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Swelling of cellulose derivative (HPMC) matrix systems for drug delivery

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ABSTRACT

The water swellable hydrogels are commonly used in the production of solid pharmaceutical dosage systems for oral administration (matrices). Their use allows to obtain the controlled drug release. The key role is played by the transport phenomena which take place: water up-take, gel swelling and erosion, increase in diffusivity due to hydration. Thus, knowledge of these phenomena is fundamental in designing and realizing the pharmaceutical systems.

In this work, tablets made of pure hydrogel, HydroxyPropyl-MethylCellulose (HPMC), were produced and immersed in a thermostatic bath filled with stirred distilled water (37 °C). The water up-take was allowed only by radial direction (from the lateral surface) by confining the tablet between two glass slides. Two distinct methods, an optical technique already described in a previous work, and a gravimetric procedure described here, were applied to measure the water concentration profiles along the radial direction in the tablets. The data obtained were used both to clarify the nature of the transport phenomena involved, and to perform a better tuning of a mathematical model previously proposed.

1. Introduction

The most common method of drug delivery are the oral solid dosage systems, basically tablets and capsules. The tablets, in particular, are most widely accepted and used for a number of reasons, such as acceptable costs, tamper resistance, ease of handling and packaging, ease of identification and manufacturing efficiency. Nevertheless, the fundamental role of a drug delivery system is to get the drug delivered to the site of action in a given amount and at the appropriate rate. So, tablet features and drug therapeutic efficacies cannot be separately considered. All that above points out that the general design criteria for tablet preparation are:

(i) accuracy and uniformity of drug content and its stability in the dosage form;
(ii) drug availability from the dosage form consistent with the intended use (immediate, IR, extended, ER, release) and in the appropriate site (without degradation);
(iii) patient acceptability (reasonable size and shape, taste, color, etc., in order to encourage compliance with the prescribed therapeutic regimen);
(iv) manufacturability (economical mass production).

In this work, the discussion is focused on the point (ii) above. The drugs orally administered have to survive to the acid pH in the stomach, to pass the intestinal membranes, to subsist after the hepatic "first pass" effect (i.e., the degradation due to the passage into the liver) and, finally, to endure the enzymatic degradation in the blood. The simplest way to overcome the degradation rate is to realize a system able to give a constant rate of delivery (zero-order systems). In this way, balancing the consumption rate due to effects listed above, the drug concentration in the plasma can be kept almost constant, within the therapeutic window (above the minimum effective concentration and below the minimum toxic concentration). Excipients are critical components in the design of a delivery system with the features above reported. The hydrogel swellable matrices, in principle, can be used to realize solid dosage systems able to produce zero-order kinetics.

Many researches are focused on the controlled drug release from swellable polymers used in tabletting manufacture. The common goal is to known the kinetics of the transport phenomena which take place after the polymer swallowing in order to design (or to improve) new oral dosage forms.

Colombo and co-workers studied the water up-take and the drug release by means of an optical technique, that allowed the water up-take only by the lateral surfaces of cylindrical tablets by confining the tablets between two Plexiglass disks (Bettini et al., 2001; Colombo, Bettini, & Peppas, 1999; Colombo, Bettini, Santi, De Ascentiis, & Peppas, 1996; Colombo, Bettini, Santi, & Peppas, 2000). They identified three main fronts: erosion (the contact between tablet and dissolution medium), swelling (the interface between the dry central core and the hydrated gel region), diffusion (the locus where most of the drug diffusion process takes place, i.e., where the drug concentration gradient has the maximum value). During their experiments with drug loaded matrix,

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they followed the evolutions of the position of the three fronts, producing valuable pieces of information to analyze the transport phenomena which take place.

Gao and Meury (1996a, 1996b) pointed out a method, based on measurements of scattered light passing through an hydrating matrix. They identified the swelling front (which they called "true water penetration front", also noting the presence of an "apparent gel front"). Working with unconfined tablet, they could follow the swelling evolution in both the radial and the axial direction. The method is really interesting and non-destructive, as it allows to follow the gel formation during the experiments.

Dürig and Fassihi (2002); Pillay and Fassihi (2000); Zuleger, Fassihi, and Lippold (2002) used the texture analysis to investigate the gel structure and the gel thickness. Of course, the texture analysis is a destructive technique, i.e., it requires the extraction of the tablet from the dissolution medium and the tablet "sacrifice" during the test.

