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Dimensional changes, gel layer evolution and drug release studies in hydrophilic matrices loaded with drugs of different solubility

Manuel Efentakis [a,*], Ioulia Pagoni [a], Marilena Vlachou [a], Konstantinos Avgoustakis [b]

[a] *Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Athens, Panepistimiopolis, Zografou, 157 71 Athens, Greece*
[b] *Pharmaceutical Technology Laboratory, Department of Pharmacy, University of Patras, Patras 26500, Greece*

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Abstract

The objective of this investigation was to explore the effects of drug solubility on the evolution of matrix dimensions and gel layer's during drug release and investigate the relationship between these effects and the mechanism and the rate of drug release.

Two hydrophilic swellable polymers Polyox (POL) and cross-linked Carbopol (CARB) were employed as carriers. Caffeine (CAF) and theophylline (THE), two drugs having similar chemical structure but different aqueous solubility, were used as model drugs.

Both drug and polymer characteristics were found to influence the dimensional changes of matrices and the development of the gel layer formed around the glassy core. The dimensional expansion in CAF matrices was always more pronounced than the THE matrices. Also the CARB matrices demonstrated greater maximum expansion and lower drug release than the POL matrices, due to a smaller degree of erosion of CARB.

The dimensions of CARB/CAF matrices, unlike all the other matrices studied, exhibited a biphasic increase at early times, which was attributed to the cross-linked structure of CARB and the high solubility of CAF. With both polymers, a thinner gel layer was developed in the matrices containing the less soluble THE compared to the CAF matrices. The thickness of the gel layer increased continuously with time in the CAF matrices whereas it increased initially and after reaching a maximum started to decrease in THE matrices. All formulations except those of CARB/THE exhibited burst release, which depended on drug and polymer characteristics. The gel layer thickness and erosion rate appeared to determine the rate of drug release from the CARB and POL formulations. The results clearly indicate that for these matrices gel thickness and fluctuation of gel thickness affect the release rate/h of drug proportionally. Analysis of the release kinetics indicated that CAF was released mainly through diffusion whereas, THE was released mainly through matrix erosion.

Keywords: Controlled release; Polyox; Carbopol; Erosion; Swelling; Dimensional changes; Gel layer; Caffeine; Theophylline

1. Introduction

The characteristics of the hydrophilic polymers employed for the preparation of matrix systems and especially their extensive swelling and erosion influence considerably the behavior of these controlled release drug delivery systems. They also determine the extent of drug release and its kinetics. It has been suggested that matrix geometry (Reynolds et al., 2002; Siepmann et al., 1999, 2000) and the dimensional changes (Colombo et al., 1995; Moussa et al., 1998) of the matrix, in addition to the formation-growth of gel layer (Colombo et al., 1987), can affect the drug release of these systems. Swelling and erosion define the gel layer thickness, which is formed around the tablet. This layer and its thickness play a very important role and is considered to be the controlling factor of drug release from hydrophilic matrices. The thickness of the gel is determined by the relative position of the moving (swelling and erosion) fronts. A number of studies have shown that the solubility of the drugs affects the rate and mechanism of drug release from the swellable delivery systems.

Nevertheless, the discussion on these studies was mainly focused on the effects of drug solubility on the evolution of the gel layer (Conte et al., 1988; Zuleger et al., 2002) and the change of the release mechanism from a drug diffusion-controlled in the matrices loaded with water-soluble drugs to an erosion-controlled mechanism in the case of matrices loaded with poorly water-soluble drugs (Bettini et al., 2001). In addition, most of the literature concerns the study of swelling and the gel thickness

* Corresponding author. Tel.: +30 210 7274 025; fax: +30 210 7274 027.
E-mail address: efentakis@pharm.uoa.gr (M. Efentakis).

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changes of hydroxypropylmethyl cellulose matrices (Bettini et al., 2001; Gao and Meury, 1996; Colombo et al., 1999), but there is a lack of information for other polymers involved in controlled release systems.

Several methods have been considered for the study of swelling, axial and radial expansion and the assessment of tablet dimensions. These methods include the tablet weighing, occasional photography of the tablet against a calibrated graticule and recently image analysis (Papadimitriou et al., 1993; Gao and Meury, 1996; Fyfe and Blazek, 1997; Rajabi-Siahboomi et al., 1994). The image analysis method allows a regular and accurate assessment of the tablet's dimensions employing a non-invasive technique, also permits an overall evaluation of the material used. Finally it ensures a reliable documentation of the dimensional changes, of the swelling process and provides excellent information for the gel layer thickness and erosion.

The objectives of the present work are two-fold. First, to study the effect of drug solubility on matrix swelling and dimension changes. Second, to investigate the relationship between these effects and drug release. The drugs utilized, were two thioxanthine derivatives, i.e., caffeine and theophylline, which have similar chemical structure but different aqueous solubility. This is a more scientific approach of studying the effects of drug solubility than using drugs of quite different chemical structure or the base (acid) form of a drug and its salt, since in the latter case the different chemical nature of the drugs may lead to different drug–polymer interactions, rendering the interpretation of the results difficult. Two hydrophilic swellable polymers with different properties, Polyox and Carbopol were employed as matrix-forming materials (Efentakis and Vlachou, 2000; Efentakis et al., 2000).

2. Materials and methods

2.1. Materials

Caffeine (CAF) and theophylline (THE) (Sigma, St. Louis, MO, USA) were used as obtained. Polyethylene oxide [Polyox, POL] of 9×10^5 MW (Union Carbide, CT) and Carbopol 974 (CARB) (BF Goodrich Chemix) were chosen as model polymers. For the determination of viscosity (1%, w/w, at 24 °C) and contact angles of Polyox and Carpool 974 polymers, a Brookfield digital viscometer model DV-II (Brookfield Engineering Lab., Massachusetts, USA) and a Kruss G40 contact angle measuring system (Kruss GmbH, Hamburg, Germany) were used, respectively.

