

Zero-order delivery of a highly soluble, low dose drug alfuzosin hydrochloride via gastro-retentive system

Quan Liu, Reza Fassihi*

Department of pharmaceutical Sciences, 3307 North Broad Street, School of Pharmacy, Temple University, Philadelphia 19140, USA

Received 5 March 2007; received in revised form 1 June 2007; accepted 2 July 2007

Available online 17 July 2007

Abstract

A composite gastro-retentive matrix for zero-order delivery of highly soluble drug alfuzosin hydrochloride (10 mg) has been designed and characterized. Two systems containing polyethylene oxide (PEO), hydroxypropylmethylcellulose (HPMC), sodium bicarbonate, citric acid and polyvinyl pyrrolidone were dry blended and compressed into triple layer and bi-layer composite matrices. Dissolution studies using the USP 27 paddle method at 100 and 50rpm in pH 2.0 and 6.8 were performed using UV spectroscopy at 244 nm, with automatic sampling over a 24 h period using a marketed product as a reference to calculate the “ f_2 ” factor. Textural characteristics of each layer, the composite matrix as a whole, and floatation potential were determined under conditions similar to dissolution. Percent matrix swelling and erosion along with digital images were also obtained. Both systems proved to be effective in providing prolonged floatation, zero-order release, and complete disentanglement and erosion based on the analysis of data with “ f_2 ” of 68 and 71 for PEO and HPMC based systems, respectively. The kinetics of drug release, swelling and erosion, and dynamics of textural changes during dissolution for the designed composite systems offer a novel approach for developing gastro-retentive drug delivery system that has potential to enhance bioavailability and site-specific delivery to the proximal small intestine. © 2007 Elsevier B.V. All rights reserved.

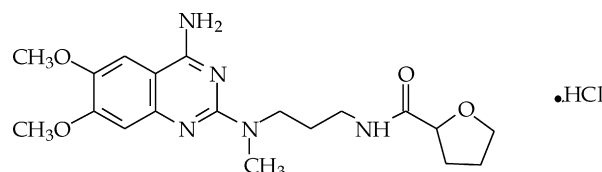
Keywords: Gastro-retentive system; Controlled release alfuzosin; Zero-order drug delivery; Composite matrix; Texture analysis

1. Introduction

Lower urinary tract symptoms (LUTS) including urinary frequency, nocturia, incomplete emptying, and urinary hesitancy are often associated with the benign prostatic hyperplasia (BPH). These symptoms can be caused by altered function of the smooth muscle tone that is regulated by the α_1 -adrenergic receptors in the prostate and its capsule, the bladder base and neck, and the prostatic urethra (Rossi et al., 2001). Presumably α_1 -adrenergic receptor antagonists maybe implicated in the pathophysiology of BPH and may cause relaxation of smooth muscles, improve in urine flow and reduction in LUT symptoms (Djavan and Marberger, 1999).

Consequently, American health care policy and research (AHCPR) guidance recommended α -blockers as a first-line therapy for BPH. Alfuzosin hydrochloride is an α -adrenergic receptor blocker approved by FDA for the treatment of symptomatic prostatic hyperplasia (BPH). It is a white to off-white

crystalline powder which is highly water soluble and melts at approximately 240 °C. The empirical formula of alfuzosin hydrochloride is $C_{19}H_{27}N_5O_4 \cdot HCl$. Alfuzosin hydrochloride extended-release tablet is currently marketed under the brand name Uroxatral®, a 10 mg gastro-retentive controlled release dosage form. Its structural formula is



Alfuzosin shows linear kinetics when administrated at doses up to 30 mg daily. The absolute bioavailability of alfuzosin is about 49% under fed condition, while the corresponding value under fasting condition is around 25% (PDR, 2005). This shows that food has a significant impact on the oral absorption of alfuzosin, potentially through the prolongation of gastric residence time. Moreover, alfuzosin is preferentially absorbed in the proximal part of the gastrointestinal tract and, in particular, jejunum appear to be the main region for absorption (Maggi et al., 2000;

* Corresponding author. Tel.: +1 2157077670; fax: +1 2157073678.
E-mail address: reza.fassihi@temple.edu (R. Fassihi).

Andrieu et al., 1995). As a result, prolongation of gastric residence time with a swellable controlled release gastro-retentive system allows continuous delivery from stomach to the intestine.

Gastro-retentive dosage forms have been the topic of interest in recent years as a practical approach in drug deliveries to the upper GI tract or for release prolongation and absorption (Moes, 1993; Singh and Kim, 2000; Talukder and Fassihi, 2004). 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 (Cooreman et al., 1993). Other candidates include drugs that are mainly absorbed in the stomach or upper small intestine, or drugs that are unstable in basic environment of distal intestine and colon or those with low solubility at elevated pH conditions (Streubel et al., 2002). Various strategies to achieve gastric-retention have been proposed and some successfully commercialized (e.g. Glucophage XRTM, containing high dose of Metformin HCl). One approach employs bioadhesive polymers to increase gastric retention time via adhering to the gastric mucosa (Akiyama and Nagahara, 1999). Swelling and expanding systems also have been researched as a mean to prevent easy passage of delivery system through the pyloric canal (Penners et al., 1997; Flashner-Barak et al., 2002). The floatation systems with or without gas generating substances also have been investigated (Sriamornsak et al., 2004; Nur and Zhang, 2000; Yang and Fassihi, 1996, 1997; Yang et al., 1997; Dave et al., 2004).

