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Image analysis studies of dimensional changes in swellable hydrophilic polymer matrices

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Studies of the fronts which are created by the process of swelling, their movement and the effect of drug solubility on release mechanisms, are presented. Tablets comprising solely of hydroxypropyl methylcellulose (HPMC) (Metolose 90 SH 100 000 SR), HPMC with sodium diclofenac (relatively soluble in the buffer solution used) and HPMC with furosemide (insoluble in the buffer solution used) were prepared. The tablets were made by direct compression in a manual hydraulic press and the matrix swelling was studied by an optical analysis technique. During the experimental procedure measurements were taken of the gel layer dimensions, the movement of the swelling, and the erosion and diffusion fronts at different time points. These measurements allowed the investigation of the possible mechanisms involved in the swelling/release process. The results showed that the rate and mechanism of drug release from swellable matrices depends on the following factors: the dissolution, the diffusion of the drug, the translocation of undissolved drug particles in the gel layer, and the solubility of the drugs used. This is supported by the following: (a) the diffusion layer thickness, which is observed as a result of the presence of undissolved drug in the gel layer, increases in the case of the water insoluble drug furosemide and as a result the diffusion front converges on the erosion front; (b) from the analysis of the dissolution data it appears that sodium diclofenac is released as a result of diffusion via the gel layer as well as due to polymer relaxation and/or matrix erosion. Conversely, the release of furosemide is only dependent on the polymer relaxation and/or matrix erosion.

KEYWORDS: swelling; gels; hydroxypropyl methylcellulose; hydrophilic polymers; image analysis system

INTRODUCTION

Swellable systems, prepared by incorporating drugs in hydrophilic polymeric matrices, have received considerable attention for the preparation of sustained release formulations.[1] Cellulose ethers, such as hydroxypropyl methylcellulose (HPMC) have been widely used for the preparation of controlled oral drug delivery systems because of their nontoxic nature and ease of manufacture.[2,3] Such formulations have been classified as swelling controlled release systems.[4]

When a hydrophilic matrix is exposed to water or a biological fluid it starts to hydrate and swell from the outer boundary towards the center. A gel layer is formed around the matrix, which significantly influences the dissolution and diffusion of the drug through the polymer. This plays an important role in determining the release mechanism. Several investigators have studied the behavior of the gel layer and its boundaries using image analysis optical techniques. Lee and Peppas[5] defined the boundary between the matrix surface and the dissolution medium, as the ''erosion front'' and the boundary between the glassy polymer and its rubbery gel state as the ''swelling front'' (Fig. 1). The presence of a third front within the gel layer was observed[6] in a matrix containing sodium diclofenac as the active substance. This was identified as the ''diffusion front'' and its boundaries are within the gel layer, between the areas in which the drug has dissolved and not dissolved (Fig. 1). Further, it has been demonstrated that the behavior of the diffusion front depends on the solubility and the quantity (or loading) of the active substance.[7] These three fronts can be observed and their movements facilitate the calculation of the parameters of the swelling/dissolution process.

Several methods have been described in the literature for the study of the gel layer. These include the penetrometer,[8] NMR imaging,[9,10] ultrasound[9] methods together with optical methods, such as image analysis.[1,11] Since each technique is applied under different experimental conditions, it is difficult to determine whether one is superior to the others. Image analysis, however, offers a qualitative and quantitative tool to study swelling and solvent transport in large matrices.

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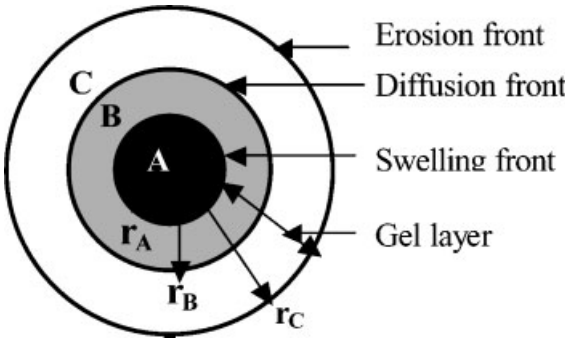

Figure 1. Schematic representation of erosion, diffusion and swelling fronts, along with the relevant layer: (A) undissolved drug in the glassy polymer layer; (B) undissolved drug in the gel layer; (C) dissolved drug in the gel layer, $r_C - r_A$ is the gel layer and $r_B - r_A$ is the diffusion layer.

