Hydrogels are materials largely used in the formulation of pharmaceuticals since, in principle, they could produce a release system of zero-order kinetics, which is of great therapeutic interest.

In this paper, a model was proposed for the description of the main transport phenomena involved in the drug release process from hydrogel matrices (water diffusion, polymer swelling, drug diffusion and polymer dissolution); the model predictions are successfully compared with a large set of experimental data, obtained working with matrices systems based on HPMC (Hydroxy Propyl Methyl Cellulose).

The proposed model was found able to reproduce main features of the observed phenomena, it can thus be adopted for prediction of the performances of drug release systems from hydrogel matrices.

Key words: Hydrogels, transport phenomena, diffusion, polymer dissolution, modeling

Introduction

Solid pharmaceutical systems (matrices) for oral administration are the most widespread method to assume drugs, for its compliance and for the large area available in the intestine to the drug adsorption. Pharmaceutical systems able to release the dose of drug with a given kinetics are highly desired. In particular, even if not only, the best goal is the so-called zero-order kinetics for the release of the drug, i.e. with a constant rate, to equate the drug consumption rate due to the metabolism. Matrices made of hydrogels seem to be able to fulfill this requirement, i.e. properly designed matrix (in terms of composition, as well as dimensions and geometry) can give tailored drug release profiles. These drug delivery systems, 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. The design of these systems requires a deep knowledge of the phenomena involved during matrix hydration/dissolution in the stomach and in the gastro-intestinal tract. The phenomena can be described in term of mathematical equations (modeling) which can be solved by a properly designed software (numerical code). The mathematical modeling of drug release can indeed significantly facilitate the development of new and the optimization of existing pharmaceutical products. The identification and the quantification of the relevant phenomena in the drugs release, by means of properly designed experimental techniques, as well as the availability of a reliable physical and mathematical model, are urgent requirements toward effective formulations of controlled release systems.

The mathematical modeling of the in-vitro drug release kinetics was the subject of recent reviews\textsuperscript{1,2}. A detailed overview of the modeling approaches to describe drug release from matrices systems proposed in literature was given by Siepmann and Peppas\textsuperscript{3}. In their analysis, the starting point was the Higuchi treatment\textsuperscript{4}, which was developed to describe the drug release from an ointment containing a suspended drug and in contact with a perfect sink. The Higuchi equation is not directly applicable to complex systems such as matrices made of polymers and drugs, which could be subject to swelling and erosion, showing a diffusivity sensible to the solvent concentration.

Peppas and co-workers developed a comprehensive mathematical theory able to describe the
full set of observed experimental phenomena, during the drug release from tablets made of swellable hydrogels. The full model was named "sequential layer" since it describes all the phenomena (water diffusion, swelling, drug diffusion, polymer erosion) layer-by-layer from the external toward the interior of the tablet. Their model was able to describe "affine" deformations, i.e. the swelling of cylindrical matrices causes the matrices to increase their size keeping their shape, and the erosion causes the matrices to decrease their size, still remaining cylinders.

More recently, the finite element methods were applied to solve the diffusion problem in tablets of various, even not simple, geometries (convex tablets, hollow cylinders, doughnuts, inwards hemispheres), also in presence of moving boundaries or in presence of slowly dissolving drugs. This approach was never applied to the description of swelling and eroding tablets, which is closer to the real situations.

Grassi and co-workers proposed several approaches, with increasing complexity, to model the drug release from solid pharmaceutical forms. A simple model based on the drug balance in the dissolution medium was developed taking into account the resistance to the release due to a layer of enteric coating. A much more complex model was developed to describe the release from tablets made of swellable hydrogels, with spherical drug particles, poly-dispersed in size and in different physical states (amorphous, crystalline). Even in these cases, despite the elegance and the completeness of the analysis proposed, the models were not able to describe not affine deformations, i.e. the change in shape of the matrices which was observed experimentally as consequence of the hydration.

Aims of this paper are to describe the steps which our research group did in the experimental study and in the modeling of the behavior for controlled drug delivery systems based on hydrogels. The experimental techniques will be described, and some of the most relevant results will be reported. The evolution in the modeling approaches will be reported, then the final, state-of-the-art model, recently proposed by our research group, will be summarized and its applications will be shown and discussed.

