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Journal of Controlled Release 122 (2007) 181 – 188
journal of controlled release
www.elsevier.com/locate/jconrel

Analysis and modeling of swelling and erosion behavior for pure HPMC tablet

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Received 11 April 2007; accepted 4 July 2007
Available online 15 August 2007

Abstract

This work is focused on the transport phenomena which take place during immersion in water of pure hydroxypropylmethylcellulose tablets. The water uptake, the swelling and the erosion during immersion were investigated in drug-free systems, as a preliminary task before to undertake the study of drug-loaded ones. The tablets, obtained by powder compression, were confined between glass slabs to allow water uptake only by lateral surface and then immersed in distilled water at 37 °C, with simultaneous video-recording. By image analysis the normalized light intensity profiles were obtained and taken as a measure of the water mass fraction. The time evolutions of the total tablet mass, of the water mass and of the erosion radius were measured, too. Thus a novel method to measure polymer and water masses during hydration was pointed out. Then, a model consisting in the transient mass balance, accounting for water diffusion, diffusivity change due to hydration, swelling and erosion, was found able to reproduce all experimental data. Even if the model was already used in literature, the novelty of our approach is to compare model predictions with a complete set of experimental data, confirming that the main phenomena were correctly identified and described.

Keywords: Controlled drug release; Swelling; Erosion; HPMC

1. Introduction

Controlled drug delivery is a key topic in modern pharmacotherapy. The main goal is to establish systems capable of giving a predetermined release profile of the drug, in order to fulfill the requirement of hematic drug concentration within the therapeutic window for as long as possible. Since preferred drug administration route is the oral one, a tablet able to give a constant rate of drug release [1] (zero order release) over a long time interval (e.g. one day) would be the best solution in many cases. The systems based on drug dispersed into hydrogel swellable matrices seem to be able to fulfill this requirement [2]. Consequently the phenomena involved in drug release from swellable matrices attract attention of researchers. Indeed, detailed knowledge of the transport phenomena involved is the key prerequisite in developing a reliable mathematical model useful for the prediction of the release kinetic as function of the formulation parameters or of the external conditions.

1.1. State of the art

Studies on controlled drug delivery from hydrophilic matrices were made to highlight the effect of a set of parameters on hydration and release kinetics. In these studies, three component systems (polymer, almost HPMC, drug and fillers) were mostly used, dissolution tests were performed using USP dissolution apparatus II and drug release was valued by spectrophotometry.

Peppas and co-workers, studying swelling and drug release kinetics from HPMC tablets, observed that relative drug release decreased if initial tablet size [3–5] or polymer molecular weight [5] increased, and if drug solubility decreased [4]. Polymer erosion rate increased with the increase of the initial tablet size [2] and with the decrease of polymer molecular weight [5]. Furthermore, a decrease in initial drug load caused a lower relative drug release [6].

Bettini et al. [7] used image analysis to investigate erosion and swelling front positions in swelling tablets, clamped between two Plexiglass slabs. They studied the phenomenon of translocation of sparingly soluble drug particles in HPMC matrix gel layer, observing that low drug solubility caused an increase in the polymer erosion rate. Colombo et al. [8] observed the effect of an

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doi:10.1016/j.jconrel.2007.07.001

