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Abstract: Controlled release by oral administration is mainly achieved by pharmaceuticals based on hydrogels. Once swallowed, a matrix made of hydrogels experiences water up-take, swelling, drug dissolution and diffusion, polymer erosion. The detailed understanding and quantification of such a complex behavior is a mandatory prerequisite to the design of novel pharmaceuticals for controlled oral delivery. In this work, the behavior of hydrogel-based matrices has been investigated by means of several experimental techniques previously pointed out (gravimetric, and based on texture analysis); and then all the observed features were mathematically described using a physical model, defined and recently improved by our research group (based on balance equations, rate equations and swelling predictions).The agreement between the huge set of experimental data and the detailed calculations by the model is good, confirming the validity of both the experimental and the theoretical approaches.

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Dear Editor,

enclosed please find the revised version of the manuscript entitled "**Controlled drug release from hydrogel-based matrices: experiments and modeling**" (IJP-D-15-00286) by Diego Caccavo, Sara Cascone, Anna Angela Barba, and myself.

First of all I want to thank you and the reviewer for the work done, and for the nice comments. We went through the manuscript and we made the change the reviewer asked for. The new text is in red in the present version. Furthermore, in the next page you can find the list of the reviewer's comments along with our answers, in red.

Look forward to hear from you

Best Regards,

Fisciano (SA), 21st March 2015

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Reviewers' comments:

Reviewer #1: This paper, dealing with the experimental and the modelling analysis of drug release from HPMC tablets, is well written and very interesting. Accordingly, its reading led to the following minor comments. In details:

1) Page 6, lines 176 - 177.
I would re-phrase this sentence as follows: From this pictures, both the swollen gel layer and the glassy core are clearly visible.

Done.

2) Page 6, lines 178 - 179.
This sentence is not clear. I suppose that the word "withdrawn" ha to be replaced by "withdrawing".

The reviewer was right, we changed the word.

3) Page 6, line 192.
The authors used HPLC to measure theophylline concentration. Is there any particular reason for using HPLC instead of the simpler and faster UV measurement?

It was a matter of convenience. We added a sentence at the end of page 6 to explain why: <<The large number of samples to be assayed has led to choose the use of HPLC over the faster UV-Vis method because of the availability of the automatized auto-sampler, which allowed to run a large number of testing overnight.>>

4) Page 7, eq.(1).
I do not understand why the matter flux depends also on the gradient of the average molar mass. Please explain.

The reason of this new terms have been explained in our previous work (Caccavo et al., 2015). However, a short sentence has been added on page 7, below Eq. 1: <<In particular, in the mass fluxes the Fick's first law for dilute systems, where the driving force is the molar fraction, has been translated for concentrate systems, where the driving force is the mass fraction. In this derivation the molar mass terms arise (Caccavo et al., 2015).>>

5) Page 7, eq.(4).
Which is the physical meaning of these equations? Which constraints do they impose to the matrix shape upon swelling?

Also these equations have been explained in our previous work (Caccavo et al., 2015). However, the text before and after Eq. 4 have been changed (extended) in order to give a better description of the physical meaning of that equations.

6) Page 7, line 251
I would replace "passes" by "elaps".

Done. (Actually, the word is "elapses", but we understood the suggestion).

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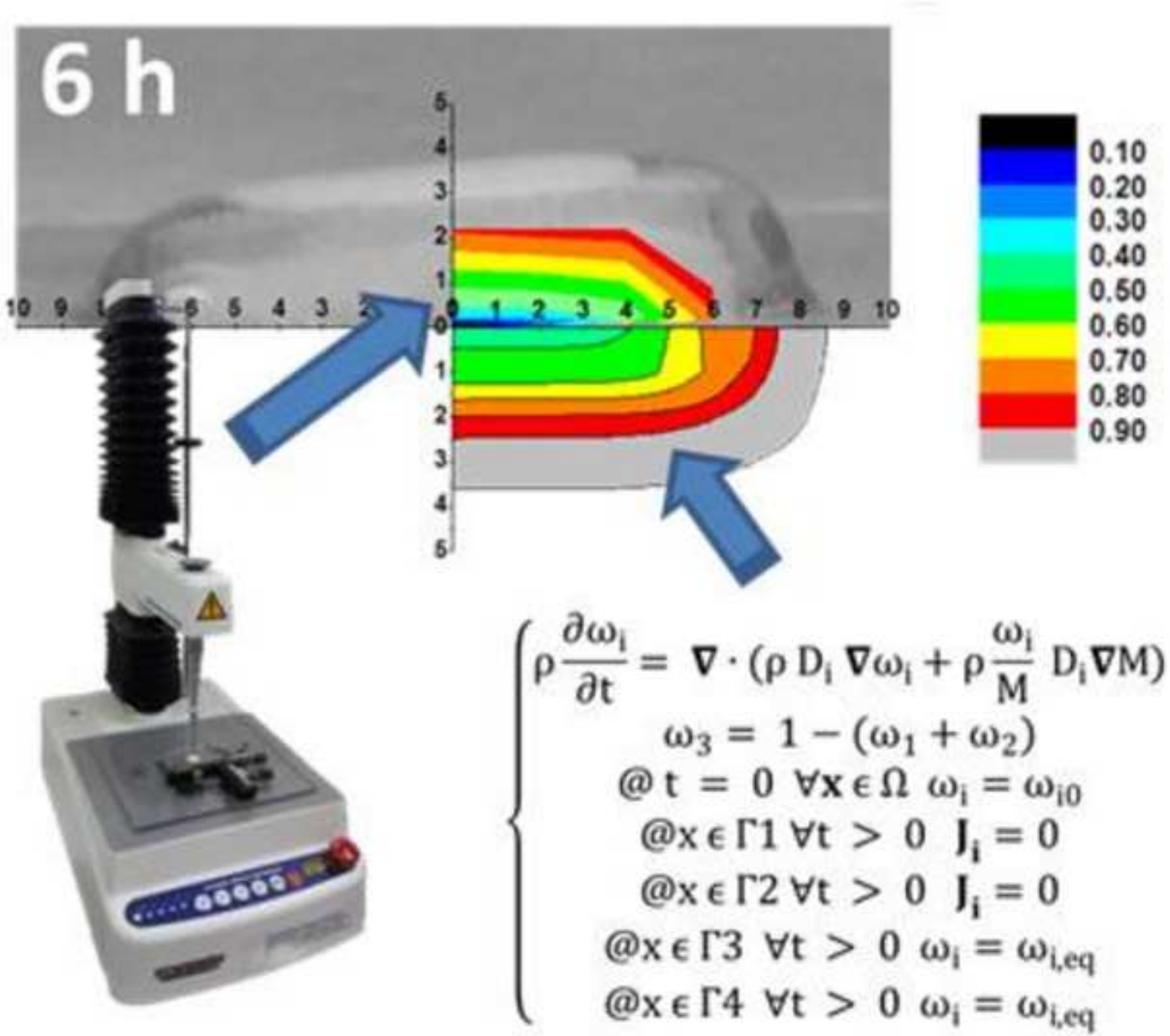
*Graphical Abstract (for review)



