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Development of a controlled release low dose class II drug-Glipizide

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Abstract

The purpose of this study was to develop a new monolithic matrix system to completely deliver glipizide, a Biopharmaceutics Classification System (BCS) Class II drug in a zero order manner over an extended time period. Two approaches were examined using drug in formulations that contain swellable hydroxypropylmethylcellulose (HPMC) or erodible polyethylene oxide (PEO). The matrices were prepared by dry blending selected ratios of polymers and ingredients using direct compression technique. Dissolution was assessed using modified USP apparatus II. Glucotrol XL push-pull osmotic pump (PPOP) was used as the reference. The interrelationship between matrix hydration, erosion and textural properties were determined and analyzed under the dissolution test conditions. Linear and reproducible release similar to that of Glucotrol XL was achieved for optimized matrices ($f_2 > 50$) independent of hydrodynamic conditions. The kinetics of drug delivery was directly related to the synchronization of swelling, erosion and fractional release. HPMC matrices showed a significantly greater degree of hydration and swelling and stronger texture property relative to PEO matrices. Results indicate that in the case of low dose/low soluble drug, total drug release in a zero order manner heavily depends on the synchronization of erosion and swelling fronts during the entire dissolution study.

Keywords: Glipizide; Controlled release; Textural behavior; Swelling; Matrix

1. Introduction

The earliest studies in the field of modified drug delivery date back to the 1950s. Since then, a large number of drug products, mainly in the form of tablet and capsule with controlled release characteristics, have been introduced. Das and Das predicted a minimum growth of 9% per year for this market through 2007 (Das and Das, 2003). This incredible growth can be attributed to several advantages that these products offer, including improved patient compliance, better therapeutic efficiency, potential for cost saving and patentability, and opportunity for extending product life-cycle.

Various technologies have been investigated in order to achieve different aims of modified release, e.g. sustained, delayed, pulsatile, targeted, and programmed release. Regardless of the delivery type, the main mechanisms associated with drug transport in these systems include diffusion, swelling, erosion, ion exchange, and osmotic effect which have been investigated in several studies (Theeuwes, 1975; Korsmeyer et al., 1983; Khurahashi et al., 1996; Colombo et al., 1999; Bettini et al., 2001; Narasimhan, 2001; Durig and Fassihi, 1999, 2002; Sako et al., 2002; Turner et al., 2004).

Among different technologies used in controlled drug delivery, hydrophilic matrix systems are the most popular because of the simplicity of formulation, ease of manufacturing, low cost, FDA acceptance, and applicability to drugs with wide range of solubility (Durig and Fassihi, 2002; Sako et al., 2002; Williams et al., 2002). Drug release from these systems is the consequence of controlled matrix hydration, followed by gel formation, textural/rheological behavior, matrix erosion, and/or drug dissolution and diffusion, the significance of which depends on drug solubility and concentration and changes in matrix characteristics as illustrated in Fig. 1.

Different factors that can influence drug release from hydrophilic matrices have been discussed and presented elsewhere (Jamzad et al., 2005; Pillay and Fassihi, 1999). Among these, the type, amount, and properties of the polymer used play a fundamental role. Hydroxypropylmethylcellulose (HPMC) and polyethylene oxide (PEO) are the most commonly used polymers in hydrophilic matrix formulations, owing to their solubility in water, availability in a range of molecular weight/viscosity grades, FDA acceptance, and unique swelling/erosion char-

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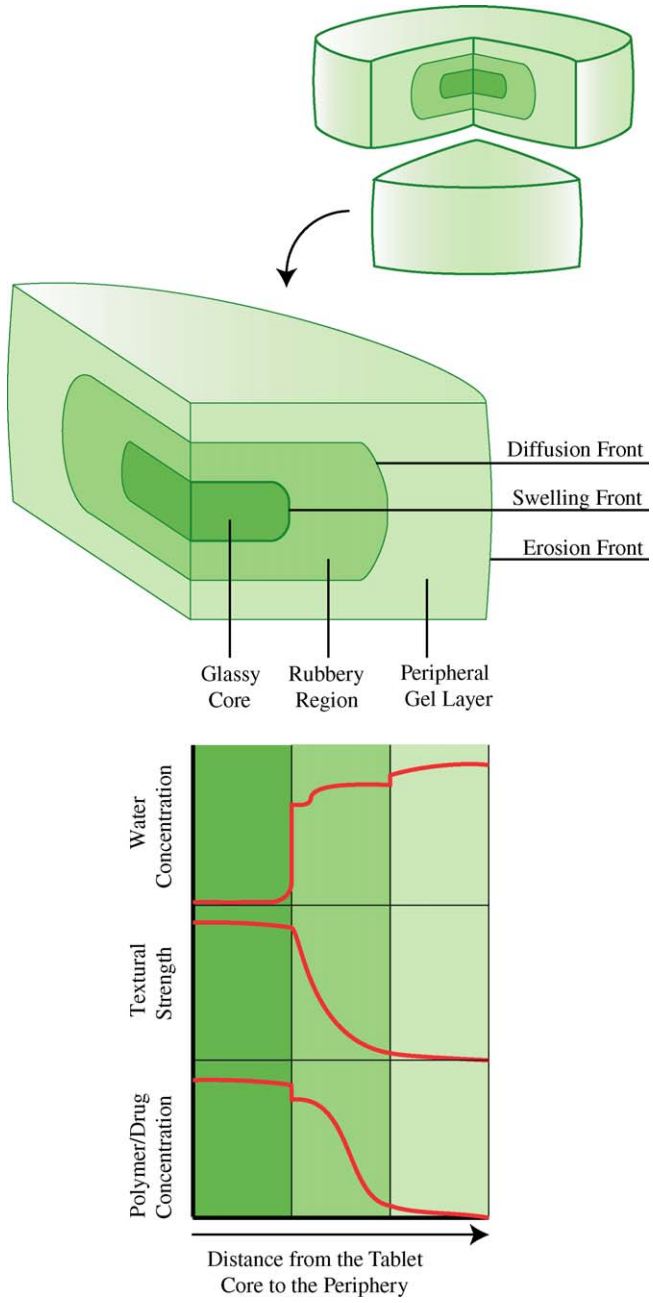

Fig. 1. Interrelationship between water concentration gradient, textural behavior, and polymer/drug concentration gradient in a swelling matrix. Reproduced from Wu and Fassihi, unpublished data.

acteristics which can be utilized in modulating drug release profile.