2.2. Tablet preparation

Drug free tablets were made from POL and CARB by weighing 450 mg of the material and directly hand filling into the die of a Carver press (Fred S. Carver Inc., Memomonee Falls, WI, USA) and compressed. Drug tablets of 450 mg were prepared by mixing together polymer and drug. The mixture consisted of 70% (w/w) of polymer and 30% (w/w) of drug. They were mixed for 10 min in a Turbula–T2C mixer (Willy A. Bachofen AG. Basel, Switzerland), then the tablets were compressed to a crushing strength of 9–10 kg, measured in the Erweka hardness tester (Erweka Heusenstamm, Germany). The diameter of the flat face tablets was 13 mm and the height was 4 mm.

2.3. Release studies

Drug release studies were carried out according to the procedure described in USP using a dissolution tester (Pharmatest, Hainburg, Germany), paddle method, in 900 ml deionized water at 37 ± 0.5 °C with the stirring at 100 rpm. Samples were withdrawn in selected time interval, filtered and analyzed at 272 nm for caffeine and 273 nm for theophylline using a Perkin-Elmer UV spectrophotometer (Norwalk, CT, USA). An equivalent volume of temperature-equilibrated fluid was replaced into the dissolution bath following the removal of every sample. The data represent the mean values of at least three separate experiments and the mean cumulative percentage of drug calculated (±standard deviation) and plotted against time.

2.4. Uptake and erosion studies

Weighed drug-free tablets were placed in flat bottom dissolution vessels, containing deionized water under the conditions of temperature and stirring described in the dissolution studies section above. To prevent floating, tablets were placed under a bell shape "tent" formed by a pre-weighted 4 cm × 4 cm metal mesh (no. 10) square. At selected time intervals (30, 60, 90, 120, 180, 240, 300, 360 and 420 min) an individual tablet was withdrawn using the mesh "tent". The mesh and the tablet were blotted to remove excess water and then weighed on a Sartrorius analytical balance. Then the wetted tablets were dried in an oven at 105 °C for a 24 h period after that, before weighing. They were cooled in a desiccator and finally weighed. This process was repeated until a constant weight was achieved (final dry weight). Three different tablets were measured at each time point, and fresh tablets were used for each individual time point. The extent of erosion (E) was determined by,

$$E\,(\%) = \frac{100(W_\mathrm{i} - W_\mathrm{f})}{W_\mathrm{i}} \quad (1)$$

where W_i and W_f are the initial starting dry weight and final dry weight of the same dried and partially eroded tablet, respectively. Also, the increase in weight (uptake) due to absorbed liquid (A) was calculated at each time point by

$$A\,(\%) = \frac{100(W_\mathrm{w} - W_\mathrm{f})}{W_\mathrm{f}} \quad (2)$$

where W_w is the mass of the wet tablet before drying.

2.5. Optical image analysis

The method we used was similar to the method described in a previous study (Gao and Meury, 1996). The recorded images were collected and analyzed with a Leica image analysis system (Leica Q 5001 W). A video camera (JVC TK-C11381, Japan) was fitted with a zoom lens (Century Precision Optics AD-5870, USA) and connected to a monitor. The light system consisted

of a fluorescent tube fitted under the beaker. The beaker was covered to prevent external light. The tablet was held on a pin and placed in a dissolution beaker (of a dissolution apparatus) with 900 ml of deionized water at 37 ± 0.5 °C at 100 rpm. The tablet was mounted in a vertical or horizontal direction to allow the observation of swelling in the axial or radial direction. The beaker was removed, at predetermined time intervals from the dissolution apparatus and was transferred to the optical image set up. The tablet was photographed by means of a video camera to record the axial and radial changes of the swelled tablet and to estimate the gel thickness growth. The gel layer appears as a light white ring due to the scattering of light by the hydrated polymer. The glassy core and the medium appear black, as they do not permit scattering of the incoming light. The swelling values of axial, radial and gel layer were obtained by calibration of the obtained image. The dimensional scale was calibrated from the known tablet size and measurement of the image obtained at $t = 0$. Results reported are averages for three different tablets.

2.6. Statistical analysis

Results given as mean ± standard deviation (S.D.), were analyzed using Student's t-test ($P < 0.05$).

3. Results and discussion

As mentioned earlier two frequently used polymers with different characteristics were employed and examined in this study namely POL and CARB. POL are hydrophilic, swellable, uncross-linked, non-anionic polyethylene oxide polymers, soluble in water with a variety of molecular weights ranging from about 100,000 to 8,000,000. Since they are non-ionic materials, no significant interaction between drug and polymers is to be expected. They have been used as controlled drug-delivery systems and the drug release is dependent on several factors (Efentakis and Vlachou, 2000; Kim, 1995, 1998). CARB is a synthetic, cross-linked, high molecular weight polymer of acrylic acid. It hydrates and swells fast, but its swelling is influenced significantly by pH. At pH over 4.5 it swells completely. It has low water solubility (Khan and Jiabi, 1998; Perez-Markos et al., 1996) and its cross-link network makes possible the physical entrapment of drugs in hydrogel domains that form when the polymer absorbs water and swells. When fully hydrated it does not dissolve, but osmotic pressure from inside breaks up the structure, mainly by sloughing off disengaged particles of the gel (Goodrich, 1994).