The aim of this research was to develop formulations for linear drug delivery and to study the release performance of the alfuzosin HCl. Asymmetric three-layer and bilayer swellable and floatable composite matrix formulations were developed in our laboratory and studied. In addition, dynamics of swelling and erosion in relation to drug release kinetics via textural analysis profiling and spectrophotometric analysis were performed.

2. Methods and materials

2.1. Materials

Alfuzosin hydrochloride (Al) was purchased from Lunan Pharmaceuticals (Linhyi, China). Marketed product was

obtained from Temple University Hospital. Hydroxypropylcellulose (HPC) (Klucel EF PHARM) was donated by Hercules Incorporated (Wilmington, DE). Microcrystalline cellulose (MCC) (Avicel pH 101) was supplied by FMC Corporation (Newark, DE). Polyethylene oxide (PEO), hydroxypropyl methylcellulose (HPMC) K4M and K15M were purchased from Dow Chemical Company (Midland, MI). Polyvinylpyrrolidone (PVP) (Plasdone C-30) was donated by ISP Technologies Inc. (Wayne, NJ). NaHCO₃, CaCO₃, lactose anhydrate, citric acid and magnesium stearate were purchased from Sigma–Aldrich (St. Louis, MD).

2.2. Methods

2.2.1. Tablet manufacturing—direct compression

Various formulations (10 batches) and powder blends were studied based on different proportions of polymers, excipients and their manufacturing processes. Formulation compositions of various layers of two selected prototype formulations (PEO M6-polyethylene oxide based and H/H M7-hydroxypropylcellulose/hydroxypropyl methylcellulose based) are provided in Table 1. Ingredients of each layer were mixed thoroughly in mortar with the help of pastel. Tablets were produced by manually feeding each layer composition into the die and compressing the entire die content together on a Carver laboratory press (Fred S. Carver Inc., Menomonee Falls, WI) using a 7 mm diameter die and a flat-face punch combination to obtain the target hardness. PEO containing formulation (PEO M6) weighed 600 ± 1 mg, thickness about 5.45 ± 0.05 mm and hardness of 7 ± 0.7 kp. HPC/HPMC based tablets (H/H M7) weighed 300 ± 1 mg, thickness of 4.24 ± 0.05 mm and hardness of 9 ± 0.8 kp. Tablet hardness was measured in six replicates using a tablet hardness tester (Mod. 2E/106 series 7410, Schleuniger & Co., Switzerland).

2.2.2. In vitro dissolution study

Dissolution study for the developed tablets containing 10 mg Alfuzosin hydrochloride was carried out under sink condition using USP 27 apparatus 2 (paddle), Vankel VK7000 dissolution

Table 1
Formulation composition of two selected and optimized prototypes

Ingredients ^a	PEO M6			H/H M7	
	Layer 1 (mg)	Layer 2 (mg)	Layer 3 (mg)	Layer 1 (mg)	Layer 2 (mg)
CaCO ₃	40				
NaHCO ₃	20		20	40	
Citric acid	4				
HPMC K4M	20		40		60
PEO 303	116				
HPMC K15M				40	
HPC				100	
PVP				20	30
Alfuzosin HCl		10			10
PEO N60-K		30	80		
MCC		30			
Lactose		30	60		

^a All ingredient were lubricated with 0.3% (w/w) magnesium stearate prior to compression.

machine (Cary, NJ) equipped with an autosampler. The dissolution media was pH 2.0 HCl and pH 6.8 phosphate buffers. During dissolution, the dissolution media were maintained at $37 \pm 0.5^\circ\text{C}$ and paddle speed was 100 rpm at pH 2.0 and 100 rpm and 50 rpm at pH 6.8. Samples through a $40\ \mu\text{m}$ filter were taken automatically at each sampling time point. Alfuzosin release was detected by UV absorbance at 244 nm using a UV spectrometer (Cary 50 UV–visible spectrophotometer, Cary, NJ). All dissolution tests were performed in triplicate. Pictures were taken at different intervals during dissolution for swelling, floating observations and physical changes associated with the delivery system.

2.2.3. Analysis of dissolution data

Release profiles of tablets were compared by calculating a statistically derived mathematical parameter, “similarity factor” (f_2) (Moore and Flanner, 1996; Costa and Lobo, 2001), using FDA approved product as the reference. Fraction released data was used for this purpose to normalize the percent drug release values for the labeled amount of alfuzosin hydrochloride present in each delivery system. The equation of similarity factor is

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

where R_t and T_t are the percent drug dissolved at each time point for the reference and test product, n the number of dissolution sample times, t the time sample index and W_t is an optional weight factor (in the current work $W_t = 1$). If the two profiles are identical, f_2 is 100. Values of $f_2 \geq 50$ indicate similarity of two dissolution profiles.

