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Controlled release from hydrogel-based solid matrices. A model accounting for water up-take, swelling and erosion

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ABSTRACT

Design and realization of drug delivery systems based on polymer matrices could be greatly improved by modeling the phenomena which take place after the systems administration. Availability of a reliable mathematical model, able to predict the release kinetic from drug delivery systems, could actually replace the resource-consuming trial-and-error procedures usually followed in the manufacture of these latter.

In this work, the complex problem of drug release from polymer (HPMC) based matrices systems was faced. The phenomena, previously observed and experimentally quantified, of water up-take, system swelling and erosion, and drug release were here described by transient mass balances with diffusion. The resulting set of differential equations was solved by using finite element methods.

Two different systems were investigated: cylindrical matrices in which the transport phenomena were allowed only by lateral surfaces ("radial" case), and cylindrical matrices with the overall surface exposed to the solvent ("overall" case).

A code able to describe quantitatively all the observed phenomena has been obtained.

1. Introduction

Drug release from solid matrices systems, made of polymer(s) and drug(s), is a basic concept for studies on controlled drug delivery. The most interesting class of polymers in this application is given by hydrogels, also pH-sensitive ones. Matrices based on hydrogels, once swallowed (during the in vitro tests, once immersed in the solvent mimicking the body fluid), start to absorb water from the surroundings (water up-take). The absorbed water causes a number of phenomena: hydrogel swelling, polymer plasticization (lowering of the glass transition temperature), diffusion coefficient increase, erosion phenomenon (due to polymer disentanglement). Therefore, the drug can diffuse through the hydrated hydrogel and then it can be released.

To design such kind of systems, a deep knowledge of what happens during the hydration/dissolution, in the gastro-intestinal tract, to these matrices is required. Then, all the hypothesized/observed phenomena can be translated into mathematical equations (the act of modeling). In turn, the set of equations can be solved using an *ad hoc* designed software (numerical code). The description of release process by mathematical model can be a powerful tool to develop novel dosage forms, as well as to optimize existing pharmaceuticals. An adequate identification of the physical and mathematical model, toward the description of the real behavior for a pharmaceutical, allows a reliable simulation of the effect of the design parameters for the device on the release kinetics. In other words, availability of a reliable model allows the *a priori* prediction of the formulation parameters to give a tailored drug release profile.

1.1. State of the art

Some recent reviews dealt with the mathematical modeling of drug release (Grassi and Grassi, 2005; Grassi et al., 2007; Siepmann and Siepmann, 2008). The controlled drug release from hydrogel based matrices was treated in a detailed overview by Siepmann and Peppas (2001), which in particular focused their attention to the modeling approaches reported in literature. The starting point of their analysis was the treatment due to Higuchi (1961). Higuchi described how a suspended drug was released from an ointment, when it was placed in contact with a perfect sink, and his equations is probably the most famous and the most used to describe drug release processes. Fundamentally, it is the solution to the Fick's balance equation (transient mass balance), and it was obtained under some restraints: the diffusivity is constant, there are no swelling and erosion of the matrix, there is the perfect sink at the interface between the ointment and the dissolution medium. Therefore, the Higuchi equation is not applicable to matrices made of hydro-

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gels and drug, which are subject to swelling and erosion, and also exhibit a diffusivity sensible to the water concentration. The result of Higuchi equation is a drug release from a slab proportional to the square root of time. Usually, the observed experimental behavior reports a release kinetics proportional to different power of time. Then Peppas (1985) proposed the use of a semi-empirical model build by the sum of two different powers of time, accounting for the pure diffusivity phenomenon (the so-called Fickian term) and for another contribution to the release kinetics, due to the relaxation of the polymer molecules (the so-called non-Fickian or case-II "relaxational" term).

The prosecution of studies by Peppas and coworkers produced a mathematical model able to describe a rich set of experimental phenomena which take place during the drug release from matrices made of swellable hydrogels (Siepmann et al., 1999a,b, 2000; Siepmann and Peppas, 2000). The model was named "sequential layer" because it accounts for all the phenomena (water diffusion, swelling, drug diffusion, polymer erosion) from the outer layers toward the interior layers of the matrices, shaped as cylinders. The main limitation of their model is that the model was able to describe only "affine" deformations, i.e. no matters what phenomenon takes place (swelling, erosion), the initial cylinder remains a cylinder (increasing its size because of the swelling or decreasing its size because of erosion).

A similar model, able to describe what happens to matrices with different shapes (slabs, finite cylinders, cylinders, spheres) was proposed and tuned, working with pure HPMC (Chirico et al., 2007), then describing the behavior of matrices made of HPMC and TP (Barba et al., 2009b).

Under the restraint of constant diffusivities, in absence of swelling and erosion, the drug diffusion problem in a finite cylinder was faced up and solved analytically (Fu et al., 1976). Recently, the drug diffusion problem, in matrices of various shape (even not simple: convex tablets, hollow cylinders, doughnuts, inwards hemispheres) was solved by the finite element methods (Wu and Zhou, 1998), in presence of moving boundaries (Wu and Zhou, 1999), in presence of slowly dissolving drugs (Frenning et al., 2005). This interesting approach, to our knowledge, was not applied in the description of swelling and eroding matrices.

Several approaches with increasing complexity were proposed by Grassi and coworkers to model the drug release from solid pharmaceuticals (Grassi and Grassi, 2005). The balance of the drug in the dissolution medium constitutes the core of a simple model proposed to take into account the resistance to the release due to a layer of enteric coating (Grassi et al., 2004). The release from an ensemble of spherical particles made of drug and swellable hydrogels, poly-dispersed in size and with the drug present in different physical phases (amorphous, crystalline), was described by a much more complex model. In this case, the fluxes of water and drug, due to both the diffusion and to the relaxational effects due to the swelling phenomenon, were calculated and also the volume increase due to the swelling was accounted for (layer-by-layer, i.e. dividing the sphere in shells). Also the balance of the release drug was calculated (Grassi et al., 2000). In this case the analysis proposed is very elegant and complete, but the model is not able to describe deformation different than the affine one. i.e. the change in shape of a matrix due to the hydration, which is a well known experimental evidence, cannot to be described by these models.

1.2. Aim of this work

Aim of this work is to point out a model and the related numerical code, which has to be able to describe the complex behavior observed during the drug release from hydrogels based matrices. In particular, the attention will be paid to the change in shape of the matrices caused by swelling and erosion, since this is a well known aspect from experimental point of view, but never dealt with in the modeling.

