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Analysis of macromolecular changes and drug release from hydrophilic matrix systems

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Abstract

The influence of water-soluble and insoluble excipients on dynamics of hydration, front movement, erosion, and drug release from hydrophilic matrix tablets containing water-soluble drug was studied. Tablets were manufactured by direct compression, and their un-constrained swelling behavior and gel strength were assessed with a texture analyzer. Dissolution was performed using USP 26 apparatus II modified by insertion of a mesh to prevent sticking of tablets to the bottom of the vessel and to allow free three-dimensional matrix swelling. Significant release differences between tablet batches were observed and this was consistent with changes in swelling rate, gel thickness, and swelling front movement within the tablets. Matrices containing approximately 30% drug load and water-soluble lactose, demonstrated more pronounced swelling front movement and hence drug release relative to the matrix tablets containing dicalcium phosphate dihydrate. The observed differences in release were verified by calculating the similarity and difference factors. The interdependence of front movement and mass erosion in relation to excipient types on progression of swelling front movement and alteration of water penetration, erosion, and drug release are explained. It is concluded that unlike in conventional dosage forms inclusion of excipients in hydrophilic controlled-release tablets containing water-soluble drugs should be carefully analyzed as their various physico-chemical properties may have significant implications on swelling dynamics, front movement, drug release kinetics, and consequently in vivo performance.
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Keywords: Non-ionizable soluble and insoluble excipients; Release kinetics; Swelling dynamics; HPMC; Monolithic matrix systems; Front movement determination

1. Introduction

Modified-release dosage forms with various formulation technologies have gained widespread importance in recent years and offer many advantages including flexible release kinetics and improved drug

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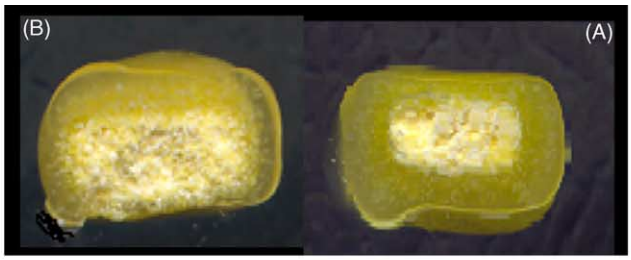
therapy and patient compliance. In its simplest form, monolithic systems can be produced by incorporating the drug and appropriate excipient(s) in a hydrophilic gel-forming matrix (Sako et al., 2002; Velasco et al., 1999; Durig and Fassihi, 2000). Such delivery systems are widely used to control drug release due to their low cost, broad FDA acceptance, ease of manufacturing, their favorable in vivo performance and their use in controlling the release of drugs with a wide range of physico-chemical properties (Williams et al., 2002; Durig and Fassihi, 2002).

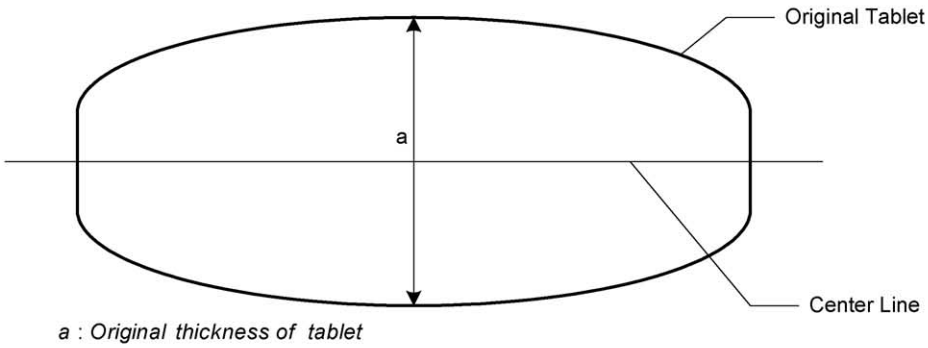
Cellulose derivatives and polyethylene oxide polymers are the most widely used hydrophilic materials in controlled-release systems due to their favorable functionality (Shah et al., 1993; Khurahashi et al., 1996; Reynolds et al., 1998; Yang et al., 1996). There are several formulation factors which influence the drug release rate from hydrophilic based matrices. These factors include but are not limited to the drug loading, drug solubility, drug:polymer ratio, drug particle size, polymer viscosity, and the addition of different types and levels of excipients and release modulators (Velasco et al., 1999; Shah et al., 1993; Khurahashi et al., 1996; Durig and Fassihi, 2002; Pillay and Fassihi, 1999). In monolithic systems typically an initial burst effect in release rate is observed especially when the drug solubility is high and loading dose in the matrix is large (Velasco et al., 1999). The physical properties of the polymer also influence drug release rate and include polymer viscosity, particle size, and amount used in the matrix (Velasco et al., 1999; Khurahashi et al., 1996; Reynolds et al., 1998). For example as viscosity of the HPMC increases, the drug release rate decreases mainly as a result of slower diffusion and extensive swelling (Reynolds et al., 1998). Particle size has a significant effect on drug release when polymer content is low; however as polymer content increases its effect on release is diminished (Mitchell et al., 1993). It has also been demonstrated that in addition to high drug solubility and dose a burst effect may be due to lack of critical polymer concentration threshold and distribution in the matrix (i.e. percolation threshold limit has to be met in all three dimensions of the tablet) (Mitchell et al., 1993). Additionally when polymer concentration is low, the hydrated matrix would be highly porous with a low degree of tortuosity leading to low gel strength, rapid erosion of the matrix, and rapid diffusion of the drug from the matrix (Khurahashi et al., 1996). It appears that the drug:polymer ratio is the most important factor affecting the rate and kinetics of the drug release from the matrix-based tablets. In general, an increase in the polymer concentration and ionic strength within the matrix causes an increase in viscosity of the gel as well as decrease in drug release rate (Velasco et al., 1999; Pillay and Fassihi, 1999).