2.2.4. Swelling and erosion study

The swelling and erosion behavior of individual layer and formulation were evaluated gravimetrically. For each time point, two samples of each layer or the tablet as a whole were weighed and subjected to 900 ml pH 2.0 HCl buffer medium under condition similar to the dissolution studies. At predetermined time points, swollen samples were removed from the dissolution vessel, patted gently with tissue paper, weighed and dried at 70°C until constant weight was reached. Percent of weight gain from hydration and weight loss due to erosion were calculated using the following equation:

$$\% \text{Weight gain} = 100 \times \frac{\text{wet weight} - \text{dry weight}}{\text{dry weight}} \quad (2)$$

$$\% \text{Weight loss} = 100 \times \frac{\text{original weight} - \text{remaining (dry) weight}}{\text{original weight}} \quad (3)$$

2.2.5. Texture analysis and swelling behavior

Tablets or different layers of PEO M6 and H/H M7 based formulations were exposed to 900 ml pH 2.0 HCl buffer under the same condition to the dissolution test. At predetermined times (2, 4, 6, 8 and 12 h) swollen samples were taken out and lightly patted with tissue paper to remove excess water. Texture profiling was carried out on a TA.TX-2i texture analyzer equipped with a 2 kg load cell (Texture Technologies Corp., Scarsdale, NY/Stable Micro System, Godalming, UK) using a 2 mm round end steel probe. The force–distance profile for each sample was spontaneously derived as probe penetrated the swollen system

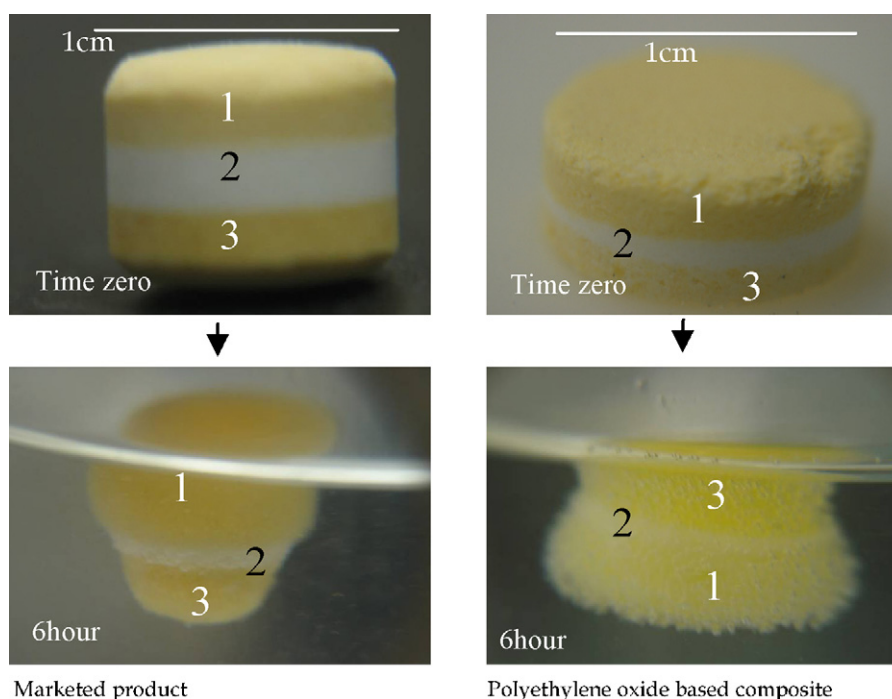


Fig. 1. Physical appearance of delivery systems as such and after 6 h of dissolution while floating on the surface of media (1, layer 1; 2, layer 2 (drug layer); 3, layer 3).

following the method described previously (Durig and Fassihi, 2002).

3. Results and discussion

3.1. Asymmetric delivery system—composite dosage form

Floating formulations of alfuzosin hydrochloride were successfully developed by two multilayer delivery systems: first formulation comprised a three-layer tablet based on PEO, while the second formulation was a two-layer tablet mainly composed of HPC and HPMC. Full composition of each system is presented in Table 1 and as an example actual appearances of PEO M6 and marketed product before and during dissolution are shown in Fig. 1.

The dissolution profiles of the marketed product, PEO M6 and H/H M7 based composite systems at pH 2.0 and 6.8 at 100 rpm are illustrated in Fig. 2. All three systems demonstrated controlled release kinetics independent of pH changes with about 99% of dose being released around 18 h. After 16 h of dissolution at pH 2.0, the third layer of both PEO M6 and the marketed product totally disappeared (see Fig. 3). As demonstrated in Fig. 2, no significant burst effect is evident for this highly soluble compound. This indicates that during initial exposure to the dissolution media barrier layers limited the available surface area for drug dissolution. Furthermore it is apparent that drug is only released through the exposed surface area of the mid-

