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Modeling the Drug Release from Hydrogel-Based Matrices

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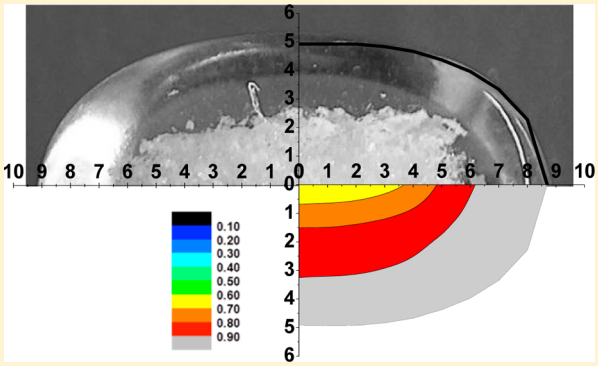
ABSTRACT: In this work the behavior of hydrogel-based matrices, the most widespread systems for oral controlled release of pharmaceuticals, has been mathematically described. In addition, the calculations of the model have been validated against a rich set of experimental data obtained working with tablets made of hydroxypropyl methylcellulose (a hydrogel) and theophylline (a model drug). The model takes into account water uptake, hydrogel swelling, drug release, and polymer erosion. The model was obtained as an improvement of a previous code, describing the diffusion in concentrated systems, and obtaining the erosion front (which is a moving boundary) from the polymer mass balance (in this way, the number of fitting parameters was also reduced by one). The proposed model was found able to describe all the observed phenomena, and then it can be considered a tool with predictive capabilities, useful in design and testing of new dosage systems based on hydrogels.



KEYWORDS: *hydrogels, swelling, controlled release, transport phenomena, modeling*

INTRODUCTION

Hydrogel-based matrices are the most common controlled release devices among all the solid oral dosage forms. Their success is mainly related to their simplicity of production, their low development costs, and their high adaptability to delivery of different kinds of active molecules. Despite their spread in practical applications, the drug release mechanisms resulting from these systems are rather complex, and, depending on the polymer carrier, several aspects have to be taken into account. One of the main important hydrophilic carrier materials is hydroxypropyl methylcellulose (HPMC), which shows a peculiar release mechanism where diffusion and tablet swelling both play important roles. Indeed when a dry HPMC-based tablet is immersed in a physiological fluid, the solvent starts to penetrate inside the polymer matrix. As soon as the solvent concentration exceed a threshold value, polymeric chains unfold so that a glass−rubbery transition occurs and a gel-like layer is formed.[1] The moving front at which this process takes place is called the "swelling front", which separates the swollen from nonswollen matrix.[2] In the swollen region the polymeric chains assume an elongated configuration that allows the contained drug molecules to easily diffuse toward the outer dissolution medium, once they are dissolved. Indeed depending on the drug solubility, in the swollen layer there could be a zone in which the drug coexists in the dissolved and dispersed forms.[3] The front that separates the swollen matrix, containing only dissolved drug, from the swollen part, containing both dissolved and dispersed drug, is called the "diffusion front". Additionally, on the zone at which the swollen matrix is in contact with the outer medium, a third front can be defined: the "erosion front". On this boundary the polymer network becomes extremely hydrated and a process like chain disentanglement takes place, "eroding" the matrix.[4]

Recently, several methods have been developed to study the main phenomena involved in the drug release from a hydrogel-based matrix. These approaches vary from the consideration of thermodynamic parameters of activation to discriminate between diffusion and relaxation control for the solvent penetration and the drug release processes[5] to the measurement of the swelling and erosion fronts[6] varying the dissolution time. In fact, the understanding of swelling kinetics and erosion behavior can help in the prediction of drug release mechanism and kinetics. Swelling progression and mobility of water molecules inside polymers have been investigated by several techniques, including magnetic resonance imaging (MRI), atomic force microscopy (AFM), texture analyzer, and ultrasound techniques, all of them summarized in ref 7.

Polymer erosion plays an important role in modulating drug release from hydrophilic matrices.[8] To calculate the degree and rate of polymer erosion, the amount of polymer that leaves the matrix and reaches the dissolution medium has to be quantified, taking into account that also different compositions of the same polymer can lead to different results.[9] This can be done using a gravimetric analysis, in which the masses of the matrix components are quantified, weighing the matrix before and after the dissolution,[10] or a phenol−sulfuric acid assay technique, in which the amount of polymer is determined

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after the sample preparation by spectrophotometric analysis.[11] To measure and study the swelling phenomenon, defining an elastic modulus or the force necessary to penetrate the sample provides a general way to compare sample behavior,[12] while oscillatory indentation experiments can be used as a technique for conducting small-scale rheological experiments, in order to measure the evolution of viscoelastic behavior of the gel layer as it swells.[13] The progress of water penetration and the water mass content into the hydrated gel can be evaluated by gravimetric technique, or by more complex techniques such as the use of texture analyzer[12] or MRI.[14] Each technique offers its own advantages which suit different study purposes.

In order to design tailored drug delivery systems based on hydrogels, the knowledge of the mechanisms that affect drug release during the dissolution process is needed. A substantial aid could be given from the mathematical modeling of physical phenomena. By mathematical approach the main features of the hydrogel dissolution could be clarified and, if the model has predictive properties, its use could help in the development and optimization of hydrogel formulation and production, sensibly reducing the time and costs required by purely experimental tests. Conscious of this, several researchers have tried to describe this peculiar process with different mathematical approaches, and most of them are summarized in the several reviews on the subject.[4,15,16]

The first modeling attempt can be traced back to the semiempirical model of Higuchi[17] in 1961 where the fractional drug release from an ointment (thin film) was related to the square root of the time. A generalization of the Higuchi equation was proposed by Peppas and co-workers in 1985[18] where the fractional drug release was related to the power "n" of the time, where the exponent "n" was an index, function of the kind of drug transport regime. For a thin film, with a values of n of 0.5, 1, or a value between them, the process was respectively described as a pure diffusion process (the same as Higuchi's), a swelling-controlled drug release (also known as case-II transport), or an intermediate behavior (also called anomalous transport). However, both of these models are based on very strict assumptions, among which are constant diffusion coefficients and negligible swelling, which for the HPMC are very far from real behavior. Therefore, these two models can give only a limited insight into the release mechanism and caution should be paid when they are applied to complex systems like the HPMC-based one. Since then, several mathematical models were proposed with increasing complexities, starting from monodimensional problems, including the swelling of the system and diffusivity function of the hydration level.