**Experimental**

**Materials**

The hydrogel used was the Hydroxypropyl methylcellulose (HPMC, Methocel K15M, a gift from Colorcon, Varese, Italy). The model drug was the theophylline (TP, CAS no. 58-55-9, purchased from Sigma Aldrich, Milan, Italy). Both the materials are powders with mean diameter of the order of 100 μm. The materials were used as obtained, obtaining cylindrical matrices (tablets) by powder mixing and compression (see the Methods section). Distilled water was used as dissolution medium.

**Methods**

The studies were organized following a two-steps approach. First, tablets made of pure polymer were prepared and hydrated, in order to analyze the swelling, the erosion and the water diffusion phenomena; then, tablets made of polymer and drug were prepared and hydrated, in order to analyze also the drug release phenomena.

*Pure HPMC studies*. 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, using a loading force of 50 kN kept for 5 minutes.

To allow the water uptake only through radial direction, the tablets were confined between two glass slides. This system was placed in a thermostatic bath, in which the dissolution medium was distilled water, kept at 37 °C and stirred using a magnetic paddle. All the runs were performed in triplicate.

At given immersion times, the sample was withdrawn from the bath and photographed by a digital camera (HP Photosmart 945) in controlled light exposure. 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. The light intensities were related to the water content by means of a relationship developed and tuned purposely.

After each photograph was taken, the cover slide was carefully removed, and the swollen tablet was cut by several thin-walled metallic punch, the gel layer external to the punch wall was carefully recovered and quantitatively transferred on a glass holder. The cutting 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. The amount of water in each sample was thus obtained; at same time, the amount of polymer in each sample was determined. By this method, the
water mass fraction and the polymer mass fraction were obtained as functions of the radial direction. For different immersion times, the mass fractions were obtained as function of time. Therefore, the technique here outlined allows to obtain the evolutions of mass fractions with both the time and the radial direction. The technique is described with more details in a previous paper by our research group\textsuperscript{15}.

Both the techniques, the image analysis and the gravimetric method, were developed and applied to the water/polymer measurement, with the aim of observing and quantifying the hydration and the erosion phenomena, in matrices systems. The methods were applied firstly to drug-free systems.

**HPMC systems loaded with Theophylline**\textsuperscript{16, 17}. Mixtures of HPMC and TP 50:50 w/w were obtained by powders direct mixing 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) by a Carver Press, with a loading force of 50 kN kept for 5 minutes.

In a first set of runs, the matrices were confined between two glass slides, in order to allow the water uptake only through radial direction\textsuperscript{18}. This method – named the “radial” experiment – is the extension to drug loaded matrices of the method described in the previous section, which was pointed out working with pure HPMC matrices\textsuperscript{15}. Each run were carried out in triplicate. The “sandwich” (glass-tablet-glass) was immersed in the vessel of an USP XXVIII type II apparatus (AT7 Smart by Sotax). The dissolution medium was 0.9 L of distilled water kept at 37 °C. After selected immersion times, the sample was withdrawn from the dissolution vessel, it was photographed by a camera (HP Photosmart 945) and the cover slide was carefully removed. Then, the swollen matrix was cut by several thin-walled metallic punches with decreasing diameters. The gel layer external to the $i$-th punch’s wall was carefully recovered and quantitatively transferred on a glass holder. The sample was dried in an oven at 105°C until it reaches a constant weight. Finally, each dried sample was fully dissolved in 500 mL of distilled water, and the TP contents were assayed spectrosopically by an UV-visible spectrometer (Lambda 25 by Perkin Elmer), in quartz cuvettes with optical path length of 10 mm, at $\lambda = 276$ nm (the water solutions of TP were found to follow the Lambert and Beer law, $A = aC$; for concentrations up to 20.0 mg/L, the constant value was found to be $a = 0.0764$, thus the limit for absorbance was around 1.5. Of course solutions which showed absorbance outside of the calibration range were diluted of a known factor and assayed once more, accounting for the dilution in the subsequent drug mass calculation). At last, the water, drug and polymer masses were obtained, as functions of time and radial direction.