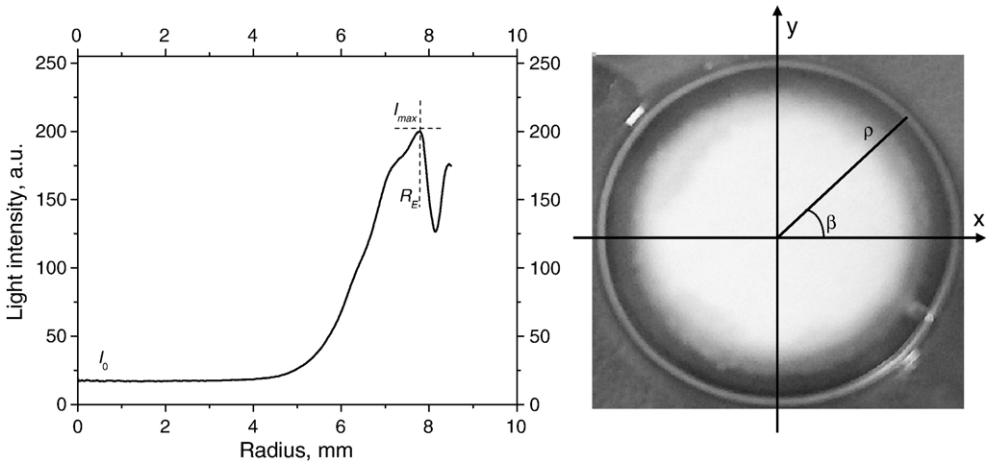

Fig. 1. (On the right) matrix with rectangular and polar co-ordinates, (on the left) the obtained light intensity profile.

initial high load of a soluble drug which caused fast water penetration in the matrix and a high polymer erosion rate (in agreement with Siepmann and Peppas [6]).

Through an analysis of macromolecular changes in hydrophilic systems, Jamzad et al. [9] pointed out that the presence of soluble excipients caused faster water penetration, faster release and faster polymer erosion.

Peppas and Colombo [10] studied partially coated tablets, observing faster release and faster water penetration not only for tablets without coating, but also for tablets having lateral area coated, since the surface for drug release is however high.

Pillay and Fassihi [11,12], using texture analysis in order to evaluate the gel strength (resistance to probe penetration) and fronts movement, observed that the presence of electrolytes assured a limited release and an increase of gel strength.

1.2. Aim of this work

Despite widespread research in this field, a thorough description of the phenomena involved is still lacking. The fundamental step in clarifying these phenomena is to consider systems made up of pure polymer tablets, to elucidate the role of penetrating water in glass transition temperature lowering, in diffusivity increase and in polymer swelling. The erosion kinetics of the polymer also should be evaluated. The full knowledge of the phenomena taking place during tablet hydration needs for the subsequent modelling of the process, which in turn is a step of great interest since the availability of a model significantly improve the design of a pharmaceutical system. Only a very limited amount of work was done with pure HPMC tablet. In particular Siepmann et al. [2] investigated the evolution of polymer mass with time, estimating the erosion kinetics of the polymer. Deeper investigations, with measurements of erosion radius, polymer and water masses, as well as radial profiles of water concentration within the tablets during hydration, to our knowledge were never performed. In the present work, all these phenomena were observed and quantified by image recording and analysis, relating the light intensity profiles to the water mass fraction profile along tablet radial direction. Actually, the aim of this work is to point out a non-destructive test to determine the water mass fraction radial profile during the hydrating of a pure HPMC tablet, and to model the phenomena related to hydration. The work was thus limited to the first characterization of the water transport phenomena in the swelling matrix; the drug's transport phenomena were not taken into consideration at this stage; the study of drug-loaded tablets' behavior is currently under consideration in our laboratory. The final goal of the research is the identification and the validation of a full model for the drug release process from swellable tablets.

2. Experimental

2.1. Material

Hydroxypropyl methylcellulose (Methocel K15M Premium Grade) kindly supplied by Colorcon.

2.2. Methods

Pure HPMC tablets (0.35 g, 13 mm diameter, 2.3 mm thickness) were prepared by compressing the polymer powder in a tabletting machine (Specac PN3000, equipped with flat-faced punches, diameter 13 mm) by a Carver Press, with a loading force of 50 kN kept for 5 min.

Erosion and swelling experiments were carried out. Water uptake was allowed only through radial direction. This was achieved by confining the tablet between two glass slides, as previously performed by Bettini et al. [7]. This system was placed in a thermostatic bath and stirred using a magnetic paddle. The dissolution medium was distilled water kept at 37 °C. To analyze the phenomenon of water uptake into the tablet, the system was video-recorded and the video camera (Sony H39E) was programmed to catch a frame every 60 s. Since the recording can go on up for a week, with changes in external lighting conditions, in order to standardize the lighting of recorded frames, the thermostatic bath and the video camera were placed in a dark room, lighted by a neon lamp. A glass

