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Research Paper

Application of a novel symmetrical shape factor to gastroretentive matrices as a measure of swelling synchronization and its impact on drug release kinetics under standard and modified dissolution conditions

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Abstract

Objectives We have assessed the kinetics of drug release in relation to the full or partial hydration and swelling of matrices under standard and modified United States Pharmacopeia (USP) apparatus II using a novel index, defined as the symmetrical shape factor. The symmetrical shape factor describes the regularity of the hydration rate of the matrix perimeter relative to its central regions.

Methods Monolithic and three-layer matrices based on hypromellose, polyethylene oxide, Kollidon SR, theophylline, diltiazem hydrochloride and alfuzosin hydrochloride were subjected to dissolution testing.

Key findings Our results indicated that Kollidon SR matrices and the three-layer composite systems with and without effervescing components were not significantly affected by the dissolution conditions. However, in the case of the floating monolithic systems based on hypromellose and polyethylene oxide, both release profiles and swelling dynamics in accordance with the similarity factor (f_2) and symmetrical shape factor values were significantly influenced.

Conclusions The symmetrical shape factor values were positively impacted. Consequently the drug release kinetics were more predictable and reproducible. The modified USP method resulted in a more synchronized axial and radial swelling with symmetrical shape factor values approaching unity. Data further indicated that the modified USP method provided for complete matrix hydration and swelling as the dosage form remained fully submerged, allowing for more reliable release mimicking the in-vivo conditions.

Keywords dissolution testing; gastroretentive systems; swelling matrices; symmetrical shape factor; synchronized hydration

Introduction

As an important analytical tool, in-vitro dissolution has an extensive application in all stages of drug development. Since it is sensitive enough to discriminate variables in formulation and processes, dissolution testing has been employed as a quality control tool in all official pharmacopoeias for solid oral dosage forms to evaluate batch-to-batch consistency. With well defined in-vitro and in-vivo correlation, dissolution can not only verify formulations with the most desirable release, but can be used as a surrogate for in-vivo bioavailability, in scale-up and post-approval changes as well as in bioequivalency studies for lower strength generic versions of similar formulations.[1,2]

Gastroretentive dosage forms have been the topic of interest in recent years as a practical approach in drug delivery to the upper gastrointestinal tract or for release prolongation and absorption.[3–5] These dosage forms are particularly suitable for drugs that have local effects on the gastric mucosa in the stomach, such as delivery of drugs used for *Helicobacter pylori* treatment.[6] Other drug candidates include drugs that are mainly absorbed in the stomach or upper small intestine, or drugs that are unstable in the basic environment of distal intestine and colon or those with low solubility at elevated pH conditions (i.e. weak bases).[7] Various strategies to achieve gastric retention have been proposed and some successfully commercialized (e.g. matrix tablets containing a high dose of metformin hydrochloride or a low dose of alfuzosin hydrochloride).[8] Among these strategies, the swellable low-density floating hydrophilic matrix systems have been studied extensively in the last two decades.[9–12]

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For in-vitro dissolution studies of gastroretentive systems numerous approaches have been proposed.[1,4,13] Among various United States Pharmacopeia (USP) recommended dissolution methods, the USP basket method is not considered by the scientific community due to limited space within the basket and sticking issues. Instead, the USP apparatus 2 (paddle) is frequently employed for the evaluation of swellable and floating dosage forms. However, one of its major drawbacks is the incomplete exposure of the floating dosage form to the dissolution medium. During dissolution one radial surface or portion of the floating system is exposed directly to the air above the surface of the media. Thus the hydration of the exposed area and its periphery will be adversely impaired, and drug release suppressed from these areas. Several papers have highlighted the importance of full exposure and have proposed modifications to the standard USP methods.[13–15] One of the strategies suggested was adding a wire mesh at a height of 72 mm from the bottom of the vessel or a ring and mesh assembly below which the dosage form is placed.[14,15] Another modification described insertion of two meshes in the vessel and the floating system was placed between those two meshes.[13] For these modifications, the floating dosage forms have to be placed into the dissolution vessel before addition of media. In addition, placement of the mesh assembly in the dissolution vessel usually causes deviation from the standard hydrodynamic conditions.