In a separate set of tests\textsuperscript{19}, the tablets were immersed in an 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 was 5 cm in diameter and 4 cm in height, i.e. it was larger than the tablet, even after a given time of immersion). In these tests, the hydration, the erosion, and the drug release are thus allowed through the full tablet surface. The experiment was thus named the “overall” experiment. After selected 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 as function of the time, allowing to gather the experimental evolutions, for all the masses: drug, polymer and water, with time. One matrix for each immersion time was drawn from the bath, cut along one diameter and photographed. Size (diameter and thickness) and shape of the hydrated matrices were obtained from image analysis.

The experiments (both the “radial” and the “overall” ones) served as the basis to observe and quantify the drug diffusion and release phenomena, beyond the hydration, swelling and erosion of the matrices.

**Modeling**

**Models evolution**

The hydration and erosion phenomena were firstly analyzed by a simple model based on the water and drug mass balance in the matrices\textsuperscript{20}. The calculation code was developed by our research group by solving the balance equations with finite difference schemes. For simple geometries the PDE (time and one-direction independent variables) were solved directly and compared successfully with known analytical solutions (which are available for simple cases of non-moving surfaces and constant diffusivities). The code abilities were improved allowing the solution for moving boundaries and variable diffusivities. Furthermore, following a suggestion taken from literature\textsuperscript{21}, the behavior of a finite cylinder was described in term of the behavior of an infinite cylinder (i.e., with the height very large with respect to the radius), by means of a
properly defined correction factor. The code, even if very simplified, was found able to describe some real behaviors of controlled drug delivery systems, both taken from literature and experimentally investigated by our research group.

The need for the description of more complex geometries (e.g. convex tablets) calls for a different approach, since the simple finite difference codes were not enough to deal with this kind of problems. Therefore, the use of commercial finite element based software was required\(^1\). Some simple cases were successfully simulated, taken from literature\(^8\)\(^,\)\(^10\). Also, the comparison with the results of the previous code, based on finite difference, was successfully carried out. The code was also applied in describing some data (drug release from bioceramics, ibuprofen release from MCM-41 matrices) never analyzed before from the modeling point of view\(^2\), and then in the analysis of data (drug release from bioceramics, zoledronate release from SBA-15 matrices) produced in collaboration with other research group\(^24\), confirming the great interest that the modeling abilities arouse in the drug release field of study.

Then, a model for the description of all the phenomena observed (hydration, swelling, water and drug diffusion, erosion) was proposed and tuned by comparison with experimental data produced within our research group\(^15\). By this way the model was proven to be fully descriptive of the phenomena observed. Therefore, the model was applied ab-initio to a different set of experimental data taken from literature\(^22\), produced working with a different system (HPMC of various powder size loaded with Diclofenac of various powder size, the tablets were obtained varying the drug-to-polymer ratio and the compression force) and it was found able to nicely reproduce the data\(^26\). By this way the model was proven to be fully predictive, since it was found able to describe the data without the need for any parameter optimization.

Once the controlled release was described, another big issue for pharmaceutical science arise. What happens to the drug once administered to living beings? Are we able to describe the drug fate from a modeling point of view? Our research group dealt with this problem, i.e. the study of the drug pharmacokinetics. At first\(^27\), a compartment modeling approach was followed: the human body was considered as some well mixed vessels (compartments) in which the drug is administered. They (the compartments) are able to exchange the drug between them (distribution) and to reproduce the metabolic as well as the excretion processes which take place in the body. The full set of phenomena is indeed known as ADME (Administration-Distribution-Metabolism-Excretion). The proposed model was successfully applied to some case histories taken from literature. The compartment approach, even if very simple and thus potentially useful, suffer of a major drawbacks since it is not very linked to the real physiology of the living being. Therefore, the model parameters have to be fitted and they have no physical meaning. Furthermore, the description of the body is very far from the reality. Therefore, a different approach has been followed, toward the building and the validation of a physiologically-based pharmacokinetic model (PBPK).