2. Experimental

2.1. Materials

The hydrogel used was the hydroxypropyl methylcellulose (HPMC, Methocel K15M). It was a gift from Colorcon (Varese, Italy). The model drug was the theophylline (TP, CAS no. 58-55-9) was purchased from Sigma Aldrich (Italy), and it was purchased from Sigma Aldrich (Milan, Italy). According to the manufacturer data, both the materials are spherical powder with the maximum particle size lower than 500 μm and the mean volume diameter of the order of 100 μm. The materials were used as obtained. Distilled water was used as dissolution medium. Along all the paper, the water is the component 1; the drug is the component 2; the polymer is the component 3.

2.2. Methods

2.2.1. Matrices preparation and hydration

Blends of HPMC and TP 50:50 (w/w) were obtained by mixing the powders in a mortar. The cylindrical matrices (0.35 g, 13 mm diameter, 2.0 mm thickness) were prepared by compressing the powder in a tabletting machine (Specac PN3000), equipped with flat-faced punches, diameter 13 mm, with a compression force of 50 kN (by a Carver Press) kept for 5 min. In both the radial test and in the overall test, described below, the matrices were immersed in distilled water stirred and kept at 37 °C. During the hydration, small quantities of the dissolution medium were withdrawn, assayed for the drug content (by UV spectrometry, $\lambda = 275$ nm), and then they were re-added to the dissolution medium. This analysis allows to determine the amount of released drug, and then the fractional drug release evolution with time.

2.2.2. The "radial" test

The radial test experiments were not carried out in the frame of the present work. The technique was pointed out previously (Barba et al., 2009a,c), and the experimental results obtained working with 50:50 HPMC:TP matrices were already published (Barba et al., 2009a). The technique was described here just for the sake of clarity.

The tablets, clamped between two glass slides to allow the water uptake only by the lateral surfaces, were immersed in distilled water stirred and kept at 37 °C for given time intervals. After the immersion, the samples were removed from the bath, and then the partially hydrated tablets were cut by annular punches of different size, obtaining several annuli, and one core disc. The different amounts of partially hydrated polymer in different annuli were carefully weighted, dried, weighted once more. In this way it was possible to determine the average concentration of water in each annulus, i.e. as a function of tablet radius. Then, the dried samples were totally dissolved and the drug contents were assayed by a spectrometer, $\lambda = 275$ nm. Thus, the average mass fractions of water and drug in each annulus, and in the core, were measured.

2.2.3. The "overall" test

The tablets were immersed in a USP dissolution tester type II containing distilled water kept at 37 °C. The tablets were placed in a suitable sample holder to avoid the sticking of the matrices on the bottom of the vessel (a cylinder made of stainless iron wire with a large mesh size. The cylinder is 5 cm in diameter and 4 cm in height, i.e. it is larger than the tablet, even after a given time of immersion). After given immersion intervals, hydrated samples were removed, weighted, dried, weighted once more and at last they were fully

dissolved, to allow the drug content assaying (each test was carried out in triplicate). By this way the water absorbed as well as the polymer and drug residual into the tablet were determined. One matrix for each immersion time was drawn from the bath, cut and photographed. Size (diameter and thickness) and shape of the hydrated matrices were obtained from image analysis.

3. Modeling

3.1. Balance equations

The transport of water and drug in the matrix can be viewed as two pseudo-diffusion phenomena, which can be described by two transient mass balances ($k = 1$ for the water and 2 for the drug). The balances should to take into account the masses accumulation and the transport phenomena which takes place. In principle, the movement of the solvent and the drug in a matrices of swelling hydrogel is due to the diffusion of both the substances (with diffusivities variable with the hydration levels) and to the convection which arise because of the volume expansion. There are several ways to take into account of both the phenomena (Wu and Brazel, 2008). Peppas and co-workers focused on the relevance of the so-called Case II or non-Fickian transport phenomenon (in which the convection plays a relevant role) (Brazel and Peppas, 1999a,b, 2000). The origin of the convective flux in the stress relaxation has been pointed out and some models have been proposed to take it into account (Camera-Roda and Sarti, 1990; Grassi et al., 1998, 1999; Harmon et al., 1987). Here the convective fluxes were neglected, limiting the attention to the diffusive fluxes and accounting for the polymer relaxation following the suggestion of Camera-Roda and Sarti (1990), as detailed in Section 3.3.

$$\rho \frac{\partial \omega_k}{\partial t} = \vec{\nabla} \cdot (\rho D_k \vec{\nabla} \omega_k) \tag{1}$$

In Eq. (1), the matrix density is ρ, ω_k are the water and drug mass fractions, D_k are the pseudo-diffusion coefficients.

The initial conditions for integration are given by Eq. (2), in which Ω is the integration domain (i.e. the matrix) and $\omega_{k,0}$ are the initial homogeneous mass fraction of water ($k = 1$) and drug ($k = 2$).

$$@t = 0 \quad \forall \vec{x} \in \Omega \quad \omega_k(t = 0, \vec{x}) = \omega_{k,0} \tag{2}$$

The boundary conditions are defined on the moving boundary $\Gamma(t)$, and they are given by Eq. (3).

$$@\vec{x} \in \Gamma(t) \quad \forall t > 0 \quad \omega_k(t > 0, \vec{x} \in \Gamma(t)) = \omega_{k,eq} \tag{3}$$

In Eq. (3), the $\omega_{k,eq}$ are the equilibrium values for water ($k = 1$) and drug ($k = 2$) mass fraction. The moving boundary, $\Gamma(t)$, is represented by the erosion front (the interface between the matrix and the dissolution medium) both for the water and the drug. The equilibrium drug mass fraction $\omega_{2,eq}$ was determined by the perfect sink conditions (i.e. the drug in the dissolution medium is negligible, therefore the partition rule gives a null concentration also in the matrix side at the interface). This hypothesis was also experimentally confirmed by direct measurement of the drug concentration in the swollen gel layer (Barba et al., 2009a).

