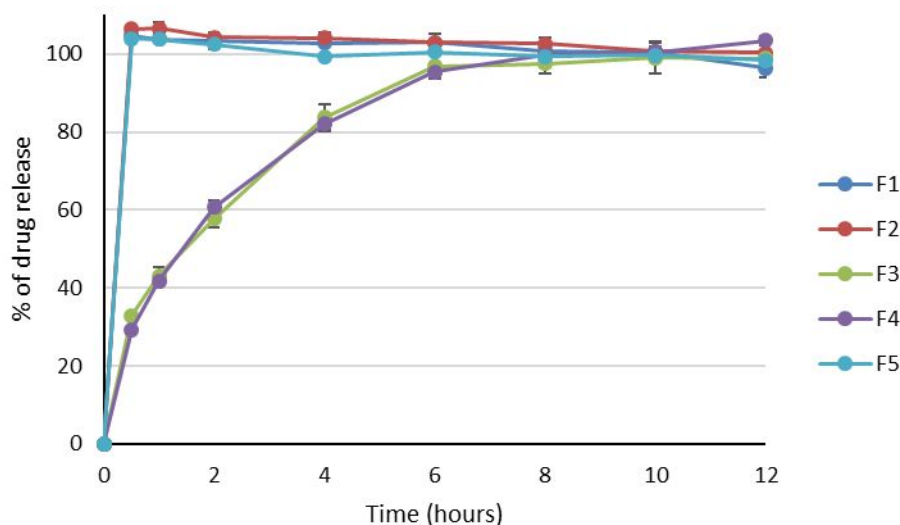


Fig. 5: Percentage of drug release of F1-F5 floating tablets in 0.1 M HCl medium before granulation.

Notes: The data represents the mean $\pm$ SD of three determinations. The compression force of the prepared tablets was adjusted to give 59-64 N crushing strength level. No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time. For formulation composition, refer to Table 1.

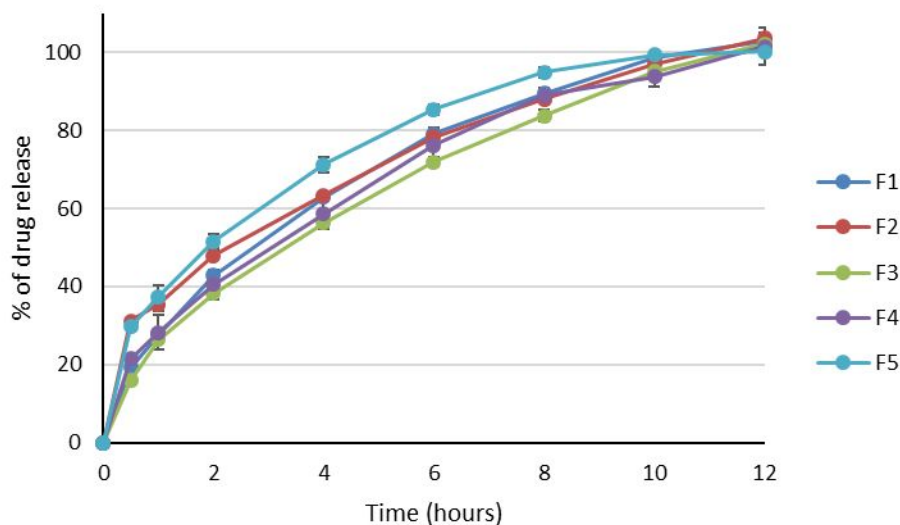


Fig. 6: Percentage of drug release of F1-F5 floating tablets in 0.1 M HCl medium after granulation.

Notes: The data represents the mean $\pm$ SD of three determinations. The compression force of the prepared tablets was adjusted to give 59-64 N crushing strength level. No significant change in the dissolution medium, macroenvironment, pH was recorded through the experiment time. For formulation composition, refer to Table 1.