The purpose of this study was to develop a rationally and scientifically sound modification to the USP apparatus 2 to provide complete media exposure of the swellable gastroretentive dosage forms without compromising the required dissolution specifications, hydrodynamic conditions and calibration compliances.

Materials and Methods

Materials

Alfuzosin hydrochloride was purchased from Lunan Pharmaceuticals (Linyi, China). Kollidon SR was donated by BASF Corporation (Ledgewood, NJ, USA). Polyethylene oxide N60-K and hypromellose (hydroxypropyl methylcellulose) K15M were purchased from Dow Chemical Company (Midland, MI, USA). Theophylline, diltiazem hydrochloride and magnesium stearate were purchased from Sigma-Aldrich (St Louis, MO, USA).

System design

A stainless steel mesh (mesh no.16) was introduced into the vessel as a modification to the USP apparatus 2, as shown in Figure 1. When the dissolution vessel was filled with 900 ml dissolution media, the inserted mesh was in contact with the surface of the dissolution media fully submerged. The mesh was positioned at a fixed height with the help of proper supporting racks with lengths of approximately 4 cm. Two openings in the mesh were produced to provide for the insertion of the paddle shaft and sampling pipette. Once floatable tablets or capsules were dropped in the vessel, they would eventually float, but would remain fully submerged under the mesh during the dissolution study.

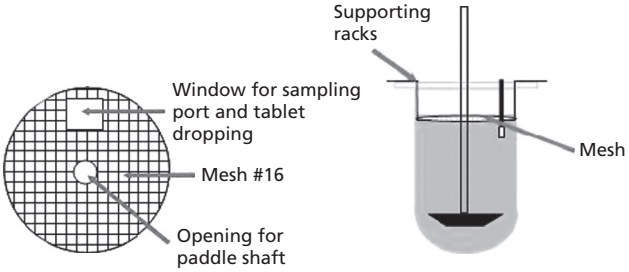

Figure 1 Modified USP apparatus II for release determination of floating delivery systems

Evaluation of various formulated matrices

To investigate the impact of mesh on the performance of floating systems, monolithic, three-layer composite tablets with and without effervescent were investigated. Monolithic noneffervescent matrices involved were based on hypromellose K15M, Kollidon SR and polyethylene oxide N60-K, respectively. The effervescent multilayer tablet based on polyethylene oxide similar to previous work was used.[12] Model drugs incorporated in different polymeric matrix composites were theophylline (sparingly soluble), diltiazem HCl and alfuzosin HCl (highly water soluble drugs). Finally, a noneffervescent three-layer commercialized tablet (Uroxatral, Sanofi-aventis, Bridgewater, USA) containing 10 mg alfuzosin HCl, obtained from the university hospital, was tested also.

All monolithic matrices contained 300 mg release-rate retarding polymer and 10 mg active ingredient. Ingredients of the formulation were mixed thoroughly in a mortar and pestle. Tablets were produced by direct compression on a Carver laboratory press (Fred S. Carver Inc., Menomonee Falls, WI, USA) using a 7 mm diameter flat-face punch. Magnesium stearate in acetone was used to lubricate the die. The monolithic matrices produced had a hardness of 70 ± 5 N with thickness of 3.10 ± 0.05 mm. The polyethylene oxide-based multilayer formulation weighed 600 ± 5 mg, had thickness of 5.45 ± 0.05 mm and hardness of 70 ± 7 N. Tablet hardness was measured in six replicates using a tablet hardness tester (model 2E/106, series 7410, Schleuniger & Co., Solothurn, Switzerland).

Dissolution study

Dissolution studies were carried out under sink conditions in pH 2.0 HCl buffer using a modified and USP 27 standard apparatus 2, in a Vankel VK7000 dissolution machine (Cary, NJ, USA) equipped with an autosampler. During dissolution the dissolution media were maintained at 37 ± 0.5°C and the paddle speed was 100 rev/min, in compliance with generally accepted hydrodynamics representing stomach conditions. Samples through a 40-μm filter were taken automatically at each sampling time point. Drug release from monolithic matrices of hypromellose, polyethylene oxide and Kollidon SR and composite layered matrices were detected by UV absorbance (theophylline at 271 nm, diltiazem HCl at 240 nm and alfuzosin HCl at 244 nm) using a UV spectrometer (Cary 50 UV-visible spectrophotometer, Cary, NJ, USA). All dissolution tests were performed in triplicate.