It combines ease of manipulation with low instrument cost and high precision. Characterization of solvent gradients is also achieved without the use of markers.[12] Optical techniques have a number of advantages (e.g. *in situ* experimentation, relative simplicity and the ability to determine various parameters such as tablet geometry, thickness of the gel layer, and even the ability in many instances to determine the diffusion front) over alternative methods. In this report, an optical imaging method based on the technique developed by Gao and his coworkers[13] has been used. This method directly measures both the dimensional changes of a matrix tablet and the gel layer growth during swelling. It also provides a semiquantitative estimation of HPMC concentration profiles across the gel layer.

The present work involves the study of the fronts formed during the swelling process in the transport of two uncolored drugs. The effect of the drug solubility on swelling is described and it is shown how this influences the formation and the behavior of the fronts. An account of the effect of front movement on the release mechanism is then presented.

EXPERIMENTAL

Materials

HPMC (Metolose 90 SH 100 000SR, Shin-Etsu chemical) was used as polymer carrier, sodium diclofenac (Sigma Chemical Co. St. Louis, MO) and furosemide (Hoechst, Germany) were used as model drugs, magnesium stearate (BDH company) was used as lubricant.

Techniques

Tablet preparation

Three types of Metolose tablets were prepared. The compositions of formulations used are listed in Table 1. The powder of each formulation was blended in a Turbula mixer (Willy A. Bachoten AE, Basel, Switzerland) for 10 min. The tablets were prepared by direct compression in a manual hydraulic press (Carver 3393, Fred S. Carver, Inc., Menomonee Falls, WI). The tablets were flat, 10 mm in diameter, weighing 200 mg, and their hardness was 8–10 kp.

Table 1. Formulation composition

Formulation Material	M	MD	MF
Metolose SR (mg)	200	99	99
Furosemide (mg)	—	—	99
Diclofenac (mg)	—	99	—
Magnesium stearate (mg)	—	2	2

M: pure Metolose; MD: Metolose with sodium diclofenac; MF: Metolose with furosemide.

Release studies

Tablets were subjected to the dissolution study at $37 \pm 0.5°C$ with stirring at 100 rpm (paddle method) in the USP XXIII dissolution apparatus II (Pharmatest, Hainerp, Germany), in 900 ml of phosphate buffer (pH 7.4). Samples (5 ml) were withdrawn at predetermined time intervals, filtered and analyzed at $\lambda_{max} = 276$ nm for sodium diclofenac and furosemide using a Perkin–Elmer UV spectrophotometer (Norwalk, CT). All experiments were performed in triplicate.

Measurement of fronts movement

The swelling, the geometric characteristics of the tablets and the position of the fronts were assessed by image analysis (IAS). Image taking and processing was performed in the Leica Q500IW Image Analysis system, equipped with a JVC TK-C 1381 color camera, combined with a Century Precision Optics C15838 (+7) lens for better image magnification (Fig. 2A). The tablets were placed in a dissolution vessel containing a phosphate buffer at pH 7.4 in suitable position (horizontal or vertical direction), as shown in Fig. 2(B), for the observation of the swelling in the axial direction. At fixed time intervals the vessel was removed from the dissolution apparatus, placed under the camera and the structure of the tablet was recorded. The experiments were carried out under the conditions described in the release studies section. Figure 3(A) shows a typical image of a swellable tablet in the radial direction and Fig. 3(B) in the axial direction. The gel layer appears as a light ring due to the scattering of light by the hydrated polymer. The glassy core and the dissolving medium appear black as they do not permit scattering of the incoming light. The two boundaries of the gel (swelling front and erosion front) are qualitatively indicated in Fig. 3(A) by the dark and the light ring in the image, respectively.

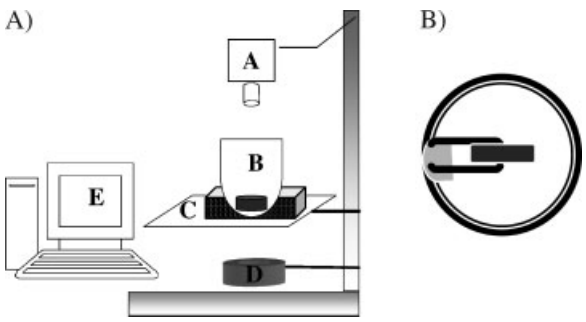

Figure 2. Schematic representation of (A) image analysis equipment and (B) the tablets placed in the dissolution vessel in the axial direction.