The purpose of this study is to develop a controlled release monolithic system for the low solubility/low dose drug glipizide, an oral antidiabetic. The reference product used to compare dissolution profiles was the commercial product Glucotrol XL, a push-pull osmotic pump (PPOP) system. Such systems are not affected by either hydrodynamics or pH, due to the fact that the release mechanism is based on osmotic pump principle, which can be appropriately controlled by compositional modifications of the core and the semi-permeable membrane, and/or by size adjustment of the delivery orifice (Wong et al., 1992). On the contrary, systems that undergo swelling and erosion could be highly sensitive to the changing environment of human GI tract (Konard et al., 1998; Kavanagh and Corrigan, 2004).

Glipizide is a weak acid ($pK_a = 5.9$), practically insoluble in water and acidic environment, and highly permeable (Class II drugs in accordance to Biopharmaceutics Classification System, BCS). The oral absorption is uniform, rapid, and complete; its bioavailability is nearly 100% and its elimination half-life is 2–4 h (Budaveri et al., 1996; British Pharmacopoeia, 2000; Physicians' Desk Reference, 2004). In this work glipizide tablets were prepared by dry blending selected ingredients and direct compression technique. Matrix properties and mechanism of release were investigated through dissolution profiling, hydration and erosion studies, and analysis of textural profiles. The effect of hydrodynamics and pH on the release characteristics of the selected developed formulation was also evaluated.

2. Materials and methods

2.1. Materials

Glipizide was obtained from Sigma–Aldrich (St. Louis, MO). Hydroxypropylmethylcellulose (Methocel K100M, K15M, K100LV Premium CR) and Polyethylene oxide 4,000,000 (Polyox WSR 301) were obtained from the Dow Chemicals Company (Midland, MI); spray dried lactose monohydrate NF from Formost (Baraboo, WI); and microcrystalline cellulose (MCC, Avicel PH 101) from FMC Corp. (Philadelphia, PA). Colloidal silicon dioxide (Syloid) was supplied by GraceDavison (Columbia, MD) and magnesium stearate NF was supplied by Mallinckrodt (St. Louis, MO). Glucotrol XL tablets were purchased from Temple university hospital (Philadelphia, PA).

2.2. Methods

2.2.1. Preparation of matrix tablets

The tablets were prepared by dry blending the ingredients followed by direct compression. In each formulation (see Table 1), all ingredients except for magnesium stearate and colloidal sil-

Table 1
Formulations composition

Ingredients	Amount per tablet in formulation (mg)						
	H1	H2	H3	H4	P1	P2	P3
Glipizide	10	10	10	10	10	10	10
HPMC K100M	90	45					
HPMC K15M			45	35			
HPMC K100LV		45	45	55			
Spray dried lactose monohydrate	50	50	50	50			
PEO (4,000,000)					60	50	40
Microcrystalline cellulose					100	100	100
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Colloidal silicone dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	152.25	152.25	152.25	152.25	172.25	162.25	152.25

icon dioxide were screened through a 20-mesh sieve and manually blended for 3 min. Colloidal silicon dioxide was added next and blended for 2 min. Finally magnesium stearate, which was screened through a 60-mesh sieve, was added and mixed for an additional 2 min. Tablets were compressed on a manual hydraulic press (Fred S. Carver Inc., Wabash, IN) using a 7 mm die and a flat-faced punch assembly to provide a desirable hardness. HPMC-based formulations weighed 152.0 ± 1 mg, had thickness of 3.57 ± 0.05 mm and hardness of 8 ± 0.6 kp, and will be referred to as H1 to H4. PEO formulations will be referred to as P1 to P3 and had thickness of 3.56 ± 0.14 mm and hardness of 14 ± 4 kp with a full description of formulations provided in Table 1.

2.2.2. Dissolution testing

Dissolution study was conducted in 900 ml pH 6.8 phosphate buffer maintained at 37 °C using USP 27 apparatus II (paddle) at 75 rpm (VK 7000, Vankel, Cary, NC). Additionally, dissolution of the selected HPMC formulation was evaluated in pH 6.8 phosphate buffer at 100 rpm and in pH 2 HCl/KCl buffer and pH 4.4 acetate buffer at 75 rpm. In cases of tablet sticking to the bottom of the dissolution vessel a single ring-mesh device was placed within the vessel in order to provide unconstrained hydration and swelling in all directions (Durig and Fassihi, 2000). Samples were taken automatically and passed through a 35 μm filter. UV absorbance was determined at 276 nm (Cary-50 UV–vis spectrophotometer), compared against the calibration curve, and % dissolved versus time profiles were constructed.

2.2.3. Statistical analysis of dissolution data

Release profiles of tablets were compared by calculating two statistically derived mathematical indices, difference factor (f_1) and similarity factor (f_2) (Moore and Flanner, 1996), using Glucotrol XL as the reference. Fraction released data was used for this purpose to normalize the % release values for the amount of glipizide actually present in each dosage form. The pull points at 30 min intervals, beginning from the first 30 min up to one point above 85% released (for reference formulation Glucotrol XL), were included in calculations. $t_{25\%}$, $t_{50\%}$, and $t_{75\%}$ were determined from the dissolution profiles for each formulation.