Dissolution data analysis

To compare the dissolution profiles of the same delivery system under different dissolution test conditions or different formulations with the same active ingredient, two indices or fit factors were used.[16] This approach is model independent, and it uses mathematical indices to define difference and similarity factors (f_1 and f_2, respectively) for comparison of entire dissolution profiles:

Difference factor, f_1:

$$f_1 = \left(\sum_{t=1}^{n} |R_t - T_t| \Big/ \sum_{t=1}^{n} R_t \right) \times 100 \quad (1)$$

Similarity factor, f_2:

$$f_2 = 50log\{[1 + 1/\mathrm{n} \times \sum_{t=1}^{n} W_t(R_t - T_t)^2]^{-0.5} \times 100\} \quad (2)$$

Where R_t and T_t are the percent of drug dissolved at each time point for the reference (i.e. dissolution under standard conditions) and test product (i.e. dissolution under modified conditions proposed in this work), respectively, n is the number of dissolution sample times, t is the time sample index and W_t is an optional weight factor (in the current work $W_t = 1$). In general, to ensure sameness between the profiles, f_1 should be in the range of 0–10, and f_2 in the range of 50–100. To calculate the fit factors, the mean dissolution values from both profiles at each time interval were used, including only one pull point at greater than 85% level of drug release to avoid bias in the similarity assessment. In addition, appropriate statistical tests (i.e. Student's t-test, Mann–Whitney test) were performed to identify the differences observed under various conditions in the research work.

Dynamic texture analyses of swelling matrices

At predetermined intervals during dissolution the partially hydrated and swollen matrices were removed and subjected to textural profiling to determine gel layer thickness and movement of the water penetration front at the matrix perimeter and central region of the tablets. Three tablets were subjected to testing for each time point and tested tablets were discarded. Textural analysis was performed using a TA.XT2 Texture Analyser equipped with a 5 kg load cell and Texture Expert software (Texture Technologies Corp, Scarsdale, NY/Stable Micro Systems, Godalming, UK). The force–displacement–time profiles associated with the penetration of a 2 mm, flat-tipped steel probe into the swollen matrices (i.e. peripheral and central regions of hydrated matrix) were monitored at a data acquisition rate of 200 points/s. Once a trigger force of 0.005 N was detected the probe was advanced into the sample at a test speed of 0.1 mm/s until it reached the glassy region.[13] In this work a novel index, the symmetrical shape factor (SSF), has been proposed and defined as the ratio of the peripheral gel thickness to the central gel thickness, its value indicating the potential asymmetrical swelling of the entire matrix at a particular time point:

$$SSF = T_p/T_c \quad (3)$$

where T_p and T_c are the peripheral and central gel thickness, respectively. The peripheral thickness was measured approximately 2 mm from the swelling matrix edge. All measurements were carried out in triplicate. The SSF value of one represents uniform hydration and swelling of the entire matrix, while values smaller or greater than one indicate non-uniform swelling of the matrix.

Results

Figure 1 demonstrates the schematics of modification to the standard dissolution apparatus for swelling gastro-floatable systems. In Figure 2 the results of dissolution profiles for various matrices studied under modified and standard dissolution conditions are presented. The inset in Figure 2 represents release profiles when standard apparatus was used. Figures 3 and 4 show the results obtained when matrices made of hypromellose and polyethylene oxide were subjected to dissolution studies with and without mesh insertion into the dissolution vessels. The SSF values calculated at different time points, together with their variations and actual photographs of swollen matrices, demonstrated significant differences under the given conditions. Figure 5 illustrates the associated changes measured when Kollidon SR matrices were subjected to dissolution conditions with and without mesh. Calculations of density changes were based on wet and dry weight comparisons at different time points. In Figure 6 the relationship between the SSF value and time for the multilayer composite matrix containing effervescent ingredients as a floating aid in the system under standard and modified dissolution conditions is presented. Analysis of release profiles were fitted to equation 4 to identify the possible release mechanisms associated with each matrix composition and comparative results of release similarities among all the dosage forms studied in this work are presented in Table 1.