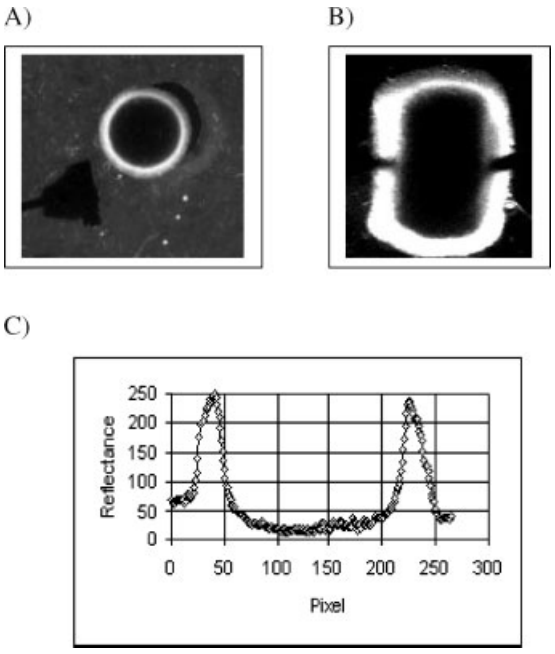

Figure 3. (A) Optical image of a HPMC matrix tablet observed *in situ* in the radial direction after swelling for 5 hr. (B) Gray level profile of the image obtained by applying a horizontal rectangular measuring frame through the center of the tablet. (C) Gray level profile where measurements are taken horizontally along the diameter of the tablet.

Figure 3(C) shows the horizontal profile (gray level) where measurements were taken horizontally along the diameter of the tablet. The two peaks are caused by the presence of gel layer on both sides of the tablet.

RESULTS AND DISCUSSION

From visual observation it is clear that as soon as the tablets are exposed to water, the liquid penetrates into their mass and the hydrated polymer swells to form a gelatinous layer around the tablet. Figure 4 shows typical photographs taken by I.A.S in the radial direction of the three tablets, pure Metolose (M) (Fig. 4A), a mixture of Metolose with sodium diclofenac (MD) (Fig. 4B) and a mixture of Metolose with furosemide (MF) (Fig. 4C). The photographs are shown after 2, 4, 6 and 8 hr and it can be seen that the build up of a gel layer rapidly occurs around the matrix. The gel layer is formed more rapidly in M and MD tablets than in MF tablets.

The results of the change in tablet dimensions during swelling are presented as normalized values of the radial and axial dimensions, with reference to the initial values (dry tablet), as a function of time (Fig. 5). Each point on the curve is the average of three repeat measurements and the standard deviations of the values are given.

The tablets undergo fast hydration due to rapid liquid penetration and in less than 30 min a significant expansion is observed. As can be seen, the M tablets displayed a significant dimensional change in the axial direction. Subsequently, the axial change of the tablets gradually increased. After 8 hr the axial dimension of the M tablets had increased four-fold, that of the MD tablets three-fold, while that of the MF tablets 2.8 fold. However, there is a smaller but progressive increase in diameter throughout the course of the experiment. Compared to the pure polymer tablets, the preparations which contain the active substance and the polymer showed smaller axial and radial swelling throughout the experiment. The presence of materials other than the polymer, such as drug or excipients, affects the osmotic pressure within the