2.2.4. Hydration and erosion studies

The formulations' capacity for hydration (buffer medium uptake) and their extent of erosion were evaluated gravimetrically. For each time point, two tablets of each formulation were weighed individually and exposed to 900 ml pH 6.8 phosphate buffer medium under conditions similar to the dissolution test. At specific time points, tablets were removed from the medium, patted gently with a tissue paper, weighed, dried at 60 °C until constant weight was achieved, and then were discarded. Percent weight gain (hydration) and % mass loss (erosion) were calculated according to the following equations using original, wet, and dry weight values obtained from the testing.

$$\%\text{Weight gain} = 100\frac{\text{wet weight} - \text{dry weight}}{\text{dry weight}} \quad (1)$$

$$\%\text{Mass loss} = 100\frac{\text{original weight} - \text{remaining (dry) weight}}{\text{original weight}} \quad (2)$$

2.2.5. Textural analysis and swelling behavior

Swelling characteristics and gel strength for the selected formulations were evaluated by the textural analysis of hydrated tablets at different time points. Tablets were exposed to 900 ml pH 6.8 phosphate buffer under the same conditions as the dissolution test. At predetermined times (2, 4, 6, and 8 h) tablets were taken out and lightly patted with tissue paper to remove excess water. Textural profiling was performed on a TA.XT2i texture analyzer equipped with a 5 kg load cell (Texture Technologies Corp. Scarsdale, NY/Stable Micro Systems, Godalming, UK), using an 11 mm diameter flat-faced probe. During a run, the probe advanced towards the swollen tablet in an axial direction at a speed of 0.5 mm/s. Data acquisition started as soon as the trigger force of 0.005 N was sensed by the probe as it contacted the gel layer on the surface of the tablet. The Probe, exerting pressure, compressed the swollen tablet at a speed of 1.0 mm/s, until the maximum force of 50 N was reached. At the end of this process, the matrix structure was totally deformed.

Thus, due to the very low trigger force, the probe displacement represents the entire thickness of the swollen tablet, which also encompasses the erosion front (Jamzad et al., 2005). The work done with the probe is equivalent to the area under the force–displacement curve and is a measure of the textural strength of the hydrated matrix as described by Eq. (3):

$$W = \int F\mathrm{d}D \quad (3)$$

where W is the work done by the probe, F the force applied, and dD the total probe displacement.

3. Results and discussion

3.1. Drug release study

Formulation of glipizide in a monolithic matrix system was pursued via two approaches, one based on a predominantly swellable/non-erodible system using HPMC, while the other was based on a swellable/erodible principle using PEO (Table 1). Dissolution profiles for various HPMC and PEO based formulations are depicted in Figs. 2, 3 and 6, respectively and $t_{25\%}$, $t_{50\%}$, and $t_{75\%}$ values are shown in Table 2.

Table 2
Time to 25, 50, and 75% dissolution

	Tablet formulations						
	H1	H2	H3	H4	P1	P2	P3
$t_{25\%}$ (h)	8.4	7.3	6.4	5.2	7	6.4	5.3
$t_{50\%}$ (h)	18.7	13.6	11.8	9.5	12.7	11.2	9.8
$t_{75\%}$ (h)	27.7	22	19	15	15.7	15	14.3

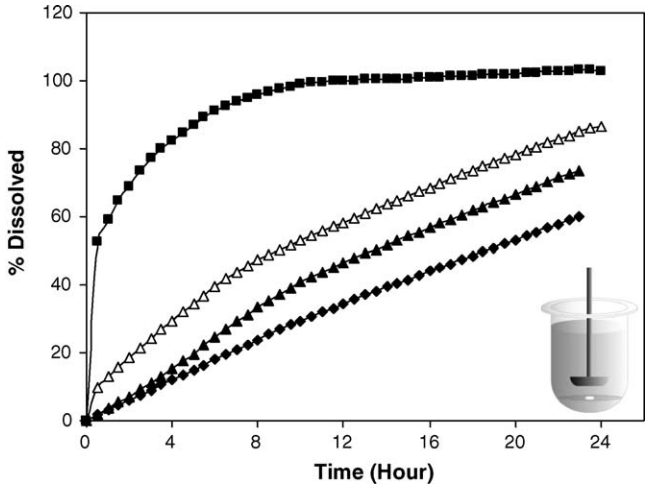

Fig. 2. Dissolution profiles of HPMC-based glipizide formulations with increasing lactose to HPMC K100M ratio: (♦) 1:1.8 in H1, (▲) 1: 1, (△) 2:1, (■) 4:1.

3.1.1. HPMC-based formulations

The formulation composition for various HPMC-based matrix is shown in Table 1. In H1, high molecular weight HPMC (Methocel K100M) and lactose at the given ratio provided linear release with a maximum of 60% of the drug released in 23 h (Figs. 2 and 3). At this time a significant portion of swollen matrix was still floating in the dissolution medium. In order to increase both the rate and extent of drug release the ratio of lactose to polymer was systematically increased. Lactose, by its water soluble and hydrophilic nature, provides for greater matrix hydration, facilitates gel formation, and promotes free volume (Gao et al., 1996). The rate of release was successfully increased, although linearity was compromised at higher release rates. The observed tailing of release profiles is likely the result of extensive swelling, lack of matrix erosion, and consequently, greater diffusional path length. Typical dissolution profiles based on this approach are shown in Fig. 2.

In order to overcome this, in the second step, instead of increasing the amount of lactose, half of the high molecular weight HPMC was replaced by low viscosity grade Methocel K100LV to reduce the gel viscosity and allow some degree of polymer disentanglement to take place. Drug release was improved to 80% at 24 h in H2 formulation (Fig. 3). Apparently, incorporation of low molecular weight and more soluble polymer facilitated drug diffusion through a relatively weaker gel structure.