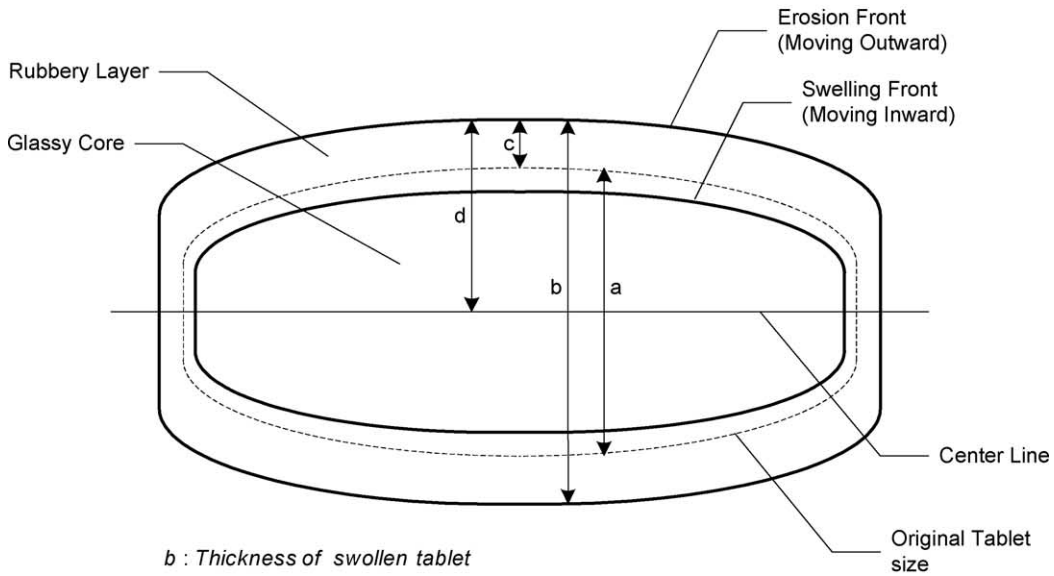
At the molecular level, drug release is determined by polymer swelling, front movement, drug dissolution, diffusion, and matrix erosion. These phenomena depend upon the interaction between water, polymer, matrix contents and the drug. Water has to penetrate the polymer matrix leading to polymer swelling and drug dissolution before the drug can diffuse out of the matrix. In effect, water decreases the glass transition temperature of polymer to the experimental temperature (e.g. HPMC T_g of 184 °C to lower than 37 °C) resulting in the transformation of glassy polymer into a rubbery phase. The enhanced mobility of the polymeric chains favors the transport of water and the dissolved drug. In vitro, release of water-soluble drugs is mainly controlled by diffusion out of the gel layer, whereas release for poorly soluble drugs is likely to be controlled by polymer relaxation–dissolution (Sako et al., 2002; Bettini et al., 2001; Colombo et al., 1999, 2000). The kinetics of these phenomena has been studied by analysis of swelling, diffusion, and erosion fronts (Bettini et al., 2001). The swelling front separates the rubbery region from the glassy region while the erosion front separates the matrix from the dissolution media as shown in Fig. 1.

Other important factors in modulating drug release from monolithic matrix tablets include the type and quantity of excipients. It has been reported that the use of insoluble excipients such as dicalcium phosphate dihydrate in matrix tablets containing insoluble drug alprazolam and 40% HPMC K4M decreased the rate and extent of drug release compared with the same matrix containing soluble excipients like lactose (Williams et al., 2002). No explanation was provided regarding the effect of these excipients on the dynamics of hydration and front movements within the matrix as well as role of excipients on actual release mechanism(s).