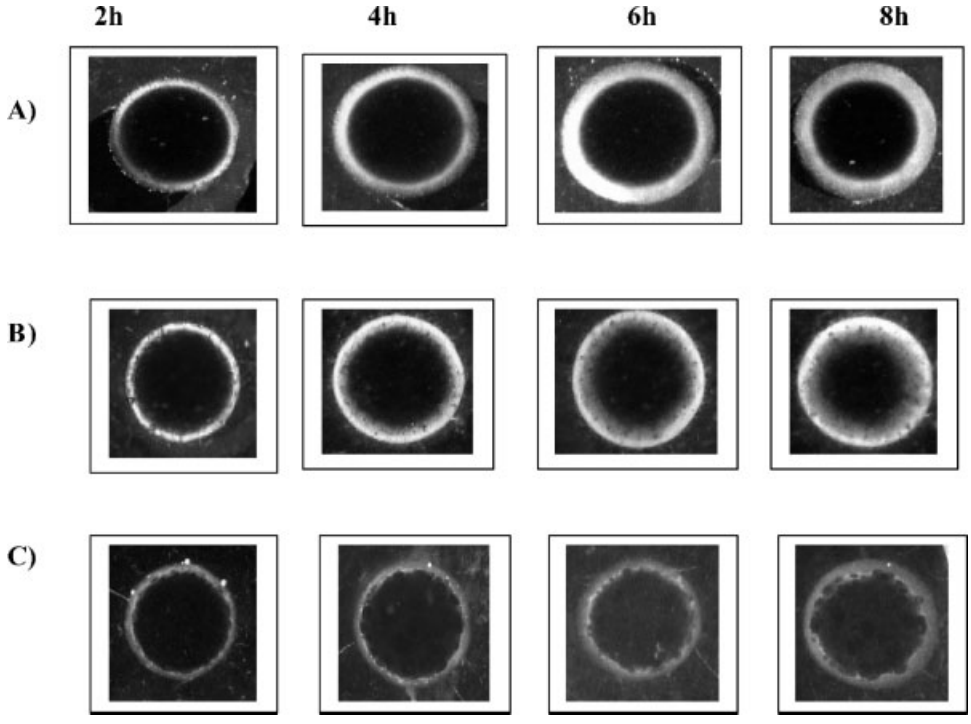

Figure 4. Pictures of the matrix taken at four different times during swelling for the formulations: (A) M; (B) MD; (C) MF.

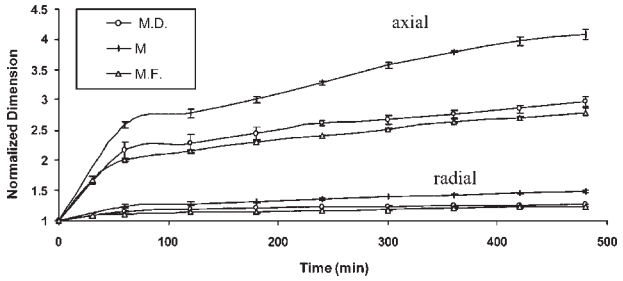

Figure 5. Normalized radial and axial tablet dimensions of the swelling Metolose tablets.

tablet/solvent system, and also the viscosity of the tablet's peripheral gel. The latter is altered due to adsorption of water or biological fluids, which results in decreased swelling.[14] In general, an anisotropic feature of the swelling process of Metolose tablets is clearly indicated by the preferential expansion in the axial relative to the radial dimension, for all formulations. These results are in good agreement with earlier studies reported in the literature.[13,15]

Further, as shown in Fig. 5, the degree of solubility of the drug affects the dimensional changes of the tablets during their hydration. Thus, furosemide has a solubility of 8,961 Cs (mg/ml) while sodium diclofenac has a solubility of 18,79 Cs (mg/ml) in buffer (pH 7.4) and furosemide tablets display a smaller axial and radial swelling. This phenomenon can be attributed to the amount of water absorbed by the matrix during hydration. In the case of the relatively soluble sodium diclofenac, the particles dissolve upon the contact of the tablet with the liquid, leaving micro cavities which facilitate (a) penetration of an increased amount of liquid into the matrix and (b) greater relaxation of the polymer chains. In the case of the less soluble furosemide, the particles take longer to dissolve, thus decreasing the penetration of the solvent and the relaxation of the polymer chains.[16,17]

The growth of the gel layer of the pure Metolose tablet was measured as a function of time (Fig. 6). The dimension of the gel layer in the axial direction is always slightly greater than that in the radial direction. This difference may be due to the axial expansion, as reported in earlier studies with Metolose tablets.[18] Since these differences are not statistically significant (*t*-test) and the continuous variable (CV) is estimated to be no greater than 10%, the gel layer dimension described in the present study is the average of those of the radial and axial gel layers. These dimensions are in good agreement with