3.1. Radial/axial dimensional changes

In Fig. 1a and b, the radial (RAD) and axial (AX) dimensional changes (normalized to the dry tablet) with time for all types of matrices are shown up to 5 or 6 h. After that, tablet deformation occurred and it was difficult to calculate accurately the dimensional changes. All formulations underwent fast hydration, due to rapid water penetration into hydrophilic materials. In less than 30 min, a considerable dimensional expansion was observed. An anisotropic swelling behavior was observed by

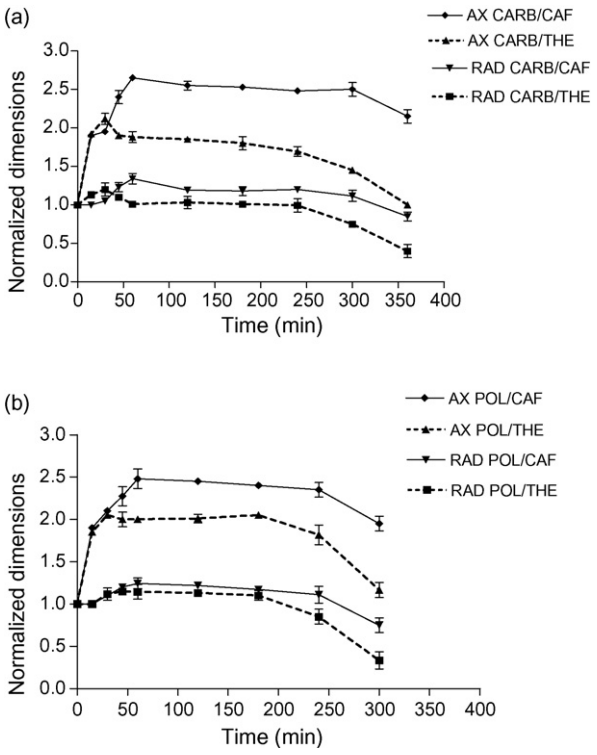

Fig. 1. (a and b) Radial and axial dimensional changes for POL and CARB matrices loaded with CAF or THE. Each point represents the mean value of the three samples and error bars show ±S.D.

preferential expansion in the axial dimension relative to the radial dimension for all formulations, in accordance with earlier studies (Papadimitriou et al., 1993; Maggi et al., 2000).

The dimensional changes of the matrix with time appeared to be both drug and polymer dependent (Fig. 1a and b). In CARB/CAF tablets, both dimensions reached rapidly a maximum in 60 min, followed by a plateau and a limited decrease after the fifth hour (Fig. 1a). CARB/THE matrices reached faster the maximum increase, in 30 min, and then a similar plateau was observed, followed (after the fourth hour) by a gradual and progressive decrease.

The CARB/CAF showed a greater maximum axial increase (over 2.8-fold) compared to CARB/THE 2.1-fold. In contrast the radial increase was smaller and rather similar for both formulations (1.35-fold for CARB/CAF and 1.2-fold for CARB/THE).

In parallel, POL/CAF matrices demonstrated also a greater expansion compared to the POL/THE matrices (Fig. 1b). The dimensional changes in both directions were comparable, but smaller (especially in axial dimension) to that of the CARB/CAF tablets. The maximum increase of POL/CAF matrices was 2.5-fold and 1.3-fold for axial and radial dimensions, respectively, whereas POL/THE matrices displayed 2.0-fold and 1.1-fold for axial and radial dimensions, respectively. After the first hour, in both dimensions, a plateau was observed between the first and third hours and then a relatively rapid decrease in both dimensions (more distinctive for THE) confirming earlier studies (Kim, 1995).

With both polymers, the expansion in CAF-loaded tablets was always greater compared to the expansion in THE-loaded

tablets. This could be attributed to the higher solubility of CAF and the development of an osmotic pressure, which facilitates the penetration of an increased amount of the liquid into the tablet, and the creation of channels (due to rapid drug dissolution) that allow a faster access of the liquid, increased hydration and finally greater swelling.

As it is known, CAF, aside from its higher solubility, 21.7 g/l (Talukdar and Kinget, 1995) is less hydrophobic (contact angle 43) than the less soluble, 11.2 g/l (Freichel and Lipold, 2000), and more hydrophobic (contact angle 48) THE. Hence, CAF allowed increased liquid penetration whereas THE impeded hydration and swelling.

The presence of less soluble THE appeared to induce matrix erosion, preventing the expansion of THE matrices to the degree observed in the case of CAF matrices. Enhanced erosion/dissolution of the polymer mass and a more abrupt decrease of both matrix dimensions, particularly after the third hour for POL/THE and the fourth hour for CARB/THE, was observed in the case of THE matrices compared to CAF matrices (Fig. 1a and b). It was noticed that, after the fourth hour, particles were removed from the THE tablets. This was most likely due to attrition and confirmed the erosion phenomenon.

CARB/CAF matrices showed, in both dimensions, a rather two stage expansion at early times followed by a plateau whereas in CARB/THE matrices a rapid expansion was observed, which was followed by a small decrease and then a plateau. This could be related to the different drug solubility. Thus, upon contact of the liquid with the polymer, the soluble CAF located on and close to the surface dissolved rapidly and facilitated an immediate and sharp liquid penetration (first phase of swelling/expansion).

The cross-linked structure of CARB withstood the osmotic pressure generated due to surface drug dissolution and the expansion of the matrix was temporarily slowed down. However, further liquid uptake dissolved a greater quantity of drug. Then more channels are formed allowing further liquid penetration. This increased the osmotic pressure within the gelled polymer and induced further swelling (second expansion phase) until equilibrium, was reached between swelling and polymer dissolution/erosion (manifested by the plateau phase).

In CARB/THE matrices a different profile was observed, due to the lower solubility of THE. After a rapid initial expansion, a local erosion of the polymer surface occurred (Aldeman, 1984), decreasing matrix dimensions. In this case, THE did not induce significant increase of the osmotic pressure and, as a consequence, the second expansion phase was eliminated.

From the above, it is clear that CARB/CAF matrices exhibited a two phase's expansion in dimensions and the maximum increase whereas all the other matrices demonstrated one stage expansion and lower increase.

The uptake (Fig. 2) results of drug-free tablets show that CARB can finally absorb and withhold greater amount of water than POL, due to smaller erosion (Fig. 3). It is obvious that up to the 4 h there is a rather slow water uptake in CARB matrices. This is attributed to its cross-linked structure, which delayed water penetration into the tablet.