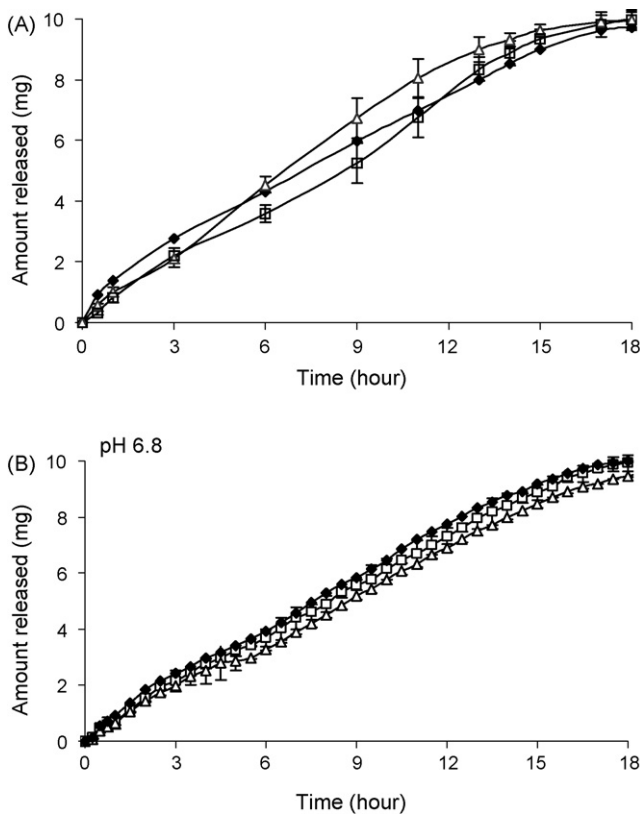


Fig. 2. Dissolution profiles of composite based on PEO (M6), HPMC/HPC (M7) and the marketed product at pH 2.0 (A) and pH 6.8 (B) at 100 rpm ($n=3$): marketed product (◆), H/H M7 (□), PEO M6 (△).

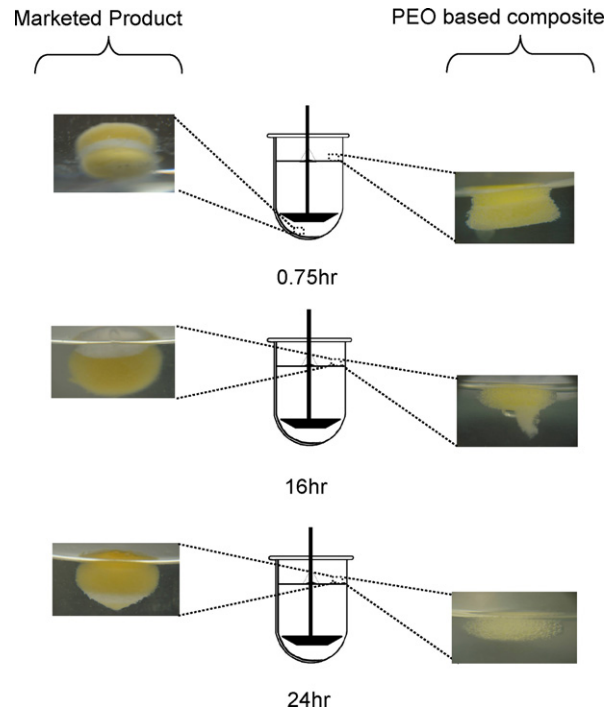


Fig. 3. Actual photograph and relative location of the swollen matrices in the vessels during dissolution studies in pH 2.0 and 100 rpm using USP apparatus 2.

dle layer of the composite matrix. Fig. 4 clearly demonstrates the significant difference in drug release profile when a simple HPMC based monolithic matrix against a three-layer PEO based composite matrix is evaluated.

Complete floatation of PEO M6 and H/H M7 took place in less than 1 min, while it took the marketed product 0.5–1 h to float (Fig. 3). The rapid floatation associated with the developed formulations can be attributed to rapid water uptake and overall system swelling which is highly desirable for the gastro-retentive dosage forms. This rapid swelling property was not apparent in the case of marketed product potentially due to the

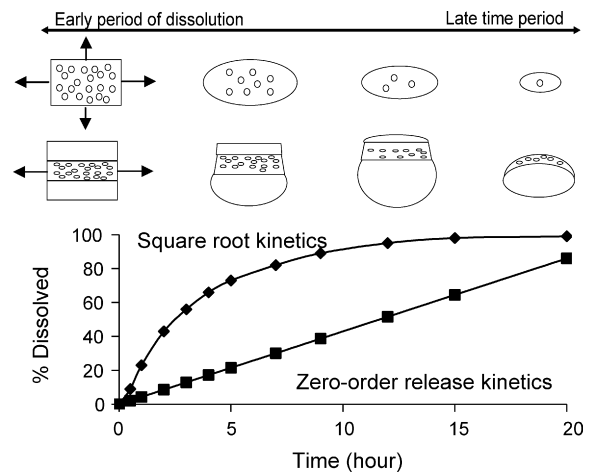


Fig. 4. Illustration of matrix dynamics and release kinetics during dissolution from a simple monolithic (HPMC based) or composite (PEO based) matrix systems.

Table 2
Kinetic considerations of data treated from Fig. 2A

Formulation	k (h^{-n})	n
PEO M6	0.0722	1.0093
Marketed product	0.1225	0.7210
H/H M7	0.695	0.9488

types of polymers used and formulation composition. Presence of sodium bicarbonate in the developed matrix formulation generally resulted in generation of carbon dioxide gas within the hydrating matrix thus complementing the swelling rate of the dosage form. This initial rapid swelling behavior is consistent with the rapid weight gain observed (see Fig. 6). Furthermore as an additional option citric acid was also included in one of the layers of PEO M6 based formulation (see Table 1) to assure that an acidic microenvironment within the swelling matrix is maintained. This may contribute to continuous generation of carbon dioxide gas in the matrix itself independent of external changes in the pH environment.