Discussion

The in-vitro assessment of gastroretentive dosage forms is especially challenging and important as there are no well

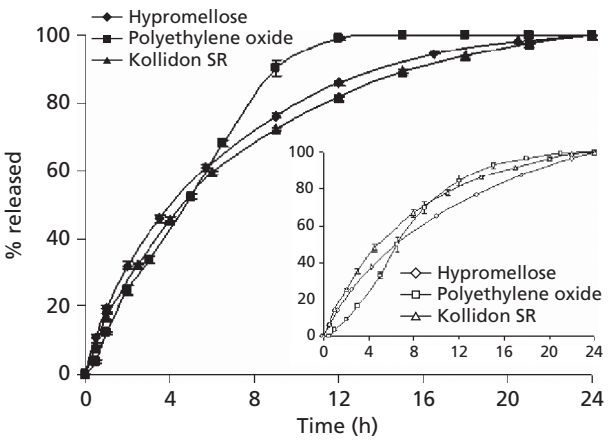

Figure 2 In-vitro release profiles for theophylline and diltiazem HCl from swellable matrices using modified and standard (inset) USP dissolution apparatus. The matrices for theophylline were based on hypromellose K15M and polyethylene oxide N60-K, and for diltiazem HCl from a Kollidon SR-based matrix. $n = 5$.

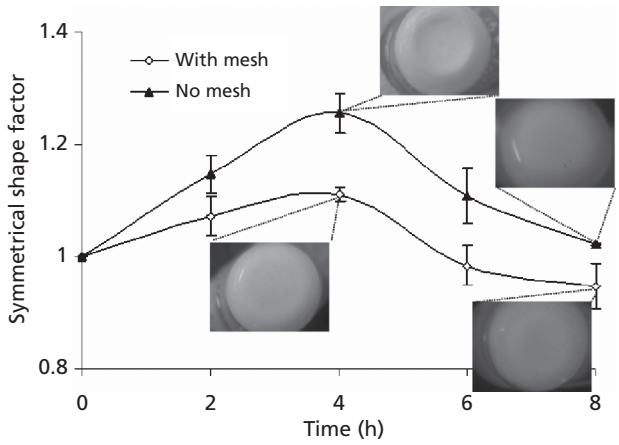

Figure 3 Relationship between symmetrical shape factor and time for hypromellose K15M matrices. HCl buffer, pH 2.0, at 100 rev/min was used (n = 3).

established dissolution methods for swelling gastro-floatable delivery systems. In the following we have assessed drug release and floating issues related to the various dosage forms and have made pertinent recommendations relevant to each system.

Monolithic matrices based on hypromellose K15M

The dissolution profiles of each monolithic matrix with both the modified and standard paddle apparatus are depicted in Figure 2. For matrices based on hypromellose K15M, the introduction of mesh (proposed modification) significantly promoted the release of theophylline. With mesh approximately 50% of the drug was released after approximately 250 min, while it took 490 min to achieve the same level of drug release with the standard USP apparatus 2 (Figure 2, inset). Correspondingly a shorter *t80%* of approximately 600 min was associated with the modified apparatus, compared with 800 min for the standard USP apparatus.

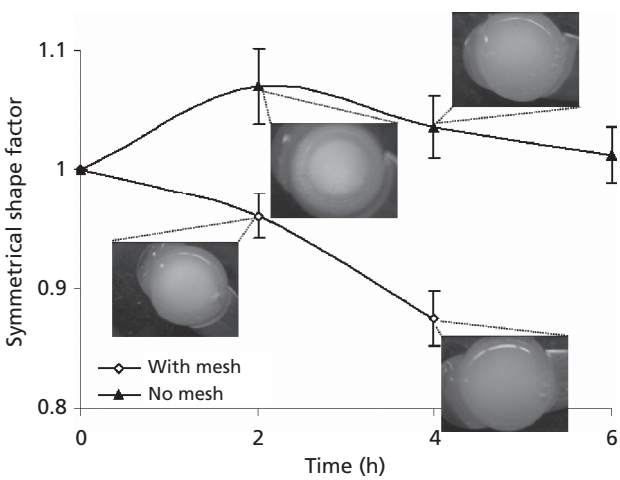

Figure 4 Relationship between symmetrical shape factor and time for polyethylene oxide N60-K matrices. HCl buffer, pH 2.0, at 100 rev/min was used (n = 3).