After that CARB tablets displayed further increase in liquid uptake, while in contrast POL tablets exhibited a decrease, after

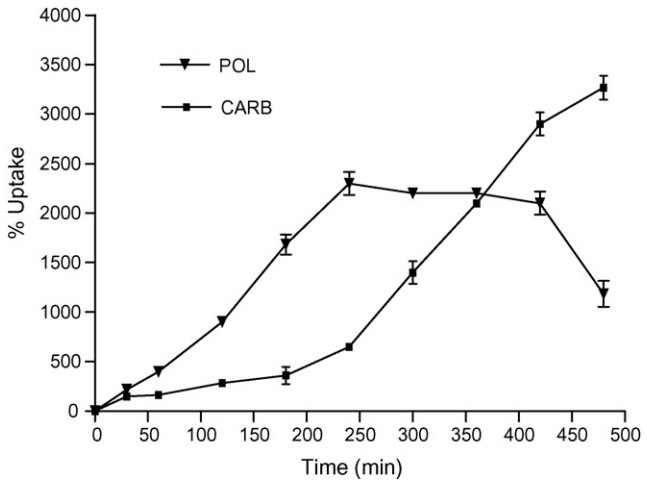

Fig. 2. Percentage of weight change (water uptake) as a function of time in deionised water, for POL and CARB tablets. Each point represents the mean value of the three samples and error bars show ±S.D.

7 h. The erosion of POL completed in 8 h, while CARB exhibited only a 75% erosion at the same time. The decreased erosion rate of CARB compared to POL (Fig. 3) allowed for the higher (maximum) expansion of drug-loaded CARB matrices compared to drug-loaded POL matrices with both drugs studied.

3.2. Gel layer changes

The relative movement of the erosion and swelling fronts represents the gel layer thickness which underscores the difference in positions between those two fronts (Colombo et al., 1987, 1999). Typical images of CAF/CARB and CAF/POL tablets undergoing hydration after 30, 60 and 120 min in the radial and axial plane are shown in Fig. 4.

The formation of the hydrated swollen polymer layer (gel layer) and its changes around the still glassy tablet core with time

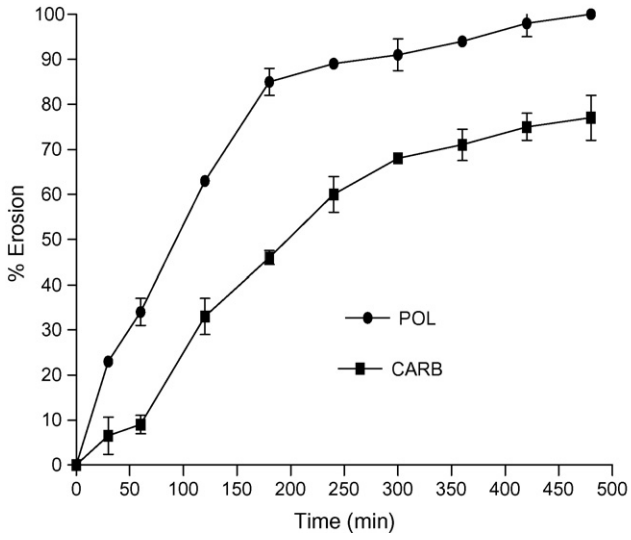

Fig. 3. Percentage of weight loss (erosion) from tablets dried after exposure to deinonised water for POL and CARB tablets. Each point represents the mean value of the three samples and error bars show ±S.D.

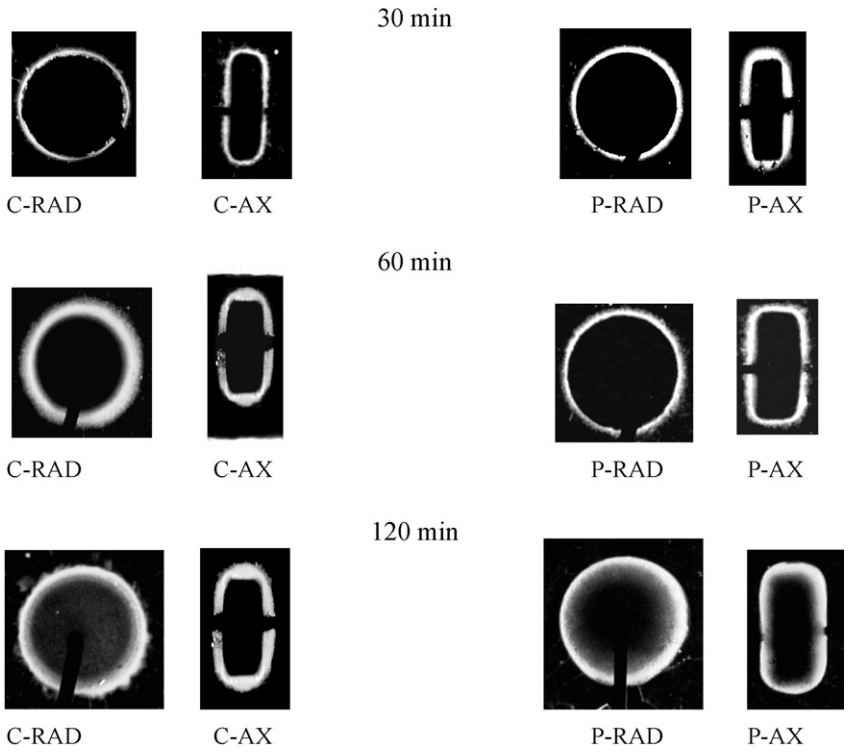

Fig. 4. Morphological changes of the matrix during dissolution. Typical images of CAF/CARB and CAF/POL matrices undergoing hydration after 30, 60 and 120 min in the radial (RAD) and axial (AX) plane. C = CARB; P = POL.

is clearly visible and indicates the variations in the thickness. The rate and the extent of gel growth were different between radial and axial direction (not shown here).