A milestone in drug release modeling is represented by the works of Siepmann et al.[19−21] in which a 3D model, accounting for drug release from a swelling HPMC matrix, including erosion phenomena, was developed. The so-called "sequential layer" model was able to describe the drug release and water uptake through Fick's second law in dilute systems with "Fujita-type"[22] diffusion coefficients, whereas the polymer mass was obtained from a macroscopic balance with a constant dissolution rate. However, the model was based on the hypothesis of affine deformations, therefore the initial cylindrical shape was maintained during the dissolution process whereas the volume was able to increase according to the amount of substances transported through the system.

The assumption of affine deformations was first implemented in a general code,[23] and then removed by Lamberti et al.[24] considering the swelling as driven by the water flux. In particular it was considered that part of the total inlet water flux was responsible for the tablet swelling whereas the rest was responsible for the inner layer hydration. This, with the introduction of an additional parameter, namely, the swelling constant "k_{swe}", allowed a local swelling velocity to be obtained on the erosion front that, coupled with an ALE (arbitrary Lagrangian−Eulerian) moving mesh method, was used to describe the observed swelling behavior along with the drug release. The evolution of the polymer mass, similarly to Siepmann's model, was derived from a macroscopic balance. However, with this approach the system was not constrained in terms of mass fractions, possibly leading to unrealistic results in some domain points.

Kaunisto et al.[25] analyzed the behavior of an HPMC matrix loaded with a poorly soluble drug, under the assumption of constant density, coupling the polymer mass description with the transport equations for drug and water through the mass fraction constraint. The transport equations were based on a simplified version of the generalized Fick equation[26] where the driving force was the species gradient concentration. Despite the elegant approach, all the multicomponent interactions, except those with the solvent, were assumed to be zero and the multicomponent Fick diffusivities were interpreted as "pseudo-binary". For the water−polymer diffusivity a "Fujita-type" form was used. Even in this case, like in Lamberti's model, the swelling was described through an ALE moving mesh method, but the swelling velocity was derived from a polymer/solid drug mass balance on the erosion boundaries.

The diffusion in concentrated systems, the local polymer mass balance, the deformed mesh analysis, and the reduction of fitting parameters are thus the unfulfilled goals of the state-of-the-art literature models. Therefore, the aim of this work is to develop a mathematical model able to predict the behavior of the hydrogel-based delivery systems on the basis of all the previously mentioned considerations. The final scope is to obtain a model (and the related calculation code), able to *describe* the observed behavior of hydrogel-based systems, which can evolve into a model able to *predict* the expected behavior of new hydrogel-based pharmaceutical systems.

MATERIALS AND METHODS

Materials. Powders of hydroxypropyl methylcellulose (HPMC, Methocel K15M, kindly supplied by Colorcon, Varese, Italy) and theophylline (TP, CAS number 58-55-9, Sigma-Aldrich, Milan, Italy) were used to produce the tablets. Distilled water was used as dissolution medium.

Methods. *Matrix Preparation and Dissolution Tests.* HPMC and TP powders were mixed (50% TP/HPMC wt/wt) and compressed in cylindrical tablets (radius 6.5 mm and thickness about 2 mm, weight of 350 ± 5 mg) using a tableting machine (Specac PN3000, equipped with flat-faced punches, diameter 13 mm, and with a Carver Press), applying a loading force of 50 kN, kept for 5 min.

To perform the dissolution tests, a conventional USP Apparatus II (AT7 Smart by Sotax) was used. The tablets were immersed in a bath containing 900 mL of distilled water kept at 37 °C. To avoid the sticking of the tablets on the bottom of the vessel, a homemade sample holder was used, consisting of a wire basket with a large mesh size. The basket was conceived to have size (both diameter and height) larger than the size of a swollen tablet. A system of metal weights was provided to guarantee the stability of the holder at the bottom

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of the vessel and to ensure the reproducibility of the fluid dynamic conditions. In these tests, hydration, erosion, and drug release are thus allowed through the full tablet surface. After predetermined immersion times, the basket was withdrawn from the bath and the tablets carefully removed to perform the tests described below. Each test was performed in triplicate, and experimental results were thus expressed as mean values with standard deviation (SD).

Swollen Matrix Characterization. To evaluate the total amount (in mass) of the three components (drug, polymer, and water) present in the tablet after different stages of hydration, each partially swollen tablet was removed from the basket, weighed, and dried in an oven at 105 °C until a constant weight was reached to ensure the total evaporation of water. Then, the dried tablet was weighed again and, comparing the weight before and after the drying, the uptake of water during the dissolution was obtained. After that, the dried tablet was completely dissolved, to determine the drug content by spectrophotometric assay. In this way, the residual amount of drug was quantified. The residual polymer mass was easily obtained knowing the total weight after the hydration and the drug and water masses. Repeating these analyses for several hydration times, the drug, the polymer, and the water mass evolution inside the tablet, function of the hydration time, have been obtained.

To evaluate the size of the tablet during the hydration stages, an image analysis technique was applied. Once the basket was withdrawn from the bath, the tablet was carefully removed and an overhead photo was taken; from this image the diameter of the swollen tablet was measured. Similarly, to measure the thickness and evaluate the shape of the hydrated matrix, after each immersion time, the tablet was photographed from the side.

To obtain the mass fractions of the three components inside the hydrated matrix, a technique previously developed was applied.[10,27] Briefly, once the tablet was recovered from the dissolution medium, it was cut using a cylindrical hollow punch centered in the center of the tablet. The gel layer external to the punch wall was carefully recovered and quantitatively transferred to a glass holder. The cutting procedures were repeated by using punches of decreasing radius, obtaining several annuli and a central core, which could not be further cut. Each single annulus and the central core were placed on a different glass holder. All the samples were dried in an oven at 105 °C until they reached a constant weight. Thus, the amount of water in each sample was obtained. The dried tablet sections were completely dissolved, to allow the determination of the drug content and thus the determination of the polymer fraction. For different immersion times, the mass fractions were obtained as a function of time. Therefore, the technique described allows one to obtain the evolutions of the mass fractions, averaged along the thickness direction, as a function of both the time and the radial direction. All the runs were performed in triplicate, and experimental results were thus expressed as mean values with standard deviation (SD).