3.2. Constitutive equations

To solve Eq. (1), the pseudo-diffusion coefficients, D_k (for $k = 1, 2$), have to be evaluated. In polymeric systems subjected to swelling, the diffusion coefficients are not constant, being low in the dry polymer and increasing as the water content increases (into the gel). They can be modeled according to (Siepmann et al., 1999b):

$$D_k(\omega_1) = D_k^* \cdot \exp\left[-\beta_k \cdot \left(1 - \frac{\omega_1}{\omega_{1,eq}}\right)\right] \tag{4}$$

where $D_k^*/\exp(\beta_k)$ are the values (for $k = 1, 2$) of the pseudo-diffusion coefficients in the dry matrix ($\omega_1 = 0$), and D_k^* are the values of the pseudo-diffusion coefficients in the fully swollen matrix ($\omega_1 = \omega_{1,eq}$).

The density of the partially hydrated matrix can be calculated by the simplest mixing rule which can be written for the specific volume:

$$\frac{1}{\rho} = \frac{\omega_1}{\rho_1} + \frac{\omega_2}{\rho_2} + \frac{1 - \omega_1 - \omega_2}{\rho_3} \tag{5}$$

where ρ_1, ρ_2 and ρ_3 are the water, the drug and the polymer densities, respectively.

3.3. Modeling of the swelling and of the erosion

The water up-take causes the matrix swelling, and the polymer disentanglement at the matrix surface causes the matrix erosion. Thus, these two phenomena, swelling and erosion, cause the matrix surface to be a moving boundary. Mathematically, there is a trace of this statement in Eq. (3), where the surface has been described by the term $\Gamma(t)$. Therefore, there is the need for modeling the two phenomena, with the aim of obtaining the function $\Gamma(t)$.

Thus, the movement of a surface element is due to the swelling phenomenon (which causes the increase of the matrix size) and to the erosion phenomenon (which causes the decrease of the matrix size). In term of element velocity, v, the governing equation is:

$$v = v_{swe} + v_{eros} \tag{6}$$

In which v_{swe} is the size-increase velocity due to the swelling (a positive value) and v_{eros} is the size-decrease velocity due to the erosion (a negative value).

According with the Camera-Roda and Sarti model (Camera-Roda and Sarti, 1990), the flow of the solvent, j_1 in the present case, 1 being the water, in a swelling system can be obtained by summing up two contribution, one due to the diffusion and the other due to the swelling phenomenon itself. The first one, $j_{1,diff}$, is thus described by the Fick law of diffusion, the second one, $j_{1,swe}$, should account for a diffusion term plus a relaxation term:

$$j_1 = j_{1,diff} + j_{1,swe} = (\rho D_1 \nabla \omega_1) + \left(\rho D_{swe} \nabla \omega_1 + \rho \tau \frac{\partial j_{1,swe}}{\partial t}\right) \tag{7}$$

The water diffusion and the drug release are phenomena which takes hours to be completed. The molecular relaxation, on the other side, takes just a few seconds. Michailova et al. (2000) reported, for HPMC based hydrogels, a zero-relaxation time of the order of 20–30 s, depending of the medium pH. Therefore, the relaxation term could be neglected (i.e. the time scale of the relaxation is assumed to be lower than the time scale of the diffusion, $\tau \to 0$). Furthermore the swelling diffusion coefficient is hypothesized to be proportional to the diffusion coefficient itself (i.e. $D_{swe} = k_{swe} D_1$, in which k_{swe} is a proper constant, to be evaluated); then the water flow due to the swelling is given by:

$$j_{1,swe} = \rho k_{swe} D_1 \nabla \omega_1 \tag{8}$$

A water balance on a surface element of thickness δ and of surface A, which is subject to the swelling phenomenon due to the water uptake, is depicted in Fig. 1 (top left). The net water flux (total flux minus diffusive flux, i.e. the swelling part) give rise to the swelling phenomenon (the volume increase proportional to the $\Delta\delta$ value), whereas the remaining flux pass through the element of thickness δ and diffuses toward the internal of the matrix. The surface element is of negligible thickness, therefore its density could be assumed constant, on the value given by the total density multiplied by the