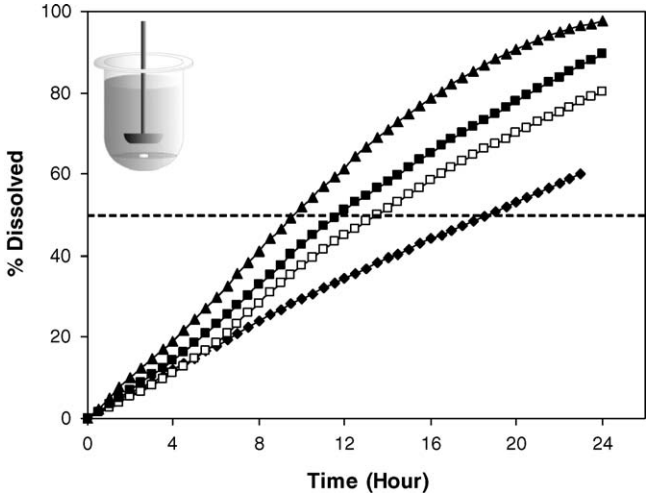

Fig. 3. Dissolution profiles of HPMC-based glipizide formulations ($n = 6$): H1 (♦), H2 (□), H3 (■), H4 (▲).

Total replacement of the remaining high molecular weight polymer with Methocel K15M (medium viscosity grade HPMC) in H3 increased the drug release to 90% (Fig. 3). Final adjustment by changing the ratio of the two viscosity grades HPMC in H4 formulation resulted in a more linear release profile ($R^2 = 0.9984$ for up to 80% release) having similarity to the reference product Glucotrol XL ($f_2 = 58$) as shown in Fig. 7b. In this case, drug release was complete (Fig. 3) and the matrix was extensively dissolved at the end of the experiment.

By reducing and selecting appropriate molecular weight of the polymer in the matrix, the rate of matrix hydration, and by implication, the rate of achieving disentanglement threshold can be controlled. Therefore, mechanism of drug release is based on the sum of diffusion and polymer relaxation. Rapid swelling and gel formation of the prepared matrix in this work minimized burst release of the glipizide which tends to be soluble in pH 6.8 buffer. The consistency of the dissolution results obtained from the H4 tablets as observed by small standard deviations, suggests the precise control of the drug release by the matrix composition.

Fig. 4 depicts effect of hydrodynamics on the release profile of Glucotrol XL (4a) and H4 formulation (4b). In both cases the difference in dissolution profile at 100 rpm and 75 rpm are statistically insignificant ($f_2 > 50$). It is known that in osmotic pump systems release is insensitive to hydrodynamics, while in hydrophilic matrix systems the opposite is true. Increase in stirring rate can facilitate polymer chains detachment from the periphery of the matrix where polymer concentration has reached the disentanglement threshold, thus enhancing drug release especially when drug is insoluble. This effect can be more pronounced whenever erosion is the predominant part of release mechanism or when the gel structure is weak and likely to collapse under fluid flow shear stress at high agitation rates. It is shown that H4 formulation swells to a large extent, produces a firm gel, and releases drug predominantly via swelling/diffusion mechanism. As is apparent in Fig. 4b rate of release at 100 rpm after first hour has increased to some extent, though not significantly, based on f_2 calculation ($f_2 = 58.55$). This slight rate increase may be attributed to the high fluid flow intensity and enhancement of mass transport from the tablet periphery. The linearity of the drug release beyond 4 h is most likely related to the formation and maintenance of uniform gel layer where front synchronization is met (see Figs. 8a and 10).

Effect of pH on release from Glucotrol XL and H4 formulation was studied in pH 2, 4.4, and 6.8 at 75 rpm and results are depicted in Fig. 5. As expected, dissolution rate was significantly lower in the acidic pH media for both systems tested, compared with release in pH 6.8 medium. This is attributed to low solubility of glipizide in acidic media. In addition, we noted that sink condition in the acidic pHs is never met since satura-

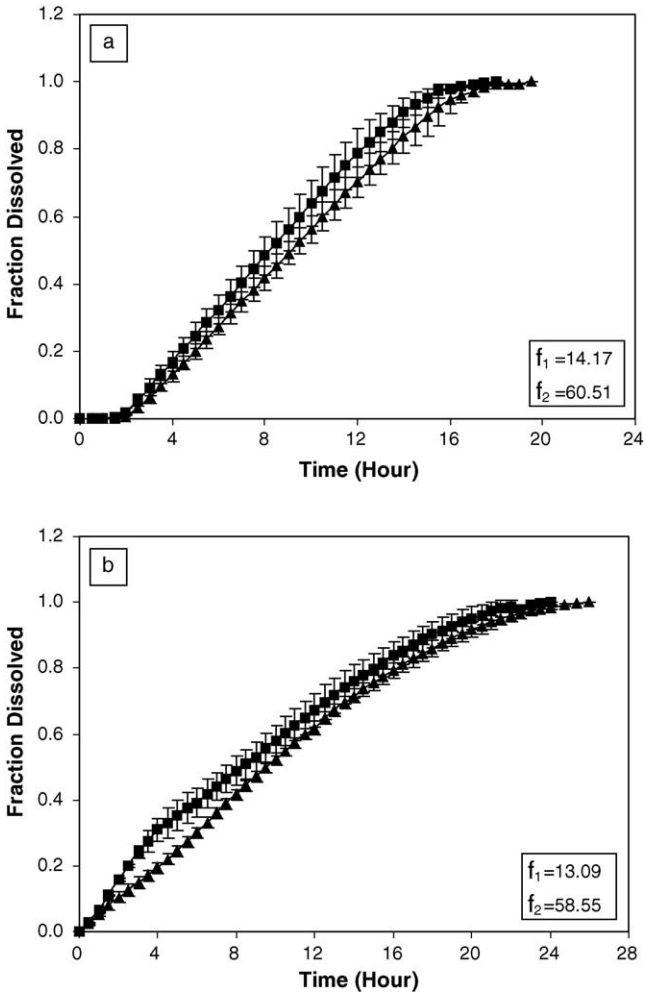

Fig. 4. Effect of hydrodynamics on drug release from (a) Glucotrol XL push-pull osmotic pump and (b) formulation H4 at: 75 rpm (▲) and 100 rpm (■).