The evolution of the gel layer (the average radial and axial values of the gel layer thickness were used; Gao and Meury, 1996) up to 5 h for all types of matrices studied is shown in Fig. 5. Soon after, a deformation of the matrices was observed and the swollen gel phase started to collapse, making difficult the accurate measurement of the gel layer thickness.

With all four formulations, the gel thickness increased rapidly in the beginning, but later the rate of gel growth decreased considerably in CAF matrices or began to decrease progressively in THE matrices. It is also noted that the gel layer growth of the soluble CAF, in both polymer tablets, increased from the beginning to the end of the measurements.

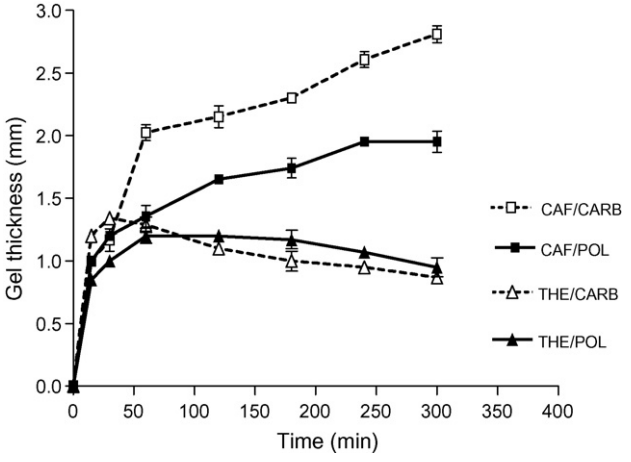

Fig. 5. Gel thickness increase versus time in POL and CARB matrices loaded with CAF or THE. Each point represents the mean value of the three samples and error bars show ±S.D.

The gel thickness was greater in the case of the CARB/CAF matrices compared to the POL/CAF matrices, reaching 2.8 and 2.0 mm, respectively, at the end of the examination period (5 h). This could be attributed to the lower erosion of CARB compared to POL (Fig. 3). With both polymers, a thinner gel layer was developed in the matrices of the less soluble THE compared to the CAF matrices. The thickness of the gel in the THE matrices started to decrease slowly with time after reaching a maximum (Fig. 5) probably because THE induced gel erosion. The maximum thickness observed was 1.4 mm for the CARB/THE matrices and 1.2 mm for the POL/THE matrices.

The existence of undissolved THE particles in the gel layer probably resulted in a reduced integrity of the gel and thus it became easily erodible. As a consequence the gel suffered an attrition phenomenon that limited the development of the gel and shortened the travel distance of the dissolved drug from the dissolution front to the surrounding medium, indicating that drug solubility considerably affects the integrity of the layer. The data in Fig. 5, clearly indicate that the presence of THE causes a profound attrition, which incites the disruption of the gel layer, a fact which was not noticed in the presence of CAF.

In addition the rate of POL swelling after the fourth hour apparently became equal to the dissolution rate of the swollen gel (Fig. 5), resulting in synchronization of the swelling and erosion fronts and stabilization of gel layer thickness (Kim, 1995). In contrast, in CARB tablets synchronization of the swelling

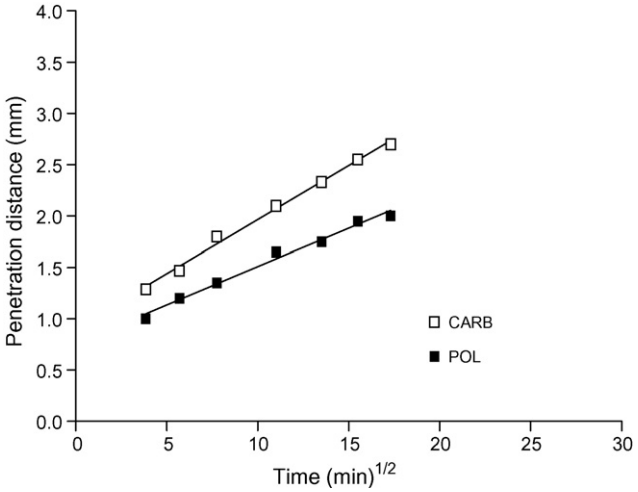

Fig. 6. Gel thickness increase plotted versus the square root of time of CAF matrices.

and erosion fronts was not observed and the gel layer thickness increased slowly.

Fig. 6 shows the growth of gel thickness, i.e., the penetration distance of the liquid into the tablet versus the square root of time up to fifth hour. As shown, the movement of the liquid penetration front is dependent on the square root of time, which underscores a Fickian diffusion, for CARB/CAF matrices. POL/CAF matrices exhibited a Fickian diffusion, up to the fourth hour, followed by a rather relaxation process. On the contrary, THE tablets do not display any similar behavior (not shown).

3.3. Core changes

Liquid penetration can be expressed, either as a change of the glassy core or, as the distance of water movement toward the center of the tablet. The length of the glassy core in the axial and radial directions was calculated by subtraction of the gel layer thickness from the overall tablet expansion. The glassy core disappeared after 5 h from the tablets as it is shown in Fig. 7.

The radial direction of the core in the CARB/CAF and the CARB/THE matrices (Fig. 7a) exhibited initially a sharp shrinking, indicating an immediate and rapid water penetration. This movement was terminated after 30 min and then a rebound was observed followed by a plateau from first to the third hour suggesting a constant phase. A progressive decrease followed suggesting a further slower water access into the tablet. The fact is corroborated by the change in the tablets' dimensions displayed in Fig. 1a and b. Likewise, the POL/CAF and POL/THE matrices exhibited a similar behavior with the difference that the liquid penetration appears rather sharper and with a smaller plateau between the first to the second hour, followed by a faster decrease of the glassy core. This indicates a rapid water penetration (Fig. 7b).