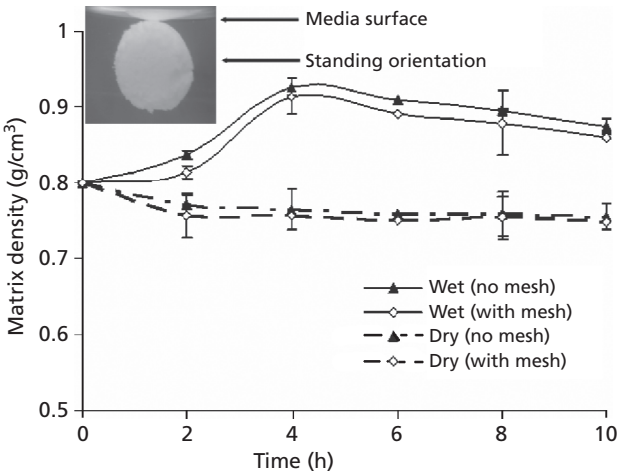

Figure 5 Calculated density change for Kollidon SR-based matrices during dissolution. Dissolution was under wet or dry conditions using the modified or standard USP methods. Floating orientation in the absence of mesh is depicted in the insert picture (n = 3).

Generally drug release from a hydrophilic delivery system follows diffusion, system erosion or the combination of both mechanisms. For a delivery system based on hypromellose, the active ingredient may be released by both direct dispersion via system erosion and diffusion through the gel layer around the hydrated matrix. With the standard USP apparatus 2 it was observed that one surface of the floating tablet was exposed to the air above the media. The exposed regions negatively impacted the extent of system swelling and erosion. With the introduction of mesh, all tablet surfaces remained in contact with the dissolution media which in turn allowed for greater symmetry in system swelling and erosion. The shape changes of systems were assessed by the SSF as a function of time (Figure 3). Under perfect conditions the SSF should have a value close to unity. Since the penetration of dissolution media into the matrix takes time and the

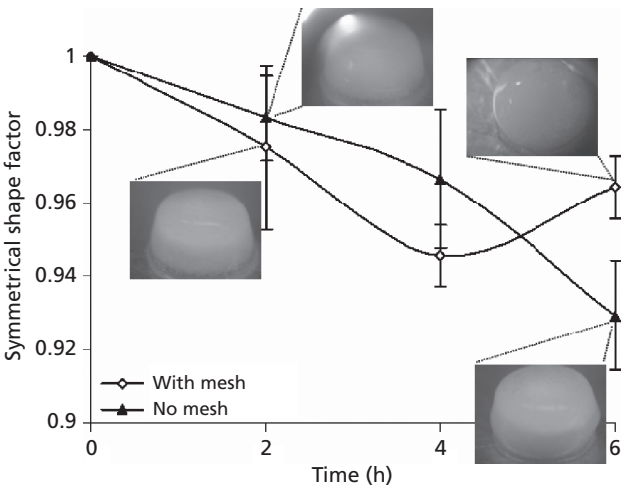

Figure 6 Relationship between symmetrical shape factor and time for an effervescent multilayer composite. HCl buffer, pH 2.0, at 100 rev/min was used (n = 3).

Table 1 Release profile curve fitting to equation 4 ($M_t/M_\infty = kt^n$) and dissolution data analysis[a]

Formulation	k (min^{-n})		n		f_{1*}	f_{2*}
	Mesh	No mesh	Mesh	No mesh		
Hypromellose K15M	2.38	1.26**	0.56	0.62	34	45
Polyethylene oxide 60-K	0.28	0.08**	0.92	1.07*	59	40
Kollidon SR	1.42	1.34	0.63	0.66	3	92
Uroxatral	0.65	0.64	0.73	0.72	10	68
Effervescent system	0.02	0.04**	0.96	1.00	10	74

[a]In fit factor data analysis USP standard paddle method at 100 rev/min dissolution data were used as reference (R_t). *$P < 0.05$ (Student's t-test, $n = 3$).