Analytical Methods. To evaluate the drug content, both in the residual tablet after the dissolution time and in each punched section after the gravimetric analysis, each dried sample was fully dissolved in 500 mL of distilled water, and the TP contents were assayed by a UV−visible spectrometer (Lambda 25 by PerkinElmer) using quartz cuvettes with optical path length of 10 mm, at λ = 275 nm. The water solution of theophylline follows the Lambert and Beer law (the value of the absorbance was found to increase proportionally with the concentration of drug: $A = kc$, for concentrations up to 20 mg/L). The constant of proportionality value, after a calibration procedure, was found to be k = 0.0764 L/mg. The solution samplings showing an absorbance value outside the calibration range were diluted, and for the evaluation of the mass this dilution was taken into account.

MODELING

The computational domain was built, due to the symmetry, as a quarter of the whole tablet, represented by a rectangle in the 2D-axial symmetric configuration (Figure 1). The initial radius

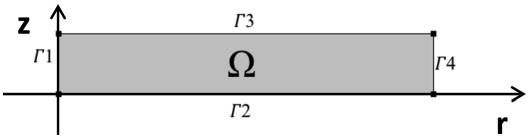

Figure 1. Computational domain representing a quarter of the tablet in 2D-axial symmetric geometry.

was fixed to 6.5 mm (experimental data), and the semithickness was measured for each tablet (it is roughly equal to 1 mm). In Figure 1 it is possible to distinguish the external boundaries Γ3 and Γ4 that represent the zone at which the tablet gets in contact with the dissolution medium (erosion front) and the internal boundaries Γ1 and Γ2 that characterize the internal symmetry regions.

The system under investigation is made by three components: water (i = 1), drug (i = 2), and polymer (i = 3). Initially the tablet is completely dry, being formed by drug and polymer perfectly mixed and pressed. As the time passes, the water penetrates inside the tablet, generating the swelling of the polymeric network, the drug release, and the matrix erosion. All these phenomena have been described through the transport equations treated in the next paragraphs with the following assumptions:

i. There is no volume change upon mixing (ΔV_{mix} = 0, ideal thermodynamic behavior).
ii. The drug dissolution within the matrix is fast compared to drug diffusion.
iii. Perfect sink conditions for drug and constant critical solvent concentration on the erosion front are maintained.
iv. There is negligible mass average velocity (convection) contribution to the species transport.
v. The relocation of the polymer due to the water inlet and drug outlet generate the tablet swelling and shape variation without contributing to the polymer release.
vi. The erosion mechanism is a function of the external fluid dynamics and of physicochemical interactions between tablet and external fluid that remain the same during the dissolution tests.

Transport Equations. The water and drug transport inside the system was considered as a pseudodiffusion phenomenon. Starting from the equation of continuity for the ith components or species:[26]

$$\frac{\partial \rho_i}{\partial t} = -(\nabla \cdot \rho_i \mathbf{v}) - (\nabla \cdot \mathbf{J}_i) + r_i \quad (1)$$

Considering that $\rho_i = \rho\omega_i$ and the equation of continuity for a multicomponent mixture,[26] eq 1 can be rewritten as

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$$\rho\frac{\partial\omega_i}{\partial t} = -\rho\mathbf{v}\cdot\nabla\omega_i - (\nabla\cdot\mathbf{J}_i) + r_i \tag{2}$$

In the system described, there is no chemical reaction ($r_i = 0$) and the diffusion-induced convection contribution to the species transport is not considered ($\rho\mathbf{v}\cdot\nabla\omega_i = 0$), as reported in most of the literature.[21,24,25] This last hypothesis was shown to be reasonably true when the apparent species densities are similar in magnitude and when the mixture can be considered ideal (therefore the volume change on mixing is negligible).[28] Therefore, eq 2 becomes

$$\rho\frac{\partial\omega_i}{\partial t} = -(\nabla\cdot\mathbf{J}_i) \tag{3}$$

Considering a diffusive flux in concentrate systems, $\mathbf{J}_i$ can be expressed as

$$\mathbf{J}_i = -\left(\rho D_i\nabla\omega_i + \rho D_i\omega_i\frac{\nabla M}{M}\right) \tag{4}$$

where $M = (\sum_i(\omega_i/M_i))^{-1}$ is the average molar mass. To the best of our knowledge, no one considered the species molar masses in previous models, despite that the derivation from Fick's first law for dilute systems, where the driving force is the molar fraction, to concentrated systems, where the driving force is the mass fraction, is quite straightforward and leads to the appearance of molar mass terms.[29] D_i are the pseudodiffusion coefficients, described in the next paragraph. Using eq 4 the transport equations (eq 3) for water and drug can be rewritten as

$$\rho\frac{\partial\omega_i}{\partial t} = \nabla\cdot\left(\rho D_i\nabla\omega_i + \rho D_i\omega_i\frac{\nabla M}{M}\right) \quad i = 1, 2 \tag{5}$$

whereas the polymer mass fraction can be obtained from the mass fraction constraints:

$$\omega_3 = 1 - \omega_1 - \omega_2 \tag{6}$$

This step is an improvement with respect to Siepmann et al.[21] and Lamberti et al.,[24] where the constraints on the mass fractions were not used, leading to a weak or null control on the polymer mass fraction. To solve eqs 5 proper initial and boundaries conditions have been applied.