$$\begin{cases} \rho\dfrac{\partial \omega_i}{\partial t} = \nabla\cdot(\rho\, D_i\, \nabla\omega_i + \rho\dfrac{\omega_i}{M}\, D_i \nabla M) \\ \omega_3 = 1-(\omega_1+\omega_2) \\ @\, t = 0 \;\; \forall \mathbf{x}\in\Omega \;\; \omega_i = \omega_{i0} \\ @\mathbf{x}\in\Gamma 1 \;\forall t > 0 \;\; J_i = 0 \\ @\mathbf{x}\in\Gamma 2 \;\forall t > 0 \;\; J_i = 0 \\ @\mathbf{x}\in\Gamma 3 \;\; \forall t > 0 \;\; \omega_i = \omega_{i,eq} \\ @\mathbf{x}\in\Gamma 4 \;\; \forall t > 0 \;\; \omega_i = \omega_{i,eq} \end{cases}$$

Controlled drug release from hydrogel-based matrices: experiments and modeling

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Abstract

Controlled release by oral administration is mainly achieved by pharmaceuticals based on hydrogels. Once swallowed, a matrix made of hydrogels experiences water up-take, swelling, drug dissolution and diffusion, polymer erosion. The detailed understanding and quantification of such a complex behavior is a mandatory prerequisite to the design of novel pharmaceuticals for controlled oral delivery. In this work, the behavior of hydrogel-based matrices has been investigated by means of several experimental techniques previously pointed out (gravimetric, and based on texture analysis); and then all the observed features were mathematically described using a physical model, defined and recently improved by our research group (based on balance equations, rate equations and swelling predictions).The agreement between the huge set of experimental data and the detailed calculations by the model is good, confirming the validity of both the experimental and the theoretical approaches.

Keywords

Hydrogels, Water uptake, Texture analysis, Transport phenomena, Modeling.

Chemical compounds

HydroxyPropyl-MethylCellulose - HPMC (PubChem CID: 57503849); Theophylline (PubChem CID: 2153)

24 # Nomenclature

A	Infinitesimal surface $[m^2]$	$\mathbf{v}$	Mass average velocity $[m/s]$
D_i	Pseudo-diffusion coefficient $[m^2/s]$	$\mathbf{v_{er}}$	Erosion velocity $[m/s]$
$D_{i,eq}$	Effective diffusion coefficient of the ith species in the fully swollen matrix $[m^2/s]$	$\mathbf{v_{swe}}$	Swelling velocity $[m/s]$
dr	Radial displacement $[m]$	Z	Reference axial coordinate of the mesh/material frame $[m]$
dz	Axial displacement $[m]$	z	Axial coordinate of the spatial frame $[m]$
$H(r)$	Tablet semi-thickness, function of the radial position, during the dissolution process $[m]$	z_0	Initial tablet semi-thickness $[m]$
$\mathbf{J_i}$	Diffusive mass flux of the ith species $[kg/(m^2\ s)]$	β_i	Fujita-type equation concentration dependence parameter of the ith species $[-]$
k_{er}	Erosion constant $[m/s]$	Γ_i	ith boundaries $[m]$
M	Average molar mass $\left(\left(\sum \frac{\omega_i}{M_i}\right)^{-1}\right)$ $[g/mol]$	ρ	System density $[kg/m^3]$
M_i	Molar mass of the ith species $[g/mol]$	ρ_i	Density of the ith species $[kg/m^3]$
R	Reference radial coordinate of the mesh/material frame $[m]$	Ω	Computational domain $[m^2]$
r	Radial coordinate of the spatial frame $[m]$	ω_i	Mass fraction of the ith species $[-]$
r_0	Initial tablet radius [m]	$\omega_{i,0}$	Initial mass fraction of the ith species $[-]$
r_i	Source term of the ith species $[kg/(m^3\ s)]$	$\omega_{i,eq}$	Equilibrium mass fraction of the ith species $[-]$
t	Time [s]	$\langle\omega_i\rangle(r)$	Average mass fraction on the axial direction function of the radial position $[-]$

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1. Introduction

Hydrogels are widely used in the pharmaceutical preparations and, among them, the HydroxyPropyl MethylCellulose (HPMC) is the most extensively appreciated due to its physical, chemical, and biological properties (Phadtare et al., 2014). In fact, this polymer plays a key role in solid and liquid preparations, sustained and controlled release formulations, capsule production, gel and bio-adhesive preparations (Huichao et al., 2014). For the administration of pharmaceuticals, the oral route has been and probably will continue to be the most exploited one thanks to the high patients compliance. The development of controlled release devices suitable for this application has seen in the hydrogel-based tablets the best option to the purpose. These systems benefit from their simplicity of production, low development costs and their highly adaptability in delivering different active molecules.

The drug release from HPMC tablets is a complex process, which has been the topic of extensive research in the past few decades. If an hydrogel-based tablet enters in contact with a solvent, which penetrates inside the matrix, the polymer undergoes a relaxation process, due to the unfolding of the polymeric chains. A glass-rubbery transition occurs and a gel-like layer is formed (Grassi et al., 2007). In this region, the elongated chains allow the dissolved drug to easily diffuse and reach the dissolution medium. Once the polymer network have been completely hydrated and the chains disentanglement takes place, the matrix starts to erode. For hydrophilic polymer-based systems, swelling and erosion are the most important mechanisms and, while the swelling implies an increase of the matrix volume, the erosion causes a volume decrease, thus the time dependence of matrix volume is determined by the combined and opposing action of these two phenomena (Grassi and Grassi, 2014). Concerning the drug release from hydrophilic matrices, it can be influenced by several factors, which depend on the drug (such as its molecular weight, solubility, particle size distribution, and the initial dose), on the polymer used (such as its molecular weight, composition, structure, and viscosity) (Tahara et al., 1995), on formulation (such as the geometry of the matrix, excipients presence, and manufactory process) (Sung et al., 1996), on external factors (such as the dissolution medium composition, ionic strength, and temperature) (Maderuelo et al., 2011; Zuleger and Lippold, 2001). Thus, it is clear the difficulty of a full understanding and characterization of all the phenomena involved in the drug release from these systems.