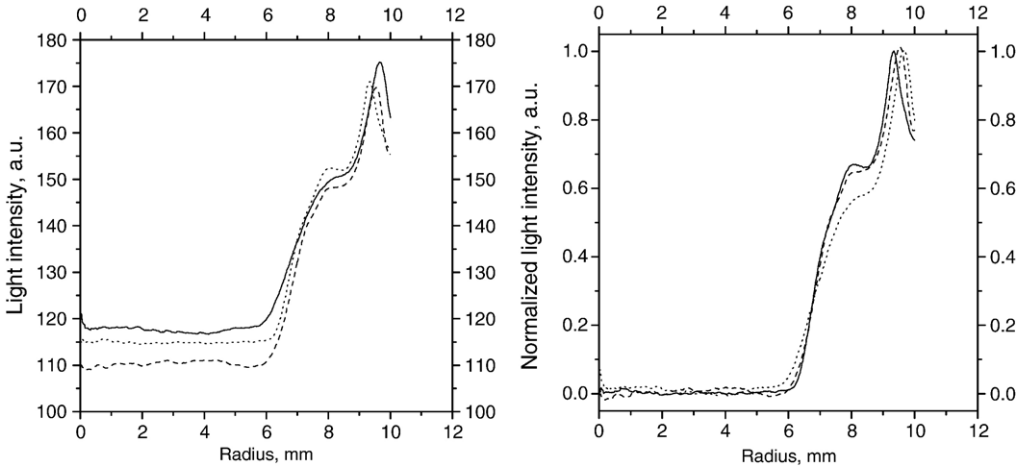

Fig. 2. (On the left) Three light intensity profiles after the same immersion time, for three different tablets; (on the right) the same data reported on the left, in terms of normalized light intensity profiles.

cover was placed between the video camera (set in horizontal position) and the thermostatic bath to avoid lens clouding by steam. Since it was difficult to detect the gel fronts positions when the tablet was immersed in water a colorant named Trypan Blue (Sigma Aldrich), was added to the dissolution medium. Furthermore, in order to remove dissolution medium interference, the sample was withdrawn at predetermined time intervals and was photographed by a camera (HP Photosmart 945) which gave more defined pictures. These photos were used for checking the information acquired by the video camera.

The long-lasting experiment, consisting in systems (glass slab–tablet–glass slab) immersion up to 1 week, was performed in triplicate. The recorded films were taken for each experiment and the photos were taken, for each experiment, after the same immersion intervals.

Light intensity profiles from pictures (obtained from both frame and single photos) of pure HPMC tablets were evaluated by image analysis. The analyses were performed by considering the picture as a matrix of pixels with intensity values ranging from 0 (white) to 255 (black). An example of such a matrix is shown in Fig. 1, together with the reference system chosen (ρ = radial axis, β = azimuthal angle).

Azimuthal intensity average reduced the errors caused, for instance, by reflections and surface imperfections. The light intensity curve, which ranged between the value of plateau (I_0), observed at tablet axis, and the highest value (I_{max}) corresponding to erosion front at radius R_E, see Fig. 1, was normalized and these values were used to measure water mass fraction in hydrating tablet.

In Fig. 2 there are three profiles, obtained by three different experiments for the same immersion time. On the left, the light intensity profiles were obtained. They show different levels for I_0 and I_{max}, due to the different lighting conditions. On the right, the same profiles after normalization, from which the effects of external lighting conditions have been eliminated. These three last profiles are in a good mutual agreement, confirming the method repeatability. The (limited) data span in ordinate direction is an estimate of error of measure (on the average, less than 5%). The other light intensity profiles reported in this work are the mean values of three measurements.

Image analysis and data elaborations were carried out by a code developed for the purpose, by using Mathcad© software (Mathsoft Engineering & Education, Inc.).