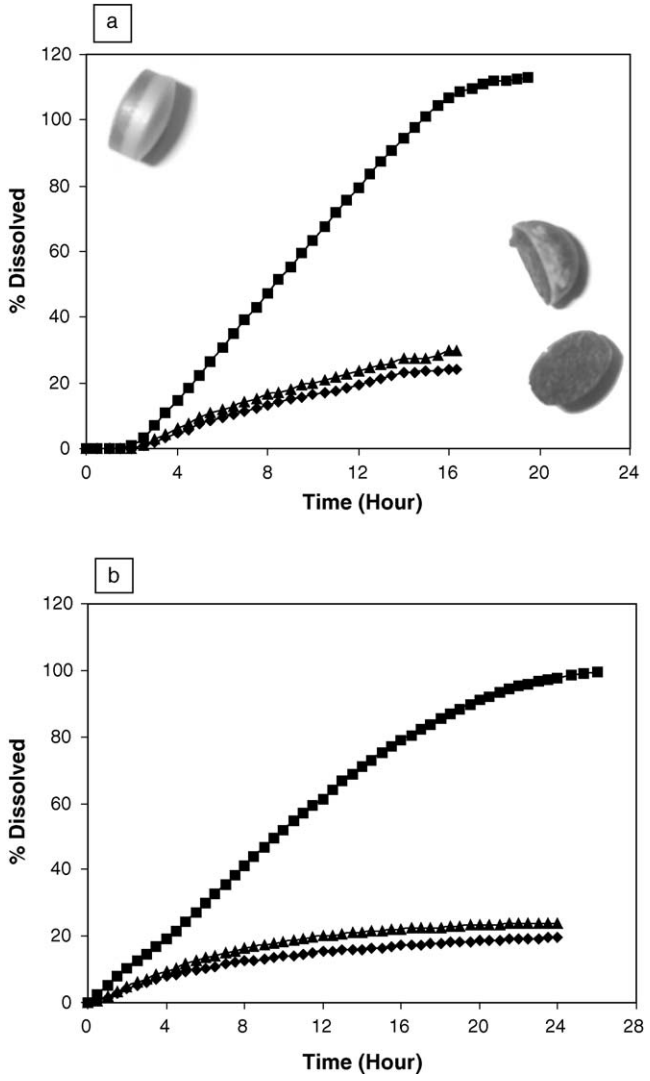

Fig. 5. Effect of pH on drug release from (a) Glucotrol XL push-pull osmotic pump and (b) formulation H4 at: pH 2 (♦), pH 4.4 (▲), and pH 6.8 (■). Inset: Glucotrol XL original tablet with top coat removed (left) and cross section after 17 h of dissolution in pH 2 (right).

tion solubility of glipizide in pH 2 and 4.4 was extremely low, 1.0949 and 1.3183 μg/ml, respectively. The cross section of Glucotrol XL push-pull osmotic pump shell at the end of dissolution experiment in all pHs only showed the existence of push layer; all the drug layer was completely delivered (Fig. 5a inset). This observation along with break up of H4 tablets at the end of the dissolution run under all pH conditions suggest that both systems completely delivered their drug content during the time course of the experiment, but drug tended to remain insoluble in the acidic pHs. While drug micro particles were released at pH 2 and 4.4, the dissolution process was impaired as a result of insolubility and the absence of sink conditions.

3.1.2. Rational for use of ring-mesh device during dissolution studies

In the initial dissolution tests with HPMC formulations, it was noticed that tablets stuck to the bottom of the dissolution vessels for the greater part of the experiment. As a result, dissolution rates and extent were low and data variation was high. When studying the dissolution behavior of a drug delivery system, it is essential to simulate conditions of the gastrointestinal tract as much as possible in order to obtain a profile prognostic of the in vivo performance of the dosage form (Dressman et al., 1998). Upon oral administration of a matrix tablet, all surfaces of the dosage form are in contact with the GI fluid, and at the same time the delivery system is under considerable physical and hydrodynamic influence of GI motility and contractions. In order to provide full matrix exposure in the dissolution medium and fluid flow, in our study, a mesh was inserted below the paddle in the dissolution vessels and the tablets were placed on top of the mesh (Figs. 2 and 3 inset) as previously described by Durig and Fassihi (2000). By this modification tablets could hydrate and swell freely in all dimensions.

3.1.3. PEO based formulations

In the second approach, the combination of high molecular weight PEO (4,000,000) with MCC was used in the matrix preparation. PEO has been studied as an alternative to HPMC in controlled release formulations (Royce, 1993; Kim, 1995, 1998; Maggi et al., 2000; Yang et al., 1996). PEO was shown

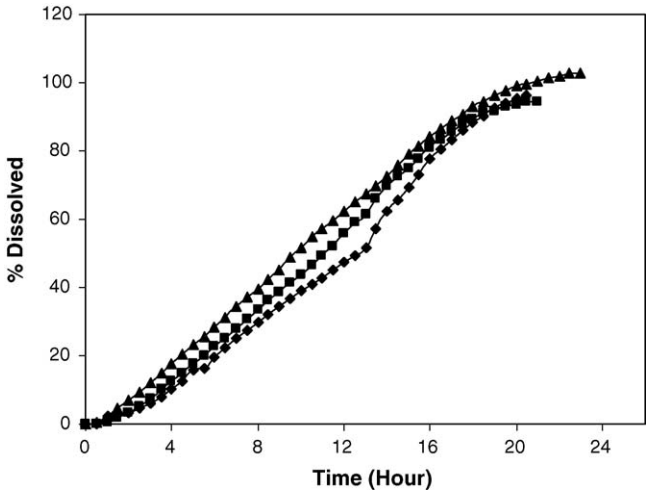

Fig. 6. Dissolution profiles of PEO based glipizide formulations ($n = 3$): P1 (♦), P2 (■), P3 (▲).