With respect to the axial direction, all formulations initially show an axial expansion of the glassy core. This could be the result of discharge and the relaxation of tablet compression forces imposed during tabletting (Papadimitriou et al., 1993).

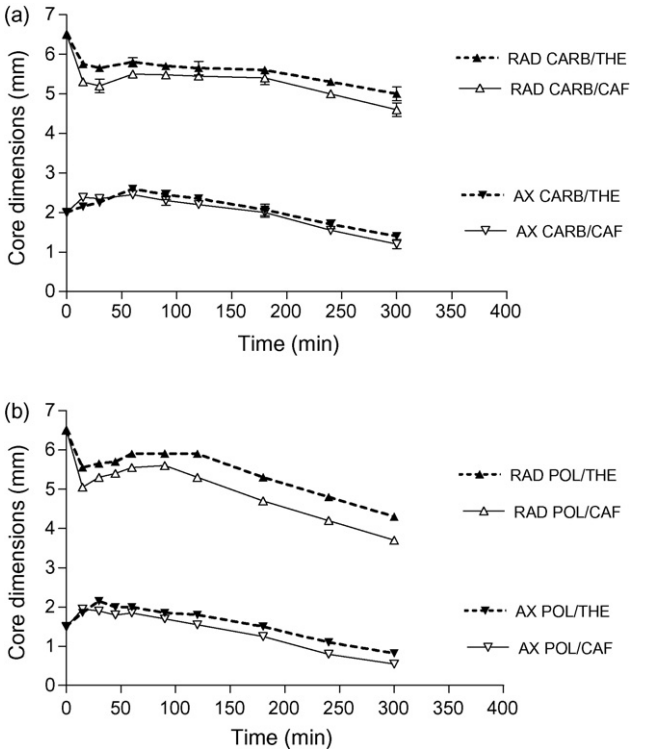

Fig. 7. (a and b) Dimensional changes in the glassy core of POL and CARB matrices loaded with CAF or THE during hydration. Each point represents the mean value of the three samples and error bars show ±S.D.

Following the expansion, at later times, the core decreases probably due to further liquid penetration. The core of both CARB/CAF and CARB/THE matrices exhibited a similar small expansion/increase up to the first hour followed by a continuous but slow progressive decrease (Fig. 7a). Analogous behavior was demonstrated by the POL/CAF and the POL/THE matrices (Fig. 7b).

In both cases, the CAF tablets showed faster radial core shrinking compared to the THE tablets. This is due to the increased liquid penetration, and could be attributed to faster dissolution of the CAF particles that consecutively facilitates rapid water penetration. In addition, a more intense liquid penetration was observed into the POL tablets (corresponding to the faster disappearance of the glassy core), in contrast to the CARB ones, since the liquid penetrates into the cross-linked material rather slower. The results are in agreement with earlier studies (Rajabi-Siahboomi et al., 1994), even though different findings reported elsewhere (Maggi et al., 2000).

3.4. Drug and polymer effects on drug release

Drug release profiles are shown in Fig. 8. The amount of drug released at a certain time point is, irrespective of the polymer, higher for CAF matrices compared to THE matrices. Furthermore, the rate of drug is higher from the POL matrices and the rate of CAF release was higher than that of THE, due to the higher aqueous solubility of CAF. All formulations, except the CARB/THE matrices, exhibited burst release in the first 30 min. POL/CAF matrices exhibited the highest burst release (27%),

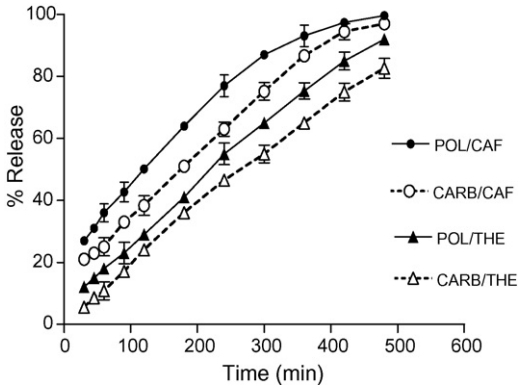

Fig. 8. CAF and THE release profiles from POL and CARB matrices.

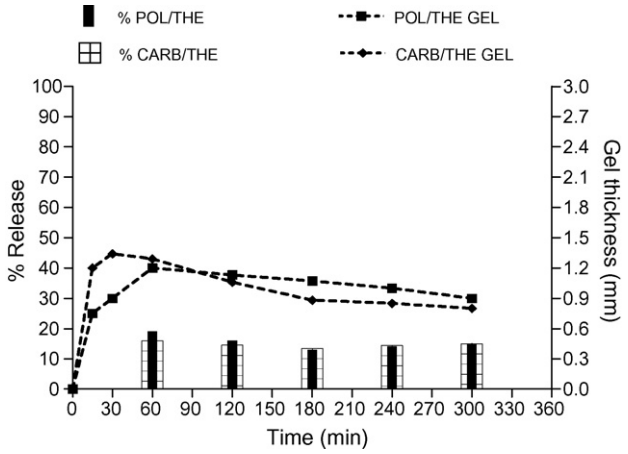

Fig. 10. Change of drug release rate/h and gel thickness with time from THE matrices.

followed by CARB/CAF (21%) and the POL/THE (12%). The higher burst release of CAF can be attributed to the fact that its matrices are more hydrophilic than the THE matrices, since CAF is more hydrophilic (contact angle with water 43°) than THE (contact angle 48°), thus CAF matrices are expected to exhibit a higher wettability and water penetration rate. Finally, the POL matrices (Figs. 9 and 10), exhibited higher a burst release than CARB matrices (with CAF or THE) probably due to the higher initial hydration and erosion rate of POL matrices.

THE has approximately half the solubility of CAF, 11.2 and 21.7 g/l, respectively. Although their solubility differs considerably their release is not that different and in 8 h 100% of CAF and 92% of THE was released from POL matrices. Similarly 97 and 85% was released from CARB matrices. In view of these results and in order to explore how drugs with considerably different solubility demonstrate comparable release from their matrices, we examined dimensional changes, changes of the glassy core and development of gel layer thickness, since these characteristics are important and play a decisive role in drug delivery.