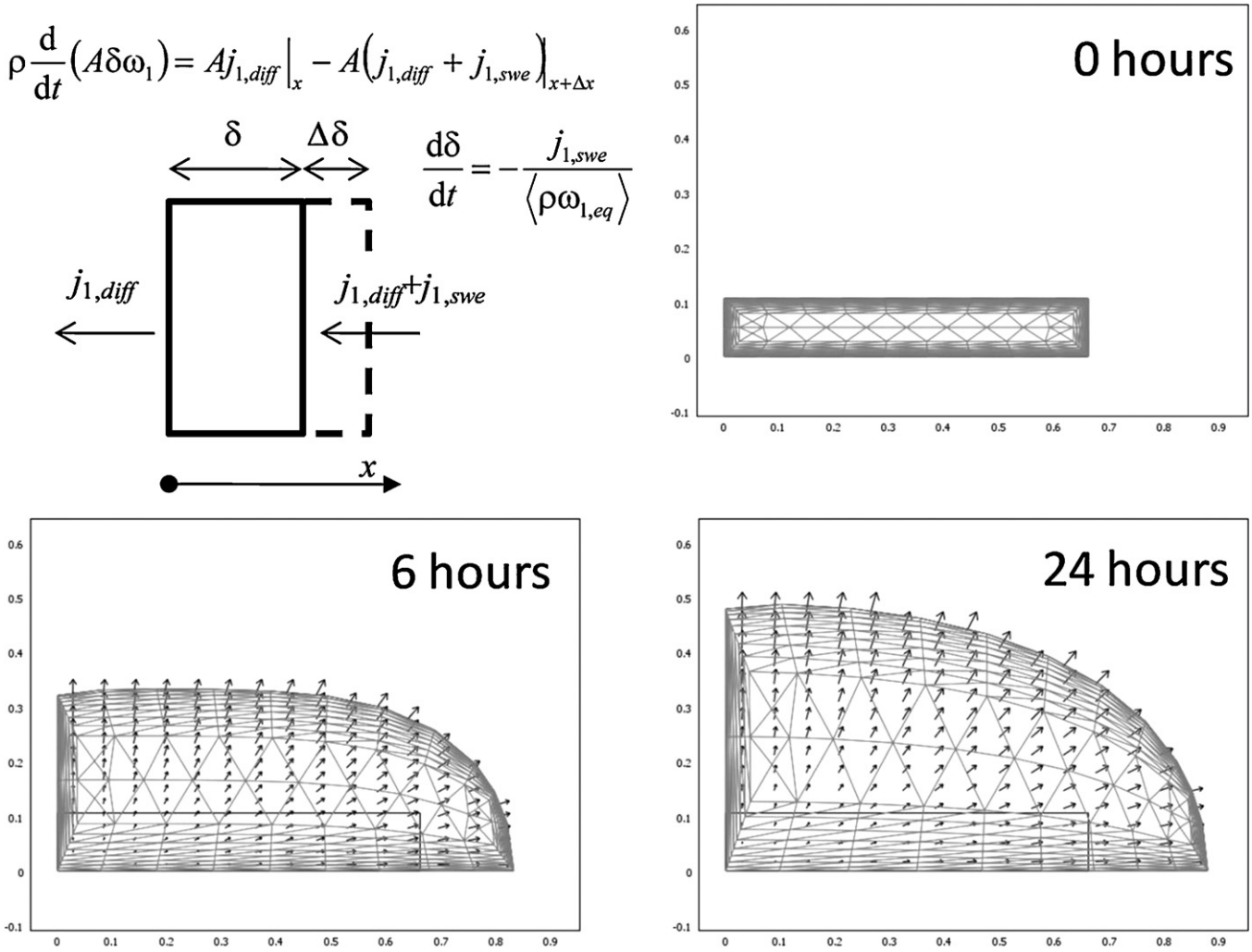

Fig. 1. The details of the mass balance on a boundary element of surface *A*, giving Eq. (9), and the deformation of the mesh due to the hydration, for the initial domain (0 h) and for two immersions times (6 and 24 h). The arrows show the calculated displacement of the mesh size.

equilibrium water mass fraction. The mentioned balance gives:

$$v_{swe} = \frac{d\delta}{dt} = -\frac{j_{1,swe}}{\rho} = -\frac{k_{swe}j_{1,diff}}{\rho} \tag{9}$$

Locally on the surface, the diffusion normal flux is negative (inward), thus the velocity given by Eq. (9) is a positive value (causing the size increase). Properly, the balance which gives Eq. (9) should be carried out on an element placed in correspondence of the swelling front (the surface moving inward the matrices in correspondence of which the polymer undergoes the transition from dry to hydrated state). The volume increase due to the hydration causes a network movement, which propagates toward the erosion front (the interface between the matrices and the solvent). Due to mathematical difficulties in implementation, the code was built in an alternative way, imposing the movement to the erosion front, whereas the remaining of the integration volume was allowed to undergo free displacements, to follow the surface movement, while the elements on the radial axis cannot move in the radial direction and the elements on the symmetry plane cannot move in axial direction. This mathematical shortcut, however, in principle is able to capture the features of the swelling matrices, and, accurately tuned, the resulting code was found able to reproduce the real observed behavior. The displacement of the full integration domain is shown in Fig. 1, which reports the initial mesh distribution (top right) and what happens to the mesh after six (bottom left) and after twenty four (bottom right) hours of hydration. The boundary as well as the deformed mesh elements are reported. The propagation of the surface velocity on the mesh is clearly evident. Furthermore, for each mesh element an arrow indicate the calculated displacement which will take place in the next time step. The surface velocity is actually due to both the swelling and the erosion phenomena, because of Eq. (6), the reasoning reported above applying to the total velocity.

The boundary movement velocity due to the erosion phenomenon is accounted for as a constant velocity, since the erosion is a phenomenon dictated by chemical and physical features of the interface between the matrices and the outer medium, and these features are constant along all the process:

$$v_{eros} = -k_{eros} \tag{10}$$

In Eq. (10) k_{eros} is a proper constant, and the minus sign accounts for the inward nature of the erosion.Both k_{swe} and k_{eros} have to be optimized by comparison with experimental data.

3.4. Code solving

The FEM software used in this work to implement the simulations is COMSOL Multiphysics® 3.4 (Copyright © 1994–2007 by COMSOL AB, Tegnérgatan 23 SE-111 40 Stockholm). This software allows transforming conventional models for each kind of physical

Table 1
Values of the parameters used in the simulations.

Input parameters					
m_{10}	Initial water mass [mg]	7.5	ω_{10}	Initial water fraction [–]	0.0217
m_{20}	Initial drug mass [mg]	160.35	ω_{20}	Initial drug fraction [–]	0.4644
m_{30}	Initial polymer mass [mg]	177.42	ω_{30}	Initial polymer fraction [–]	0.5139
R_0	Initial radius [cm]	0.65	ρ_1	Water density [mg cm^{-3}]	1000
H	Initial thickness [cm]	0.2	ρ_2	Drug density [mg cm^{-3}]	1200
V_0	Initial volume [cm^3]	0.2654	ρ_3	Polymer density [mg cm^{-3}]	1200
β_1	Diffusive coefficient, 1 [–]	3	β_2	Diffusive coefficient, 2 [–]	9
ω_1^*	Equilibrium water fraction [–]	0.97	ω_2^*	Equilibrium drug fraction [–]	0
Parameters optimized in the simulation of the "radial" test					
D_1^*	Critical water diffusivity [cm^2 s^{-1}]	1.6×10^{-6}	D_2^*	Critical drug diffusivity [cm^2 s^{-1}]	1.5×10^{-6}
k_{swe}	Swelling constant [–]	4.35	k_{eros}	Erosion constant [cm s^{-1}]	0.83×10^{-7}
Parameters optimized in the simulation of the "overall" test					
k_{swe}	Swelling constant [–]	5.32	k_{eros}	Erosion constant [cm s^{-1}]	1.97×10^{-7}

model into multi-physics models, which solve coupled physics phenomena simultaneously. The development and implementation of the simulations have been carried out with the help of a workstation based on the processor Intel® Core™2 Duo E8500, with a clock rate of 3.16 GHz and a RAM of 3 Gb, 800 MHz.

Before to deal with the very complex problem depicted in the present work, some preliminary problems, with known analytical solutions or already solved by other numerical methods were simulated to test the reliability of the approach and of the code (Galdi and Lamberti, submitted for publication). The details of the code implementation are available in (Galdi, 2009).