During the last decades, several approaches have been used to describe the behavior of these systems, from both the experimental and the modeling point of view. To study the swelling behavior of a matrix, theoretical considerations are usually the starting points useful to define the release mechanism (i.e. assessment of swelling controlled release mechanism based on the use of dimensionless analysis (Ferrero et al., 2010), use of thermodynamic parameters of activation to discriminate between diffusion and relaxation control for the solvent penetration (Ferrero et al., 2013), evaluation of the self-diffusion of the solute and of the water in hydrogels to explain deviations from Fickian diffusion (Ferrero et al., 2008)). To evaluate the water uptake into a tablet, different experimental methods have been proposed in literature, ranging from weighing the swollen and the dried matrix (Mamani et al., 2012) to NMR microscopy (Rajabi-Siahboomi et al., 1994). Swelling progression and mobility of water molecule inside polymers have been investigated by several technologies, including magnetic resonance imaging (MRI) (Kikuchi et al., 2012), atomic force microscopy (AFM), texture analyzer, ultrasound techniques (Huanbutta et al., 2013). To quantify the swelling phenomena, a rheological analysis to measure the evolution of viscoelastic behavior of the gel layer as it swells using an oscillatory indentation (Hewlett et al., 2012), the use of a stereoscopic microscope (Choi et al., 2014), an optical image analysis (Gao and Meury, 1996; Gao et al., 1996) have been proposed. To measure the matrix erosion and the consequent polymer dissolution, a phenol-sulphuric acid technique using a spectrometric analysis can be applied (Ghori et al., 2014). Moreover, a combination of determination of the expansion factor, texture analysis, visual swelling observation of dye containing

tablets, and photomicroscopy used together allows the investigation of dimensional changes, swelling velocity, thickness, appearance and strength of the gel layer and front movements (Zuleger et al., 2002). To evaluate the drug, polymer, and water amount residual in a matrix after a certain dissolution time, a combination of gravimetric and image analysis techniques can be used (Barba et al., 2009a; Barba et al., 2009b; Chirico et al., 2007).

Recently, the texture analysis as approach to pharmaceutical research and development has been extensively used (Li and Gu, 2007; Li et al., 2008). In general, from a compression experiment a force-time diagram is obtained and the hardness of the system, the work of cohesion (the work necessary to overcome the internal bonds of the material), and the work of adhesion (the work necessary to pull the probe away from the swollen tablet) can be evaluated (Conti et al., 2007). Using this device the correlation between drug dissolution and polymer hydration from a modified release matrix can be obtained, measuring the work necessary to penetrate the swollen matrix after a certain dissolution time and correlating it to the water uptake (Jamzad et al., 2005; Lamberti et al., 2013). The simultaneous measurements of the dimensional changes in the swollen gel and in the glassy core during the dissolution of a matrix can be achieved using a texture analyzer equipped with a special probe (Nazzal et al., 2007).

Due to the complexity of the phenomena involved during the hydration of hydrogel-based matrices, in the study and in the development of these systems the use of mathematical modeling can be of great aid. Several modeling approaches have been proposed in literature during the years, starting from the semi-empirical model of Higuchi (Higuchi, 1961), where a square root dependence of drug release from time (for a thin film geometry) was found, later generalized by Peppas and his coworkers (Peppas, 1984), until the recent approach followed by (Caccavo et al., 2015), where a model based on the transport equations coupled with a deforming domain through the ALE (Arbitrary Lagrangian Eulerian) method has been proposed. The release rate from hydrophilic matrices can be described using simplified approaches, i.e. considering that diffusion is the sole mechanism of drug release (ignoring the swelling mechanism) (Gao et al., 1995), considering that determined system specific model parameters (such as apparent drug diffusion coefficients in the polymeric matrix) can be biased using simplified theories (Siepmann et al., 2013). Increasing the complexity a 3D model, taking into account both the drug release from a swelling hydrogel-based matrix and the erosion phenomenon was proposed (Siepmann et al., 1999a; Siepmann and Peppas, 2000; Siepmann et al., 1999b). The major drawback of this model was the hypothesis of affine deformations, therefore the initial cylindrical shape is maintained during the dissolution process and the matrix volume increase as the water penetrate into the system. These limiting hypotheses were later removed considering that the inlet water flux is the driven force for the swelling (Lamberti et al., 2011). In this model, the polymer mass was derived from a macroscopic balance and the unconstrained mass fractions could lead to some local unrealistic results. This inaccuracy was overcome coupling the polymer mass description with the mass transport equations for drug and water by the use of mass fraction constraints (Kaunisto et al., 2010; Kaunisto et al., 2013).

1.1 Aim of the work

The aim of this work is then to make use of the recently proposed model (Caccavo et al., 2015) to describe all the phenomena which take place during the complex process of hydrogel-based matrices hydration, by comparison with the very large set of experimental data gathered by several experimental techniques, including the detailed water content distribution obtained by texture analysis (Cascone et al., 2014).

2. Materials and Methods

2.1 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) have been used to produce the matrices. Deionized water, HCl (37% w/w, Sigma–Aldrich, CAS number 7647-01-0) and sodium phosphate tribasic dodecahydrate (Sigma–Aldrich, CAS number 10101-89-0) have been used for the dissolution media preparation.

2.2 Matrices preparation

HPMC and TP powders have been mixed (TP/HPMC 50% wt/wt) and compressed using a cylindrical tableting machine (Specac PN3000, equipped with flat-faced punches), applying a loading force of 50 kN, kept for 5 min by a press. For the 'radial dissolution' tests, the matrices dimensions are: radius 6.5 mm, thickness 2 mm, weight 350 ± 5 mg; for the 'semi-overall dissolution' tests: radius 6.5 mm, thickness 1 mm, weight 175 ± 2 mg.

2.3 Dissolution methods

To reproduce the matrix behavior after its administration, different media have been used to reproduce the gastrointestinal environments during the dissolution tests. In fact, a pharmaceutical form is firstly ingested from the mouth and arrives into the stomach, where it finds an acidic environment. To reproduce this condition, the dissolution medium in this first phase has been kept at pH 1 preparing a solution containing 6.25 mL of HCl diluted with deionized water to 750 mL for two hours, the average physiological residence time in the stomach. To simulate the passage into the intestinal environment, which is almost neutral, the dissolution medium has been neutralized adding 250 mL of deionized water containing 19 gr of sodium phosphate tribasic dodecahydrate. The medium during all the tests has been kept at 37°C and at constant rotation speed of 100 rpm in a USP II apparatus (AT7Smart, Sotax, Allschwil, Switzerland). The dissolutions have been performed under the same conditions for all the tests.