With the initial condition, the initial mass fractions have been specified, mathematically:

$$@t = 0 \quad \forall\,\mathbf{x}\in\Omega \quad \omega_i(t = 0, \mathbf{x}) = \omega_{i,0} \tag{7}$$

With the boundary conditions, instead, the behavior of the system at the edges has been described:

$$\begin{aligned}
&@\mathbf{x}\in\Gamma3 \quad \forall\, t > 0 \quad \omega_i(\mathrm{t} > 0, \mathbf{x}\in\Gamma(t)) = \omega_{i,\mathrm{eq}}\\
&@\mathbf{x}\in\Gamma4 \quad \forall\, t > 0 \quad \omega_i(\mathrm{t} > 0, \mathbf{x}\in\Gamma(t)) = \omega_{i,\mathrm{eq}}\\
&@\mathbf{x}\in\Gamma1 \quad \forall\, t > 0 \quad \mathbf{J}_i = 0...\\
&@\mathbf{x}\in\Gamma2 \quad \forall\, t > 0 \quad \mathbf{J}_i = 0...
\end{aligned} \tag{8}$$

On Γ3 and Γ4 the mass fractions of drug and water have been imposed.[21,24,25] For the drug the perfect sink conditions have been applied, meaning that all the resistance to the drug transport is concentrated within the matrix and it is negligible in the outer medium. The validity of this hypothesis was also confirmed experimentally by measurement of the drug concentration in the swollen layer.[10] For the solvent, instead, a critical polymer/solvent concentration was used, therefore assuming that, as soon as the tablet gets in contact with the dissolution medium, the water concentration in an infinitesimal layer close to the erosion front reaches and maintains the maximum hydration value. Even this hypothesis was confirmed by experiments.[30]

Constitutive Equations. *Diffusion Coefficients.* The pseudodiffusion coefficients, D_i (for i = 1, 2), have been described with a "Fujita-type" equation. This approach, based on the free volume concept,[22,31−33] has been intensively utilized in the literature to describe HPMC-based systems during diffusion−swelling processes.[19−21,24,25,34,35] In this manner it has been possible to consider low diffusivity values in the dry matrix core and increasing values along with the water concentration:

$$D_i = D_{i,\mathrm{eq}}\exp\left[-\beta_i\left(1 - \frac{\omega_1}{\omega_{1,\mathrm{eq}}}\right)\right] \tag{9}$$

where $D_{i,\mathrm{eq}}/\exp(\beta_i)$ are the values of the effective pseudodiffusion coefficients in the dry matrix ($\omega_1 = 0$), and $D_{i,\mathrm{eq}}$ are the values of the effective pseudodiffusion coefficients in the fully swollen matrix ($\omega_1 = \omega_{1,\mathrm{eq}}$).

System Density. The density of the partially hydrated matrix was calculated considering ideal mixing rule, which has been written for the specific volume:

$$\frac{1}{\rho} = \frac{\omega_1}{\rho_1} + \frac{\omega_2}{\rho_2} + \frac{\omega_3}{\rho_3} \tag{10}$$

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

Modeling of the Swelling and the Erosion. In modeling drug release from HPMC tablets, the swelling phenomenon has to be considered. Indeed this mechanism, increasing the length of diffusion pathways and changing the matrix morphology (mobility), greatly contributes to the final drug release kinetics.[4] On the other hand, the surface erosion has to be included as well, since this mechanism accounts for the polymer release, mainly due to disentanglements, leading to matrix shape modifications and in turn to modified drug release behavior.

Both these mechanisms can be mathematically translated in a deformable domain, therefore Ω in Figure 1 is treated as Ω(t). In this work the ALE (arbitrary Lagrangian−Eulerian) method has been applied to describe the tablet/domain deformation: $\Omega(t) = \{(r(R,Z,t), z(R,Z,t))|_{(R,Z)\epsilon\Omega_0}\}$. Briefly with "$R$" and "$Z$" are indicated the reference coordinate of the mesh/material frame (mesh and material frame are identical in this application), fixed to their original position, and with "r" and "z" are specified the spatial coordinates of the spatial frame in which all the previous equations have been defined. The domain deformation has been modeled considering that the domain is freely deformable and the deformation is driven by the movements of the boundaries Γ3 and Γ4. The relocation of the internal mesh nodes has been obtained accordingly to Laplace smoothing equations:[36,37]

$$\begin{aligned}
&\frac{\partial^2}{\partial R^2}\left(\frac{\partial r}{\partial t}\right) + \frac{\partial^2}{\partial Z^2}\left(\frac{\partial r}{\partial t}\right) = 0\\
&\frac{\partial^2}{\partial R^2}\left(\frac{\partial z}{\partial t}\right) + \frac{\partial^2}{\partial Z^2}\left(\frac{\partial z}{\partial t}\right) = 0
\end{aligned} \tag{11}$$

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It is worth specifying that the mesh convection induced by eqs 11 does not have any physical meaning in the current model. Equations 11 have been solved with the initial condition

$$@t = 0 \quad (r(R, Z, t), z(R, Z, t)) = (R, Z) = (r_0, z_0) \tag{12}$$

and with the following boundary conditions:

$$@x\epsilon\Gamma 3 \quad \forall\, t > 0 \quad \frac{\partial z}{\partial t} = (\mathbf{v}_{swe} + \mathbf{v}_{er})\Big|_z$$

$$@x\epsilon\Gamma 4 \quad \forall\, t > 0 \quad \frac{\partial r}{\partial t} = (\mathbf{v}_{swe} + \mathbf{v}_{er})\Big|_r$$

$$@x\epsilon\Gamma 1 \quad \forall\, t > 0 \quad dr = 0...$$

$$@x\epsilon\Gamma 2 \quad \forall\, t > 0 \quad dz = 0... \tag{13}$$

where $\mathbf{v}_{swe}$ and $\mathbf{v}_{er}$ are the swelling (directed outside of the matrix) and erosion (directed inside of the matrix) velocities, respectively, derived from the following considerations.

Swelling and Erosion Velocities. The swelling velocity has been derived through a polymer mass balance on the erosion front. It has been considered that the polymer movement generated, due to the water inlet and drug outlet, contributes only to the swelling phenomenon, without resulting in a polymer release. Therefore, the polymer flux reaching the erosion front goes to increase the outer layer dimension, without being released (Figure 2). Mathematically:

$$\mathbf{J}_3 A = \rho\omega_3 A \frac{d\mathbf{x}}{dt} \tag{14}$$

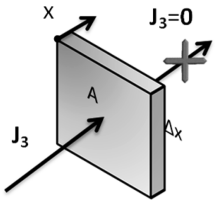

Figure 2. Polymer flux on a differential surface element on the erosion boundary.