Aim of this study is to define a method to measure the water concentration profile during dissolution tests of a pure hydrogel swellable excipient based on cellulose polymer. This methodology may have a relevant role in the understanding of the phenomena taking place after the tablet swallowing. These phenomena are of great interest for the design of new pharmaceutical systems and/or for the optimization of the existing ones that show a "programmed" release kinetics.

The detailed knowledge of water concentration in cylindrical tablets of pure HPMC will be investigated by means of a properly pointed out gravimetric technique. The obtained data will be used to validate an optical technique based on image analysis, previously pointed out. At last, the observed data will be of aid in the better tuning of a mathematical model of the process.

2. Materials and methods

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.

To allow the water up-take only through radial direction, the tablets were confined between two glass slides (Fig. 1a). This system was placed in a thermostatic bath, which was stirred using a magnetic paddle. The dissolution medium was distilled water, kept at 37 °C.

After the given immersion time, the sample was withdrawn from the bath and photographed by a digital camera (HP Photosmart 945) in controlled light exposure, and the cover slide was carefully removed (Fig. 1b).

Light intensity profiles from pictures 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). Azimuthal intensity average was performed to reduce the errors caused, for instance, by reflections and surface imperfections. Some more details on the image analysis were given in Chirico, Dalmoro, Lamberti, Russo, and Titomanlio (2007). Here, the image analysis technique was reconsidered on the basis of the gravimetric technique results (see Section 4).

The swollen tablet was cut by a thin-walled metallic punch, and the gel layer external to the punch wall was carefully recovered and quantitatively transferred on a glass holder, previously weighed (mass m_{V1}). The holder + recovered gel was weighed, its mass being m_{U1} (Fig. 1c).

These last two steps were repeated by using punches of decreasing radius, obtaining several annuli and a central core, which could not be further cut (Fig. 1d). Each single annulus, and the central core, were placed on a glass holder of known mass (m_{Vi}), and all of them were weighed (m_{Ui}).

All the samples were dried in an oven at 105 °C until they reached a constant weight (m_{Si}) (Fig. 1e). The amount of water in each sample was obtained by the difference $m_{Wi} = m_{Ui} - m_{Si}$; at same time, the amount of polymer in each sample was $m_{Pi} = m_{Si} - m_{Vi}$. Thus, the mass fraction of water could be obtained as $\omega_{Wi} = m_{Wi}/(m_{Pi} + m_{Wi})$. For different annuli, the water mass fraction was obtained as function of the radial direction. For different immersion times, the water mass fraction was obtained as function of time. Thus, the technique here outlined allows to obtain the function $\omega_1 = \omega_1(t, r)$ (1 being the water). All the runs were performed in triplicate.

3. Modeling

The model used was described in details in a previous paper (Chirico et al., 2007). Here, it is briefly summarized.

The water up-take, and the subsequent polymer swelling and erosion, takes place with a complex mechanism, still not fully clarified, also because of the lack of experimental data. This paper aims to point out methods to obtain reliable data to fulfill this lack.

The simplest way to describe the water up-take in matrix polymer systems is to consider it in analogy to the diffusion phenomena (thus it is usually named pseudo-diffusion), even if the swelling phenomena should be described in term of two contributes (the pure diffusive one, or Fickian, and a viscoelastic one). The most reliable model to account for viscoelastic effects was proposed by Grassi, Grassi, Lapasin, and Colombo (2007) on the basis of a previous idea by Camera-Roda and Sarti, and it was found able to describe the kinetics of swelling/de-swelling for a thermoreversible polymer. However, the use of such a model requires the determination of a number of material parameters, and also two adjustable parameters, which for our systems are unknown. To circumvent this difficult, we model the process in analogy to a pure diffusive process (pseudo-diffusion). This choice allowed to use the well known mathematics developed to describe the diffusion phenomena. The complexity of the phenomena involved was thus lumped into a hydration-dependent diffusion coefficient.