The purpose of this study was to investigate in detail the influence of excipient type on the kinetics of matrix hydration, erosion, and drug release from HPMC-based matrix system containing water-soluble drug, with the aid of a texture analyzer. This task was accomplished







$$c : (MTV) = \frac{\left(Swollen\ thickness - Original\ thickness\right)}{2}$$

$$d : \frac{Swollen\ thickness}{2}$$

Fig. 1. Cross-sectional scan of formulation A and B tablets after 5 h exposure to swelling medium (top), the schematic of various fronts for a tablet before (middle) and after (bottom) swelling.

Table 1
Components of formulation A, B, and control

Component	Tetracycline HCl 100 mg	HPMC K4M 150 mg	Spray-dried lactose monohydrate 100 mg	Dicalcium phosphate dihydrate 100 mg	Magnesium stearate (1.0%)	Micron–sized fumed silica (0.5%)
Formulation A	X	X	X	–	X	X
Formulation B	X	X	–	X	X	X
Control	X	X	–	–	X	X

Tablet weight: for formulations A and B containing excipient was 355.25 mg and for control without excipient was 255.25 mg. The tablet hardness was around 5–7 kP for all tablets.

via combined evaluation of dissolution studies, texture analysis of the matrix over time, front movement determination and erosion of the tablets containing lactose monohydrate or dibasic calcium phosphate dihydrate as possible release modulators using tetracycline hydrochloride as the drug model. The importance of non-ionizable but soluble versus insoluble excipients on solute transport, boundary movement and gel strength relative to control tablets containing no excipient is also discussed.

2. Materials and methods

2.1. Materials

Tetracycline hydrochloride USP was obtained from Zenith Laboratories Caribe Inc. (Cidra, PR), and hydroxypropylmethylcellulose (HPMC) K4M from the Dow Chemical Company (Michigan, USA). The additives/fillers used included: dibasic calcium phosphate dihydrate NF (Emcompress, Amend Drug & Chemical Company, Irvington, NJ) and spray-dried lactose monohydrate NF (Foremost, Baraboo, WI). Micron-sized fumed silica was obtained from GraceDavison (Columbia, MD) and magnesium stearate NF from Malinckrodt (St. Louis, MO).

2.2. Preparation of the matrix tablets

Three batches of tablet formulations were produced and will be referred to as formulations A, B and control in the article (Table 1). Tetracycline hydrochloride USP, HPMC K4M, and spray-dried lactose monohydrate NF (mean particle size of 85 micron) constituted formulation A and dibasic calcium phosphate dihydrate NF (mean particle size of 150 micron) in place of spray-dried lactose was used in formulation B. These materials were screened through a sieve number 20, and blended for 10 min in a laboratory-scale V-shaped blender (The Patterson-Kelly, East Stroudsburg, PA). Magnesium stearate NF screened through a sieve number 60 and micron-sized fumed silica were added and mixed for additional 5 min. Final blends were compressed into tablets using a single punch tablet press (Stockes, Model 511-7, Bristol, PA) at constant pressure of 70 MN/m^2. Control tablets containing drug, HPMC K4M, magnesium stearate, and fumed silica were prepared under identical conditions. The final tablet weight and hardness were determined as reported in Table 1.

2.3. Dissolution testing

Tablet dissolution was assessed using three tablets per batch and standard USP 26 Apparatus II (paddle) at 75 rpm using buffer at pH 2.2 and 37 °C (Vankel, Cary, NC). To avoid the adhesion of the hydrating tablets to the bottom of the dissolution vessel the apparatus was modified by the inclusion of stainless steel ring mesh devices in each vessel as previously described (Durig and Fassihi, 2000). The drug concentration was determined every one hour by UV spectrophotometer at 278 nm (diode array spectrophotometer, HP 8452A, Hewlett Packard, Wilmington, DE). Dissolution studies were performed on tablet batches (formulation A, B, and control) independent of swelling and erosion experiments.

2.4. Water uptake and erosion studies

Water uptake and erosion for each time point were studied under the same condition as explained for dissolution test. At predetermined time intervals, tablets

were removed from the medium and lightly patted using tissue paper, weighed and dried under vacuum at 70 °C until constant weight was achieved and discarded. The following equations were used to determine percent weight gain (water uptake) and percent mass loss:

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

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

2.5. Textural analysis of swelling behavior

The swelling behavior of the formulations was investigated through textural analysis of swollen tablets. Tablets were placed in the dissolution vessels under conditions identical to those described above for dissolution testing. The hydrated tablets were removed at predetermined intervals, patted lightly with tissue paper, and subjected to textural profiling to determine gel layer thickness, movement of the erosion and swelling fronts, and total work of probe penetration into the entire matrix. All measurements were carried out in triplicate for each time point and tablets were discarded. Textural analysis was performed using a TA.XT2i texture analyzer 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 round-tipped steel probe into the swollen matrices were monitored at a data acquisition rate of 200 points per second as previously described (Pillay and Fassihi, 2000). Probe approached the sample at pretest speed of 1.0 mm/s. Once a trigger force of 0.005 N was detected (at contact of the probe with tablet) the probe was advanced into the sample at a test speed of 0.5 mm/s until the maximum force of 40 N was reached. Swollen thickness was determined by measuring the total probe displacement value recorded and by the observation of textural profiles. Percent axial swelling was calculated according to the following equation:

$$\text{Axial swelling (\%)} = \frac{\text{swollen thickness} - \text{original thickness}}{\text{original thickness}} \times 100 \quad (3)$$

Swollen thickness in this work reflects the entire free axial swelling thickness of the matrix without any constraint imposed on the swelling. This approach is entirely novel and different to the visually observed swelling reported by some authors where thin discs of pure polymers are sandwiched between two Plexiglass plates and radial expansion of the constrained discs are investigated (Bettini et al., 2001; Colombo et al., 1999, 2000). Total work of penetration, which is a measure of gel strength and resistance to probe penetration, was also determined from the textural profiles.

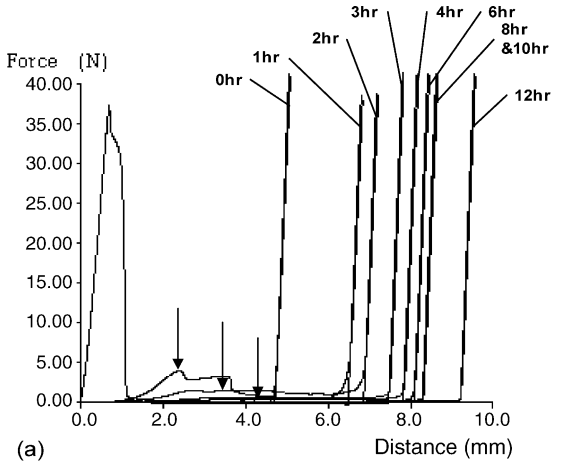
$$\text{Total work of penetration} = W_T = \int F \mathrm{d}D \quad (4)$$

3. Results and discussion

3.1. Textural analysis (TA)

Textural profiles were used to study the dynamics of gel strength and movement of gel boundaries at different depths in matrices containing soluble and insoluble excipients in the presence of soluble drug. This would help to better understand solute transport in the presence of various mesophases. Fig. 2 shows series of TA profiles for formulations A and B achieved at different times after matrix exposure to the swelling medium in the dissolution vessels under similar conditions to that described under dissolution studies. The force required for probe to penetrate the swollen tablet decreases with increasing time as the swelling proceeds and gel strength is reduced. Force transition regions in a force–displacement textural profile of a swollen tablet has been defined earlier by Pillay and Fassihi (2000) and Durig and Fassihi (2002).

The total work of penetration calculated as the area under the force–displacement curve indicates matrix stiffness or rigidity. Fig. 3 depicts the change in work of penetration versus time as the exposure to swelling medium is extended and hydration is increased. A sharp decrease in work of penetration from 0 h (dry tablet) to



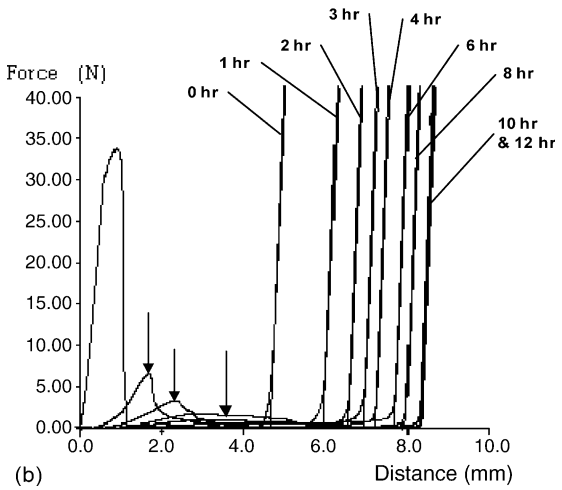


Fig. 2. Force–displacement profiles for formulation A (a) and formulation B (b) at different time points.Note: The initial resistance to probe penetration into the core (up to 3 h, arrows) and overall tablet swelling thickness which is >9 mm for formulation A and >8 mm for formulation B.