3. Modeling

3.1. Diffusion

The tablets are cylindrical in shape, with a large diameter/thickness ratio, thus they could be approximated by slabs. However, as the transport phenomena can only be allowed in radial direction, they can be treated as infinite cylinders. The main transport phenomenon is the pseudo-diffusion of water from the medium into the tablet; this phenomenon can be modeled by the one-dimensional transient mass balance (subscript 1 will identify water; subscript 2 will identify the polymer):

$$\frac{\partial \omega_1}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(rD_1\frac{\partial \omega_1}{\partial r}\right) \tag{1}$$

where ω_1 is the water mass fraction, t is the time, r is the radius and D_1 is the pseudo-diffusion coefficient of the water into the tablet. The balance equation requires initial and boundary conditions. They are summarized as follows:

$$\text{I.C.} \quad @t = 0, \quad \forall r, \qquad \omega_1 = \omega_{10} \tag{2a}$$

$$\text{B.C.1} \quad @r = 0, \forall t, \qquad \frac{\partial \omega_1}{\partial r} = 0 \tag{2b}$$

$$\text{B.C.2} \quad @r = R_E(t), \forall t, \quad \omega_1 = \omega_{1eq}. \tag{2c}$$

The initial condition (2a) states that the tablet initially contains water at mass fraction ω_{10} (in our experiments the tablets were initially absolutely dry, $\omega_{10}=0$), the axial boundary

condition (2b) is a standard symmetry (no flux) condition, the surface condition (2c) takes into account that, at the erosion radius (R_E) the water mass fraction is in equilibrium with the outer medium, ω_{1eq}. To solve Eq. (1) the pseudo-diffusion coefficient, D_1, has to be evaluated. In polymeric systems subjected to swelling, the diffusion coefficient is not constant, being low in the dry polymer and increasing as the water content increases (into the gel). It can be modeled according to Siepmann et al. [3]:

$$D_1 = D_1^* \cdot \exp\left[-\beta_1 \cdot \left(1 - \frac{\omega_1}{\omega_{1eq}}\right)\right] \tag{3}$$

where $D_1^*/\exp(\beta_1)$ is the value of pseudo-diffusion coefficient in the dry tablet ($\omega_1=0$), and D_1^* is the value of pseudo-diffusion coefficient in the fully swollen tablet ($\omega_1=\omega_{1eq}$). Since the pseudo-diffusion coefficient is concentration dependent, and since the outer boundary is moving, $R_E=R_E(t)$, Eq. (1) has to be solved numerically. The erosion front position $R_E(t)$ was calculated on the basis of the tablet's mass and density, this step then required the knowledge of water and polymer mass in the tablet at any given time instant, t.

3.2. Water mass calculation

At each time step, the resolution of the diffusion equation (1) gives the water mass fraction profile, $\omega_1(t,r)$, and a proper integration of this profile gives the actual value of the water mass ($m_1(t)$, by Eq. (4) below and the value of the water mass fraction averaged on the volume of the tablet ($\langle\omega_1(t)\rangle$ by Eq. (5)):

$$m_1(t) = \int_V \rho(\omega_1)\omega_1(t,r)\mathrm{d}V \tag{4}$$

$$\langle\omega_1(t)\rangle = \frac{1}{V}\int_V \omega_1(t,r)\mathrm{d}V = \frac{\pi H}{\pi H R_E^2}\int_0^{R_E(t)} \omega_1(t,r) r \mathrm{d}r. \tag{5}$$

3.3. Polymer mass calculation

The polymer mass, $m_2(t)$, is given by the resolution of a balance equation which accounts for the erosion phenomenon, postulated to be proportional to the surface area, $A_E(t)=2H\pi R_E(t)$, with H = tablet thickness:

$$\begin{cases} \dfrac{\mathrm{d}m_2}{\mathrm{d}t} = -k_E A_E(t) \\ m_2(t=0) = (1-\omega_{10})m_{tot.in} \end{cases}. \tag{6}$$

At each time step the erosion radius, R_E, and thus the erosion surface, A_E, are known, allowing for the calculation of the polymer mass by solving Eq. (6), once a proper value for erosion constant, k_E, is given.