4. Results and discussion

Experiments were carried out by immersion of tablets for several time intervals, following both the protocols outlined in Section 2.2. All the results obtained were summarized in the following sub-sections. The model parameters were obtained by direct measurements (initial masses and mass fractions, matrices initial dimensions) and some of them were estimated from previous works, both experimental, carried out by our group (e.g. equilibrium water fraction (Chirico et al., 2007)) or from literature (e.g. diffusive coefficient (Siepmann et al., 1999a)). All the input parameters were reported in Table 1. A limited number of parameters were fitted to allow the model to reproduce experimental data. They were reported in separate rows in Table 1, and they were discussed in the following sub-sections.

4.1. The "radial" test

During radial test, the swelling and the erosion phenomena did not cause a significant shape modification, due to the presence of the two glass slabs which confine the matrices subjected to hydration. Therefore, the matrices keep their initial cylindrical shape, even if their radius change (it increases due to the swelling, then it decreases due to erosion).

The cutting procedure outlined in Section 2.2.2, and better detailed elsewhere (Barba et al., 2009a,c), allows to measure the mass fraction values of water and drugs along the radius of the matrices, for different immersion times. In Fig. 2 the profiles of water and drug were reported for two immersion times (24 and 72 h). Experimental data were reported as symbols, model calculations were reported as curves. It is worth to note that, to our knowledge, these kind of data were never reported before our previous work (Barba et al., 2009a), and they constitute a powerful piece of information to the understanding of the phenomena which take place during the matrices hydration. The agreement between the data and the model, even if not perfect, is fair and indicates that, at last, all the main phenomena were correctly taken into account by the model.

The four remaining parameters (D_1^*, D_2^*, k_{swe}, k_{eros}) were optimized to reproduce the profiles collected after several immersion times (6, 12, 18, 24, 48, 72, 96 h, most of these profiles are reported in (Barba et al., 2009a)), and their values were reported in Table 1. The critical diffusivities were obtained by (little) modifications of the values reported in literature (Siepmann et al., 1999b), the first

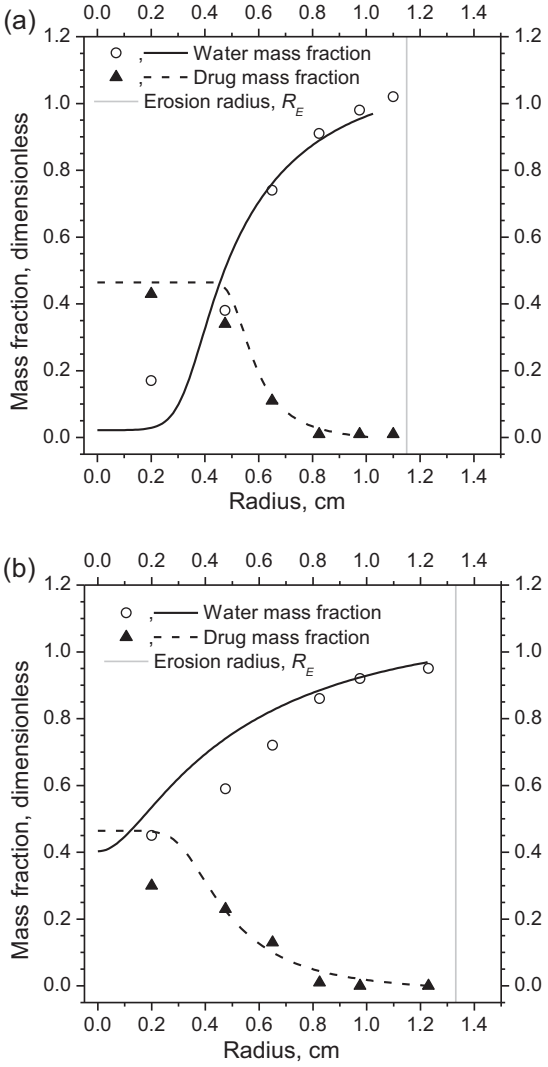

Fig. 2. Water and drug mass fraction along the radius direction in the HPMC-TP 1:1 matrices subjected to the lateral hydration ("radial" test). Symbols, experimental data (○, water mass fraction, ▲, drug mass fraction; the experimental data were taken from Fig. 2 in (Barba et al., 2009a)); curves, model calculations (continuous, water; dashed, drug). (a) After 24 h of immersion; (b) After 72 h of immersion.

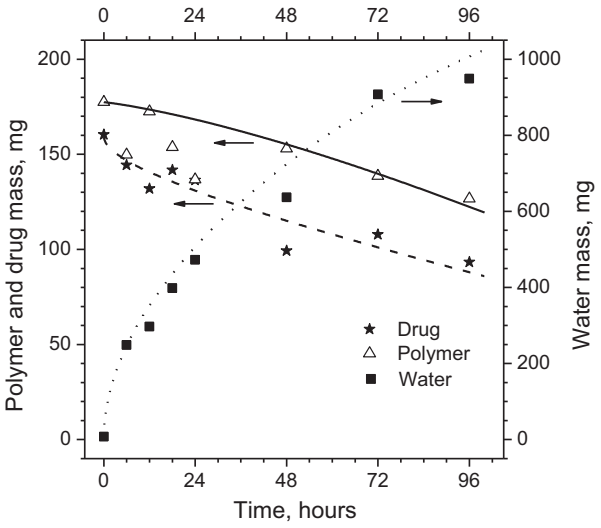

Fig. 3. Time evolutions of polymer, drug and water mass in the HPMC-TP 1:1 matrices subjected to the lateral hydration ("radial" test). Symbols, experimental data (△, polymer, ⋆, drug, ■, water; the experimental data were taken from Fig. 5 in (Barba et al., 2009a)); curves, model calculations (continuous, polymer; dashed, drug; dotted, water).