1 h is observed which reflects the initial high rate of hydration of tablets which incidentally coincides with high rate of water uptake and gel formation shown in Figs. 4 and 5. Between 2 h and 10 h formulation A shows lower values for work of penetration which is attributed to the soluble nature of lactose and drug in providing for greater water penetration and subsequently weakening of the gel structure. In the case of formulation B containing dicalcium phosphate the gel strength was greater over the same time period. This is also consistent with lower hydration and gel thickness

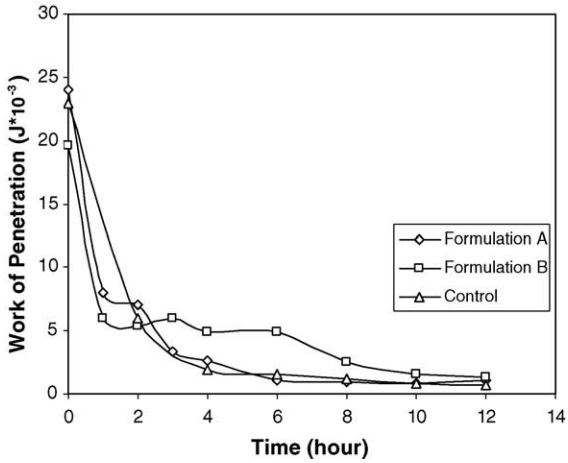


Fig. 3. Total work of penetration at different time points for formulation A, B, and control.

shown in Figs. 4 and 5. The inward movement of the fully hydrated region as well as increase in total thickness of swollen tablet for each time point is apparent in all TA profiles as shown in Fig. 2.

Determination of total tablet thickness and swelling front movement using force-displacement profiles provided more evidence that the rate and extent of gel formation is significantly influenced by the nature of excipient used. As has been described in Fig. 1, swelling front moves inward toward the center of tablet. As shown in Fig. 6 hydration and swelling increase (see

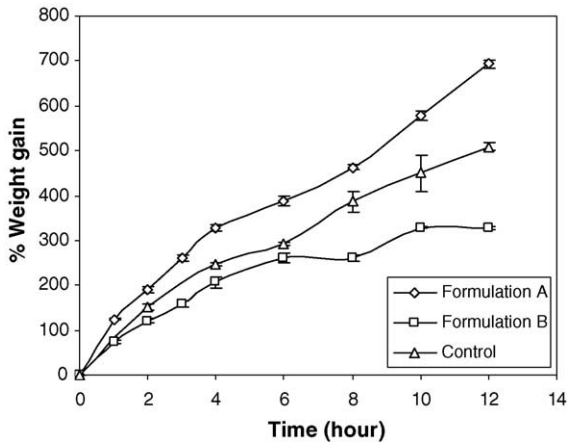


Fig. 4. Percent weight gain (water uptake) at different times for formulation A, B, and control.

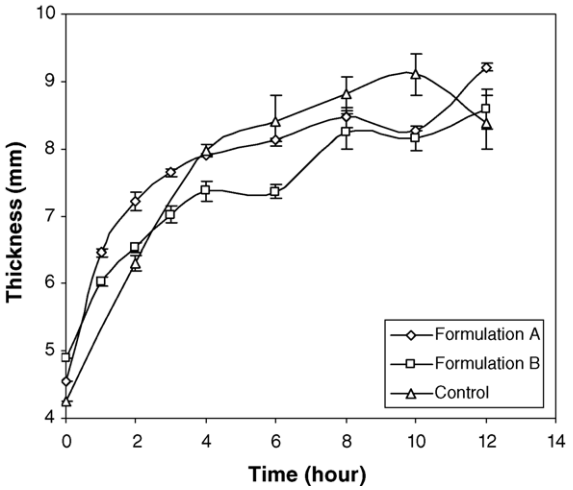


Fig. 5. Axial thickness of hydrated tablets at different times for formulation A, B, and control.

also Figs. 4 and 5) and the core weakens until the solid core disappears and gelation is complete. The rate of movement of swelling front remains high while the rate of changes in overall tablet thickness decreases after 4 h (Fig. 5). It may be concluded that in HPMC-based systems the rate of core hydration is greater than the rate of erosion at the tablet peripheries. In addition front synchronization in these formulations does not seem to actualize and therefore the deviation of release profiles from zero-order kinetics is understandable.

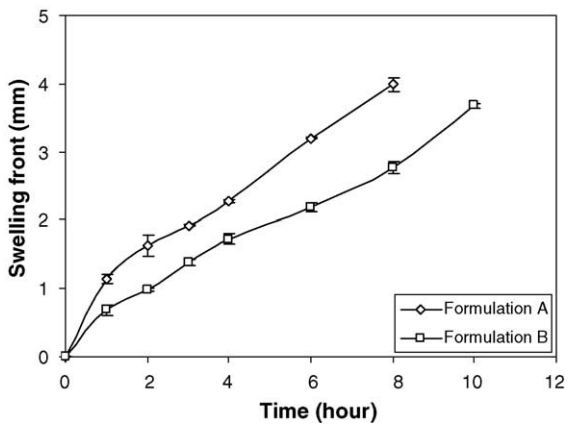


Fig. 6. Swelling front movement for formulation A and B.