Rapid system floatation is highly desirable for gastro-retentive dosage forms and can potentially prolong gastric residence time and improve the bioavailability of drug substances with narrow window of absorption. The significance of rapid floatation and prolongation of gastric retention has been recently investigated (Steingotter et al., 2003), using magnetic resonance imaging for the three dimensional visualization of stomach volume and floating tablet position on the meal surface in human volunteers. The application of gamma scintigraphy in evaluation of gastric retentive formulation and the benefits of such delivery systems is also demonstrated by others (see Burke et al., 2007).

3.2. Drug release mechanism

The quantity of drug released from a thin slab is generally expressed as an exponential: $M_t/M_\infty = kt^n$, where M_t/M_∞ is the fraction of drug released, k a constant and the exponent n can range from ~ 0.5 to >1.0 . The dissolution data presented in Fig. 2A were subjected to the kinetic analysis using above general equation. The diffusional exponent n for H/H M7 and PEO M6 was found to be 0.9488 and 1.0093, respectively (see Table 2), which indicate case-II transport mechanism (i.e. swelling, disentanglement and system erosion) with zero-order release kinetics resulting from constant surface area and controlled swelling/erosion provided by the changing geometry of the system. The n value of the marketed product was 0.7210, which also shows significant swelling and erosion in agreement with the literature reports (Lindner and Lippold, 1995; Durig and Fassihi, 2002). The approach of achieving constant releasing area is the same for both of the developed formulations. Each formulation contains one swelling layer which swells to a greater extent relative to other layers, thus suppressing the burst release of drug in the first stage of dissolution. While one of the layers contains some erosion promoters so as to provide increasing contact surface for active ingredient diffusion in the following stages of dissolution. For example in the case of PEO M6 formu-

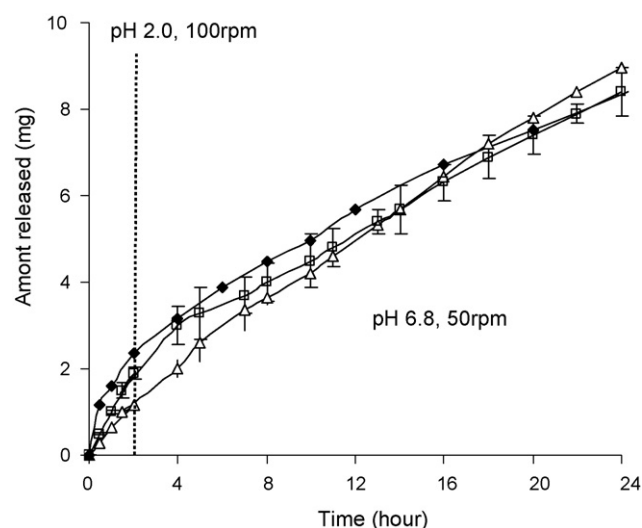


Fig. 5. Comparative dissolution profiles of composite formulation based on PEO (M6), HPMC/HPC (M7) and marketed product in pH 2.0 followed by pH 6.8 ($n=3$): marketed product (\blacklozenge), H/H M7 (\square), PEO M6 (\triangle).

lation, the barrier layer contained PEO 303 with high molecular weight (about 7,000,000), which would swell and prevent drug diffusion. While in the second barrier layer, PEO N60-K with lower molecular weight (about 2,000,000) and lactose monohydrate as erosion promoter were used, leading to disentanglement of PEO N60-K, erosion and greater drug release as dissolution time is prolonged.

To compare the dissolution profile of the developed formulations with that of the marketed product, statistically derived mathematical parameter, “similarity factor” (f_2) was employed. The similarity factor for PEO M6 and H/H M7 were 68 and 71, respectively, using the marketed product as reference. This indicates the sameness of release profiles (Jamzad and Fassihi, 2006).

In order to find the impact of rapid pH changes on formulation performance, dissolution study with pH combination was also carried out (see Fig. 5). The first 2 h of dissolution was carried out in pH 2.0 HCl buffer at 100 rpm, then tablets were removed from acidic media and dropped into pH 6.8 phosphate buffer at 50 rpm. It has been reported that forces of GI contractions are generally weaker in the intestinal region relative to that of stomach (Kamba et al., 2000). Therefore different paddle speeds (hydrodynamics) were used to both mimic small intestine contraction forces and understand the nature of drug release, should the gastric residence time and the assumed floatation mechanism fail due to unpredictable motility patterns. Under this condition the drug release still follows zero-order kinetics. However, the total amount of drug released for all tablets were slightly reduced at elevated pH. This might be due to the matrix exposure to the air and rapid textural changes (i.e. buffer/electrolyte effect) on the periphery of the swollen matrix during transfer from low pH environment to the higher pH. In addition changes in the hydrodynamic conditions from 100 to 50 rpm may contribute to the total amount of drug released. The dissolution profiles of the developed systems at variable pH conditions were comparable with that of the marketed product.