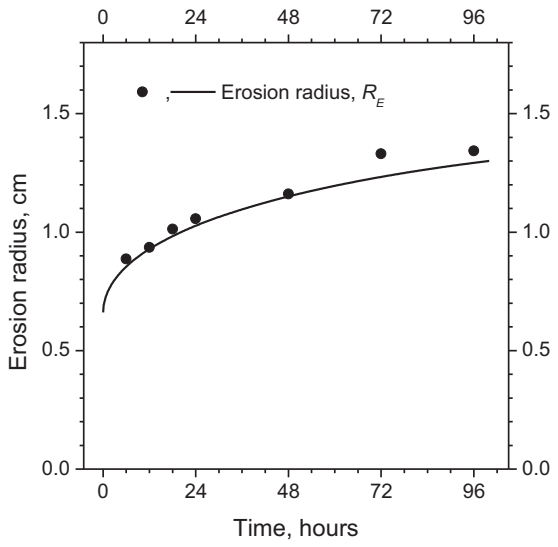

Fig. 4. Time evolutions of erosion radius for the HPMC-TP 1:1 matrices subjected to the lateral hydration ("radial" test). Symbols, experimental data, taken from Fig. 3 in (Barba et al., 2009a); curve, model predictions.

estimation of the two constants were obtained by the procedures outlined in the appendix (from which $k_{swe} = 3.27$ and k_{eros} is of the order of 10^{-7} cm^{-1} s^{-1}). The optimized value of $k_{swe} = 4.35$ is larger than the first estimation. Indeed, it should be noted that the value obtained by the estimation procedure is lower than the real one, since the erosion phenomenon has been neglected (and it causes a decrease in Ω observed), and the long immersion time is not the equilibrium (maybe some more water could enter into the matrix, thus, again, the Ω observed is lower than Ω_{eq}).

After the cutting procedure, and for each immersion time, the total mass of each component can be obtained easily by summation of the masses of each annulus and the core. Therefore, Fig. 3 reports the masses evolution with time of drug, polymer and water in the matrices. The experimental data are reported as symbols and they were taken from (Barba et al., 2009a), the model calculations are the curves. No more optimization step were required at this point, and the agreement of the model with experimental data was found to be very good.

The model was able also to predict the matrices radius, and its calculations are reported in Fig. 4. The agreement with experimental data (from (Barba et al., 2009a)), once more, is very good.

At last, the model was compared with the data of fractional drug release. This is the only kind of experimental data which can be obtained by using the USP type II apparatus. Thus, by traditional dissolution method this is the only data useful in model validation or in a new formulation testing.

In Fig. 5, the direct output of the spectrometer connected to USP type II apparatus is reported as small symbols (high number of symbols close each other and limited at the first 12 h). After the first 12 h, the automatic procedure has to be stopped because the drug concentration become too high (it exceeded the reliability range of Lambert and Beer's law) and the operator has to switch to a – much less frequent – manual sampling procedure, followed by a proper dilution and then by the spectroscopy assaying of the drug. The model nicely fits both the data series.

It is worth to note that usually the data in Fig. 5 are the only kind of experimental data available studying the release from solid matrices using the USP Type II apparatus, and thus the tuning of other model parameters, proposed in literature, were often carried out on the basis of such a limited number of experimental data.

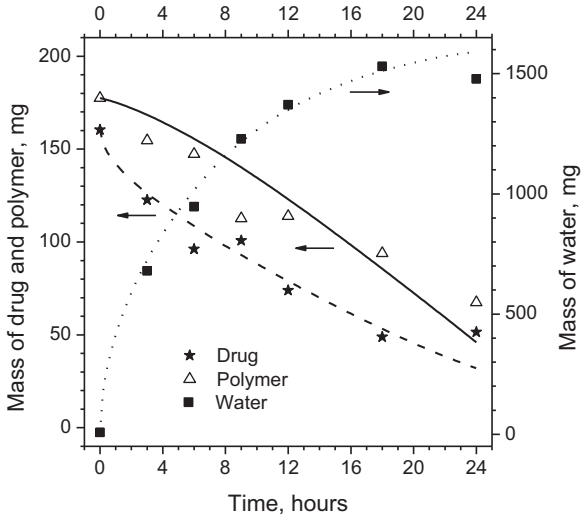

Fig. 5. Time evolutions of polymer, drug and water mass in the HPMC-TP 1:1 matrices subjected to the full hydration ("overall" test). Symbols, experimental data (△, polymer, ⋆, drug, ■, water); curves, model calculations (continuous, polymer; dashed, drug; dotted, water).

Summarizing, by using a limited number of parameters – four – and by optimizing them by comparison with one set of experimental data (and the optimization does not give values far from the first estimation), the proposed model was found able to reproduce the complex behavior exhibited by the matrices during their hydration.

4.2. The "overall" test

In Fig. 6 data similar to those presented in Fig. 3 were reported. In this case, they were obtained during the "overall" test, i.e. when the entire tablet's surface is in contact with the dissolution medium. Even in this case, the model reveals itself able to capture all the phenomena observed. Indeed, the model curves nicely fit the experimental data.

Only the two parameters k_{swe} and k_{eros} were further optimized, and their values are in Table 1. In this case, since the hydration causes a large shape modification, the estimation of Ω_{eq} is quite difficult. Considering the matrix as a cylinder, and calculating the

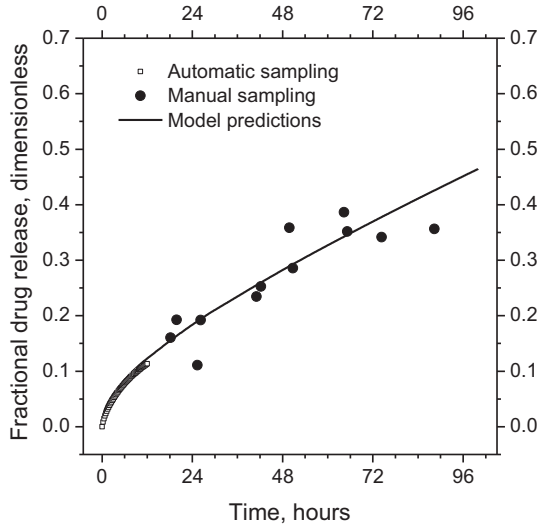

Fig. 6. Fractional release of the drug for the HPMC-TP 1:1 matrices subjected to the lateral hydration ("radial" test). Symbols, experimental data (□, automatic sampling, ●, manual sampling); curve, model calculations.

volume of the fully swollen matrix as the cylinder of the same radius and height, the k_{swe} estimated is larger than the real value (because the calculated volume is larger than the real one). The value estimated is k_{swe} = 7.6, the optimized value is k_{swe} = 5.32. The value optimized is different than the one obtained for the radial test. The reason of this could be ascribed to the differences between the two tests: the swelling is dominated by the chemical nature of the polymer, the temperature, the solvent (and all these features are the same in the two kind of tests) and the stress level in the gel. During the radial test, the confining in glass slides causes an increase in the stress level, then the hydration is somewhat limited, and then the expected swelling extent has to be lower. The found data are in agreement with this hypothesis. The estimated value for k_{eros} is of the order of 2×10^{-7} cm s^{-1} (the optimized value is 1.97×10^{-7} cm s^{-1}). It is worth to note that a similar parameter was introduced by Siepmann et al. (1999a), the k_{diss} value which has the sense of $k_{eros} \cdot \rho_3$, is around 5.5×10^{-5} mg cm^{-2} s^{-1}, having the same order of magnitude for the erosion phenomenon. Mod-