Two different dissolution tests have been performed on the matrices, the first type, the 'radial dissolution' has been performed on matrices confined between two glass slides to ensure only the lateral uptake of water. Using this method, the matrix swells only in radial direction and preserves its thickness. Once the matrix has been withdrawn from the dissolution medium, the superior slide has been removed and the matrix has been subjected to the gravimetric or mechanical analysis. References for further details (Barba et al., 2009a; Barba et al., 2009b). The second type of dissolution experiments, the 'semi-overall dissolution' tests, has been performed on matrices glued in a small center-part on a glass slab paying attention to overlap the centers of the tablet and of the glass slab. The matrix is free to swell both in axial and in radial direction, and the glass slide could be seen as the symmetry plane orthogonal to the z-axis (the cylinder axis) of a tablet with a thickness twice the one used in this test.

2.4 Gravimetric, optical, and mechanical methods

The gravimetric method has been used to evaluate the mass amounts of the three components (polymer, drug, and water) in the swollen matrix according to a previously developed technique (Barba et al., 2009a). This technique has been applied only for the radial dissolution and the water content measured has been used as calibration to obtain the relation between water content and force-penetration diagram obtained from the mechanical tests, as described in (Cascone et al., 2014). At given immersion times, the sample has been withdrawn and the superior slide has been removed. Then, the swollen matrix has been cut by several thin-walled metallic punch, and each portion has been recovered and quantitatively transferred on a glass holder. The cutting procedures have been repeated by using punches of decreasing radius, obtaining

several annuli and a central core, which have been placed on different glass holder. All the samples have been dried till reaching a constant weight to obtain the amount of water in each section. Then, the dried tablet sections have been completely dissolved, to allow the determination of the drug content and thus the determination of the polymer fraction. These operations have been repeated for all the dissolution time considered (for radial dissolution: 24, 48, 72, and 96 hours), obtaining the evolutions of mass fractions with both the time and the radial direction. All the runs were performed in triplicate, and results have been showed as average values, with their proper standard deviation.

With reference to the semi-overall dissolution, only the total mass amounts of the components after the hydration (for semi-overall dissolution: 2, 3, 4, 6, 8, and 24 hours) have been evaluated. To evaluate the water up-take of the matrix, it has been weighted, dried, and then weighted again, the water mass entered in the matrix during the dissolution can be thus evaluated, from the difference between the two weights. The dried matrix has been completely dissolved, to determine the drug content by the use of the High Performance Liquid Chromatography (HPLC) method described in the next section. The residual polymer mass has been 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 masses evolution inside the tablet, as functions of the hydration time, have been obtained.

To evaluate the swollen matrix size, an image analysis technique has been applied. Once withdrawn from the dissolution medium, the matrix has been carefully removed and an overhead photo has been taken. From this image the diameter of the matrix after erosion and swelling phenomena has been measured. To measure the thickness and evaluate the shape of the hydrated matrix, after each dissolution time, the matrix has been carefully cut along a diameter and photographed from the side. From these pictures, both the swollen gel layer and the glassy core are clearly visible.

The drug release, for both the radial and the semi-overall dissolution methods has been evaluated withdrawing a sample of the medium after the dissolution and analyzing it according to the analytical method described in the next section.

The mechanical tests have been performed according to a previously described procedure (Cascone et al., 2014). Indentation tests using a texture analyzer (TA.XT Plus Stable Micro System Godalming, UK equipped with a needle probe and a 5 kg loading cell) have been performed on swollen matrices for both the radial and semi-overall systems. Matrices have been penetrated axially at several distances from the center. The indentation test velocity has been kept constant at 0.03 mm/s, the instrument measuring the force necessary to penetrate into the swollen matrix. Data acquisition starts when the probe touches the sample (i.e. where the sample offers a not negligible force to penetration) and it ends when the probe reaches the 90% of the total sample thickness with a recording rate of 100 points/s. To ensure reproducibility of the data, every test has been performed in triplicate and results have been shown as average values.

2.5 Analytical methods

In the present work, the analytical determinations to evaluate the amount of theophylline in solution have been performed using an Agilent 1200 Infinity Series HPLC (Agilent Technologies, Milano, Italy). The analyses have been performed using a C-18 column (Nucleodur 100-5 ec C18, by MACHEREY-NAGEL) equipped with a column guard and the detection has been performed at 275 nm wavelength. The flow rate of the eluent phase has been set on 2 mL/min of a solution composed by acetonitrile and acid acetic/water 0.2% vol solution, according with the gradient elution described in Table 1. The large number of samples to be assayed has led to choose the use of HPLC over the faster UV-Vis method because of the availability of the automatized auto-sampler, which allowed to run a large number of testing overnight.

3. Modeling

The dissolution process has been virtualized using the model proposed by (Caccavo et al., 2015) where the whole matrix release behavior is described using mass transport equations, to describe the species diffusion, coupled with the ALE (Arbitrary Lagrangian Eulerian) method, to consider the system swelling.

The computational domains in this work have been a quarter and half of the whole tablet, respectively for the radial and the semi-overall dissolutions, represented by a rectangle in the 2D-axial symmetric configuration (Figure 1).

The transport equations employed, with the proper initial and boundary conditions, have been the same as in (Caccavo et al., 2015), for water (i=1) and drug (i=2), while the polymer (i=3) has been derived from the mass fraction constraint:

Radial

$$\begin{cases} \rho\dfrac{\partial \omega_i}{\partial t} = \nabla\cdot(\rho\, D_i\, \nabla\omega_i + \rho\dfrac{\omega_i}{M}\, D_i \nabla M) \\ \omega_3 = 1-(\omega_1+\omega_2) \\ @\, t = 0 \;\; \forall \mathbf{x}\in\Omega \;\; \omega_i = \omega_{i0} \\ @x\in\Gamma 1\; \forall t > 0 \;\; \mathbf{J_i} = 0 \\ @x\in\Gamma 2\; \forall t > 0 \;\; \mathbf{J_i} = 0 \\ @x\in\Gamma 3\; \forall t > 0 \;\; \mathbf{J_i} = 0 \\ @x\in\Gamma 4 \;\; \forall t > 0 \;\; \omega_i = \omega_{i,eq} \end{cases}$$