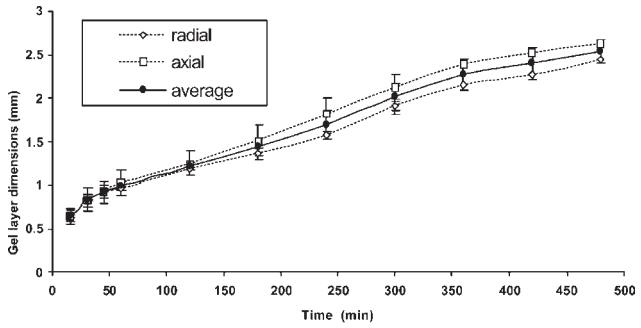

Figure 6. Gel layer dimensions of the swelling pure Metolose tablets observed in the axial and radial directions and the average of the both.

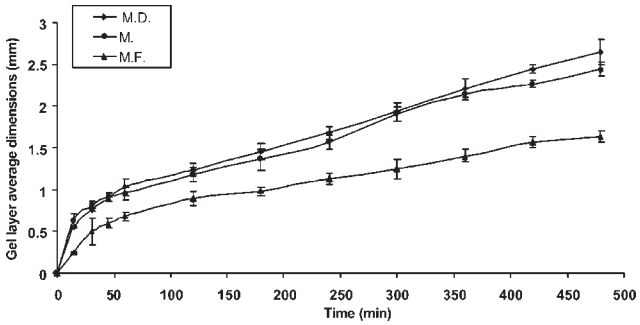

Figure 7. Gel layer average dimensions of the swelling tablets versus time.

earlier findings, which claim a similar dimension of the gel layer for Metolose tablets in both the radial and axial directions during swelling.[9,18]

The apparent growth and expansion of the average gel layer was measured as a function of time and is plotted in Fig. 7. It is obvious that the size of the gel layer in all three tablets, with and without the active substances, progressively increases. The increase of the gel layer occurs in two distinct phases. There is an initial rapid increase in the size of the gel layer within a short period of time ($t < 90$ min), followed by a more gradual increase ($90 < t \approx 480$ min). In the initial stages of matrix swelling the liquid is in direct contact with the polymer and liquid penetration is faster than the chain disentanglement, resulting in a rapid build up of the gel layer thickness taking place around the matrix. When the liquid penetration rate decreases with the increase in the diffusional distance, then there is little change in the gel layer because the liquid penetration and polymer disentanglement rates are similar.[19,20] Furthermore, it was noticed that the presence of sodium diclofenac in the Metolose tablets does not affect the increase in dimension of the gel layer compared to pure polymer tablets, whereas the presence of furosemide halves the increase. This observation can be linked to the fact that sodium diclofenac is almost twice as soluble in buffer solution (pH 7.4) as furosemide. The effect that furosemide exerts in the gel layer dimension is also depicted by the bar graph of Fig. 8, which illustrates the relative increase in gel thickness of the aforementioned drugs versus time. Specifically, in the first 30 minutes the increase noticed in the rate is, as expected, more rapid. Subsequently, the rate

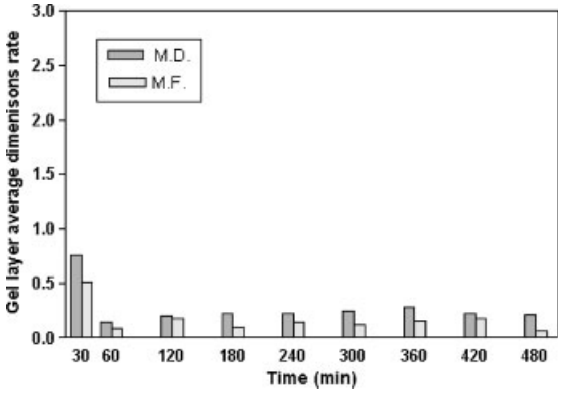

Figure 8. Rate of gel layer average dimensions as a function of time.