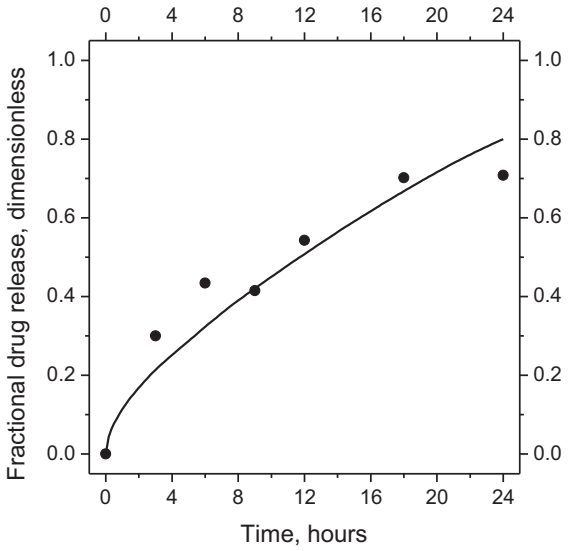

Fig. 7. Fractional release of the drug for the HPMC-TP 1:1 matrices subjected to the full hydration ("overall" test). Symbols, experimental data; curve, model calculations.

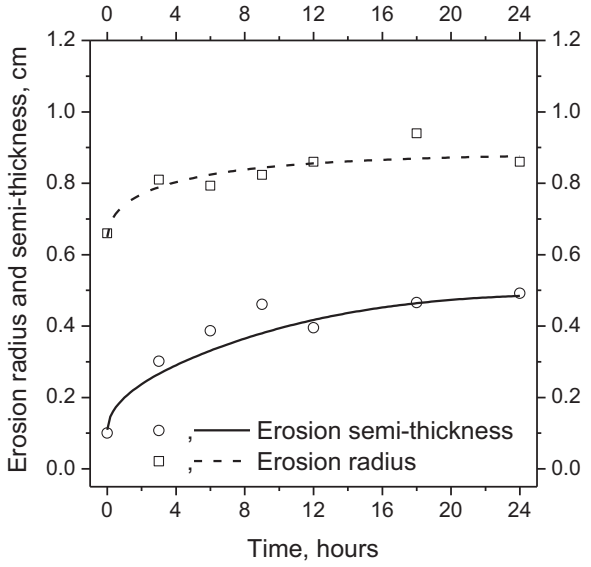

Fig. 8. Time evolutions of erosion radius and semi-thickness for the HPMC-TP 1:1 matrices subjected to the full hydration ("overall" test). Symbols, experimental data (◯, erosion semi-thickness, □, erosion radius); curve, model calculations (continuous, erosion semi-thickness, dashed, erosion radius).

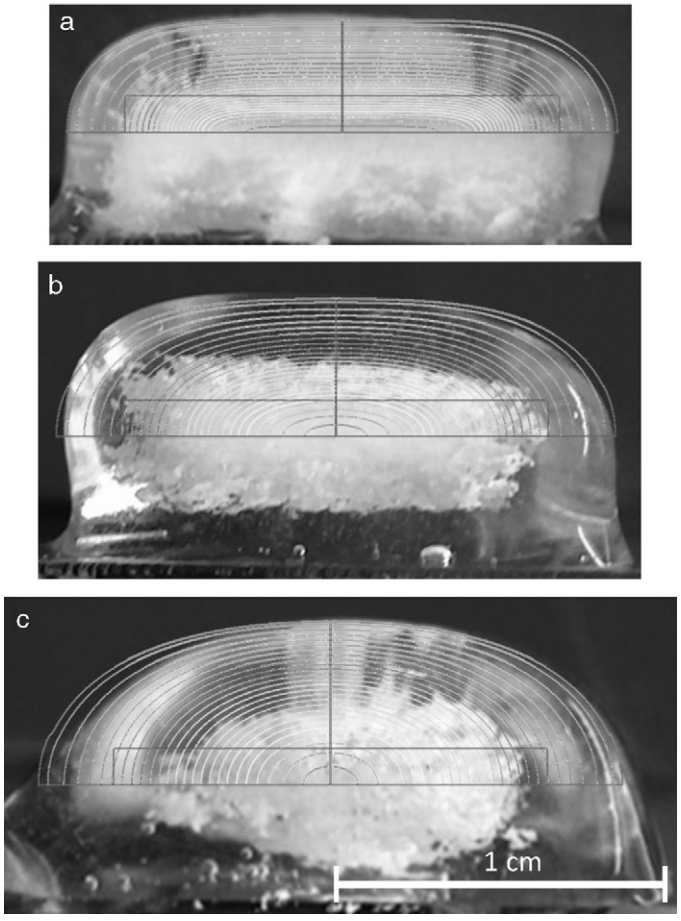

Fig. 9. Shape and hydration levels for the HPMC-TP 1:1 matrices subjected to the full hydration ("overall" test). Snapshots of cut matrices (experimental) and superimposed simulated profiles (model). The initial, non-swollen half-matrices shape is reported as a rectangle (diameter 13 mm, semi-thickness 1.1 mm). (a) After 6 h of hydration, (b) after 12 h of hydration, (c) after 24 h of hydration.

ifying the experiment from the "radial" test to the "overall" test can cause these two parameters to vary, because the presence of the confining glass slides in the "radial" configuration causes less erosion (the fluid-dynamic of eroding solvent is limited by the presence of the glass slides, and also the glass slides limit the swelling of the gel, acting as physical barriers). Fig. 7 reports the fractional drug release evolution with time, both experimental (symbols) and model (curve) results. Of course, without any further optimization, the model was able to predict the kinetic of the drug release.

The most important result, to our knowledge never obtained before, is the ability of the code to predict even the shape assumed by the swelling/eroding matrices during the hydration. Once the code has been tuned (i.e. each single parameter has been determined by fitting the experimental data from Fig. 6), the shape of the matrices as predicted by the code was compared with the real one as observed by cutting and photographing the hydrated matrices.