In this approach, the body was described by several compartments mimicking some organs, and the connections between them were designed to reproduce real transport phenomena which take place in the body\(^28\). The proposed model was found able to nicely describe what happens to a drug once administered for several physiologies (rat, humans) and for several administration routes (injection, oral administration of delayed release drug delivery systems). The model revealed itself to be a powerful tool also in the analysis of release data in a particular case\(^29\), when an enteric delayed release tablet for the administration of Diclofenac was tested both following the USP protocol (pH = 1 for the first two hours, and then pH = 6.8 for the following six hours) and an home-made release test, build to reproduce the real physiology of the human stomach (with a slowly decreasing pH in the first two hours). The expected plasma levels of the drug are very different if the controlled release system was tested in the USP apparatus (they stay in the therapeutic window for a long time, i.e. the concentration of the drug is higher than the minimum effective concentration, M.E.C., and lower than the minimum toxic concentration, M.T.C.), or in the apparatus which mimic better the real stomach (the release is faster, the plasma concentration quickly overcame the M.E.C. and then decays, exiting from the therapeutic window). By this study, the relevance of the modeling was confirmed once more: there was no need for a study involving human beings (which is expensive and which has ethical issues), to predict that the controlled release system will not perform at its better.

To describe and to discuss the pharmacokinetic model is beyond the scope of the present work, therefore it is not reported here. It can be found in the first paper of the serie\(^28\). However, the most interesting application would be the coupling of the model able to describe the release kinetics from hydrogel based matrices (the main subject of this work) with the pharmacokinetic model. A first attempt was done by simulating the drug plasma levels after the oral administration of a HPMC-TP matrix\(^30\). Once more, the availability of such a tool could avoid un-necessary testing on living beings, again proving the importance of mathematical modeling.
**Model equations**\textsuperscript{17,26}

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).

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

The balances take into account the masses accumulation and the transport phenomena which takes place. In eq. (1), the matrix density is $\rho$, $\omega_k$ are the water and drug mass fractions, $D_k$ are the pseudo-diffusion coefficients. The balances have been written neglecting the convective terms, which in the un-diluted systems such as the swelling hydrogels is a strong approximation. However, this effect is somehow taken into account in the modeling of the swelling phenomenon, described below.

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

$$
\begin{align*}
@ t = 0 & \quad \forall \vec{x} \in \Omega \quad \omega_k(t = 0, \vec{x}) = \omega_{k,0} \\
@ t > 0 & \quad \forall \vec{x} \in \Gamma(t) \quad \omega_k(t > 0, \vec{x} \in \Gamma(t)) = \omega_{k,eq}
\end{align*} \quad (2)
$$

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

$$
\begin{align*}
@ \vec{x} \in \Gamma(t) & \quad \forall t > 0 \quad \omega_k(t > 0, \vec{x} \in \Gamma(t)) = \omega_{k,eq}
\end{align*} \quad (3)
$$

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.

To solve equations (1), the pseudo-diffusion coefficients, $D_k$ (for $k = 1, 2$), have to be evaluated, accounting for the increase in diffusivity due to the hydration:\textsuperscript{5}

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

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:

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

where $\rho_1$, $\rho_2$ and $\rho_3$ are the water, the drug and the polymer densities, respectively.

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. Therefore, there is the need for modeling the two phenomena, with the aim of obtaining the evolution of the boundary, $\Gamma(t)$. In term of element velocity, $v$, the governing equation is:

$$
v = v_{swe} + v_{eros} \quad (6)
$$

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).

The swelling phenomenon has been modeled by:

$$
v_{swe} = \frac{d\delta}{dt} = -\frac{j_{swe}}{\rho} = -\frac{k_{swe} j_{1,diff}}{\rho} \quad (7)
$$

In eq. (7), the $j_{1,diff}$ is the flux of water due to pure diffusive transport, i.e. due to the concentration gradient, and the $j_{swe}$ is the flux of water which is required by the swelling phenomenon, i.e. the water which remains into the gel networks after the swelling. The basic idea of the modeling is that the swelling contribution was taken as proportional to the diffusion contribution, by the model parameter $k_{swe}$.

It should be noted that the proposed model (eq. 7) actually does not describe the real behavior of the swelling matrix. Properly, the swelling phenomenon takes place 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). By this way, the convective flux omitted in eq. (1) is somehow taken into account since its effect is reproduced by the movement of the fully swollen network (the layers from the swelling front toward the erosion front).

Furthermore, 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:

$$
v_{eros} = -k_{eros} \quad (8)
$$
In eq. (8) \( k_{\text{eros}} \) is a constant, and the minus sign accounts for the inward nature of the erosion. The equations code were solved using the parameters value summarized in Table 1.