From the findings presented above, it is obvious that significant changes were observed during the dissolution process in

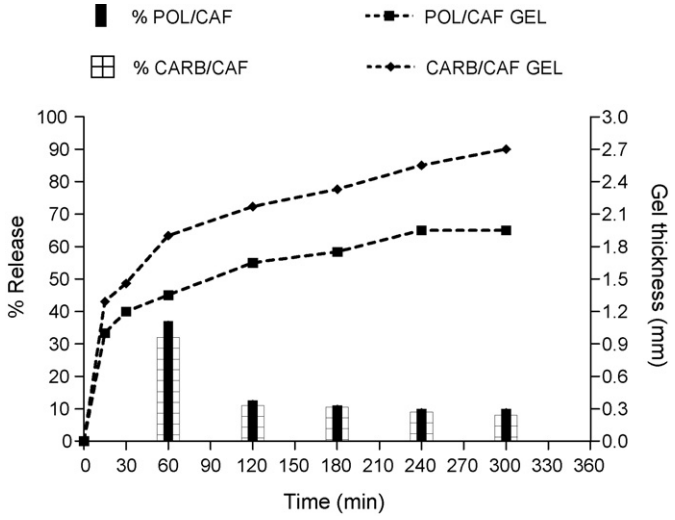

Fig. 9. Change of drug release rate/h and gel thickness with time from CAF matrices.

tablet dimensions and characteristics. The CARB tablets displayed greater dimensional expansion and gel layer thickness compared to the POL ones. The faster penetration of liquid into the POL tablet mass (Fig. 7b) resulted in a rapid shrinking of the glassy core, in contrast to the CARB tablets (Fig. 7a). This behavior may explain the initially enhanced drug release rate from POL tablets. Also, the increased penetration of liquid into the CAF tablets (Fig. 7a) might have affected its faster release. The findings indicate that these changes affect the release of a drug and may be responsible for differences in release between the formulations.

Overall, it appears that among all the characteristics examined, gel layer thickness changes may play the most important role. As can be seen in Fig. 5, the gel thickness of CARB/CAF tablets was greater than that of POL/CAF tablets. This fact explains the smaller rate of release of CAF from the former, since in these tablets the diffusion path length appears to be longer and the drug molecules have to travel a greater distance. In parallel, THE tablets displayed less gel growth within the some time period (i.e., up to the 30th minute), followed by a gradual and progressive decrease. This was due to erosion of the gel layer. The phenomenon of less gel growth/thickness may explain the increased release of THE (given its limited solubility) compared to CAF, i.e., the THE molecules have to travel along a shorter diffusion path length. The difference in gel layer growth/thickness between the two polymers could be attributed to their different chemical characteristics and structure. POL is a linear polymer soluble in water. These materials (particularly those with lower molecular weight), form softer gels that are more liable to erosion (Kim, 1995). Therefore, they erode and dissolve faster than the CARB ones that consist of a cross-linked polymer with limited solubility in water (Goodrich, 1994). The erosion studies confirmed this finding (Fig. 3).

Gao and Meury (1996), have suggested that gel layer growth depends on polymer viscosity. In addition Bonferoni et al. (1992) reported that higher polymer viscosity reflects a stronger ability of the polymeric chains to produce entanglements and consequently matrices with slower erosion. Our measurements show that POL has a viscosity of 180 cP, while CARB has a viscosity

of 6800 cP. It appears that POL (with lower viscosity) displayed slower gel growth and a thinner gel layer due to increased erosion and dissolution, whereas CARB exhibited the exact opposite characteristics. These findings suggest that the high viscosity gel layer that formed around the CARB tablets is more resistant to extended erosion. In contrast, the POL tablets with a more erodible gel showed greater drug release. The presence of less soluble THE particles in the gel layer reduced the entanglement of polymer chains and affected gel integrity and erosion. As a consequence the THE matrices became more erodible (Bettini et al., 2001). From visual observations it was noticed that after the fourth hour, particles were released from the THE tablets. This is most likely due to attrition and confirms the erosion phenomenon.

As shown, in Fig. 9, the drug release rate from CARB/CAF matrices appears to increase rapidly up to 60 min when the thickness of the gel layer is still rather small. As a result the release from these matrices reached a total 32%, while that from the POL/CAF matrices was 37%. As gel thickness increased with the passage of time, a decrease in the release rate was observed in both cases. This corresponds to a small but progressive increase in thickness after the second hour.

Thus, as can be seen in Fig. 9 the release rate/h from POL/CAF matrices is 12.5, 11, 10 and 10% at 2, 3, 4, and 5 h, respectively. While, on the other hand the release rate/h from CARB/CAF matrices was 11, 10.5, 9 and 8%, respectively.

In parallel the gel thickness in THE matrices (Fig. 10), after an initial increase was followed (2 h) by a progressive decrease. The release rate was lower, than that of the CAF tablets in 1 h, i.e., 16% from CARB/THE and 19% from POL/THE, respectively. After the second hour, when the gel layer starts to decrease, a progressive small increase in release rate was demonstrated. POL/THE matrices exhibited 13, 14 and 15% release for 3, 4 and 5 h.

Similarly the release rate for CARB/THE matrices was 13.5, 14.5 and 15%, respectively. These results clearly indicate that gel thickness and its fluctuation inversely affect the rate of drug release from these matrices. Moreover, it is obvious that the fluctuation of gel's thickness is reflected quantitatively in the rate of drug release/h.