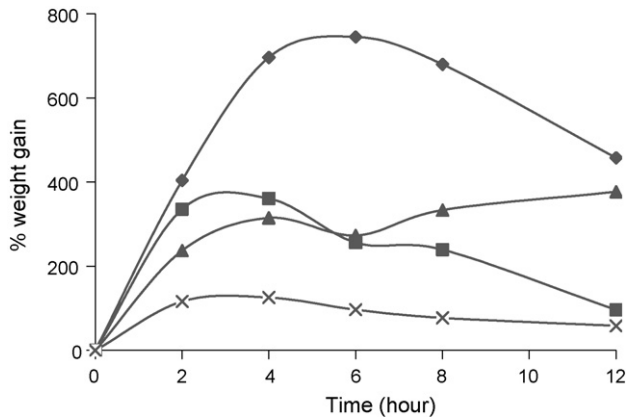


Fig. 6. Changes in percent weight gain for composites and its layers: layer 1 of PEO M6 (◆), layer 3 of PEO M6 (■), PEO M6 (▲), two layer composite based on HPMC/HPC (×).

3.3. Weight gain and erosion behavior

Investigation of matrix hydration and erosion directly by gravimetric analysis is a valuable approach to understand the mechanisms of release and the relative importance of participating parameters (Durig and Fassihi, 2002). Figs. 6 and 7 show typical results of such studies for PEO and HPMC based matrix compositions.

It is evident that percent of weight gain during the 12 h of study has a changing trend for each layer and the entire composite systems. Changes in layer 1 of PEO M6 follow a parabolic trend with a maximum around 6 h (see Fig. 6). While weight

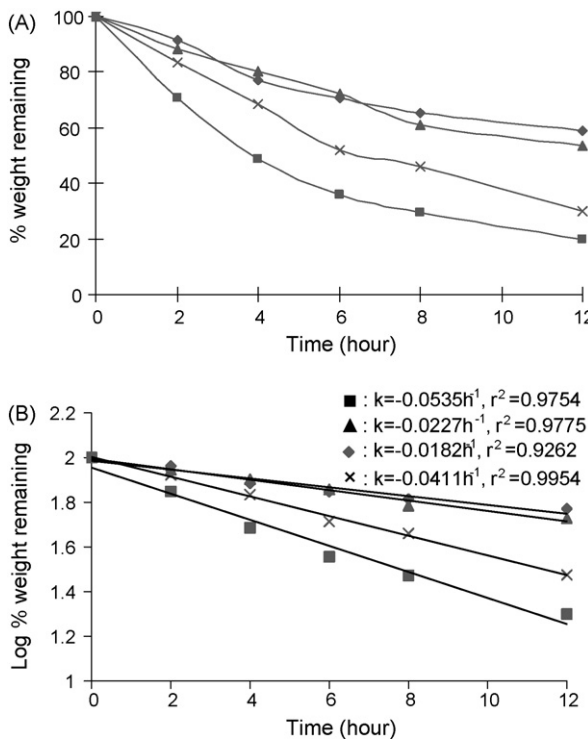


Fig. 7. Changes in erosion with time (A) and log value of percent weight remaining vs. time (B) for composites and its layer: layer 1 of PEO M6 (◆), layer 3 of PEO M6 (■), PEO M6 (▲), two layer composite based on HPMC/HPC (×).

loss for this layer is gradual (see Fig. 7A). On the contrary data for layer 3 of PEO M6 indicate slight weight gain initially followed by continuous and extensive weight loss (Figs. 6 and 7A). Both composite systems as a whole appear to moderately change in terms of weight gain and erosion. It was noted that percent weight gain for HPMC based composite system was minimal and its overall erosion rate was greater than PEO based composite system. The log values of percent weight remaining versus time (see Fig. 7B) indicate the rate constant of erosion calculated from the slope of the lines. It clearly demonstrates that individual layers and composites have variable erosion rates (see k values in Fig. 7B), thus providing for controlled surface area changes during dissolution, consequently leading to zero-order kinetics.

3.4. Texture analysis study

Hydration and erosion study of each layer of PEO M6 and H/H M7 and whole tablet of PEO M6 and H/H M7 were carried out on texture analyzer TX 2i. The force–distance profiles for H/H M7 system and its second layer at pH 2.0 is depicted in Fig. 8A and B, the single first layer as such disintegrated within 2 h and its swelling behavior could not be determined. Thus no profile is provided for this layer. The second layer (drug layer) alone swells to its largest extent around 6 h with a thickness of about 3.3 mm, after which time erosion was more dominant and thickness continuously decreased as shown on Fig. 8A. H/H M7 composite swelled to the maximum thickness about 6 mm of around 8 h and then gradually decreased (see Fig. 8B). None of the samples showed any detectable peak prior to the final ascending curve, indicating the absence of any brittleness or hard core (existence of glassy core) in the system.