Thus, the main transport phenomenon is considered to be 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:

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

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

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

The initial condition (2a) states that the tablet initially contains water at mass fraction ω_{10} (in our experiments the tablets were ini-

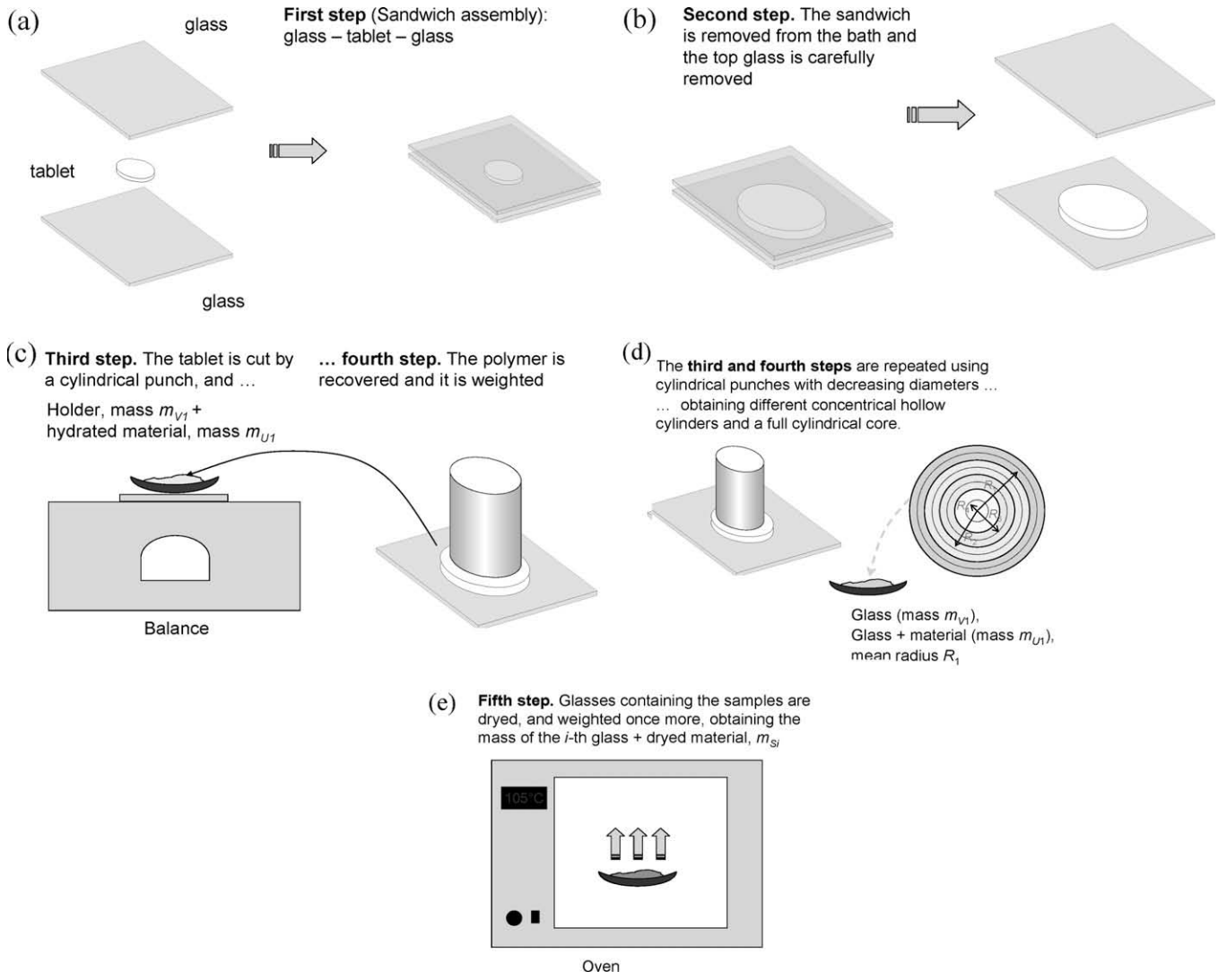

Fig. 1. The steps of the gravimetric technique (see the text).

tially 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}.

The solution of the model requires the knowledge of the erosion radius, R_E. This latter is a function of time, because of swelling and erosion phenomena (causing the first one an increase of R_E, the second one a decrease of R_E). As discussed at the beginning of this section, the pseudo-diffusion coefficient, D_1, is concentration-dependent (it increases in hydrated gel). It can be modeled according to Siepmann, Kranz, Bodmeier, and Peppas (1999):

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

where $D_1^*/\exp(\beta_1)$ is the value of the pseudo-diffusion coefficient in the dry tablet ($\omega_1 = 0$), and $D_1{}^*$ is the value of the pseudo-diffusion coefficient in the fully swollen tablet ($\omega_1 = \omega_{1eq}$).