hydration process at the periphery and central regions differ due to the density variations associated with compression force and physicochemical properties of polymers used, the SSF tends to be less than unity in the early phase of dissolution and closer to unity in the late phase. The nature of hydration and swelling is also dependent on the intrinsic characteristic of each material, which is closely related to its physicochemical and textual properties. With the modified apparatus, in the first 4 h of dissolution the SSF or matrices based on K15M showed less deviation from unity compared with those with the standard dissolution apparatus. In the former a relatively more symmetrical system swelling and erosion in the early time period was observed, while the SSF in the latter case was significantly greater. The SSF values beyond 4 h gradually shifted toward unity and in the case of the modified USP method the overall erosion rate resulted in a SSF value of < 1.0 (Figure 3). The SSF values between modified and standard dissolution conditions were analysed using the Mann–Whitney test and were found to be significantly different ($P < 0.05$).

The impact of changes in SSF value on release kinetics was also evaluated. An exponential equation can be used to fit the two dissolution profiles up to 80% release:

$$M_t/M_\infty = kt^n \quad (4)$$

The corresponding values of constant k for release profiles with modified apparatus was nearly two-times greater than the one derived from the standard USP dissolution condition (i.e. = 2.375 $min^{-0.56}$ vs 1.259 $min^{-0.62}$, $P < 0.05$, Table 1), while the values of exponent n were relatively close (i.e. n = 0.56 vs n = 0.62). Thus the dissolution system modification promoted swelling and erosion of the matrix in a more synchronized manner relative to the standard USP conditions for matrices based on K15M (see Table 1). Correspondingly, the value of both f_1 and f_2 factors demonstrated absence of dissolution similarity (Table 1).

Monolithic matrices based on polyethylene oxide N60-K

In polyethylene oxide specifically the extent of polymer swelling and/or erosion is fundamentally controlled by the degree of polymerization. Hydrophilic polymers with relatively low molecular weight would undergo an extensive but fast swelling and erosion, while for those with a higher molecular weight erosion and swelling would be slow. In general release rates up to approximately the 50% level were similar for all the matrices. However, due to the nature and low molecular weight of polyethylene oxide N60-K, theophylline was released at a higher rate from these matrices relative to hypromellose K15M beyond the 50% level (Figure 2). For polyethylene oxide N60-K-based matrices complete drug release with the modified dissolution condition occurred at approximately 11 h compared with 22 h under standard USP dissolution conditions.

The change of SSF as a function of time for monolithic matrices based on polyethylene oxide N60-K is depicted in Figure 4. With the modified apparatus, the corresponding values of SSF decreased in a semi-linear manner, indicating continuous system swelling and erosion. No measurements were taken beyond 6 h. In general, polyethylene oxide-based matrices demonstrated more uniform swelling and erosion relative to hypromellose K15M matrices. At 2 h with the standard USP apparatus 2 only the peripheral parts of the upper surface of matrices of polyethylene oxide N60-K were hydrated (Figure 4, see insert). This resulted in much lower theophylline release compared with release from the modified dissolution apparatus, where full hydration of the matrix was accomplished (9 vs 24%). At 4 h there were no apparent differences in the physical appearance between the swollen matrices of either system; however, release profiles were significantly different, as evident from the f_1 and f_2 values (see Table 1). This indicated that the textural character of the matrix interior significantly influenced the kinetics of drug release (see Table 1). Values of SSF calculated under the two different dissolution conditions were significantly different ($P < 0.005$, using Mann–Whitney test).