The force–distance profile of PEO M6 and its first and third layer at pH 2.0 is depicted in Fig. 9. The individual second layer

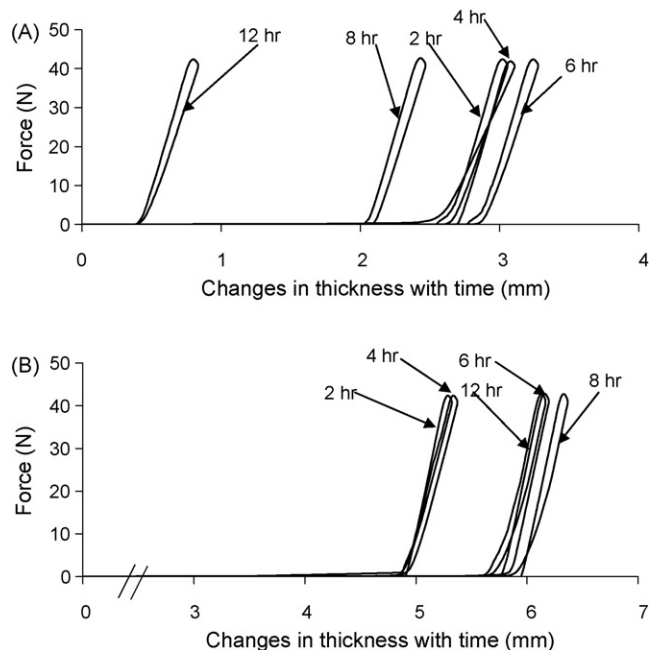


Fig. 8. Texture profiles representing force–distance relationship for H/H M7 based system: (A) layer 2 (drug layer); (B) composite tablet as a whole.

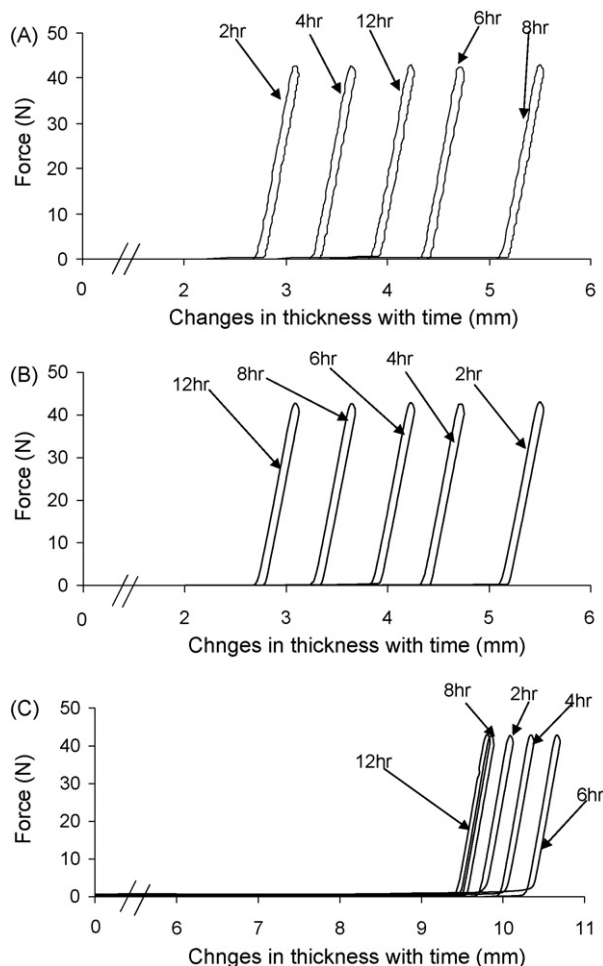


Fig. 9. Texture profiles representing force–distance relationship for PEO M6 based system: (A) layer 1; (B) layer 3; (C) composite tablet as a whole.

as such (drug layer) disintegrated once being introduced into dissolution media. The first layer alone swells to its largest extent around 8 h with a thickness of >6.5 mm, after which time erosion was dominant as shown by various time points (arrows) in Fig. 9A. The thickness of third layer rapidly increased within the first 2 h, and then gradually decreased with time. It showed significant erosion rate as a result of low molecular weight polymer and the added lactose monohydrate as an erosion promoter showing continuous decrease in swollen layer thickness with time (see Fig. 9B). In the case of whole tablet of PEO M6 composite (see Fig. 9C) it gradually swelled reaching its maxima around 6 h and then eroding. There was no detectable peak prior to the final ascending curve indicating the absence of glassy core. The observed swelling and erosion characteristics measured via the novel texture analysis work demonstrate significant impact of system geometry and composition on the dynamics of physical changes and their associated effect on maintaining constant surface area and achievement of zero-order kinetics.

4. Conclusion

Two swellable and floatable composite delivery systems for alfuzosin hydrochloride have been successfully developed and

evaluated. The dynamics of swelling, erosion, weight gain and weight loss were assessed. Study demonstrated that maintenance of constant surface area during dissolution is critical for zero-order drug delivery. Both PEO M6 and H/H M7 have comparable dissolution behavior relative to each other and that of the marketed product as measured by similarity factor “ f_2 ”. Each formulation contains barrier layers that swell and erode differentially with respect to each other as confirmed via texture analysis and data profiling. The burst release suppression effect brought about by rapid initial swelling and controlled erosion of layers provided for programmed controlled delivery and enhanced floatation. The developed formulations further demonstrated to be superior to the marketed product as far as their rate of floatations and swelling is concerned. Presence of highly swellable polymers and generation of gas within the developed systems provided for rapid swelling and floatation. Clearly benefits of gastric retention and floatation for drugs with narrow window of absorption or other challenging therapeutic situations is evident and has been pursued by both academia and industry. The composite design approach and the proposed matrix evaluation may offer formulation scientists with greater opportunity to successfully develop and evaluate variety of swelling and floating drug delivery systems for highly soluble drugs.