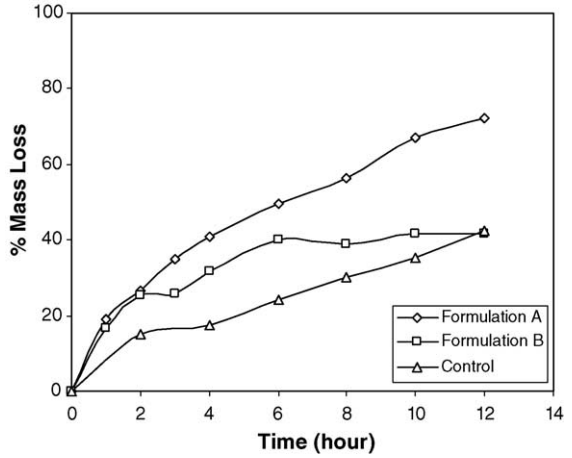


Fig. 7. Mass loss for formulation A, B, and control.

3.2. Water uptake and mass loss study

Gravimetric evaluation of hydration and mass loss revealed that rate and extent of water uptake were significantly greater in lactose containing formulation than in control and formulation B (Fig. 4). Lactose as a water-soluble excipient facilitates penetration of water into the matrix, leaches out and therefore leaves behind more pores to be filled with more water. On the contrary the lower water uptake in formulation B is explained by insoluble nature of dicalcium phosphate dihydrate. Greater mass loss observed in both formulations A and B compared to control is probably attributed to the depletion of excipients and greater polymer dissolution (Fig. 7).

In order for a polymer to dissolve, a disentanglement threshold must be reached. Because of higher original concentration of HPMC in control tablets (Table 1) more time is required before such threshold is reached. Therefore the degree of polymer erosion up to the last sampling time was relatively low in the control formulation. This is also manifested in the constant increase in thickness of hydrated tablets during the same period of time.

3.3. Determination and analysis of front movement

In order to determine the swelling front, an experimental method was developed using analysis of dimensional changes as shown in Fig. 1. Thickness of

swollen tablet was determined first and compared to the original thickness to provide the extremes of the axial swelling boundaries values. The minimum theoretic value (MTV) at each time point was calculated as follows:

$$\text{MTV} = \frac{\text{swollen thickness} - \text{original thickness}}{2} \quad (5)$$

and the maximum possible swollen value (when no glassy core remains) is calculated by dividing the thickness of swollen tablet by factor 2. In order to determine swelling front values relevant portions of the up curving textural profiles of the swollen tablets were measured at specified forces, from minimum of 0.1 to maximum of 1 N depending on the relative strength of the core. As time of exposure to the medium (pH 2.2 HCl/KCl buffer) increased, the gel layer thickness increased and the swelling front shifted toward the core center. To select and assure the relevant force representing the real swelling front, cross-sections of swollen tablets at different time points were scanned and the ratio of the rubbery region to the total thickness was determined. At respective time points a force value in the TA profile, which coincided best with the observed swelling front of the scanned tablets, was selected. The maximum swelling when the glassy core completely disappeared was confirmed by observing the cross-section of tablet at late time period.

Based on the combined scans and textural information the swelling front at all time points was determined. It is noteworthy that the core consistently loses its strength as swelling progresses. Fig. 1 (top) shows a typical scan of cross-section of a swollen tablet. Note the difference in gel thickness between matrices containing dicalcium phosphate dihydrate as excipient versus tablet containing lactose. Due to the solubility and probably an osmotic effect of lactose and drug in the matrix greater swelling and gel thickness is observed. Fig. 1 (middle and bottom) is a schematic representation of minimum and maximum value determination for the swelling front. Positive values of swelling front represent the increasing distance between erosion front and glassy front (i.e. swelling front). Since the boundaries are not well defined, the values measured are estimates and appear to be consistent with the front locations visually observed on the actual scans at different time points.

Fig. 6 shows the nature of front movement for matrices containing soluble and insoluble excipients. The difference in front movement appears to follow similar trend to percent weight gain shown in Fig. 4. In addition a comparison between front movement profiles and mass erosion profiles shown in Fig. 7 also demonstrates meaningful relevancy between these factors. As mass erosion progresses, so is the front movement, indicating that erosional kinetics and swelling front movement are interrelated. Presence of excipients with soluble or insoluble characteristics seem to have significant impact on front movement and consequently on drug release kinetics. At early times, in the case of tablet containing lactose the rapid swelling and outwardly expansion results in pulling the diffusion and swelling front and hence thicker gel layer formation (Fig. 1, scan A).