Therefore:

$$\mathbf{v}_{swe} = \frac{d\mathbf{x}}{dt} = \frac{\mathbf{J}_3}{\rho\omega_3} = -\frac{(\mathbf{J}_1 + \mathbf{J}_2)}{\rho\omega_3} \tag{15}$$

where the definition $\sum \mathbf{J}_i = 0$ has been applied. This swelling formulation is different from the theoretical hypothesis in which the swelling occurs on the swelling front causing the movement of the hydrated external layer (the ones between the swelling and erosion fronts) toward the external environment. However, it has been equally able to capture all the features of the system, not requiring any fitting parameter.

The erosion phenomenon is related to the system fluid dynamics and to physicochemical interaction between the tablet interface and the outer medium. If these features are constant during the dissolution process and uniform around the swelling matrices, the erosion velocity can be accounted for using a constant value (which is a fitting parameter):

$$|\mathbf{v}_{er}| = -k_{er} \tag{16}$$

Code Solving. The previous partial differential equations (PDEs), along with all the initial and boundary conditions, have been solved with the finite element methods (FEM) using the commercial software COMSOL Multiphysics 4.3b. The development and the implementation of the simulations have been carried out using a workstation based on the processor Intel Core i7-4820K with a clock rate of 3.7 GHz and a RAM of 64 GB.

RESULTS AND DISCUSSION

The section has been divided into "whole-matrix" and "distributed" results to emphasize the model ability to describe aspects related to the whole matrix (macroscopic), like global drug release, as well as distributed (microscopic) aspects, like the mass fraction profiles inside the tablet. All the model parameters are reported Table 1. Some of them have been obtained by direct measurements, some others have been estimated from previous works, and a few of them have been used as fitting parameters, starting from literature values and optimizing the model prediction on the experimental data. In particular the transport parameters and the erosion constant ($D_{1,eq}$, $D_{2,eq}$, β_1, β_2, k_{er}) were optimized against the macroscopic results: water, drug, and polymer masses in the tablet during the dissolution process. The initial guess values for the diffusivities in the fully swollen layers have been the self-diffusion coefficient of water in water (3.027×10^{-9} (m^2/s) @ 37 °C[38]) for $D_{1,eq}$ and the diffusion coefficient of theophylline in water (8.21×10^{-10} (m^2/s) @37 °C[39]) for $D_{2,eq}$. In both cases the best fitting parameters assumed smaller values than the guessed one, but keeping the same order of magnitude. This seems to agree with the fact that the diffusion in the fully swollen region is somewhat limited by the presence of polymer chains ($3\%_{w/w}$). However, in a swelling hydrogel system the variables that could affect the species transport are several:

Table 1. Values of the Parameters Used in the Simulations

	From Experiments/Literature	
m_{10}	initial water mass (mg)	0
m_{20}	initial drug mass (mg)	160.35
m_{30}	initial polymer mass (mg)	177.42
r_0	initial tablet radius (mm)	6.5
z_0	initial tablet semithickness (mm)	1
ω_{10}	initial water mass fraction	0
ω_{20}	initial drug mass fraction	0.475
ω_{30}	initial polymer mass fraction	0.525
ρ_1	water density (kg/m^3)	1000
ρ_2	drug density (kg/m^3)	1200
ρ_3	polymer density (kg/m^3)	1200
M_1	water molecular weight (g/mol)	18
M_2	drug molecular weight (g/mol)	180.16
M_3	polymer molecular weight (g/mol)	120000
	From Experiments/Hypotheses	
$\omega_{1,eq}$	equilibrium water mass fraction	0.97
$\omega_{2,eq}$	equilibrium drug mass fraction	0
	From Literature/Optimization	
$D_{1,eq}$	water effective diffusivity in the fully swollen matrix (m^2/s)	2.2×10^{-9}
$D_{2,eq}$	drug effective diffusivity in the fully swollen matrix (m^2/s)	1×10^{-10}
β_1	water Fujita-type equation coefficient	5
β_2	drug Fujita-type equation coefficient	4
k_{er}	erosion constant (m/s)	55×10^{-9}

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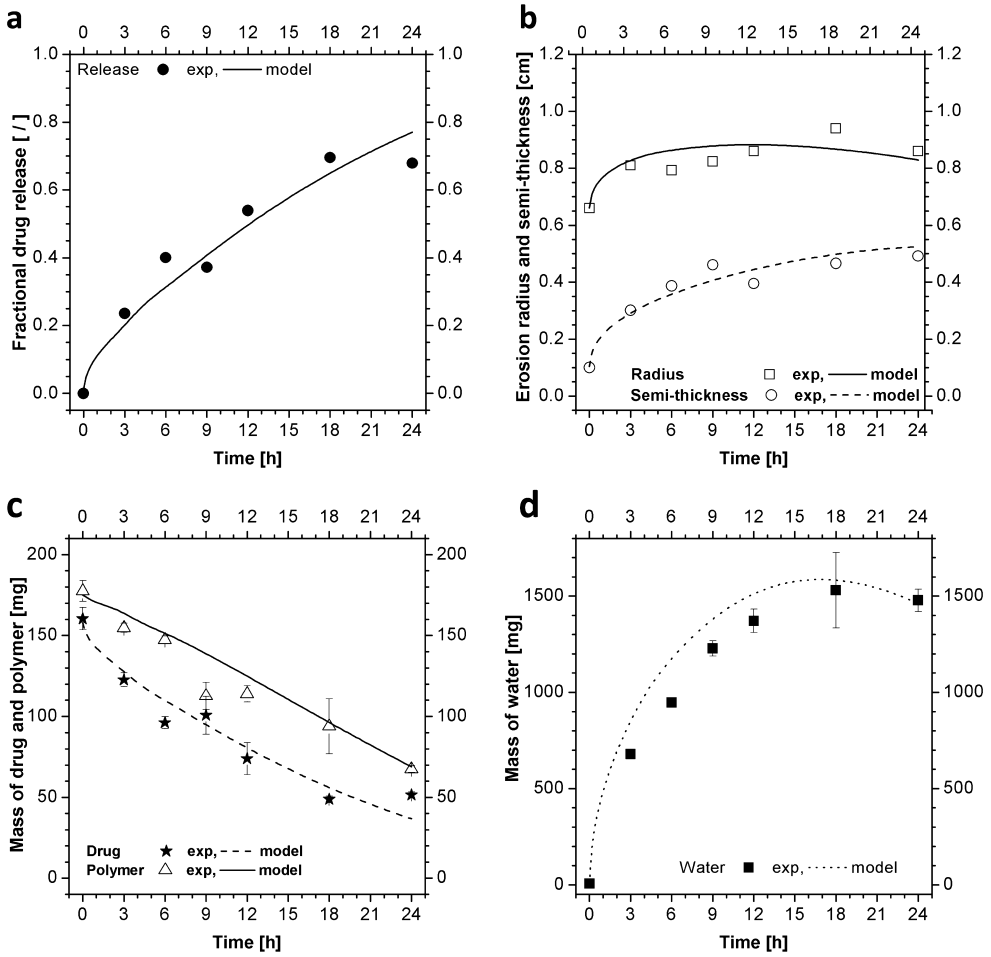