In Fig. 8 the radius and the semi-thickness of the hydrating matrices (i.e. of the cylinder which includes the swelling matrix) were reported both as experimental data (symbols) and as model calculation (curves). The agreement is very good.

At last, Fig. 9 shows some examples, after 6, 12 and 24 h of hydration. The code calculations fit perfectly the experimental data. The hydrating matrices do not keep their original shape (cylinder), thus the basic hypothesis of the most interesting modeling works published in the past (Barba et al., 2009b; Siepmann et al., 1999a,b; Siepmann and Peppas, 2000) was not verified. Instead, the code proposed in this work has been proven not only to be descriptive of all the phenomena observed, but also to be predictive of some peculiar features of the process. This result was achieved also thanks to the large sets of experimental data obtained during previous research activities within our group, which allowed the quantification of all the phenomena (the swelling and the erosion, the mass evolutions, the mass fraction profiles, the shape and size evolutions).

5. Conclusions

In this work the problem of the modeling of controlled drug release from matrices made of hydrogels and drugs was faced out and solved.

Cylindrical tablets were prepared by mixing and compressing powders of a model hydrogel (HPMC K15M) and a model drug (theophylline), in the ratio of 1:1. These matrices were subjected to hydration following two distinct protocols, allowing the water uptake and the drug release only by the lateral surface ("radial" tests) or by the full tablet surface ("overall" tests). At different times, the matrices were removed from the hydration bath and analyzed to obtain their size, shape and drug, water and polymer content. A rich set of experimental data was thus obtained for each kind of test.

In parallel, a model able to describe all the phenomena observed, i.e. the water uptake, the drug release, the matrices swelling and the matrices erosion was formulated. The corresponding code was written and solved, and the model calculations were successfully compared with the full set of experimental data for each kind of test. The model was found fully descriptive of the experimentally observed behavior.

The model, able to describe the full process of controlled drug release, could be a powerful tool in the design of novel matrices systems and in shortening the trial tests needed in designing and realizing novel formulations.

Appendix A. Parameter estimation

The parameters to be used in Eq. (4) to give the water and drug diffusivity were firstly given in Siepmann et al. (1999b) as $D_1^* = 5.6 \times 10^{-6}\ \mathrm{cm^2\ s^{-1}}$, $\beta_1 = 2.5$, $D_2^* = 6.3 \times 10^{-7}\ \mathrm{cm^2\ s^{-1}}$, $\beta_2 = 9.5$ (the values are for the same polymer, HPMC K15 M, but for a different drug, propranolol hydrochloride). In the present work, the diffusive coefficients, β_1 and β_2, were taken from the literature, while the critical diffusivities were used as free parameters in the optimization, starting from the literature values. The values of parameters used in the simulations are summarized in Table 1.

A.1. Estimation of k_{swe}

The mass of water within the matrix could be calculated by integrating the concentration profile over the full matrix volume, Ω (left hand side of Eq. (A1)), but it is also given (right hand side of Eq. (A1)) by the sum of initial mass of water, m_{10}, plus the time integral of the water mass rate due to the hydration, $\dot{m}_1$, and to the erosion, $\dot{m}_{1,eros}$ which is a negative contribution:

$$\int_{\Omega} \rho\omega_1 d\Omega = m_{10} + \int_0^t (\dot{m}_1 + \dot{m}_{1,eros})dt \tag{A1}$$

With the aim of an estimation of the swelling effects, the initial mass of water and the erosion phenomena could be neglected. The water mass rate could be evaluated as the integral, extended to the matrix surface Γ, of the water flux, which in turn is due to the diffusion and to the swelling (Eq. (7)). The right hand side of Eq. (A2) has been obtained considering that, according to Eq. (8), $j_{swe} = k_{swe} j_{diff}$:

$$\int_{\Omega} \rho\omega_1 d\Omega = \int_0^t \left(\int_{\Gamma} (j_{diff} + j_{swe}) d\Gamma \right) dt = (1 + k_{swe}) \int_0^t \left(\int_{\Gamma} j_{diff} d\Gamma \right) dt \tag{A2}$$

Under equilibrium conditions, Eq. (A2) gives:

$$\rho_{eq}\omega_{1,eq}\Omega_{eq} = (1 + k_{swe})I \tag{A3}$$

In which I is the last integral in the right hand side of Eq. (A2). Eq. (A3) could be written also under a limiting conditions, i.e. if the hydration does not cause any swelling ($k_{swe} = 0$, $\Omega_{eq} = \Omega_0$), and the ratio between this last with Eq. (A3) gives:

$$\frac{\rho_{eq}\omega_{1,eq}\Omega_{eq}}{\rho_{eq}\omega_{1,eq}\Omega_0} = \frac{(1 + k_{swe})I}{I} \Rightarrow k_{swe} = \frac{\Omega_{eq}}{\Omega_0} - 1 \tag{A4}$$

Therefore, a rough estimation of k_{swe} could be easily obtained subtracting one from the ratio between the fully hydrated matrix (which can be approximated by the volume of the matrix after a long immersion time) and the initial matrix volume.

A.2. Estimation of k_{eros}

Starting from Eq. (10), written locally in which n is the modulus of the vector normal to the surface

$$v_{eros} = \frac{dn}{dt} = -k_{eros} \tag{10}$$

Multiplying for $\rho_3 dA_{loc}$ and integrating over the external surface $\Gamma(t)$

$$\int_{\Gamma(t)} \rho_3 \frac{dn}{dt} dA_{loc} = -\int_{\Gamma(t)} k_{eros}\rho_3 dA_{loc} \tag{A5}$$

The left hand side of Eq. (A5) is the rate of change of polymer mass, m_3. The right hand side of Eq. (A5) can be integrated, giving an ODE which, with the initial value of polymer mass, m_{30}, describes the evolution of polymer mass within the matrix:

$$\begin{cases} \dfrac{dm_3}{dt} = -k_{eros}\rho_3 A_{tot} \\ m_3(t=0) = m_{30} \end{cases} \tag{A6}$$

Eq. (A6) can be easily integrated once the time evolution of total area, $A_{tot}(t)$, was provided (the experimental radius and semi-thickness were known and they were given in Fig. 7). Integration of Eq. (A6), and its comparison with experimental data of polymer mass, allows a straightforward estimation of the constant k_{eros}.

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