3.4. Release characterization

Dissolution profiles for formulation A, B, and control are presented in Fig. 8. Incorporation of a soluble, non-ionizable excipient, spray-dried lactose monohydrate as expected increased the rate of drug release compared to control with significant burst effect. In the presence of lactose, as anticipated, water diffusion into the matrix is enhanced and drug is diffused out of the matrix more rapidly. The favorable water solubility of lactose results in enhancement in both rate and extent of gelation at matrix periphery as shown in the cross-section of scanned tablet in Fig. 1 (top panel, scan A). This introduces more water into the system and consequently provides for gel-layer formation and drug diffusion control.

Incorporation of a non-soluble excipient, dicalcium phosphate dihydrate resulted in a slower release with more linearity in the dissolution profile (see formulation B). In general presence of dicalcium phosphate dihydrate and in this case potential for in situ complexation with tetracycline tends to reduce drug release and to some extent inhibit the overall swelling (see Fig. 1, top panel, scan B). It is also apparent that in formulations containing water-soluble drugs the polymer: matrix ratio may make the system more susceptible to water uptake and erosion (Velasco et al., 1999; Reynolds et al., 1998; Colombo et al., 1999, 2000). The balance between the aforementioned factors determines the net difference in swelling dynamics, erosion, and dissolution kinetics. In both formulations at a late-time pe-

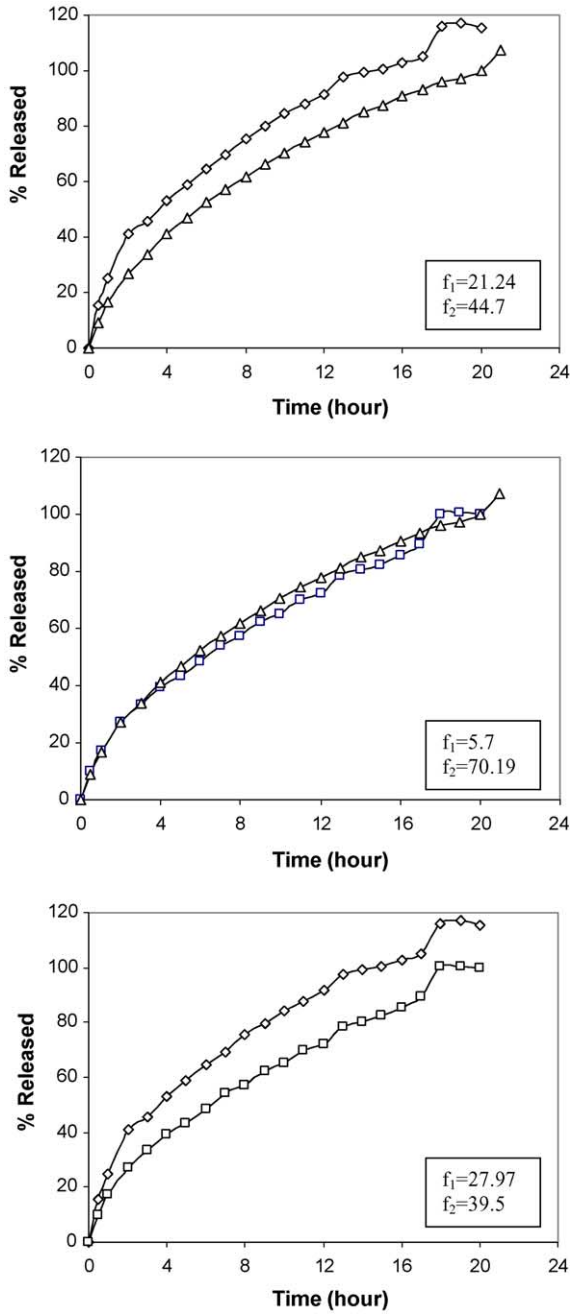


Fig. 8. Dissolution profiles for formulation A (◊), formulation B (□), and control (△).

riod (∼17 h), release tends to accelerate which may be explained by reduction in polymer concentration and consequently more rapid disentanglement of polymer chains, weakening of gel microstructure and complete dissolution of the system.