Semi-overall

$$\begin{cases} \rho\dfrac{\partial \omega_i}{\partial t} = \nabla\cdot(\rho\, D_i\, \nabla\omega_i + \rho\dfrac{\omega_i}{M}\, D_i \nabla M) \\ \omega_3 = 1-(\omega_1+\omega_2) \\ @\, t = 0 \;\; \forall \mathbf{x}\in\Omega \;\; \omega_i = \omega_{i0} \\ @x\in\Gamma 1\; \forall t > 0 \;\; \mathbf{J_i} = 0 \\ @x\in\Gamma 2\; \forall t > 0 \;\; \mathbf{J_i} = 0 \\ @x\in\Gamma 3 \;\; \forall t > 0 \;\; \omega_i = \omega_{i,eq} \\ @x\in\Gamma 4 \;\; \forall t > 0 \;\; \omega_i = \omega_{i,eq} \end{cases} \qquad (1)$$

In particular, in the mass fluxes the Fick's first law for dilute systems, where the driving force is the molar fraction, has been translated for concentrate systems, where the driving force is the mass fraction. In this derivation the molar mass terms arise (Caccavo et al., 2015).

With the constitutive equations described by the following equation for the diffusivities:

$$D_i = D_{i,eq}\exp\left[-\beta_i\left(1-\frac{\omega_1}{\omega_{1,eq}}\right)\right] \qquad (2)$$

and an ideal mixing rule for the specific volume for the system density:

$$\frac{1}{\rho} = \left(\sum\frac{\omega_i}{\rho_i}\right) \qquad (3)$$

The domain deformation has been modeled considering that the domain is freely deformable and the deformation is driven by the movements of the boundaries Γ_i, accordingly to Laplace smoothing equations (Caccavo et al., 2015; COMSOL, 2013):

Radial

$$\begin{cases} \dfrac{\partial^2}{\partial R^2}\left(\dfrac{\partial r}{\partial t}\right)+\dfrac{\partial^2}{\partial Z^2}\left(\dfrac{\partial r}{\partial t}\right)=0 \\ \dfrac{\partial^2}{\partial R^2}\left(\dfrac{\partial z}{\partial t}\right)+\dfrac{\partial^2}{\partial Z^2}\left(\dfrac{\partial z}{\partial t}\right)=0 \\ @\, t = 0 \;\; r = r_0;\; z = z_0 \\ @x\in\Gamma 1\; \forall t > 0 \;\; dr = 0, dz = 0 \\ @x\in\Gamma 2\; \forall t > 0 \;\; dz = 0 \\ @x\in\Gamma 3\; \forall t > 0 \;\; dz = 0 \\ @x\in\Gamma 4\; \forall t > 0 \;\; \dfrac{\partial r}{\partial t} = (\mathbf{v_{swe}}+\mathbf{v_{er}})|_r \end{cases}$$

Semi-overall

$$\begin{cases} \dfrac{\partial^2}{\partial R^2}\left(\dfrac{\partial r}{\partial t}\right)+\dfrac{\partial^2}{\partial Z^2}\left(\dfrac{\partial r}{\partial t}\right)=0 \\ \dfrac{\partial^2}{\partial R^2}\left(\dfrac{\partial z}{\partial t}\right)+\dfrac{\partial^2}{\partial Z^2}\left(\dfrac{\partial z}{\partial t}\right)=0 \\ @\, t = 0 \;\; r = r_0;\; z = z_0 \\ @x\in\Gamma 1\; \forall t > 0 \;\; dr = 0 \\ @x\in\Gamma 2\; \forall t > 0 \;\; dz = 0 \\ @x\in\Gamma 3\; \forall t > 0 \;\; \dfrac{\partial z}{\partial t} = (\mathbf{v_{swe}}+\mathbf{v_{er}})|_z \\ @x\in\Gamma 4\; \forall t > 0 \;\; \dfrac{\partial r}{\partial t} = (\mathbf{v_{swe}}+\mathbf{v_{er}})|_r \end{cases} \qquad (4)$$

The free-boundaries (Γ_4 for radial case, Γ_3 and Γ_4 for semi-overall case) move with a velocity due to swelling and erosion; the other boundaries describe physical constraints: for radial case Γ_1 is a symmetry axis,

whereas Γ_2 and Γ_3 are planes which don't allow vertical translations; for semi-overall case Γ_1 is a symmetry axis and Γ_2 is a plane which doesn't allow vertical translations.

The swelling velocity can be computed from a flow identity at interface, as shown by (Caccavo et al., 2015):

$$\mathbf{v_{swe}} = -\frac{(\mathbf{J_1} + \mathbf{J_2})}{\rho\ \omega_3} \tag{5}$$

whereas the erosion velocity is accounted as a constant value (fitting parameter):

$$|\mathbf{v_{er}}| = -\ k_{er} \tag{6}$$

3.1 Code solving

The previous Partial Differential Equations (PDEs) have been solved with the Finite Element Methods (FEM) using the commercial software COMSOL Multiphysics® 4.3b. The development and implementation of the simulations have been carried out with the help of a workstation based on the processor Intel® Core™ i7-4820K with a clock rate of 3.70 GHz and a RAM of 64 GB. The computational domain was divided in 725 and 385 quadrilateral elements (with dimensions between 8.25×10^{-7} and 2.44×10^{-4} m) for the semi-overall and the radial simulation, respectively, with particular high elements density close to the erosion boundaries. The results obtained are mesh-size independent and the calculation time have been 19 min for the semi-overall simulations and 37 s for the radial simulations.

4. Results and discussion

4.1 Radial dissolution

In the radial dissolution tests, the matrices behavior has been monitored for 4 days, gathering experimental data each 24 h. In Figure 2 the total mass evolution of each component inside the swollen matrix is shown. The drug release is particularly slow in this configuration, where the surface through which the system can exchange matter is only the lateral one, reaching at maximum the 60% of theophylline release in 4 days. However the release rate is higher in the first 24 h, sensibly decreasing after that time. This can be explained considering that in this configuration within the first day the drug close to the tablet lateral surface is promptly released whereas after this first part the presence of a gel layer increasing in thickness takes over and the drug transport and its release become more and more difficult, leading to a decrease of the release rate. On the other hand even the polymer dissolution is very limited, particularly in the first 48 hours, bringing to a final dissolution of about 20% of the initial polymer amount in the matrix. The water uptake considerably increases in the first 3 days, slowing down after that time. The curves in Figure 2 represent the modeling results obtained using the model proposed by (Caccavo et al., 2015). Most of the parameters (Table 2) have been applied as they were in the original model whereas the water Fujita-type equation coefficient (β_1) has been modified using the data by Gao et al. (Gao and Fagerness, 1995) and the drug effective diffusion coefficient ($D_{2,eq}$) has been slightly increased to better describe the drug release. The erosion constant has been used as fitting parameter as in the original model.