3.4. Erosion radius calculation

The average density of the partially hydrated tablet can be calculated from the simplest mixing rule which can be written for the specific volume:

$$\frac{1}{\langle\rho_{tot}\rangle} = \frac{\langle\omega_1\rangle}{\rho_1} + \frac{1-\langle\omega_1\rangle}{\rho_2} \tag{7}$$

where ρ_1 and ρ_2 are the water and the polymer densities. Once the water and the polymer masses are known, the current volume of the tablet can be calculated:

$$V(t) = \pi R_E^2(t)H = \frac{m_1(t)+m_2(t)}{\langle\rho_{tot}\rangle} = \frac{m_{tot}(t)}{\langle\rho_{tot}\rangle}. \tag{8}$$

Finally, the required value for erosion radius was obtained from the volume value.

3.5. Parameters estimation

The parameters in the pseudo-diffusion coefficient formula (3), $D_1^*=5.6\cdot10^{-10}$ m^2 s^{-1} and $\beta_1=2.5$, were taken from literature [3].

The polymer density was easily obtained as $\rho_2=1200$ kg m^{-3} by the ratio between the tablet mass (by weighting) and its volume (calculated from diameter and thickness).

The equilibrium water mass fraction, ω_{1eq}, was obtained leaving pure HPMC tablets immersed in water for more than 100 h, to be sure the matrix was fully swollen, then weighing the obtained gel, drying it and weighing it again. The value was found to be 0.97 (i.e., 97% of the fully swollen gel is water).

The erosion constant, k_E, was evaluated on the basis of Eq. (6), experimental evolutions of polymer mass and erosion surface with time are outlined in the Results and discussion section.

3.6. Numerical issues

The model equations were solved numerically, adopting the Crank & Nicolson finite difference scheme for the diffusion equation (1), and the Eulero finite difference scheme for the erosion equation (6), the integral equations (4) and (5) being approximated by summations. The code was developed using the Mathcad© software (Mathsoft Engineering & Education, Inc.).

4. Results and discussion

4.1. Normalized light intensity profiles

The hydration test consists in the immersion of the tablet, confined between the two glass slabs, in distilled water kept at 37 °C, as described in the Experimental section. Snapshots of the tablet at different immersion times, starting from case A) which is the dry tablet before the immersion are reported on the right of Fig. 3. The results of image analysis are reported as normalized light intensity on the left of Fig. 3 (symbols). The