References

- Akiyama, Y., Nagahara, N., 1999. Novel formulation approaches to oral mucoadhesive drug delivery systems. In: Mathiowitz, E., Chickering III, D.E., Lehr, C.M. (Eds.), *Bioadhesive Drug Delivery Systems Fundamentals: Novel Approaches and Development*. Marcel Dekker, New York, pp. 477–505.
- Andrieu, V., Montel, J., Wick, A., 1995. Sustained-release pharmaceutical dosage forms containing alfuzosin hydrochloride. European Patent 0673650, September 27.
- Burke, M., Staton, J., Vickers, A., Peters, E., Coffin, M., 2007. A novel method to radiolabel gastric retentive formulations for gamma scintigraphy assessment. *Pharm. Res.* 24, 695–704.
- Cooremans, M.P., Krausgril, P., Hengels, K.J., 1993. Local gastric and serum amoxicillin concentrations after different oral application forms. *Antimicrob. Agents Chemother.* 37, 1506–1509.
- Costa, P., Lobo, J., 2001. Modeling and comparison of dissolution profiles. *Eur. J. Pharm.* 13, 123–133.
- Dave, B.S., Amin, A.F., Patel, M.M., 2004. Gastroretentive drug delivery system of ranitidine hydrochloride: floatation and in vitro evaluation. *AAPS PharmSciTech.* 5.
- Djavan, B., Marberger, M., 1999. A meta-analysis on the efficacy and tolerability of 1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur. Urol.* 36, 1–13.
- Durig, T., Fassihi, R., 2002. Guar-based monolithic matrix systems: effect of ionizable and non-ionizable substances and excipients on gel dynamics and release kinetics. *J. Control. Release* 80, 45–56.
- Flashner-Barak, M., Rosenberger, V., Lerner, Y., 2002. Composition and dosage form for delayed gastric release of alendronate and/or other bisphosphonates. US Patent 6,476,006, November 5.
- Jamzad, S., Fassihi, R., 2006. Development of a controlled release low dose class II drug—glipizide. *Int. J. Pharm.* 312, 24–32.
- Kamba, M., Seta, Y., Kusai, A., Ikeda, M., Nishimura, K., 2000. A unique dosage form to evaluate mechanical destructive force in the gastrointestinal tract. *Int. J. Pharm.* 208, 61–70.
- Lindner, W.D., Lippold, B.C., 1995. Drug release from hydrocolloid embeddings with high or low susceptibility to hydrodynamic stress. *Pharm. Res.* 12, 1781–1785.

- Maggi, L., Conte, U., Gerenier, P., Vergnault, G., Dufore, A., Jarreau, F.X., Rauch-Desanti, C., 2000. Tablet with controlled release of alfuzosin chlorhydrate. US Patent 6,149,940A, November 21.
- Moes, A.J., 1993. Gastroretentive dosage forms. *Crit. Rev. Ther. Drug Carrier Syst.* 10, 143–195.
- Moore, J.W., Flanner, H.H., 1996. Mathematical comparison of dissolution profiles. *Pharm. Technol.* 20, 64–74.
- Nur, A., Zhang, J., 2000. Captopril floating and/or bioadhesive tablets: design and release kinetics. *Drug Dev. Ind. Pharm.* 26, 965–969.
- Penners, G., Lustig, K., Petersen-von Gehr, J., 1997. Expandable pharmaceutical forms. US Patent 5651985, July 29.
- Physicians' Desk Reference (PDR), 59th ed., 2005. Thomson PDR, Montvale, NJ.
- Rossi, C., Kortmann, B.M., Sonke, G.S., 2001. α -Blockade improves symptoms suggestive of bladder outlet obstruction but fails to relieve it. *J. Urol.* 165, 38–41.
- Singh, B.M., Kim, K.H., 2000. Floating drug delivery system: an approach to oral controlled drug delivery via gastric retention. *J. Control. Release* 63, 235–239.
- Sriamornsak, P., Thirawong, N., Puttipipatkachorn, S., 2004. Morphology and buoyancy of oil-entrapped calcium pectinate gel beads. *AAPS J.* 6.
- Steingoetter, A., Weishaupt, D., Kunz, P., Mader, K., Lengsfeld, H., Thumshirn, M., Boesiger, P., Fried, M., Schwizer, W., 2003. Magnetic resonance imaging for the *in vivo* evaluation of gastric-retentive tablets. *Pharm. Res.* 20, 2001–2007.
- Streubel, A., Siepmann, J., Bodmeier, R., 2002. Floating microparticles based on low density foam powder. *Int. J. Pharm.* 241, 279–292.
- Talukder, R., Fassihi, R., 2004. Gastroretentive delivery systems: hollow beads. *Drug Dev. Ind. Pharm.* 30, 405–412.
- Yang, L., Fassihi, R., 1996. Zero-order release kinetics from a self-correcting floatable asymmetric configuration drug delivery system. *J. Pharm. Sci.* 85, 170–173.
- Yang, L., Fassihi, R., 1997. Modulation of diclofenac release from a totally soluble controlled release drug delivery system. *J. Control. Release* 44, 135–140.
- Yang, L., Venkatesh, G., Fassihi, R., 1997. Compaction simulator study of a novel triple-layer tablet matrix for industrial tableting. *Int. J. Pharm.* 152, 45–52.