With this minimum parameters adjustment the model results seem to describe nicely all the "macroscopic" experimental results (Figure 2).

The so tuned model has been compared to microscopic experimental results. In Figure 3 the data from the gravimetric and the texture analyses allow to completely characterize the system in terms of components distribution inside the swollen tablets. The horizontal bars represent the radius of the tablet parts (annulus or core) analyzed, therefore the experimental point is an average value of the part examined. The texture data represent local water mass fraction that is uniform along the tablet height (Lamberti et al., 2013). As it

can be seen these two techniques are in good agreement and give precise information on the hydration of the swollen tablet. The other gravimetric data, on drug and polymer mass fractions, allow to close the mass balances on the whole system. After 24 h (Figure 3/a) the tablet core is almost not hydrated and as the dissolution time elapses the inner part of the tablet get more and more hydrated, reaching the 50% wt/wt after 96 h (Figure 3/d) in the tablet core. The drug mass fraction profiles instead highlight the phenomenon of the faster drug release rate in the first 24 h with respect to greater dissolution times. Indeed the drug mass fraction close to the erosion front (Figure 3/a) shows the depletion of drug inside the swollen tablet for several millimeters, confirming the promptly dissolution and release of the theophylline close to the erosion front, whereas in the tablet core its mass fraction is still the original one. After the initial dissolution/release behavior, the inner tablet parts play the role of a drug storage, allowing its gradual release along with the tablet hydration (Figure 3/b-d). The polymer distribution, besides confirming the equilibrium polymer mass fraction at the erosion front (3% wt/wt), shows the gradual polymer dilution along with the tablet swelling.

The modeling results have been compared to the experimental results using the mass fraction profiles along the tablet radius (at any height) that, in this system, is equal to the $\langle\omega_i\rangle(t,r)$ (Caccavo et al., 2015) since the mass fraction is constant along the axial direction. The modeling water mass fraction profiles in the first 48 h (Figure 3/a-b) slightly underestimate the experimental points whereas, at the same times, there is an overestimation in the macroscopic water uptake. This is explainable considering that a greater swollen tablet radius is predicted, and in the external layers the amount of water is predominant (97% of the total mass), bringing to an overestimation of the macroscopic water adsorption, despite the underestimation of the internal mass fraction profiles. However, the experimental mass fraction profiles are satisfactorily well described, since no further parameters adjustment is requested at this stage (zero parameter model) (Figure 3).

4.2 Semi-overall dissolution

The same HPMC-theophylline system has been used for “semi-overall” dissolution analyses. These tests, as described in the ‘Materials and Methods’ section, have been set up to reproduce the behavior of the overall dissolution tests exploiting the disc planar symmetry. Indeed half amount of components has been utilized to form tablets, with respect to the normal tablets (e.g. the tablets employed for the radial tests), and the lower tablet part has been centrally glued on a glass slab to reproduce the symmetry condition of the overall system: the null mass flux. In this way the system behavior can be characterized in terms of macroscopic data (e.g. residual masses and shape) and in terms of microscopic data (e.g. hydration via texture analyses). In the semi-overall dissolution tests the tablets behavior has been analyzed for 24 h. In Figure 4/a are reported the residual masses inside the swollen matrices as well as the percentage of drug release.

In this configuration the surfaces through which the system can exchange matter are the lateral and the top part, substantially changing the release behavior with respect to the radial experiments. Indeed, after 24 h of dissolution the drug release is close to the 97% (just the 38% in the radial tests) and the water uptake is close to 1 g (less than 0.4 g in the radial tests whereas in an overall experiment it should be 2 g). The polymer dissolution/release, like in the radial experiments, is very limited in the dissolution time analyzed. In Figure 4/b the erosion radius and thickness obtained from the photos are shown, taking the maximum radius and the central height (at r=0). As it can be seen, the axial swelling is quite pronounced, increasing of almost 6 times with respect to the initial thickness, whereas the radial expansion is somewhat less evident, despite the increment is of 1.5 times the initial radius. The model tuned on the macroscopic radial experiments has been applied with the same parameters, apart the erosion constant, (Table 2) to the semi-

overall configuration, changing the boundary conditions as shown in the 'Modeling' section. As it can be seen all the experimental results in Figure 4/a-b are well predicted by the model, allowing the complete characterization of the macroscopic behavior of the tablet dissolution in the semi-overall configuration.

In order to fully investigate the matrix behavior, the swollen matrices have been subjected to texture analyses to obtain the hydration level. The technique gives information on the water content along the axial distance: repeating the analysis at several radii it is possible to build a contour plot that shows the hydration level in the whole swollen tablet. As explained in Cascone et al. (Cascone et al., 2014) this type of analysis is not able to detect the presence of the fully swollen layer (ω_1>0.9) due to its low resistance to the needle penetration. However these simple analyses give detailed information on the internal water content that can be compared with pictures of the swollen tablet as well as with modeling results. In Figure 5 swollen tablet pictures (top left part) with texture analysis results (top right part), and modeling water mass fraction distribution (bottom right part) at several dissolution times (2, 3, 6 and 8 h) are shown.

Both the texture and the modeling data are expressed in terms of water mass fraction content, starting from zero (black) in the dry regions up to more than 0.9 in the fully swollen regions (light gray). From these graphs it is possible to see that the internal tablet hydration level, as well as the final swollen tablet shape, are well predicted by the model thanks to the comparison with the texture analysis results and the swollen matrix pictures, respectively. This confirms, once again, the validity of the model proposed by Caccavo et al. (Caccavo et al., 2015), that is able to predict in a satisfactorily manner all the phenomena involved in a tablet dissolution process, as well as the effectiveness of the experimental methods employed in the characterization of the swollen tablets.