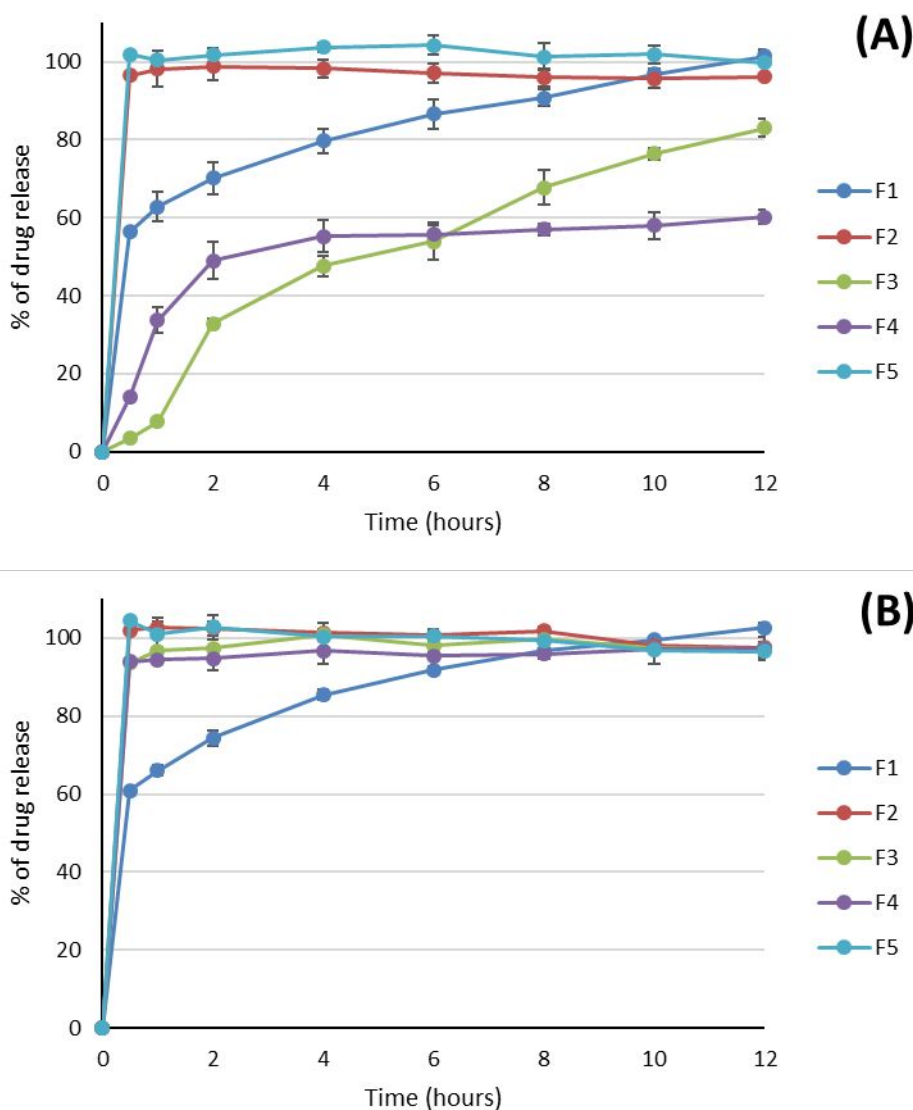


Fig. 7: Percentage of drug release of F1-F5 floating tablets in 0.1 M HCl medium after storage for 3 months at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $80\% \pm 5\%$ RH in open containers (A) and in closed containers (B). Notes: The data represents the mean $\pm$ SD of three determinations. The compression force of the prepared tablets was adjusted to give 59-64 N crushing strength level. No significant change in the

dissolution medium, macroenvironment, pH was recorded through the experiment time. For formulation composition, refer to Table 1.

Release data modeling and analysis

The *in vitro* drug release rate of the formulations F1-F5 were best explained by Higuchi's and Hixson-Crowell equations, as the highest linearity (R^2) values were obtained (Table 6). This indicates that the release of cefalexin monohydrate from the evaluated floating matrices (F1-F5) as a square root of time was dependent process based on Fickian diffusion alongside with a change in diameter and surface area of the matrices with the progressive dissolution process as a function of time. Korsmeyer–Peppas equation (Equation 11) was used, as it describes the drug release from polymeric systems, to evaluate the effect of the granulation process, and the gassing agent concentration on the drug release mechanism of the prepared tablet formulations (F1-F5) (Table 7).

The drug release results of F1-F5 tablets fitted into Korsmeyer–Peppas equation as the correlation coefficients (R^2) greater than 0.98 were obtained in all the tablets except for the tablets prepared from the granules of the formulations F2 (20% (w/w) calcium carbonate. But there were insufficient data points on the release profile in order to provide accurate values for the tablets prepared from the powder mixture of the formulations F1, F2 (Fig. 5) and F5 (Fig. 5). The values of the release rate constant (K_p) were consistent with the *in vitro* drug release results. The granulation process decreased the release rate constant (K_p) of the tablets F3 and F4 based on sodium carbonate as a gassing agent, however the effect was not clear for the other formulations due to the insufficient data points.

For calcium carbonate, increasing its level decreased the release rate constant (K_p) at 10% (w/w) concentration (F1), but, at 20% (w/w) concentration (F2), it increased K_p values up to almost similar level of the control tablets (F5, 0% (w/w)). Additionally, raising sodium carbonate content decreased the drug release rate constant (K_p) at 10% (w/w) level (F3) and slightly increased it at the higher level (F4). The effect of these factors on the drug release mechanism was also evaluated through the release exponent (n) values.