Monolithic matrices based on Kollidon SR

For monolithic matrices based on Kollidon SR, dissolution conditions with or without mesh had no impact on its release performance or physical appearance (Figure 2). The corresponding f_1 and f_2 values were 3 and 92 relative to standard conditions. This was confirmed by the calculated values of kinetic release parameters (see Table 1). Kollidon SR is a physical mixture of polyvinyl acetate and povidone or Kollidon 30. It is made by spray drying of a mixture of polyvinyl acetate and povidone (polyvinyl acetate : povidone = 4 : 1). The soluble povidone component leaches out of the matrix during dissolution, thereby creating pores for the active component to diffuse out. The polyvinyl acetate, being an insoluble component, maintained the integrity of the matrix structure during dissolution. It appeared that sustained drug release from the Kollidon SR-based matrix was mainly

via soluble polymer contents and drug dissolution and diffusion. Its sustained-release properties were unaffected by erosional dynamics, ions, salts or hydrodynamic conditions.[17–19] Theoretically the increased media exposure brought about by the application of the mesh should increase the dissolution of the povidone component of Kollidon SR and generate more pores for diltiazem HCl release. However, it appeared that the povidone dissolved rapidly and the system tended to hydrate irrespective of dissolution conditions (Figure 5). With either of the dissolution methods the total dry mass of matrices based on Kollidon SR levelled off after 2 h dissolution; this corresponded to a loss of approximately 75% of the povidone content of Kollidon SR based on dry mass calculation. The relative location and orientation of the Kollidon SR based matrices during dissolution under the modified and standard conditions did not have any effect on drug release kinetics. Under standard dissolution conditions at 100 rev/min, it was found that Kollidon SR matrices frequently kept on floating in the dissolution media, with a 'standing' position near the surface of the dissolution media instead of a generally observed horizontal orientation when modified apparatus was used (see Figure 5, insert picture). However, the corresponding wet density peaked at 4 h (0.93 and 0.91 g/cm^3 for standard and modified apparatus, respectively), then declined gradually to approximately 0.87 g/cm^3 in both cases at approximately 10 h (see Figure 5). Neither values of wet nor dry density calculated under the two different dissolution conditions were significantly different ($P > 0.05$, Mann–Whitney test).

Dissolution of the commercialized gastro-floatable three-layer tablet

The commercialized tablet contained 10 mg alfuzosin HCl as the active ingredient. It was a three-layer floating controlled-release system with the aim to continuously deliver drug in the stomach and on to the upper part of the intestine. The application of mesh had no impact on the release of alfuzosin HCl from the commercially designed system (the corresponding f_1 and f_2 values were 10 and 68, respectively). This indicated that the multilayered system was more robust than the simple monolithic systems based on hypromellose and polyethylene oxide (Table 1). It should be noted that the drug layer was sandwiched between two barrier layers and drug release mainly occurred through the radial surfaces of the middle layer. The barrier layers tend to provide for floatation and less surface exposure to achieve zero-order release.

The designed three-layered effervescent floating system

Since the floating lag time of the commercial product was 0.5–1 h, this might have increased the possibility of it being emptied out of the stomach before its full floatation. To reduce the floating lag time, a three-layer effervescent floating system was designed.[12] The newly designed system demonstrated no lag time for floating and provided comparable dissolution behaviour with that of the commercial product. Similar to the commercialized three-layer system, the mesh had no impact on the release performance of the three-layer effervescent floating system, and the calculated f_1 and f_2 values were 10 and 74, respectively (Table 1). Although significant differences between values of release constants ($P < 0.05$, Table 1) were observed, this did not influence the overall release profiles calculated by similarity and difference factors due to their small values (i.e. $k = 0.02$ and 0.04). The effervescent layered composite had two barrier layers, one layer with the aim of suppressing burst release and containing the high molecular weight hydrophilic polymer polyethylene oxide, which would undergo extensive swelling during dissolution. The other barrier layer consisting of low molecular weight polyethylene oxide, would undergo extensive swelling and erosion. It was apparent that introduction of mesh in the vessel would improve the overall swelling and erosion of the swollen matrices and it was likely to impact the shape factor too. However, the corresponding SSF values at each time point and the physical appearances of the swollen three-layer matrices (Figure 6) were similar. As each layer in the composite had its own swelling and erosion property, in the late time period at approximately 6 h the physical appearance of the swollen composite appeared to be highly asymmetrical (see Figure 6). For the multilayered effervescent system, calculated values of SSF under different dissolution conditions during the six-hour period were not significantly different (Mann–Whitney test; $P > 0.05$).