For these reasons, a numerical calculation is required. For each time-step, the solution code calculates the actual mass of polymer and water (accounting for the erosion phenomenon by a polymer mass balance, where the erosion was taken as proportional to the surface of separation between the tablet and the water), then the code estimates the average density of the tablet (by a proper integration of the polymer and water concentration profiles). Finally, from mass and density, the tablet volume is calculated (from which the erosion radius is easily obtained, since the tablet remains a cylinder of constant thickness during the hydration). More details on equations and parameters used, as well as on the solution scheme adopted, can be found elsewhere (Chirico et al., 2007).

4. Results and discussions

4.1. Experimental and modeling results

Fig. 2 reports the water mass fractions as function of the tablet radius for the three different immersion times investigated (24, 48 and 72 h). In each graph:

(1) The results of the gravimetric technique, described in Section 2.2, are reported as full black circles, connected by a continuous line. Each data point is drawn with vertical error bars, whose extension is the standard deviation of experimental data, and with horizontal error bars, used to identify the size of the annulus (or the core) assayed. For example, for the tablet immersed for 24 h, the third data point, which is approximately $\omega_1 = 0.75$, has a standard deviation of

about 0.04 and the annulus radius ranges between 6 and 8 mm. Thus, $\omega_1(t = 24\text{ h},\ 6\text{ mm} < r < 8\text{ mm}) = 0.75 \pm 0.04$, i.e., after 24 h of immersion, the average water mass fraction of an annulus of radius comprised between 6 and 8 mm ranges between 71% and 79%.