The granulation process changed the drug release mechanism for the formulation F3 (10% (w/w) sodium carbonate) from release by diffusion (Fickian) to release by diffusion and polymer relaxation (non-Fickian) and retained it by non-Fickian release for the formulation F4 (20% (w/w) sodium carbonate).

Increasing calcium carbonate concentration in the tablets of the granules origin changed the release mechanism from non-Fickian at 10% (w/w) (F1) to Fickian release at 20% (w/w) (F2). This suggests that calcium ion concentration available in the formulations F1 (10% (w/w)) was insufficient to properly cross-link with the anionic alginate molecules of the polymeric mixture. Still, the concentration was enough in the formulations F3 (20% (w/w)) as only diffusion mechanism became the controller of the drug release.

For the tablets based on sodium carbonate as a gassing agent (F3 and F4), a change in the drug release mechanism from Fickian to non-Fickian release was noted by increasing its concentration from 10% to 20% (w/w) in the tablets prepared from the powder mixtures.

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

Fickian release mechanism (release by diffusion) was reported in the control tablets (F5) prepared from the granules. Adding the gassing agents (calcium carbonate, or sodium carbonate) changed the release mechanism from release by diffusion (F5) to release by diffusion and polymer relaxation in the tablets prepared from the granules (F1-F4 respectively). This could be related to the movement of the generated carbon dioxide bubbles from the internal to the peripheral sides of the floating tablets, which increased the mass loss or the polymeric erosional behaviour.

Effects of storage stability on morphology and quality of the prepared floating tablets

In order to investigate morphological changes of all the tablets (F1-F5) before and after storage for 3 months at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $80\% \pm 5\%$ RH in closed or open containers, tablets were evaluated visually. The formulations which were loaded with sodium carbonate showed a change in the colour from white to yellow (F3) or dark brown (F4) in the open container tablets, and a very slight change in colour was seen in tablets stored in closed ones. The intensity of the colour was proportional to sodium carbonate concentrations in the related formulations. This agrees with the results of DSC and FTIR that an interaction occurred between these gassing agents and cefalexin monohydrate after storage in the open containers (Supplementary file, Fig. S9-10 and Fig. S19-20). Since sodium carbonate is water soluble, direct exposure to a stressful humidity level (80%) for 3 months could increase the pH of the matrix microenvironment in a concentration dependent rhythm causing degradation for cefalexin monohydrate as it is unstable in such conditions (10,12). F1 and F2 calcium carbonate-based formulations and F5 control formulation did not show change in colour which approves that calcium carbonate is a promising gassing agent, this agrees with the DSC and FTIR data (Supplementary file, DSC Fig. S7-8 and Fig. S11 and FTIR Fig. S17-18 and Fig. 21). Consequently, it is suggested that all cefalexin monohydrate floating systems based on such gas forming agents should be packaged by the pharmaceutical companies in tightly closed containers with an eye-catching label to direct patients for good practice.

Table 6: Release rate constants (*k*), and correlation coefficients (*R*²) calculated after fitting the release profiles of F1-F5 into of zero order, first order, Hixson-Crowell, and Higuchi drug release mathematical models.

Formulation	Origin of prepared tablets	Drug release mathematical model							
		Zero order		First order		Hixson-Crowell		Higuchi	
		<i>R</i> ²	<i>K</i> ₀ (<i>mg</i> * <i>h</i> ⁻¹)	<i>R</i> ²	<i>K</i> ₁ (<i>h</i> ⁻¹)	<i>R</i> ²	<i>K</i> _{HC} (<i>mg</i> ^{1/3} * <i>h</i> ⁻¹)	<i>R</i> ²	<i>K</i> _H (<i>mg</i> ^{1/2} * <i>h</i> ⁻¹)
F1	Powder	0.8903	-0.4031	N.A	N.A	0.8770	-0.0856	0.8780	-1.561
	Granules	0.9605	8.3348	0.9030	0.3763	0.9850	0.3179	0.9981	33.142
F2	Powder	0.9171	-0.5527	N.A	N.A	0.8955	-0.0874	0.9291	-2.170
	Granules	0.9781	7.0334	0.9311	0.3022	0.9869	0.2691	0.9972	27.702
F3	Powder	0.8477	7.0778	0.9777	0.4670	0.9500	0.3441	0.9406	29.082
	Granules	0.9809	8.0994	0.9436	0.2692	0.9884	0.2646	0.9995	31.972
F4	Powder	0.8560	7.4062	0.9204	0.6941	0.9916	0.4969	0.9501	30.436
	Granules	0.9674	7.8763	0.9840	0.2671	0.9965	0.2632	0.9945	31.151
F5	Powder	0.7387	-0.4828	0.5993	0.0811	0.6453	-0.2584	0.8332	-2.000
	Granules	0.9419	7.4527	0.9236	0.4459	0.9957	0.3343	0.9919	29.832

For formulation composition, refer to Table 1.