Figure 3. Comparison between experimental and calculated results in terms of fractional drug release (a), erosion radius and semithickness (b), mass of drug and polymer (c), and water (d) inside the tablet at different dissolution times.

presence of concentration gradients, polymer relaxation,[40] ionic species, and so on. That is why, in this work, the simplest expressions for the diffusive fluxes (Fick's first law, eq 4) modified with Fujita-type diffusivities (eq 9) have been chosen. In this manner a robust, but still simple, model has been built, leaving with the fitting parameters the necessary flexibility to deal with these complicated systems.

It has to be specified that each of these fitting parameters affects more than one model outcome and therefore they are not completely independent. For example "k_{er}" is the only parameter responsible for polymer erosion, but it has a direct impact on the tablet size and shape. In the same manner the diffusion coefficients, tuned on the mass of drug and water, influence the tablet shape and the internal mass fraction profiles. Therefore, only the right combination of these parameters can be able to describe the whole system.

Whole-Matrix Results. In Figure 3 are reported the experimental results referred to the whole matrix, from Lamberti et al.,[24] compared with the modeling results obtained in this work. The experimental fractional drug release (Figure 3a), apart from the first instants, resembles a zero order release kinetic, releasing the drug at a constant rate. As it can be seen, the modeling results, derived indirectly from the current drug mass inside the tablet, perfectly describe this release behavior.

In Figure 3b the erosion radius and semithickness are shown, that correspond experimentally and from modeling point of view to the point on $\Gamma 4$ at $z = 0$ and on $\Gamma 3$ at $r = 0$, respectively (Figure 1). Even in this case the model is able to describe the "macroscopic" nonaffine swelling. Indeed one of the strong points of this model is the possibility to describe tablet deformation different from the limiting assumption of affine swelling (like in Siepmann et al.[21]). It can be seen that whereas the semithickness still increases within the time analyzed, the radius starts to decrease. This can be explained considering that the water inlet driving force became smaller in the radial than in the axial direction, mainly due to a longer pathway generated by a thicker gel layer, letting the erosion take over.

In Figure 3c and Figure 3d the drug and polymer masses, as well as the water mass inside the tablet vs time, are respectively represented. Experimentally the masses have been determined following the procedures outlined in Methods, while the modeling results have been obtained integrating the mass concentrations of the ith species ($\rho\omega_i$) on the deformed domain:

$$m_i(t) = 2 \times \int_{\Omega(t)} \rho\omega_i \, d\Omega \tag{17}$$

The model has been found able to correctly describe the evolution of the mass species, inside the tablet, during the dissolution process.

Distributed Results. The model so formulated allows to be known in each point of the domain the mass fractions of water, drug, and polymer. Therefore, it is able to describe a microscopic aspect like the species distribution inside the

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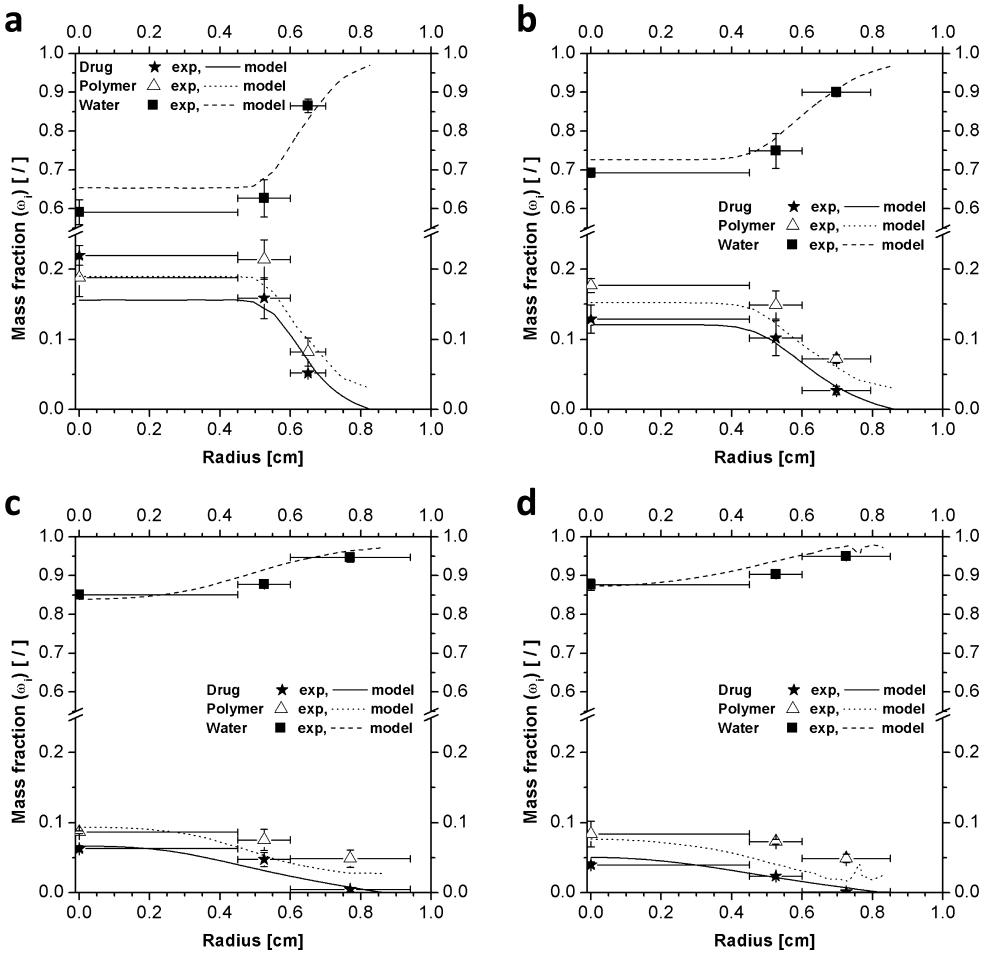