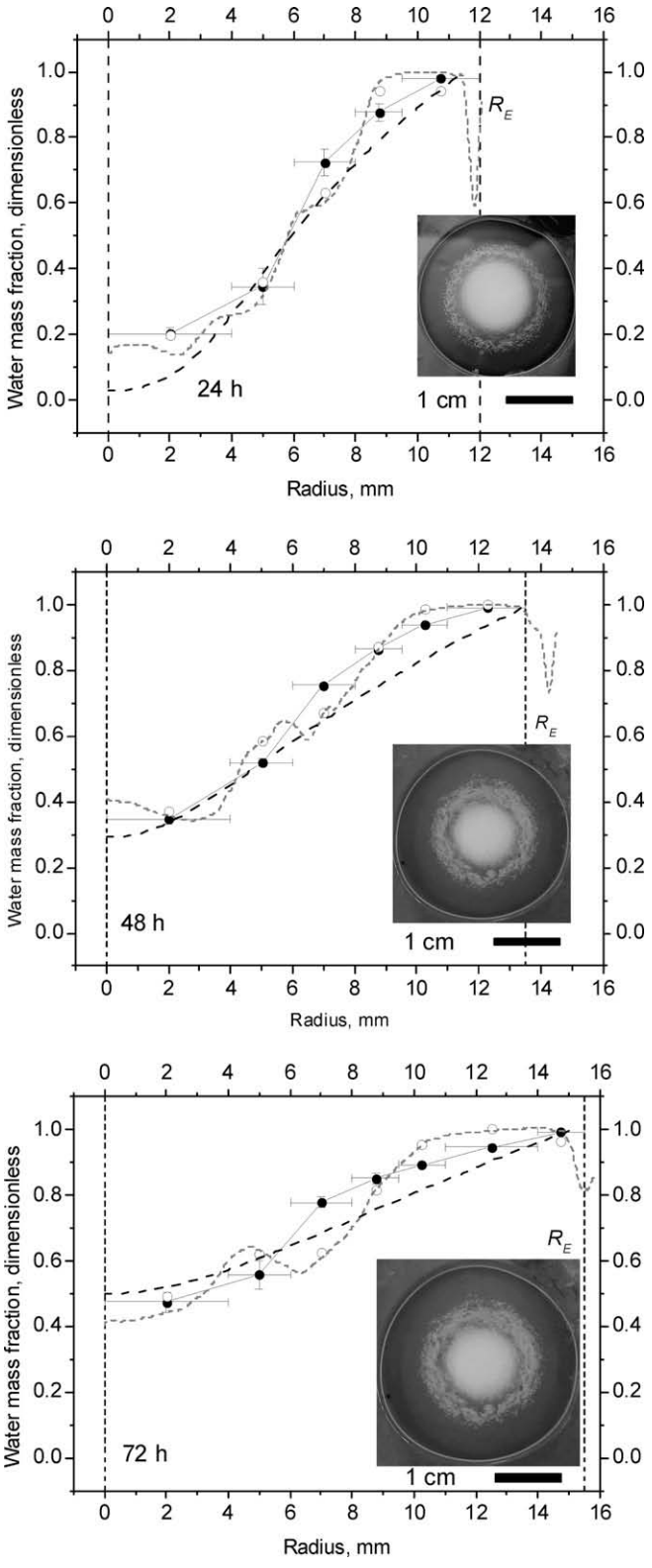

Fig. 2. Water mass fraction along the radial direction after three different immersion times: 1, 2 and 3 days. In the insets: the photos taken after sample withdrawing from the bath, used in the image analysis. Closed circles connected by a full line: results of gravimetric technique; dotted gray line: results of image analysis technique; open circles: volume–average of the image analysis results; dashed line: model predictions.

(2) The results of the image analysis technique, reconsidered as described below, are reported as a gray dotted line, together with the open circles, which represents the average of the optical data. This latter was carried out to compare the optical data with the gravimetric ones.
(3) The simulation of the model, is reported as a black dashed line, after a model tuning procedure (parameter optimization), below described.
(4) The snapshot of the hydrated tablet is shown, along with a −1 cm length – dimension bar.

4.2. Reconsideration of the image analysis technique

In our previous work (Chirico et al., 2007), we suggested a very simple way to relate the light intensity (i.e., the grayscale value of the image) to the water mass fraction. Once the values of light intensity for the dry core, I_0, and for the erosion radius, I_{max}, were identified, the normalized water mass fraction was linearly related to the normalized light intensity by using Eq. (4), in which the parameter γ was set equal to 1 to ensure linearity.

$$\left(\frac{I - I_0}{I_{max} - I_0}\right)^{\gamma} = \frac{\omega_1 - \omega_{10}}{\omega_{1eq} - \omega_{10}} \tag{4}$$

The value of I_0 and I_{max} were slightly changing from one photo to another, whereas the normalization process caused the fraction to range between 0 (dry matrix) and 1 (fully swollen matrix) anyway. This fact, together with the result of a model taken from literature which did not require any further optimization to match the experimental data from Eq. (4) with $\gamma = 1$, induced us to conclude that the couple experimental technique + model gave us the right results. Thus we described our work (Chirico et al., 2007).

Here, we got different results from the gravimetric technique, which seems to be much more reliable, since it does not require any assumption. The image analysis technique, however, would still be preferable to the gravimetric one, since it asks for much less experimental work, is non destructive and, in principle, can be applied also on-line, i.e., during the hydration experiments. Thus, we tried to better tune the image analysis method.

First of all, we standardize at maximum the external lighting conditions during the photo acquisition. By this way, we get a series of images in which the dry tablet is always represented by an average value $I_0 = 28$. At the same time, the fully swollen matrix is always depicted by an average value of $I_{max} = 220$.

Then, we look for a value of the parameter γ in Eq. (4) which makes results of image analysis technique to match with the ones of gravimetric technique. To do this, the water mass fraction from Eq. (4) were integrated within each annulus volume, to get single data points (for each annulus) to be compared with the data points obtained by the gravimetric technique, which are really volume averaged of water mass fraction. Eq. (5) was used to perform the averaging in the i-th annulus, and the resulting data point were reported as open circles in Fig. 2.

$$\langle\omega_1\rangle^{(i)} = \frac{1}{V^{(i)}}\int_{V^{(i)}} \omega_1 \mathrm{d}V = \frac{2}{((R^{(i)})^2 - (R^{(i-1)})^2)}\int_{R^{(i-1)}}^{R^{(i)}} \omega_1 r \mathrm{d}r \tag{5}$$

The tuning of the image analysis technique was thus performed by searching the value of γ which minimizes the distance between the results of the gravimetric technique (the closed circles in Fig. 2) and the results of the image analysis technique (the open circles in Fig. 2). The value found was $\gamma = 0.425$. Thus, the image analysis technique is a fast, accurate and non destructive test to get the water mass fraction profiles, once:

(i) the photos are taken under very controlled and reproducible external light conditions,
(ii) Eq. (4) is used to get the desired profile using the value $\gamma = 0.425$ (not unity).