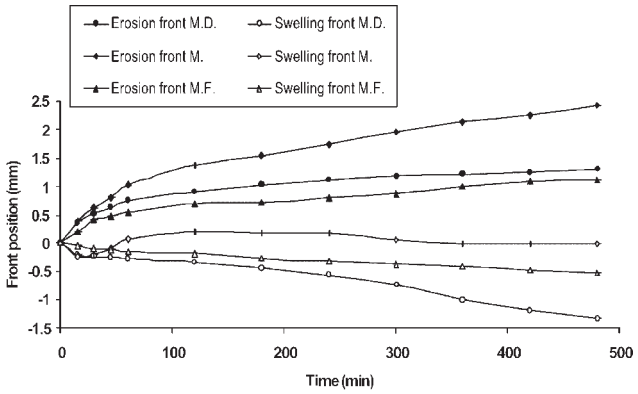

Figure 9. Erosion and swelling front positions during the swelling of the tablets versus time.

was monitored at 1 hr intervals and found to become double. This behavior has not been recorded previously in the literature. This is a quite interesting result, which could be partly attributed to the different stereoelectronic and solubility characteristics of the two drugs.

The analysis of the movements of the swelling and erosion fronts (Fig. 9) enhances the knowledge about the swelling behavior of these tablets. The interaction between the tablet mass and the liquid at the beginning of the experiment ($t = 0$) is indicated by position 0. The standard errors of the mean values are relatively small in all cases. Due to the immediate swelling of the tablet, the erosion front moves rapidly outward (an increase in total diameter) within the first 60 min for all three formulations. Subsequently, the outward movement of the front continues at a slower rate until the end of the experiment, namely after 480 min. The swelling front in M tablets shows a small expansion in the first 120 min, and then moves inwards, while in the Metolose tablets containing the drugs the swelling front moves inwards even at the early stages of the process. As shown in Fig. 9, the rates of movement of the erosion and swelling fronts decrease with decreasing drug solubility.

Of particular interest is the movement of the diffusion front in tablets containing sodium diclofenac and furosemide. These depend on the rate of dissolution of the drug in the gel layer. As shown in Fig. 10, the diffusion front in MD tablets moves outwards from the beginning of the experiment and continues expanding up to 240 min when it moves inwards. This movement of the diffusion front represents the transfer of undissolved particles of the drug within the gel layer because of polymer swelling. This is identified as the diffusion layer. The remaining part of the gel layer (Fig. 1), in which the drug is completely dissolved, is called the dissolution layer and represents the diffusion of the drug in the gel layer. For the MF tablets the diffusion front moves outwards and matches the erosion front, and thus there is no dissolution layer.

The release of furosemide occurs from the surface of the gel layer by means of erosion or escape of solid molecules from the gel.

The data on the release of sodium diclofenac and furosemide from Metolose tablets are shown in Fig. 11. The release data were fitted using the familiar empirical equation proposed by Korsmeyer and coworkers:[21]

$$\frac{M_t}{M_\infty} = k \times t^n \tag{1}$$

where M_t/M_∞ represents the fraction of the drug released at time t, k is a constant incorporating characteristics of the macromolecular network system and the drug and n is the diffusional exponent, which is indicative of the transport mechanism.

Equation (1) is only valid for the first 60% of the fractional release. The values assumed by the n exponent represent either Fickian or anomalous (non-Fickian) release kinetics.

For the case of cylindrical tablets, in particular, $n \leq 0.45$ corresponds to a Fickian diffusion release (case I diffusional), $0.45 < n \leq 0.89$ to an anomalous transport, and $n = 0.89$ to a zero-order (case II) release kinetics.

For the sodium diclofenac formulation, n was found to be equal to 0.70 ($R^2 = 0.9981$). This value points to an anomalous transport from the swellable matrix, which means that the release mechanism is a combination of diffusion and matrix erosion.

In the case of the furosemide formulation, n was determined to be equal to 0.91 ($R^2 = 0.9995$), a value which suggests that the release of furosemide is erosion dependent and follows near zero-order kinetics.

As can be seen in Fig. 11, the release of sodium diclofenac is almost two-fold higher than that of furosemide and this difference is statistically significant. The higher release of sodium diclofenac than that of furosemide is certainly due to the different solubilities of the two drugs, which considerably affects the behavior of these tablets (tablet swelling and

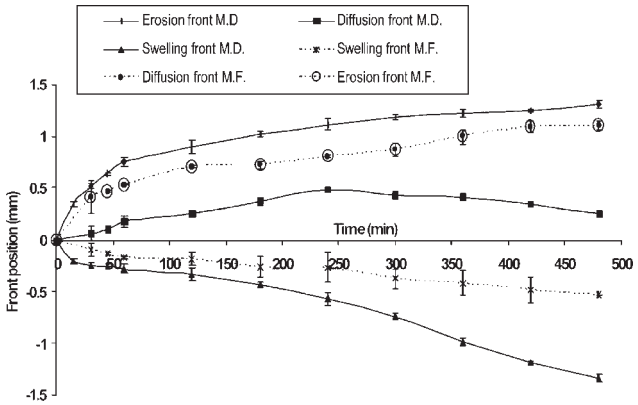

Figure 10. Erosion, diffusion and swelling front positions during the swelling of the tablets versus time.