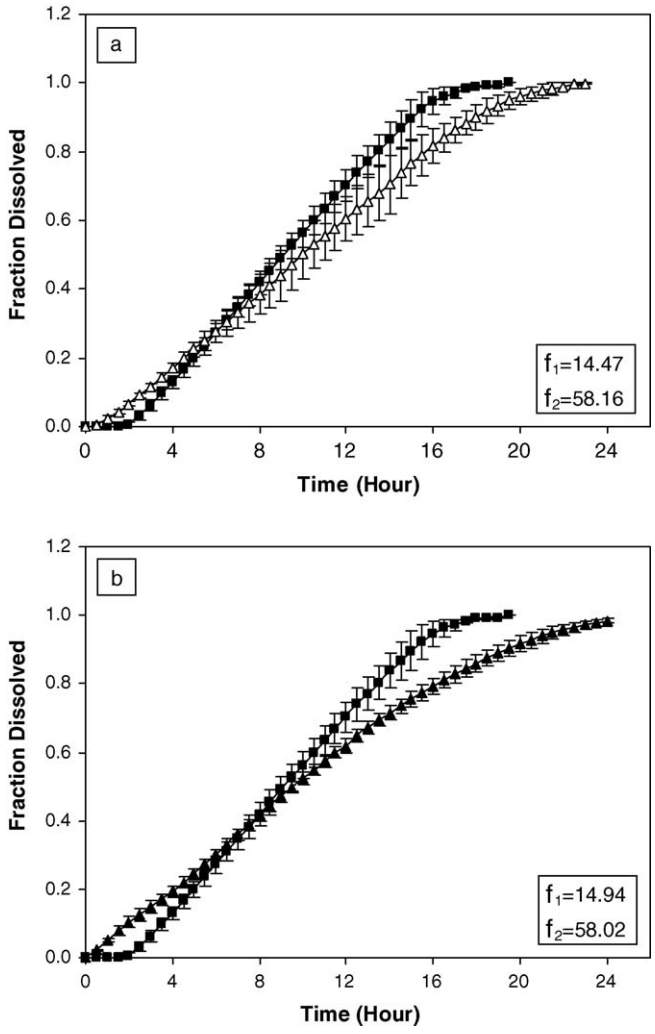

Fig. 7. Comparison of drug release profiles of (a) P3 (△) and (b) H4 (▲) with the reference product, Glucotrol XL (■).

to consolidate via viscoelastic behavior and fusion due to the low melting point, and showed very poor tabletability characteristics. As a result, PEO tablets showed low tensile strength and large axial recovery (Yang et al., 1996). MCC is known to have a high compactibility; and when sufficiently added to PEO as a compression aid, can improve manufacturability and make strong tablets. Besides, MCC is fibrous and hydrophilic in nature; and thus, can complement water uptake and improve matrix integrity and provide for modulation of matrix erosion rate.

In the PEO formulations, the amount of PEO was systematically reduced, increasing the ratio of MCC:PEO (Table 1). As shown in the release profiles (Fig. 6), the rate of drug release increased and linearity improved. The P3 formulation showed the best drug release similarity to Glucotrol XL in this series ($f_2 = 58.16$ compared to 43.66 and 50.24 for P1 and P2, respectively). The release was linear ($R^2 = 0.9998$ for up to 90% release), but standard deviations were higher than H4 formulation (Fig. 7a and b). In the PEO series, the degree of swelling was less than HPMC formulations, and the surface erosion of the tablets began from the early hours of the dissolution. The tablets were completely eroded at the end of the dissolution test with some insoluble residues visible at the bottom of the vessel.

The lag time in Glucotrol XL's release profile was not observed in either HPMC or PEO formulations (Fig. 7). The 2 h lag time in the osmotic pump system is the time required for water imbibition through the semi-permeable membrane and activation of the osmotic pump. From a pharmacokinetic point of view, especially in a chronic treatment with once a day controlled release matrix tablet, the lag time effect is insignificant. The steady state plasma drug concentration is usually achieved after equivalent of five dosing intervals, especially when drug release is linear and absorption is not the rate limiting factor.

3.2. Hydration and erosion studies

Investigation of matrix hydration and erosion directly by gravimetrical analysis is a valuable exercise to better understand the mechanisms of release and the relative importance of participating parameters (Durig and Fassihi, 2002). Fig. 8 shows the results of weight gain and mass loss studies for H4 and P3 formulations.

In the H4 formulation, weight gain and mass loss proceeded throughout the entire course of the dissolution with matrix hydration showing a near zero order kinetics (Fig. 8a). The high capacity of HPMC matrix for water retention and the osmotic pressure generated by lactose are responsible for such behavior.

In the P3 formulation, however, the rate of hydration levels off at around 6 h, possibly as a result of front synchronization and consistency of gel layer thickness. Furthermore, mass loss appears to follow the same kinetics as that of drug release (Fig. 8b). This can be attributed to a relatively more pronounced erosion mechanism. In Fig. 8c, the water uptake capacity of two developed systems are compared. The differences observed can be described by the higher osmotic effect of lactose compared to that of MCC in addition to differences in polymer content (total 90 mg or 59% in H4 compared to 40 mg or 26% in P3) and the inherent swellability differences between HPMC and PEO.