In order to describe the mechanism of drug release the n values were obtained from the following well known Peppas equation (Korsmeyer et al., 1983)

$$\frac{M_t}{M_\infty} = kt \tag{3}$$

where M_t is the amount of the drug released at time t, M_∞ the amount of drug released over a very long time that corresponds in principle to the initial loading, k the kinetic constant and n is the diffusional exponent which depends on the release mechanism. For a cylindrical matrix values $n = 0.5$ indicate Fickian release, values $0.45 < n < 0.89$ indicate anomalous release kinetics (coupled diffusion/relaxation) and $0.89 < n < 1$ indicate a zero order release also known as purely relaxation-controlled drug release.

The n values for the POL/CAF and CARB/CAF, were 0.52 and 0.58, respectively, indicating mainly diffusional drug release in combination with erosion release mechanisms for the CAF. This coincides with our findings above, in which a Fickian liquid penetration process characterized these systems. On the other hand, the n values for POL/THE, CARB/THE matrices are 0.90 and 0.94, respectively, indicating that the drug release was mainly governed by swelling/erosion and show a rather constant release rate. These findings match well with the data shown in Fig. 1, where it is obvious that drug properties affect the matrices' dimensional changes and that the THE matrices suffered increased erosion.

The above suggests that in the systems studied, drug solubility noticeably influences release rates and mechanisms. The difference in release is more distinctive at the beginning, while towards the end (eighth hour), the total fraction released is not considerably different.

Regarding drug release from the POL matrices, earlier studies show that it is complex and depends on a number of factors, such as drug solubility, drug loading, the recipient's characteristics and probably more importantly the molecular weight of the polymer. The release mechanism could be attributed either to polymer swelling and diffusion or to swelling and erosion/dissolution. Further, it was demonstrated that in matrices prepared from low molecular weight POL and containing water soluble drugs, diffusion is the controlling factor from release kinetics. Correspondingly, for less soluble drugs the swelling and erosion process is the dominating step (Maggi et al., 2000; Kim, 1995, 1998). These findings are in full agreement with our results with $n = 0.52$ and 0.90 for the POL/CAF and the POL/THE tablets, respectively. Our n values also suggest analogous release kinetics with those reported in the existing literature and strengthens their validity.

Previous studies with CARB have shown that the release mechanism and n values are affected by the pH values (Kim, 1995). The $n = 0.49$–0.70 for soluble propranolol HCI at pH 4.5 is in agreement with our value $n = 0.58$ for soluble CAF (at the pH 5.8), implying diffusion dominated release mechanisms. Further, Durani et al. (1994) reported $n = 1.08$ for THE at pH 6.5 which is not far from our $n = 0.94$, indicating erosion controlled release.

The relative contribution of each of these two mechanisms, drug diffusion or matrix erosion, was quantified by applying the two-terms release equation (Catellani et al., 1988)

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} + k_2 t \tag{4}$$

For a given time t, the first term of the right part represents the Fickian (diffusion) contribution and the second term is the case II relaxational (erosion) contribution.

The drug release data (Fig. 8) were fitted to Eq. (4) and the calculated release constants and the fraction (%) of drug released through diffusion or erosion for a total of 60% drug release are presented in Table 1. In accordance with the conclusions drawn based on the n values, the dominant mechanism of CAF release from both types of polymers was drug diffusion (the fraction of CAF released through diffusion was 97.30 and 71.00% for the POL and CARB tablets, respectively) whereas the dominant mechanism for THE release from both types of

Table 1
Results from fitting the release data in Eq. (4)

Type of tablet	Release constant, k_1	Release constant, k_2	Correlation coefficient (R^2)	Fraction of drug released by diffusion[a] (%)	Fraction of drug released by erosion[a] (%)
POL/CAF	4.569	0.010	0.9916	97.30	2.70
CARB/CAF	2.825	0.075	0.9847	71.00	29.00
POL/THE	1.070	0.155	0.9960	28.50	71.50
CARB/THE	0.208	0.173	0.9958	6.00	94.00

[a] Correspond to a 60% total drug release.

polymers was polymer erosion (the fraction of THE released through erosion was 71.50 and 94.00% for the POL and CARB tablets, respectively).

Since diffusion was the dominant release mechanism for CAF, the rate of CAF release was higher in the case of POL matrices compared to CARB matrices (Fig. 9) because the thickness of the gel layer was lower in the case of POL/CAF matrices compared to CARB/CAF matrices and, consequently, in this case, CAF molecules had to travel a smaller distance before being released into the surrounding liquid. In the case of THE, erosion of the gel layer was the dominant release mechanism. The similarity of gel development (Fig. 5), indicates that gel erosion proceeded at similar rates in POL/THE and CARB/THE matrices. This is probably the reason why the release rate of THE from the POL/THE matrices was not essentially different from that from CARB/THE matrices (Fig. 10).

4. Conclusions

Both drug and polymer characteristics were found to influence the dimensional changes with time of the drug/polymer matrices as well as the evolution of the gel layer formed around the glassy core when the matrices were immersed in the dissolution medium. Through their effects on matrix dimensions and gel layer thickness, drug solubility and polymer structure considerably influence the rate and mechanism of drug release. The dimensional expansion in CAF matrices was always more pronounced than that of the THE matrices. The CARB matrices exhibited greater maximum expansion and lower drug release than the POL matrices. The dimensions of CARB/CAF matrices, unlike all the other matrices studied, exhibited a biphasic increase at early times, due to the cross-linked structure of CARB and the high solubility of CAF. With both polymers, a thinner gel layer was developed in the matrices containing the less soluble THE. The thickness of the gel layer increased with time in the CAF matrices whereas in the THE matrices it increased initially and after reaching a maximum started to decrease. All formulations except these of CARB/THE exhibited burst release. The gel layer thickness and erosion rate appeared to determine the rate of drug release from these formulations. The results suggest that gel thickness and its changes affect the release rate/h of the drug proportionally. In addition, the fluctuation of gel's thickness is reflected quantitatively in the rate of drug release/h. Analysis of the release kinetics and mechanism indicated that CAF was released mainly through diffusion whereas THE was released through matrix erosion.

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