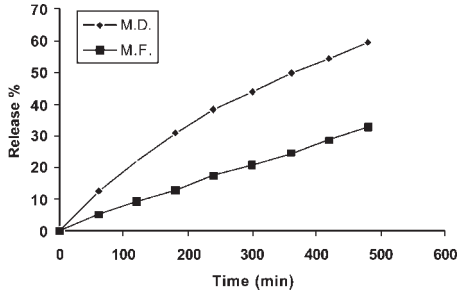

Figure 11. Release profiles from sodium diclofenac and furosemide matrices.

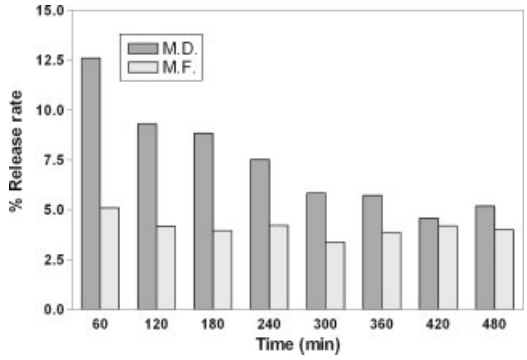

Figure 12. Rate of percent drug release as a function of time.

erosion) and leads to a greater release of sodium diclofenac. Previous studies have shown that the particles of the polymer swell when the dissolution media penetrates into swellable matrices, thus modifying the dimensions and the behavior of the matrix. These modifications depend on the solubility of the loaded drug and the characteristics of the excipients. Soluble materials can produce greater increase in the matrix swelling than less soluble materials and show faster release rates.[22,23]

The bar graph of Fig. 12, presents the percent release rate as a function of time. The bar graph clearly illustrates the initial rapid release of sodium diclofenac which then gradually decreases. Furosemide, however, shows a fairly constant release rate of about 5% per hour.

The two-fold higher release of sodium diclofenac than that of furosemide can also be concluded from the dissolution efficiency (DE) values of the matrices (16.95 for furosemide and 35.21 for sodium diclofenac).

The DE value, which was first suggested by Khan and Rhodes, is a further parameter for the evaluation of *in vitro* dissolution and is defined as follows:[24]

$$\mathrm{DE} = \frac{\int_{t_1}^{t_2} y\,\mathrm{d}t}{y_{100}(t_2 - t_1)} \times 100 \qquad (2)$$

where y is the percentage of dissolved product, and DE is the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y_{100} over the same time period. Normally $t_1 = 0$ for a tablet where there is no lag phase.

The concept of a DE value has the advantage that when a relation is to be shown between dissolution and another variable, it is perhaps more realistic to use a DE value which takes into account the dissolution profile as a whole.[25] Also, where a quantitative comparison is required DE is a more suitable parameter and when limits are set on DE it can be used for quality control in place of the conventional dissolution level.[26]

The results presented herein underline the significance of the dissolution, the diffusion of the drug, the translocation of undissolved drug particles in the gel layer, and the solubility of the drugs used to the rate and mechanism of drug release from swellable matrices.

CONCLUSIONS

This study shows that Metolose tablets mainly swell axially. The solubility of an included active substance affects the swelling, the movement of the fronts, the gel layer dimensions and the release kinetics. It is clearly shown that there is a direct relation between the solubility of the two drugs and those parameters. Specifically, it was observed that sodium diclofenac, with twice the solubility of furosemide, causes double the increase in the dimension of the gel layer and double the percentage of drug release. Furthermore, with the drug of lower solubility the diffusion front converges with the erosion front, increasing thus the dimension of the diffusion layer and affecting the release kinetics. Statistical analysis of the release results shows that sodium diclofenac is released by a combination of diffusion and matrix erosion, while furosemide is solely released by matrix erosion.

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