5. Conclusions

Hydrogels are extensively used in pharmaceutical preparations due to their peculiar behavior. In this work the main transport phenomena which take place when an hydrogel-based matrix loaded with a soluble drug is subjected to dissolution tests have been analyzed, both by experimental and modeling approaches. Two different systems have been studied, the first one, a simplified system which allows only the radial uptake of water, has been characterized in term of polymer and drug release and water uptake, together with the determination of all the three components along the swollen matrix radius. The mass amounts into the matrix have been measured using a gravimetric technique, moreover, a texture analysis has been performed to determine the water uptake along the matrix height at several radii during the dissolution. The second system analyzed, the semi-overall one, which allows the water uptake both in radial and axial directions, besides being analyzed in terms of polymer and drug release and water uptake, has been subjected to an image analysis to measure the dimensions (radius and height) of the swollen matrices after several dissolution times and to a mechanical analysis to determine the water content inside the matrix. A mathematical model previously proposed (Caccavo et al., 2015), based on the combined use of the mass transport equations and the ALE method to describe the diffusion of the species in the matrix during the dissolution and the swelling phenomenon, has been adapted to describe these systems. In particular, although most of the model parameters used have been derived from the original model, the water Fujita-type equation coefficient and the drug effective diffusion coefficient have been slightly modified and the erosion constant has been used as fitting parameter on the basis of the best fitting of macroscopic experimental results. The model, tuned by comparison with macroscopic experimental data (drug, polymer and water masses evolution with time), was found able to satisfactorily describe the matrix size and shape during the hydration. Furthermore, the availability of a recently pointed out technique for water content measurement (Cascone et al., 2014), allowed to compare the model calculations with the experimental info.

Therefore and in conclusion, in this work two tools have been successfully used to investigate the behavior of hydrogel based matrices: an easy and fast experimental technique based on texture analysis to evaluate the water content (Cascone et al., 2014); and a powerful and detailed model able to describe all the phenomena which take place during the hydration of the matrices (Caccavo et al., 2015). These tools can be of great aid for designing and testing new hydrogel-based pharmaceutical systems.

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Conflicts of interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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464

Tables and figures

No table of figures entries found.

468

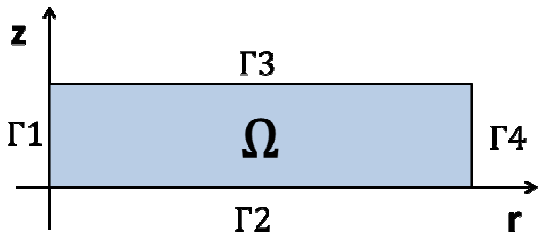
469 **Table 1. Parameters of HPLC analysis.**

Gradient elution	Time	Acetonitrile - Acetic acid/water 0.2% vol.
	min	Composition
	0	3%-97%
	6	4%-96%
	12	6%-94%
Flow rate	2 mL/min	
Injection volume	5 µL	
Temperature	25°C	
Elution time	15 min	

470

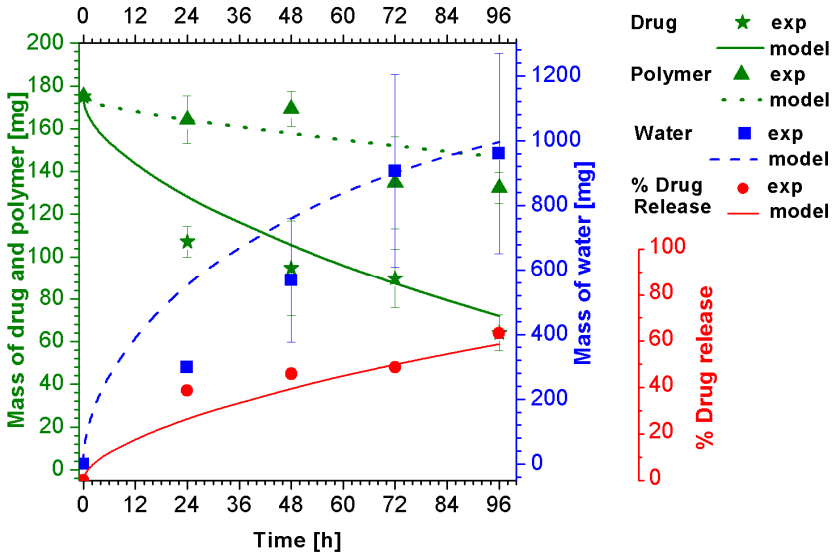
471 **Table 2. Values of the parameters used in the simulations.**

From experiments/literature		
r_0	Initial tablet radius $[mm]$	6.5
z_0	Initial tablet semi-thickness (radial) or thickness (semi-overall) $[mm]$	1
ω_{10}	Initial water mass fraction $[-]$	0
ω_{20}	Initial drug mass fraction $[-]$	0.5
ω_{30}	Initial polymer mass fraction $[-]$	0.5
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 $[m^2/s]$	1.5×10^{-10}
β_1	Water Fujita-type equation coefficient $[-]$	3.53 (Gao and Fagerness, 1995)
β_2	Drug Fujita-type equation coefficient $[-]$	4
k_{er} (radial)	Erosion constant $[m/s]$	10×10^{-9} (fitting)
k_{er} (semi-overall)	Erosion constant $[m/s]$	5×10^{-9} (fitting)



472

473 **Figure 1. Computational domain representing a quarter of the whole tablet in the radial tests and half tablet in the semi-overall**
474 **test. The physical meaning of the domain boundaries is the following. Radial tests: Γ1=axial symmetry, Γ2=plane of symmetry,**
475 **Γ3=in contact with the glass slab, Γ4=erosion boundary. Semi-overall tests: Γ1=axial symmetry, Γ2=centrally glued (0,0) on the**
476 **glass slab, Γ3=erosion boundary, Γ4=erosion boundary.**