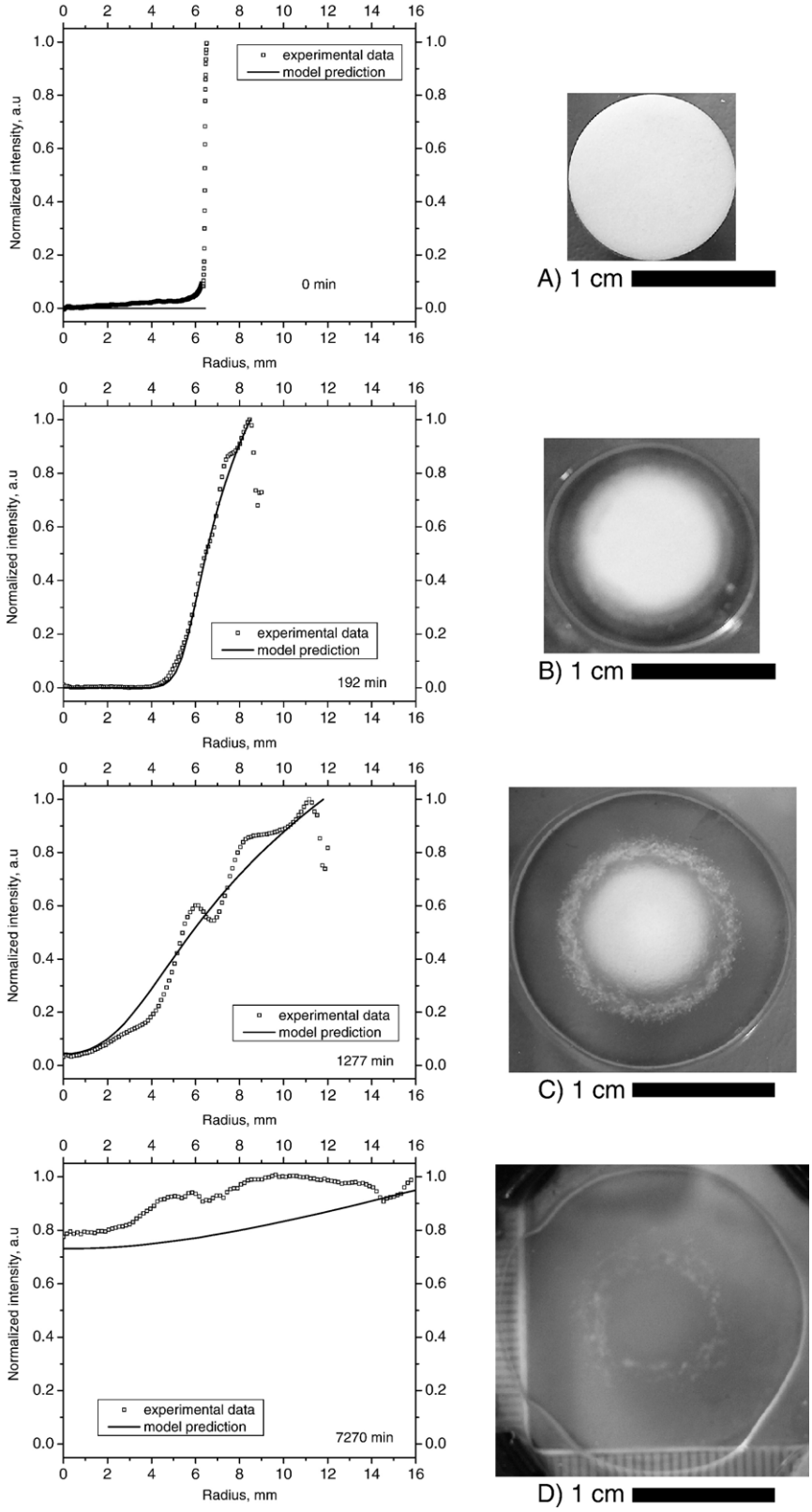

Fig. 3. Experimental data (symbols) and model predictions (curves) at different immersion time (left) and corresponding analyzed frame (right). The pictures are referred to: A) dry tablet; B) the tablet after about 3 h (192 min) of immersion; C) after about 1 day (1277 min) of immersion and D) after about 5 days (7270 min) of immersion.

hydrating phenomenon is clearly observed: in case A the normalized light intensity describes practically a step, from zero (inside the dry tablet), to one (at the tablet initial radius which corresponds to the initial value for the erosion radius); in case B (after about 3 h of immersion) the tablet is partially hydrated, and the water did not reach the tablet axis; in case C (after about 1 day of immersion), the water penetrated up to the tablet axis; in case D (after about 5 days of immersion), the tablet was practically fully swollen, and the water was close to equilibrium condition.

An unexpected phenomenon is evident in the photo of case C: the presence of a circular halo intermediate between the erosion radius (the external tablet radius, where the erosion takes place) and the swelling radius (the radius at which the water penetrated). The halo, whose origin is not clear, is also evident in the normalized light intensity profile of Fig. 3, case C, in which it takes the form of a couple of shoulders. In embryonic form, it is perceptible in case B, as well as in case D that the shoulders were still recognizable, even if fully developed. It is worth noting that we carried out our experiments by pure HPMC tablets, observing such halo. In experiments carried out with drug-loaded tablets, the halo could be source of confusion: identification of the "diffusion front" (the radial position where most of drug diffusion takes place) [8] would be affected by the presence of this phenomenon.

If a simple linear relation is assumed between light intensity and water content, the normalized light intensity (obtained as described in Experimental section) is directly related to the normalized mass fraction of water:

$$\frac{I - I_0}{I_{\max} - I_0} = \frac{\omega_1 - \omega_{10}}{\omega_{1\mathrm{eq}} - \omega_{10}} \tag{9}$$