Conclusions

A simple modified USP apparatus 2 was designed which introduced complete dissolution media exposure to the floating drug delivery systems. For monolithic systems based on hydrophilic polymers such as hypromellose and polyethylene oxide, the modified dissolution method promoted the overall system swelling and erosion in a more synchronized manner based on SSF values, so that more drug was released in a predictable manner. In the case of Kollidon SR matrices, due to the rapid release of the povidone component and absence of extensive swelling relative to hypromellose and polyethylene oxide-based matrices, the modified dissolution system had no impact on the release performance of the system. In comparison with monolithic systems, layered systems were more robust and were least impacted by the dissolution modification proposed. Both effervescent and noneffervescent floating systems have been investigated using this modified USP apparatus 2 and no significant differences in their release kinetics were observed. Although no adhesion to paddle shaft and sampling pipettes were observed in this study, matrix sticking to parts of the dissolution apparatus could be a potential problem when highly viscous polymers are used. In the proposed modification to the dissolution apparatus a more synchronized system of swelling and erosion as defined by the SSF was consistently observed. Dissolution data obtained under the modified USP method represented a more realistic in-vitro release for gastro-floatable systems based on the monolithic and swelling principle, and release data obtained may provide greater potential for establishment of a successful in-vitro–in-vivo correlation.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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References

1. Pillay V, Fassihi R. Unconventional dissolution methodologies. *J Pharm Sci* 1999; 88: 843–851.
2. Dressman J, Kramer J. *Pharmaceutical Dissolution Testing*. New York: Taylor & Francis Group, 2005.
3. Moes A. Gastroretentive dosage forms. *Crit Rev Ther Drug Carrier Syst* 1993; 10: 143–195.
4. Singh B, Kim K. Floating drug delivery system: an approach to oral controlled drug delivery via gastric retention. *J Control Release* 2000; 63: 325–329.
5. Steingoetter A *et al*. Magnetic resonance imaging for the in vivo evaluation of gastric-retentive tablets. *Pharm Res* 2003; 20: 2001–2007.
6. Cooreman M *et al*. Local gastric and serum amoxycillin concentrations after different oral application forms. *Antimicrob Agents Chemother* 1993; 37: 1506–1509.
7. Streubel A *et al*. Floating mircroparticles based on low density foam powder. *Int J Pharm* 2002; 241: 279–292.
8. Chawla G *et al*. Gastroretention: a means to address regional variability in intestinal drug absorption. *Pharm Tech* 2003; 27: 50–68.
9. Sheth P, Tossounian J. The hydrodynamically balanced system (HBS): a novel drug delivery via gastric retention. *Drug Dev Ind Pharm* 1984; 10: 313–339.
10. Yang L, Fassihi R. Examination of drug solubility, polymer types, hydrodynamics and loading dose on drug release behavior from a triple-layer asymmetric configuration delivery system. *Int J Pharm* 1997; 155: 219–229.
11. Yeole P *et al*. Floating drug delivery systems: need and development. *Indian J Pharm Sci* 2005; 67: 265–272.
12. Liu Q, Fassihi R. Zero-order delivery of a highly soluble, low dose drug alfuzosin hydrochloride via gastro-retentive system. *Int J Pharm* 2008; 348: 27–34.
13. Durig T, Fassihi R. Evaluation of floating and sticking extended release delivery systems: an unconventional dissolution test. *J Control Release* 2000; 67: 37–44.
14. Burns S *et al*. Assessment of a dissolution vessel designed for floating and erodible dosage forms. *Int J Pharm* 1998; 60: 213–218.
15. Pillay V, Fassihi R. Evaluation and comparison of dissolution data derived from different modified release dosage forms: an alternative methodology. *J Control Release* 1998; 55: 45–55.
16. Moore J, Flanner H. Mathematical comparison of dissolution profiles. *Pharm Technol* 1996; 20: 64–74.
17. Chungi S, Lin K. Stabilized, acid-free formulation for sustained release of bupropion hydrochloride. US Patent 6306436, 2001.
18. Kranz H *et al*. Development of a multi particulate extended release formulation for ZK 811 752, a weakly basic drug. *Int J Pharm* 2005; 299: 84–91.
19. Shao Z *et al*. Effects of formulation variables and post-compression curing on drug release from a new sustained-release matrix material: poly (vinyl acetate)-povidone. *Pharm Dev Technol* 2001; 6: 247–254.