Figure 4. Comparison between experimental and calculated results in terms of mass fraction (averaged along the thickness direction) profiles along the radial direction. Dissolution times of 3 h (a), 6 h (b), 18 h (c), 24 h (d).

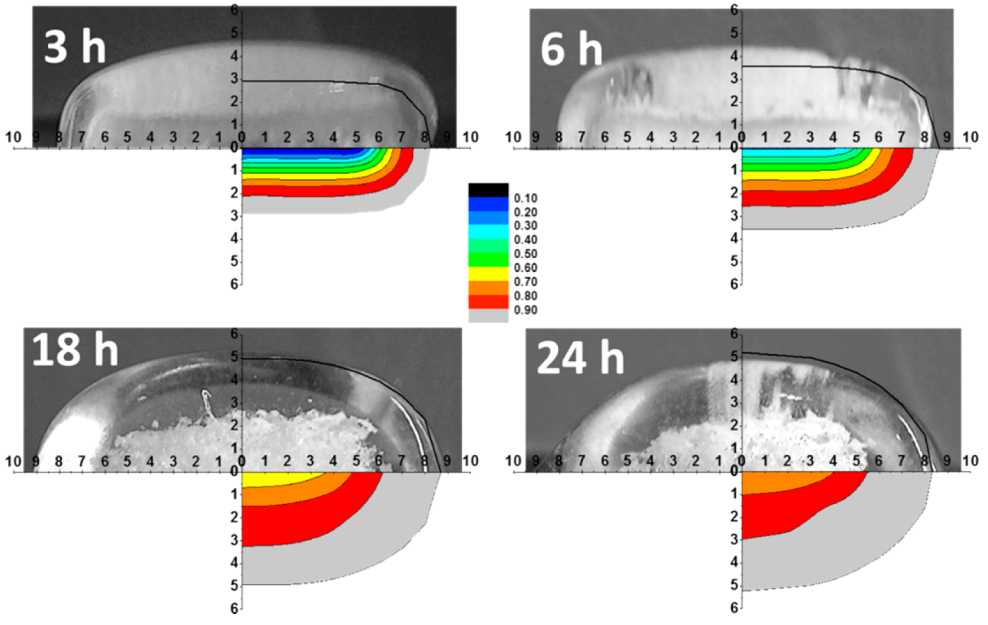

Figure 5. Comparison between experimental and modeling results. In the top part of each graph: photos, and calculated shape of the swollen matrix as a black line. In the bottom right part of each graph: calculated water mass fraction as contour plot. All the spatial sizes are in mm; color scale is referred to water content fraction (black = dry matrix; light gray = fully hydrated matrix).

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swollen tablet or, defining a solvent concentration threshold value for the glass−rubber transition, it would able to describe the matrix core position and its movements.

In Figure 4 the experimental and calculated mass fraction (averaged along the thickness direction) profiles inside the tablet are compared.

The experimental results have been obtained in this work with the "hollow punch" procedure described in Method. The horizontal bars in Figure 4 represent the radius of the tablet pieces (annulus or core) analyzed. To compare the experimental values with the calculated results, a mass fraction value averaged along the thickness direction, z, has to be defined:

$$\langle \omega_i \rangle(r) = \frac{\int_0^{H(r)} \omega_i \, dz}{\int_0^{H(r)} dz} \tag{18}$$

These are average mass fractions along the axial direction, as a function of the radial position. As it can be seen in Figure 4 the calculated profiles describe well the experimental data, confirming the model ability to reproduce the system behavior.

Other microscopic comparisons are shown in Figure 5. Tablet pictures (top part) are compared with the calculated water mass fraction contour plots (bottom right part) and with the calculated swollen tablet shapes (the black lines in the top right part). In the graphs showing the tablet after 3 and 6 h of dissolution the reader should follow the bright reflection to individuate the right swollen tablet profile since the pictures include, due to inclination of the photos, a piece of the tablet's top part. The modeling results even in this case seem to nicely describe the experimental results. The shape profiles close resemble the experimental one and, just qualitatively on the basis of the data available, the contours of the water mass fraction seem to describe well the tablet hydration levels.

CONCLUSIONS

In this work a new mathematical approach for the description of drug release from hydrogel-based matrices has been proposed.

The model has been validated against the behavior of HPMC tablets loaded with theophylline in the weight ratio 1:1. These matrices have been subjected to hydration in a USP Apparatus II, allowing all the tablet surfaces to get in contact with the dissolution medium. Experimental results in terms of swollen tablet dimensions, water, drug, and polymer masses have been taken from the "overall" tests of Lamberti et al.,[24] where the same system and the same dissolution conditions were used. To enlarge the collection of experimental data, the average mass fraction profiles inside the hydrated matrices—as radius functions—have been obtained during this work, partitioning and analyzing the pieces of the swollen tablets. In this manner a wide set of experimental data have been gathered, in order to validate the proposed model. This last has been formulated as balance and transport equations coupled with a deforming domain through the ALE method. In this way the water uptake, the drug release, and the polymer erosion along with the swelling phenomenon have been considered. In particular the use of Fickian flux equations in concentrated systems that accounts for the species molar masses, and modified with "Fujita-type" diffusivities, has been proved to be able to describe the pseudodiffusion processes involving water, drug, and polymer in the deforming system. Albeit the previous version of the model[24] was already able to describe nicely the experimental data, the use of flux equation in concentrated systems (eq 4), and the novel formulation for the swelling velocity (eq 15), constitute the specific innovations which have made the model presented here better than its previous version, also allowing reduction of the number of fitting parameters (since in the present version there is no need of a "swelling constant" to be determined, used as an adjustable parameter). In conjunction the use of the ALE moving mesh method coupled with a polymer mass balance on the erosion front has allowed, with no additional parameters, satisfying results to be obtained in the prediction of the hydrate tablet shape and size. This has avoided the need for dealing with the mathematics and the complicated assumptions regarding the swelling mechanics that, normally, is not of interest in the controlled drug release field.