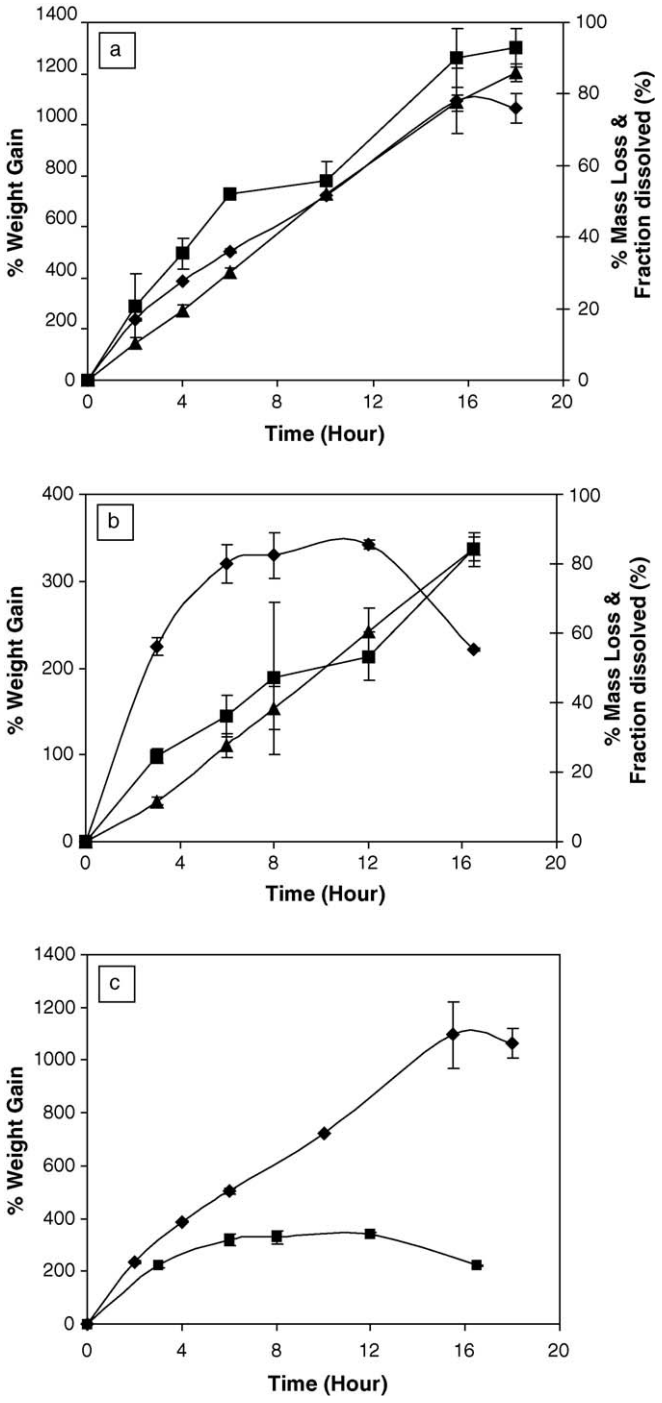

Fig. 8. % Weight gain (♦), % mass loss (■), and % fraction drug dissolved (▲) for H4 (a) and P3 (b). Comparison of % weight gain in H4 (♦) and P3 (■) (c).

3.3. Textural analysis (TA) study

In Fig. 1, the overall dynamics of the water gradient, polymer character, drug concentration gradient, as well as textural behavior within a hydrating matrix is presented. The polymer and water concentration in a hydrated matrix influences its textural behavior. Apparently, low water concentration or high polymer concentration represent a strong gel and vice versa. Gel strength is an important factor in controlling water transport and drug release in that it can influence not only drug diffusion, but also dynamics of matrix erosion. Drug diffusivity through a hydrated matrix increases as gel strength decreases (diffusion coefficient is inversely proportional to the viscosity of the diffusion medium, that is the hydrated matrix in this case).

Gel strength of the matrix system also has some additional significance in vivo since the dosage form is exposed to the destructive forces of the GI tract. Kamba et al. (2000) measured the contractional forces in the stomach to be 1.9 N under fed and 1.5 N under fasting condition (Kamba et al., 2000, 2002). In the small intestine, force of up to 1.2 N under fasting condition was measured. Weaker frictional forces during dosage form transit in the GI tract may also contribute to the matrix erosion.

Therefore, understanding the rheological properties of the matrix throughout the swelling and dissolution process can provide insight regarding drug release mechanisms as well as prognosis for in vivo performance. Textural analysis of H4 and P3 formulations were evaluated at 2, 4, 6, and 8 h and corresponding force–displacement profiles are presented in Fig. 9. The axial swelling is greater in the H4 formulation (greater total displacement at all time points) and the matrix resistance to force imposed by the probe is relatively greater (larger area under the curve) (Fig. 9). The individual profiles for both

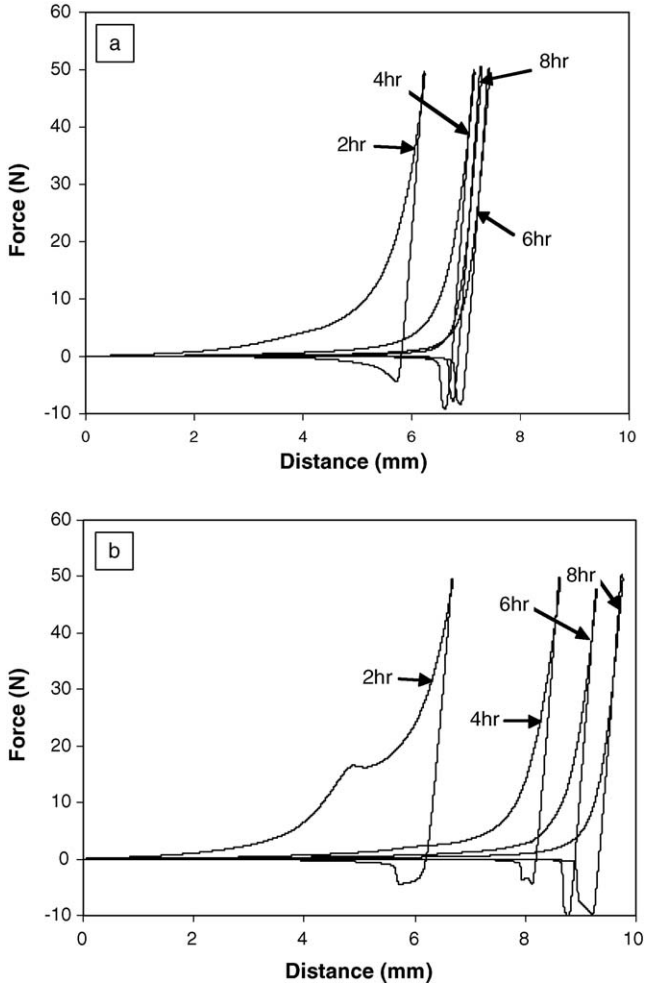

Fig. 9. Textural profiles of P3 (a) and H4 (b) determined after 2, 4, 6, and 8 h.