Linear regression analysis by Microsoft Excel was performed to fit the dissolution data to the following exponential equation (Lindner and Lippold, 1995):

$$Q = kt^n + b \tag{6}$$

where Q represents the fraction of drug released in time t, k is a diffusional rate constant and n describes the operating release mechanism. The constant b was incorporated into the equation to account for the initial burst effect. The Fickian diffusion exponent "n" varies from ∼0.5 to <1.0 for thin slabs. In our work "n" was taken as 0.43 based on the calculated aspect ratio (diameter/thickness) of the tablets (Peppas and Sahlin, 1989) and duration of Fickian release was defined as the period of time in which Q versus $t^{0.43}$ was linear with the highest correlation coefficient (Durig and Fassihi, 2002). First, regression analysis was performed for fraction released up to $Q = 0.6$. However, based on the observation of data and in order to investigate the applicability of power law to release data above $Q = 0.6$ as has been discussed by Rinaki et al. (2003) it was decided to treat data for entire profile as long as linearity was maintained (see Table 2). Interestingly in both analyses the fitting results were excellent with high correlation coefficients. It is demonstrated that the common equation $Q = kt^{0.43} + b$ is also applicable to release data in excess of $Q = 0.6$ (i.e. data for formulations A, B, and control up to $Q = 0.78$, 0.62, and 0.96 respectively).

Although this model seems to describe the dissolution profiles fairly well, based on visual observation and the results of erosion studies it is clear that substantial relaxation (erosion) of the polymer is also taking place in the process of drug release. In order to determine the predominance of diffusional and relaxational contributions, data were fitted to Eq. (7) (Peppas and Sahlin, 1989):

$$Q = k_1 t^m + k_2 t^{2m} \tag{7}$$

where Q is the fraction of drug released in time t, k_1 and k_2 represent kinetic constants associated with diffusional and relaxational release, respectively, and m

Table 2
Analysis of drug release and fickian duration Eq. (6)

Formulation	Slope (k) ($h^{-0.43}$)	Intercept	Duration of fickian release (hr)	r^2
A	0.2941	−0.0770	12	0.9974
B	0.2701	−0.1089	10	0.9983
Control	0.3019	−0.1564	18	0.9991

Table 3
Analysis of release mechanism Eq. (7)

Formulation	Diffusional rate constant k_1 ($h^{-0.43}$)	Relaxational rate constant k_2 ($h^{-0.86}$)	k_2/k_1	r^2
A	0.1996	0.0262	0.1313	0.9878
B	0.1307	0.0397	0.3037	0.9957
Control	0.1115	0.0514	0.4610	0.9959

is the purely Fickian release exponent. Sigma Plot 8.0 was used for fitting the data up to $Q = 0.6$ to the Eq. (7). Expanding the analysis to later time points, the model appeared to fit the data with high r^2 up to 85–90% of total dose (see Table 3).

The k_2/k_1 values represent the relative contribution of relaxational and diffusional mechanisms to overall release profile. Based on the calculated values in all cases diffusion is dominant ($k_2/k_1 < 0.5$), with some differences among the formulations. Presence of lactose compliments diffusional contribution (lower k_2/k_1), whereas dicalcium phosphate dihydrate tends to reduce this effect. The results of water uptake determinations (Fig. 4), work of penetration (Fig. 3), and swelling thickness data (Figs. 5 and 6) show high interdependency. Higher water uptake and gel thickness were observed with lactose-containing matrix compared with matrix containing dicalcium phosphate dihydrate while gel strength was weaker in the presence of lactose.

Further comparison of dissolution profiles was performed by calculation of difference factor (f_1) and similarity factor (f_2) (Moore and Flanner, 1996), based on which dissolution profile of formulation A is significantly different from formulation B as shown in the inset in Fig. 8.

It is noteworthy that degree of hydration and mechanical gel strength can influence in vivo drug release from swellable matrices because matrix integrity and subsequently release mechanism may change under mechanical stress applied to the dosage forms in the stomach and intestine specially during the phase III of Migrating Myoelectric Complex (MMC) (Sako et al., 2002). In general resistance to probe penetration into the hydrated matrices after 4 h was less than 2 N. The reported contraction force of stomach and small intestine on 10 mm flat faced tablets is approximately 2 and 1.2 N respectively (Kamba et al., 2000, 2002). This information is valuable and can be used in relation to in vivo performance of dosage forms through manipulation of matrix composition, gel strength, and in vitro release evaluation of the designed delivery systems.

4. Conclusion

Within the context of hydrophilic polymeric matrices containing water-soluble drug, excipients should not be regarded as neutral or simple additives as they are certainly capable of altering water penetration, erosion, and hence mechanism of drug release. The role of gel layer and its rate of growth are central and fundamental to define various fronts and understand the operating release mechanism(s). To this end textural analysis methods used for studying the dynamics of front movements offer new opportunities to better understand the nature of solute transport in these systems when substances with different solubility and ionization potential are used. Furthermore, modifications introduced for evaluation of dissolution by insertion of a mesh in the vessel to allow unrestricted matrix swelling and various interpretations presented may be of use to research scientists who are involved in design of hy-

drophilic matrix systems and can be used as formulation "finger-prints" and may aid in successful formulation optimization.

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