It is worth to note that the gamma-value obtained holds for the system investigated and for the light conditions used. Therefore, using different set-up (camera, light, exposition) it could be different. However, Eq. (4) is of general validity, thus a single tuning run (the couple of measurements by gravimetric technique and by image analysis) should be enough to get a reliable value for the constant gamma.

4.3. Tuning of the model

The model summarized in Section 4, which was detailed elsewhere (Chirico et al., 2007), and which is based on the idea of "sequential layer model" proposed by Peppas and coworkers (see for example, Siepmann et al., 1999), is based on a limited number of parameters. The most important are the equilibrium water mass fraction, which we found to be $\omega_{1eq} = 0.97$ by an independent test (Chirico et al., 2007), and the couple β_1 and D_1^*, used in Eq. (3) to describe the hydration dependent pseudo-diffusion coefficient. By using the values $D_1^* = 5.6 \times 10^{-10}\,m^2\,s^{-1}$ and $\beta_1 = 2.5$, taken from literature (Siepmann et al., 1999), the model overestimates the water up-take and the increase of the tablet erosion radius (i.e., the water mass fraction predicted are larger than the ones observed and, subsequently, the predicted tablet radius increases faster than the experimental one). After the optimization, the value $D_1^* = 4.5 \times 10^{-10}\,m^2\,s^{-1}$ was found to satisfactory describe the experimental profiles (the value of $\beta_1 = 2.5$ was found to be the best one). The results of the model are reported as dashed line in Fig. 2, and they agree with both the sets of experimental data, either gravimetric and from image analysis. It is worthy to note that the optimization changes a little the parameter values (less than 20%, i.e., not changing the order of magnitude), thus the ones provided in literature were very good estimates. Hence, the data presented here can be taken as a further confirmation for the modeling approach proposed by Peppas and co-worker, and also for the substantial correctness of their parameter estimation.

4.4. Discussions

Hydrogels were used in controlled release systems since they allow the drug release only after their transition to the rubbery phase caused by hydration. The knowledge of hydration kinetics and its extent, thus, is very useful to design systems able to give tailored drug release profiles. The techniques presented and pointed out in the frame of this work allowed to obtain data useful to understand and describe the phenomena involved.

From Fig. 2, in fact, one can see how and how fast the water penetrate the tablet.

A comparison between photo and data allows to observe that the transparent gel layer (the swollen one) is characterized by a large amount of water (more than 80%), whereas the white core is not really dry (it contains at least 20% of water).

The glass to rubber transition, which is identified by Gao and Meury (1996a, 1996b) to take place close to the swelling front during the hydration, seems to be located around $\omega_1 = 50$–60%, i.e., where the gravimetric data show a flex and the image analysis data show a shoulder (due to the presence of a circular halo, already reported in Chirico et al. (2007)).

The quantitative identification of these three zone (the fully swollen external region, the transition region and the "quasi-dry" core region), whose existence has been postulated in the past but never associated with the real water content, is a good starting point to study what happens during the drug release from drug-loaded tablet.

The gravimetric technique proposed in this work, in principle, could be applied to measure also the axial water up-take. However, a number of practical problems arise, since it is really difficult to cut and manipulate a cylinder which is made of a soft gel in thin slices. Until now, we did not get reliable data from an experiment designed to analyze the axial water up-take.

5. Conclusions

In this work, a gravimetric technique to quantify the water concentration profile along radial direction in cylindrical tablet of pure swellable hydrogel was pointed out. It consists in the hydration of matrices with the water up-take limited to the lateral surface of the cylindrical tablets; in cutting the hydrated matrix with thin-walled metallic punches; in weighing the hydrated material, drying it and weighing it again, to obtain the water and residual polymer masses. The two techniques presented in this work (the gravimetric and the optical one) are themselves useful results: these tools allow to study the phenomena which take place during swellable matrix hydration, which in turn is a key step for the drug delivery.

The data obtained were used to reconsider the method based on image analysis and to perform a better tuning of a mathematical model, both of them (the method and the model) having been proposed by us in a recent work. An interesting observation is that the "white" core, reported previously to be completely dry (this information was also used as the basis of some modeling works, see for example (Kiil & Dam-Johansen, 2003)), it is not really dry, since a certain amount of water was found in it by the gravimetric technique. As a development of this study, the gravimetric technique will be modified to be suitable in analyzing drug-loaded tablets. Also the model will be adapted and tuned by comparison with properly obtained experimental data.

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