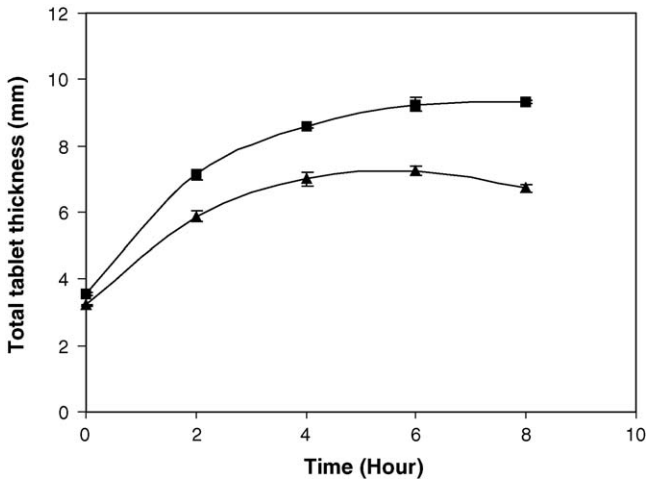

Fig. 10. Comparison of swelling behavior in P3 (▲) and H4 (■).

formulations at 4, 6, and 8 h are more comparable than the profiles obtained at 2 h. This can be attributed to the nature of polymer interaction with water, which is faster in PEO than HPMC, and resulted in a significantly faster reduction in tablet strength in P3 formulation (see profiles at 2 h in Fig. 9) even though the initial hardness was higher. The negative force values observed during the probe retraction in all profiles result from the fully deformed matrix sticking to the probe, causing resistance against the probe's retraction to its original position.

Using force–displacement profiles, thickness of the swollen tablets and the total tablet resistance to the probe's advancement were measured as depicted in Figs. 10 and 11, respectively. Swelling in both formulations follows the same trend, but the rate of swelling is higher in the HPMC formulation. Front synchronization (Conte et al., 1988) in both formulations can be noticed in Fig. 10, where after 4 h the thickness of the swollen tablet remains relatively steady. This potentially contributes to the zero order drug release kinetics observed in both formulations. Due to the extensive swelling in the late time period and the very soft nature of the matrix, technically it was not possible to perform further textural studies beyond 8 h.

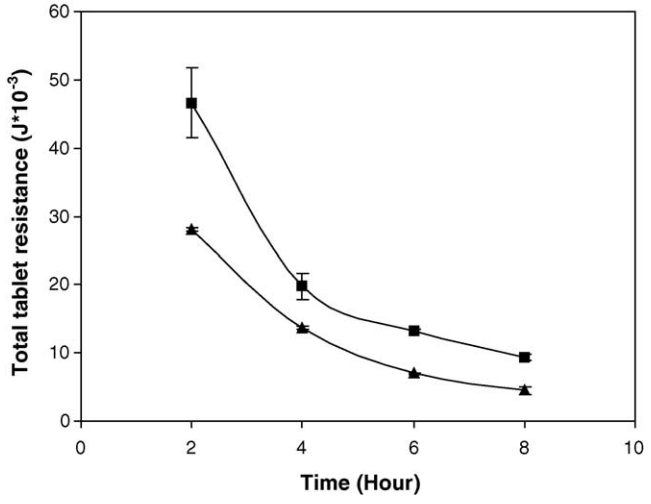

Fig. 11. Comparison of gel strength in P3 (▲) and H4 (■).

The gel strength and tablet resistance to the probe action, shown in Fig. 11, was greater in H4 formulation at all times with the maximum difference relative to P3 at 2 h. Results of this study reveal that despite a significantly higher degree of hydration and swelling, the gel structure formed by the HPMC matrix in H4 is much stronger than the P3 formulation, yet over time the matrix is totally dissolved. As noted earlier, within GI tract formulation H4 is expected to better resist the destructive forces, especially in the stomach, where a swollen matrix system may remain for many hours. This generally may provide greater and more predictable in vivo performance relative to the erodible systems.

4. Conclusion

In this study linear release of a low solubility/low dose drug, glipizide, similar to the profile of the commercial PPOP system, Glucotrol XL, was achieved with the developed monolithic matrix systems based on HPMC and PEO. Simplicity of formulation, ease of manufacturing, and complete disintegration/dissolution of system are among the advantages of the developed matrix formulations versus the PPOP. The kinetics of drug release was shown to be in accordance with kinetics of hydration/swelling in HPMC-based formulation, while in PEO system erosion kinetics dominated the release operation. Significantly greater swelling/hydration observed in HPMC-based formulation is attributed to water soluble nature of lactose and its osmotic effect, higher concentration of polymer, and inherent water retention characteristics of HPMC. The stronger gel structure of HPMC-based formulation relative to that of PEO may provide superior quality in in vivo performance in terms of matrix resistance to destructive forces within GIT. In general H4 formulation is very promising because of high reproducibility of drug release profile, stronger physical structure relative to P3 formulation, complete disintegration of the system, and insensitivity to the hydrodynamics conditions.

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