Therefore, the experimental procedures have been shown to be able to characterize the hydrogel-based controlled delivery system in terms of macroscopic as well as microscopic aspects. On the other hand, the model has been proved to be able to capture all the features involved in the drug release mechanism. Further studies will be devoted to the generalization of the fitting parameters, a necessary step to obtain a predictive model usable in the design of hydrogel-based delivery systems, shortening the expensive trial-and-error procedure needed.

APPENDIX A. FICK'S LAW APPROXIMATION IN CONCENTRATE SYSTEMS

In this appendix the mathematical derivation of the diffusive flux in concentrated systems used in eq 4 will be illustrated.

Assuming a molecular diffusion mass flux governed by a Fick's law type expression:[29]

$$\mathbf{J}_i = -\frac{\rho_i}{x_i} D_i \nabla x_i \tag{A.1}$$

That can be expressed in terms of mass fraction gradient considering that[26] $x_i = \omega_i M / M_i$

$$\mathbf{J}_i = -\frac{\rho \omega_i}{\frac{\omega_i M}{M_i}} D_i \nabla \left(\frac{\omega_i M}{M_i} \right) \tag{A.2}$$

Being M_i constant and simplifying:

$$\mathbf{J}_i = -\frac{\rho}{M} D_i \nabla (\omega_i M) \tag{A.3}$$

When M is not considered as a constant, eq A.3 evolves in eq 4.

$$\mathbf{J}_i = -\left(\rho D_i \nabla \omega_i + \rho D_i \omega_i \frac{\nabla M}{M} \right) \tag{4}$$

This expression has been employed to describe the diffusive mass fluxes in the present model.

In order to evaluate the relative importance of the two terms on the right-hand side of eq 4, the ratio between the diffusive term and the term due to the change in mixture molecular weight has to be estimated:

$$\left| \frac{(\nabla \omega_i)/\omega_i}{(\nabla M)/M} \right| \cong \left| \frac{\frac{\omega_{i,0} - \omega_{i,eq}}{(\omega_{i,0} + \omega_{i,eq})/2} \frac{1}{L_{ch}}}{\frac{M_0 - M_{eq}}{(M_0 + M_{eq})/2} \frac{1}{L_{ch}}} \right| \tag{A.4}$$

In the right-hand side of eq A.4, the gradients have been approximated by a finite difference between the initial and

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equilibrium value of each variable (which is the maximum value allowed to the gradient), L_{ch} being a characteristic length of the system; and the values out of the gradient have been approximated with the average between the initial and equilibrium values. Since, for each quantity involved, the initial and the equilibrium values are really different from each other (for example: $\omega_{1,0} = 0$ and $\omega_{1,eq} = 0.97$; M_0 is of the order of the polymer molecular weight, M_{eq} is of the order of water molecular weight), the ratio given by eq A.4 is close to unity:

$$\left|\frac{\frac{\omega_{1,0}-\omega_{1,eq}}{(\omega_{1,0}+\omega_{1,eq})/2}\frac{1}{L_{ch}}}{\frac{M_0-M_{eq}}{(M_0+M_{eq})/2}\frac{1}{L_{ch}}}\right| = \left|\frac{\frac{\omega_{1,0}-\omega_{1,eq}}{\omega_{1,0}+\omega_{1,eq}}}{\frac{M_0-M_{eq}}{M_0+M_{eq}}}\right| \cong \left|\frac{\frac{-\omega_{1,eq}}{\omega_{1,eq}}}{\frac{M_0}{M_0}}\right| = 1 \tag{A.4}$$

Therefore, both the terms in eq 4 have similar importance.

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Notes

The authors declare no competing financial interest.

Chemical compounds: hydroxypropyl methylcellulose, HPMC (PubChem CID: 57503849); theophylline (PubChem CID: 2153).

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NOMENCLATURE

A, infinitesimal surface (m^2); D_i, pseudodiffusion coefficient (m^2/s); $D_{i,eq}$, effective diffusion coefficient of the ith species in the fully swollen matrix (m^2/s); dr, radial displacement (m); dz, axial displacement (m); $H(r)$, tablet semithickness, function of the radial position, during the dissolution process (m); $\mathbf{J}_i$, diffusive mass flux of the ith species [kg/(m^2 s)]; k_{er}, erosion constant (m/s); M, average molar mass (g/mol); M_i, molar mass of the ith species (g/mol); R, reference radial coordinate of the mesh/material frame (m); r, radial coordinate of the spatial frame (m); r_0, initial tablet radius (m); r_i, source term of the ith species [kg/(m^3 s)]; t, time (s); $\mathbf{v}$, mass average velocity (m/s); $\mathbf{v}_{er}$, erosion velocity (m/s); $\mathbf{v}_{swe}$, swelling velocity (m/s); x_i, mole fraction of the ith species; Z, reference axial coordinate of the mesh/material frame (m); z, axial coordinate of the spatial frame (m); z_0, initial tablet semithickness (m); β_i, Fujita-type equation concentration dependence parameter of the ith species; Γ_i, ith boundaries (m); ρ, system density (kg/m^3); ρ_i, density of the ith species (kg/m^3); Ω, computational domain (m^2); ω_i, mass fraction of the ith species; $\omega_{i,0}$, initial mass fraction of the ith species; $\omega_{i,eq}$, equilibrium mass fraction of the ith species; $\langle\omega_i\rangle(r)$, average mass fraction on the axial direction function of the radial position

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