Table 7: Korsmeyer-Peppas kinetic parameters of F1-F5 cefalexin monohydrate tablet formulations.

Formulation	Origin of prepared tablets	Korsmeyer-Pepas		
		R^2	n	$K_p (h^{-n})$
F1	Powder	N.A	N.A	N.A
	Granules	0.9978	0.5837	0.2831
F2	Powder	N.A	N.A	N.A
	Granules	0.9492	0.3107	0.376
F3	Powder	0.9995	0.4052	0.4341
	Granules	0.9945	0.6009	0.2505
F4	Powder	0.9999	0.5267	0.4198
	Granules	0.9961	0.4877	0.2924
F5	Powder	N.A	N.A	N.A
	Granules	0.991	0.3985	0.3856

Notes: N.A: There are insufficient data points on the release profiles $\leq 60\%$ drug release in order to provide accurate values. For formulation composition, refer to Table 1.

Conclusions and future perspective

In this study, effervescent floating tablets of cefalexin monohydrate were successfully compacted using calcium carbonate, or sodium carbonate as a gas forming agent and a (1:1) binary mixture of hydroxyethyl cellulose and sodium alginate as a drug retarding polymeric matrix. All the prepared tablets through the granulation showed acceptable physical properties regarding weight and drug content uniformity tests. Friability results of calcium carbonate based formulations F1 (10% (w/w)) and F2 (20% (w/w)), and cefalexin monohydrate control tablets F5 exceeded the BP limit of friability ($< 1\%$).

Raising the gassing agent (calcium carbonate, or sodium carbonate) concentration, in the tablets prepared from the granules, decreased their floating lag time results and increased their floating duration time. Cefalexin monohydrate control tablets prepared following the granulation showed acceptable floating capacity behaviour due to the rapid swelling rate profiles which reduced their tablets density to initiate and to maintain the floating process. The drug release rate indicates a release by non-Fickian mechanism except for F2 tablets based on 20% (w/w) calcium carbonate as a gassing agent and the control tablets of cefalexin monohydrate (F5) which fitted to Fickian release mechanism. The addition of the gassing agents enhanced the movement of the generated carbon dioxide bubbles from the internal to the peripheral sides of the floating tablets which influenced the polymer erosional behaviour and changed cefalexin monohydrate release mechanism from release by diffusion (Fickian) to release by diffusion and polymer relaxation (non-Fickian). However, 20% (w/w) concentration of calcium carbonate was enough to influence the in-situ ability of the anionic alginate molecules to be cross linked and changed the drug release mechanism to release by diffusion (Fickian). The tablets could float on the surface of the dissolution medium and the drug release was sustained over 10 h.

DSC and FTIR indicate instability of the formulation based on sodium carbonate (F3 and F4) after storage for 3 months at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $80\% \pm 5\%$ RH in the open containers (Supplementary file, Fig. S9-10 and Fig. S19-20). Still, the closed containers showed better physical stability of cefalexin monohydrate loaded in such formulations. The tablets prepared with 10% (w/w) calcium carbonate (F1) were promising with respect to their floating lag time, floating duration, swelling ability, sustained drug release rate, and physical stability results. Accordingly, calcium carbonate revealed promising results not only with cefalexin monohydrate but also with pentoxifylline in our previous research (37), and this makes the chosen ingredients (for this research) and their quantities feasible to be applied with other drugs intend for gastroretentive delivery systems.

Further formulation development is worth accomplishing in the future to achieve a suitable floating tablet dosage form to benefit the pharmaceutical industry. Applying factorial design would be valuable to extend the study to cover more ratios of the polymeric mixture; and more concentrations of calcium carbonate to achieve the best possible combination. A well-designed *in vivo* study in appropriate animal model will be essential in the future to verify the *in vivo* efficacy of the most promising floating tablets formulation.

Author contribution

Safwan Abdel Rahim: writing – original draft methodology, investigation, formal analysis, visualization. Amal Ali Elkordy: supervision, conceptualization, writing – review and editing.

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No potential conflict of interest was reported by the authors.

Data availability statement

All data included in the manuscript and within the supplementary file

Additional information

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Data availability statement

All data included in the manuscript and within the supplementary file