### Results and discussion

The experimental protocols depicted in the Materials and Methods section gave us access to a very large set of experimental data. Carrying out a release test by means of the traditional USP apparatus II, which consist of a standardized thermostated vessel equipped with a stirrer blade, will allow measurements limited to the drug fraction released for several immersion times. The methods pointed out in our laboratory, on the other side, make available data about the matrix size and shape (the radius in the "radial" test; the radius, the height and the shape in the "overall" test); and on the component’s masses (the drug and the water fraction profile with the radius in the "radial" test; the mass of each component in the "overall" test). The availability of these richer sets of data allow to give a deep insight the phenomena which takes place during the drug release process. As an example, the knowledge of the drug fraction profiles with radius (in the "radial" test)\(^{18}\) allowed to confirm that the drug diffusion takes place mainly in the gel layer, as predicted by equation 4\(^{9}\), which was predicted starting from a model (the free-volume theory), but it was not confirmed experimentally before.

In Figure 1 all the experimental data gathered during “radial” tests were summarized, along with the calculation obtained with the model reported in section Modeling, and the parameters listed in Table 1. The graph above reports the sample radius, the experimental data being obtained by image analysis. The graph below reports the masses evolutions, for drug, polymer and water, the experimental data being obtained by the gravimetric/spectroscopic method described in section Materials and Methods. In the same graph, also the photographs taken for each immersion test are reported. The model calculations were drawn as lines in the same figure. The agreement with the data is clearly very good for each series of data, which means that the model is able to quantitatively reproduce all the phenomena which takes place during the drug release process. In particular, the hydrogel swelling is correctly described, both in term of swelling radius (the graph above) and in term of absorbed water (the graph below, the close squared symbols and the dotted line). Similarly, the polymer erosion was correctly predicted (the upward open triangles and the continuous line in the graph below). Last but not least, the drug release is correctly predicted (the closed stars and the dashed line in the graph below). Furthermore, the nature of the drug transport phenomena (diffusion, limited to the swollen gel layer) was confirmed by the radial drug fraction profile (data not reported here, available in the original paper\(^{18}\)). It is worth noticing that these last data (the drug release data) would be the only ones obtained by means of the conventional USP test, whereas the integrated experimental approach depicted here allowed a much more informative gathering of data.

### Table 1 — The values of the model parameters used for model simulations

| Input parameters                  | \( m_{10} \) | Initial water mass [mg] | 7.5 | \( m_{20} \) | Initial drug mass [mg] | 160.35 | \( m_{30} \) | Initial polymer mass [mg] | 177.42 |
|-----------------------------------|-------------|-------------------------|-----|-------------|------------------------|--------|--------------------------|----------------|-----------------|----------------------|
| \( \omega_{10} \)               | Initial water fraction [-] | 0.0217 | \( \omega_{20} \) | Initial drug fraction [-] | 0.4644 | \( \omega_{30} \) | Initial polymer fraction [-] | 0.5139 |
| \( R_{0} \) | Initial radius [cm] | 0.65 | \( H \) | Initial thickness [cm] | 0.2 | \( V_{0} \) | Initial volume [cm\(^3\)] | 0.2654 |
| \( \rho_{1} \) | Water density [mg cm\(^{-3}\)] | 1000 | \( \rho_{2} \) | Drug density [mg cm\(^{-3}\)] | 1200 | \( \rho_{3} \) | Polymer density [mg cm\(^{-3}\)] | 1200 |
| \( \beta_{1} \) | Diffusive coefficient, 1 [-] | 3 | \( \beta_{2} \) | Diffusive coefficient, 2 [-] | 9 |
| \( \omega_{1}^{*} \) | Equilibrium water fraction [-] | 0.97 | \( \omega_{2}^{*} \) | Equilibrium drug fraction[-] | 0 |

**Parameters optimized in the simulation of the “radial” test**

| \( D_{1}^{*} \) | Critical water diffusivity [cm\(^2\) s\(^{-1}\)] | 1.6 \( \cdot \) 10\(^{-6}\) | \( D_{2}^{*} \) | Critical drug diffusivity [cm\(^2\) s\(^{-1}\)] | 1.5 \( \cdot \) 10\(^{-6}\) |
| \( k_{\text{sw}} \) | Swelling constant [-] | 4.35 | \( k_{\text{sw}} \) | Erosion constant [cm \( \cdot \) s\(^{-1}\)] | 0.83 \( \cdot \) 10\(^{-7}\) |