where ω_{10} is the initial mass fraction of water in the tablet and $\omega_{1\mathrm{eq}}$ is the equilibrium mass fraction of water in the hydrogel. The light intensity values were already defined as the value of the plateau (I_0), observed at tablet axis, and the maximum value ($I_{\max}$), corresponding to the erosion front. The normalized water mass fraction (the right hand side of Eq. (9)) is constrained to vary between 0 (initial, dry tablet) and 1 (fully hydrated tablet). The normalized light intensity (the left hand side of Eq. (9)) is constrained to vary between 0 (the brightest image, the dry tablet) and 1 (the darkest image, the fully hydrated tablet). The simplest choice is thus a linear relationship between the normalized water mass fraction and the normalized light intensity. However, this choice needs further investigation. The light intensity distribution in the photos and in the film frames can be taken as the sources for the water mass fraction distribution, $\omega_1(t,r)$. This is a significant piece of information, if the targets are the understanding and the quantifying of the mass transport phenomena which take place during tablet hydration.

Availability of the quasi-experimental mass fraction profiles, $\omega_1(t,r)$ from image analysis, allows for the calculation of evolutions with time of the water and polymer mass, $m_1(t)$ and $m_2(t)$ respectively. This analysis does not require any modeling step and it is reported in the following section. Furthermore, image analysis gives the erosion radius evolution, $R_E(t)$, implying knowledge of the erosion surface evolution $A_E(t)$ due to the constant thickness. The erosion phenomenon can be estimated from these data: experimental, A_E via R_E; quasi-experimental m_2 via ω_1.

4.2. Masses evolution

The local density value can be evaluated by the local analogous of the average equation (7):

$$\frac{1}{\rho_{\mathrm{tot}}(t,r)} = \frac{\omega_1(t,r)}{\rho_1} + \frac{1-\omega_1(t,r)}{\rho_2}. \tag{10}$$

Therefore, on the basis of the mass fraction evolution $\omega_1(t,r)$, the total mass of the hydrating tablet, $m_{\mathrm{tot}}(t)$, can be calculated by integrating the local density over the tablet volume:

$$m_{\mathrm{tot}}(t) = \int_v \rho_{\mathrm{tot}}(\omega_1(t,r))\mathrm{d}V = 2\pi H \int_0^{R_E(t)} \rho_{\mathrm{tot}}(\omega_1(t,r))r\mathrm{d}r. \tag{11}$$

In a similar way, the water mass in the tablet, $m_1(t)$, can be obtained by a proper volume integral:

$$m_1(t) = \int_v \rho_{\mathrm{tot}}(\omega_1(t,r))\omega_1\mathrm{d}V = 2\pi H \int_0^{R_E(t)} \rho_{\mathrm{tot}}(\omega_1(t,r))\omega_1 r\mathrm{d}r. \tag{12}$$

Fig. 4 shows the total, the water and the polymer mass evolutions with time (symbols), obtained by applying Eqs. (11) and (12) to water mass fraction profiles given by Eq. (9) from normalized light intensity profiles. The polymer mass was obtained by the subtraction of water mass from total mass. The increase of water mass (the uptake of water) is in analogy to the increase of total mass, thus the polymer mass is practically constant (i.e. the erosion phenomenon is negligible).

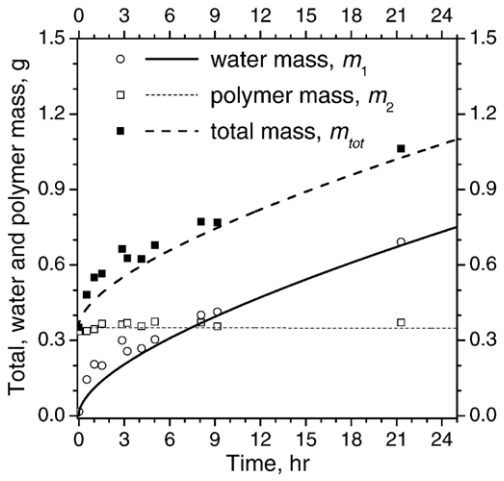

Fig. 4. Total, water and polymer masses: experimental data (symbols) and model predictions (curves).

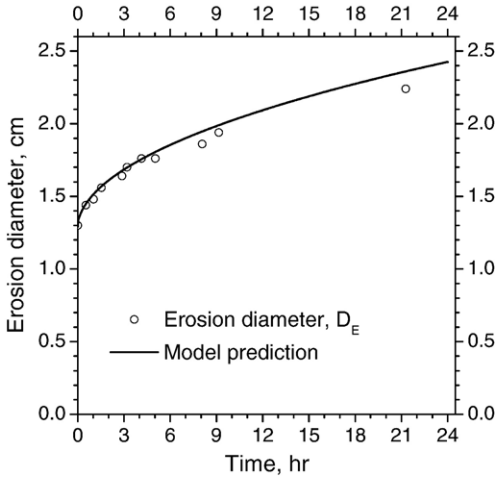

Fig. 5. Erosion diameters: experimental data (symbols) and model predictions (curves).

4.3. Erosion radius evolution and erosion constant estimation

From image analysis the erosion radius evolution, $R_E(t)$, can be easily obtained. The observed values were reported, as erosion diameter $D_E(t)$, in Fig. 5 (symbols).

The integration of Eq. (6) gives:

$$m_2(t) = m_2(t=0) - k_E \int_0^t A_E(\tau)\mathrm{d}\tau. \quad (13)$$

The polymer mass, $m_2(t)$, can be easily evaluated as the overall mass and the water mass in the tablet were known (by Eqs. (11) and (12)), the lateral surface area, $A_E(t)$, was known since the erosion radius, $R_E(t)$, was experimentally measured by image analysis and the tablet is of constant thickness, H. Thus, Eq. (13) was used to evaluate the erosion constant which results to be $k_E = 1.3 \cdot 10^{-7}$ kg m^{-2} s^{-1}, which is the same order of magnitude of the value reported in literature [2] ($k_E = 5.5 \cdot 10^{-7}$ kg m^{-2} s^{-1}). It is worth noting that the value obtained is consistent with the negligible erosion observed.

4.4. Model predictions

Once the erosion constant had been estimated, the model described in the Modeling section was solved. All the figures in the present section also displayed the model predictions. It is evident that there is a good agreement between experimental data in terms of both water mass and total mass profiles (Fig. 3); and evolutions (Fig. 4); erosion radius evaluation was nicely described (Fig. 5). It has to be noted that:

- A part of the erosion constant, k_E, and all the other model parameters were estimated by independent tests (ρ_2, ω_{1eq}), or they were taken from literature [3] (D_1^*, β_1). The erosion constant does not play a relevant role in the model predictions, provided its value is low enough, since the erosion is a secondary phenomenon in this case (the polymer mass is practically constant, see Fig. 4).
- No further optimization parameter was required or used. Thus the model has been confirmed to be fully predictive.

From the results obtained from the experiments, the model can establish the basis for the description of more complex systems (drug-loaded tablets, water uptake allowed by the overall tablet surface).

5. Conclusions

In this work, the time evolution of the water mass fraction profile along radial direction during hydration of pure HPMC cylindrically shaped tablets, with the water uptake allowed only by radial direction, was followed by means of video-recording and image analysis. The measurement of these data for pure HPMC tablets, to our knowledge, is a new result in literature.

In our experiments, the erosion radius time evolution was also achieved by image analysis. Furthermore, by proper integration of mass fraction profiles, the time evolutions of water and total mass for the hydrating tablets were obtained, too.

This is a very rich set of experimental data (the mass fraction profiles along radial direction, the total and the water mass, the erosion radius; all of these are time-functions). This set of data was taken as the basis to check a model describing all the transport phenomena involved (the water uptake by diffusion, the increase in water diffusivity due to hydration, the gel swelling, the polymer erosion). The model, whose parameters were taken from independent tests or from literature, was found able to reproduce all the observed phenomena. Thus, the physical interpretation given to the phenomena was substantially confirmed.

The advancement in knowledge due to the work done in this research is thus the availability of the water mass radial profiles and of the mass evolution with time during hydration, which was not directly measurable via traditional experimental set-ups. Furthermore, the observed data have been used to confirm a traditional interpretation of the transport phenomena which take place in the tablet during hydration. Both data and technique will be used in future investigations of more complex systems (tablets loaded with drugs, hydrated by lateral and/or overall surfaces).

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