**Parameters optimized in the simulation of the “overall” test**

| \( k_{\text{sw}} \) | Swelling constant [-] | 5.32 | \( k_{\text{sw}} \) | Erosion constant [cm \( \cdot \) s\(^{-1}\)] | 1.97 \( \cdot \) 10\(^{-7}\) |
Figure 2 summarized the experimental data produced with “overall” tests, and the model calculations obtained with the model reported in section Modeling, and the parameters listed in Table 1. Similarly to Figure 1, here all the data obtained during the “overall” tests were reported: in the graph above, the matrices radius data (open circles) and the semi-height data (open square) were reported along with the model calculations (dashed line, radius; continuous line, semi-height). The experimental data were obtained by image analysis of photos of the partially hydrated matrices cut along one diameter. Properly speaking, the swollen tablets are not cylinders thus it is not correct to talk about radius and height. The radius is measured in correspondence of the tablet mid-plane and the height is measured along the tablet axis. The calculated values were taken accordingly from the code simulations. Once again, the agreement between experimental data and model calculations is very good. In the graph below, the data reported are the masses of drug (closed stars), of polymer (upwards open triangles), and water (closed squares) evolutions with time. The data comes along the model calculations, in term of drug masses (dashed line), polymer masses (continuous line), and water masses (dotted line). The figure reported also the photos of the samples, hydrated up to a given times, than withdrawn from the hydration medium and cut along one diameter. Some of these photos (6, 12, 18 and 24 hours) shown not only the sample, but also the contour graph obtained by the model, superposed to the real tablet image. Since the contours superpose to the images, the code was found able to reproduce also the shape of the hydrating tablets.

The analysis of Figure 1 and of Figure 2 confirmed that the proposed model is able to describe all the phenomena observed in the experiments. Simulations of the “radial” and “overall” experiments required the fitting of some parameters ($D_1^*$,
$D_s$, $k_{sw}$ and $k_{er}$ for the “radial” test; $k_{sw}$ and $k_{er}$ for the “overall” test). Therefore, the model cannot be defined a predictive tool in this case. However, the proposed model has predictive abilities, since it was used to describe the release of a different drug (Diclofenac), using a different hydrogel (HPMC of different powder size), from tablets obtained under different preparative conditions (drug-to-polymer ratio, compaction force)\textsuperscript{25}, and it was able to predict the drug release kinetics without asking for a further parameter optimization\textsuperscript{26}.

The solution of the balance equations in presence of the moving boundaries requires a careful redefinition of the volume elements meshing during the process. Figure 3 shown the deformed meshes for some of the immersion times investigated (6, 12, 18 and 24 hours). The increase in size due to the swelling phenomenon, which for the investigated times overcomes the reduction in size expected because the erosion phenomenon, is evident from the graph, and it causes a deformation of the mesh shape and position, as well as the shape change, compared with the initial shape (the black rectangle). The Figure 3 reports also lines which identify the layer of identical water concentration.

As described below eq. 7, due to mathematical difficulties in implementation, the code does not localize the swelling phenomenon were it really takes place (somewhere inside the matrix). The code instead 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 Figure 3, which describes what happens to the mesh after several times 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. The surface velocity is actually due to both the swelling and the erosion phenomena, because of equation 6, the reasoning reported above applying to the total velocity.

Conclusions

In this work, the problem of controlled drug release from hydrogel based matrices was described in detail.

Some experimental techniques, pointed out in the past by our research group, were described and some interesting results were reported. The drug content in the matrices, as function of time and radial direction, were measured by means of a protocol based on gravimetric and spectroscopic measurements, providing a powerful piece of information, to our knowledge never reported before in literature.

Several modeling approaches, experienced by our research group, were summarized and the last model obtained was reported, along with some of its performances. The model was proven to be descriptive and, in some cases, predictive of what happens to a hydrogel based matrix once swallowed.

The importance of the modeling in the studies related to the controlled release of drug was thus emphasized, also mentioning the needs for the completion of the general framework by means of a reliable pharmacokinetic model.

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