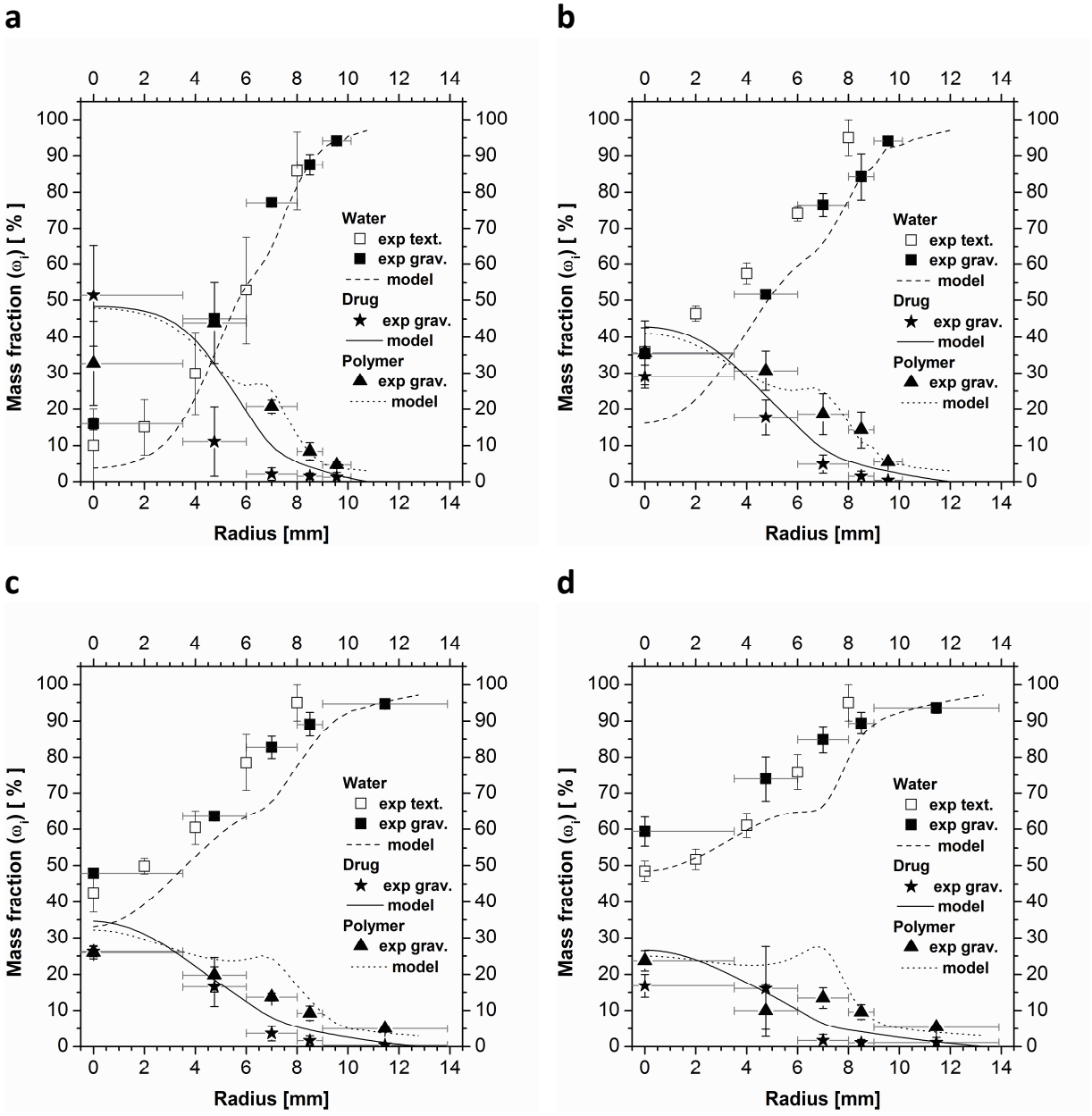


477

478 **Figure 2. Radial dissolution: mass of drug, polymer (green) and water (blue) inside the swollen tablet at different dissolution**
479 **times. In red the percentage of drug release.**

480

481



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483 **Figure 3. Radial dissolution: comparison between experimental and calculated results in terms of mass profiles along the radial**
484 **direction. Dissolution times of 24 h (a), 48 h (b), 72 h (c), 96 h (d).**

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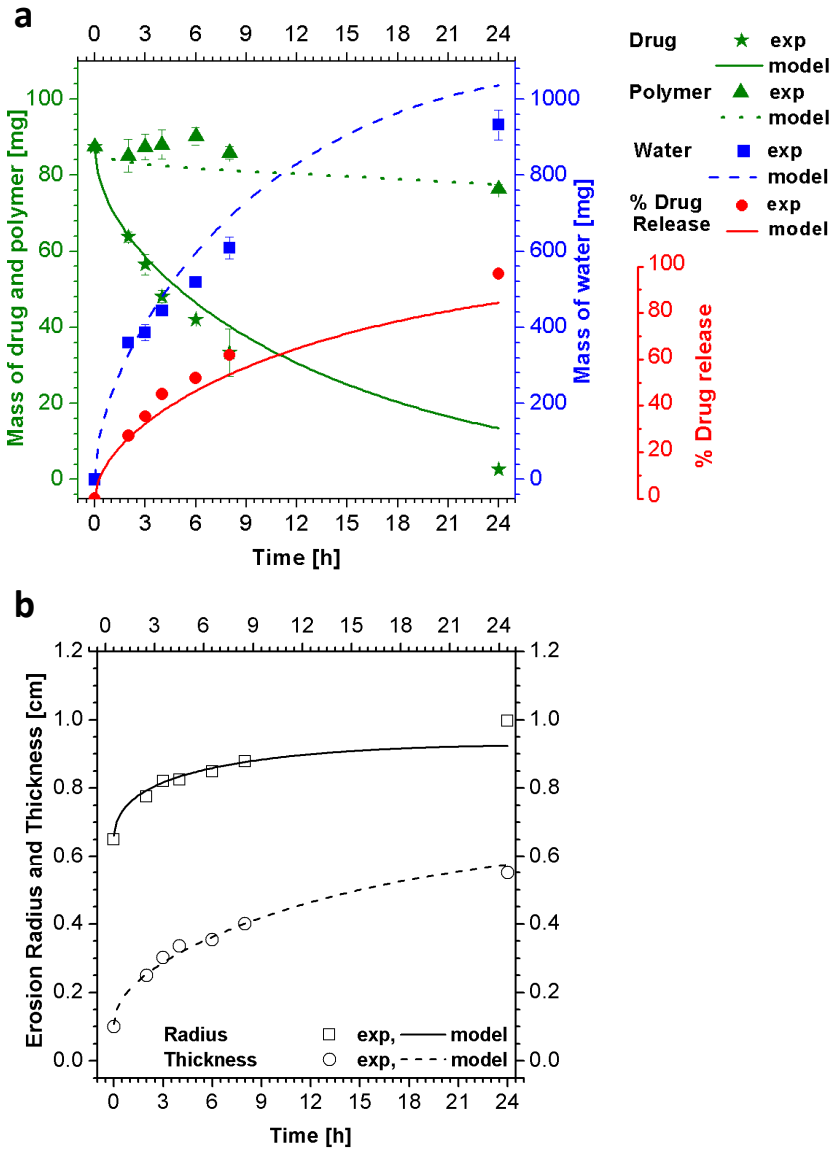

487 **Figure 4. Semi-overall dissolution: (a) mass of drug, polymer (green) and water (blue) inside the tablet at different dissolution**
488 **times. In red the percentage of drug release. (b) Erosion radius and thickness of the swollen tablet.**

489

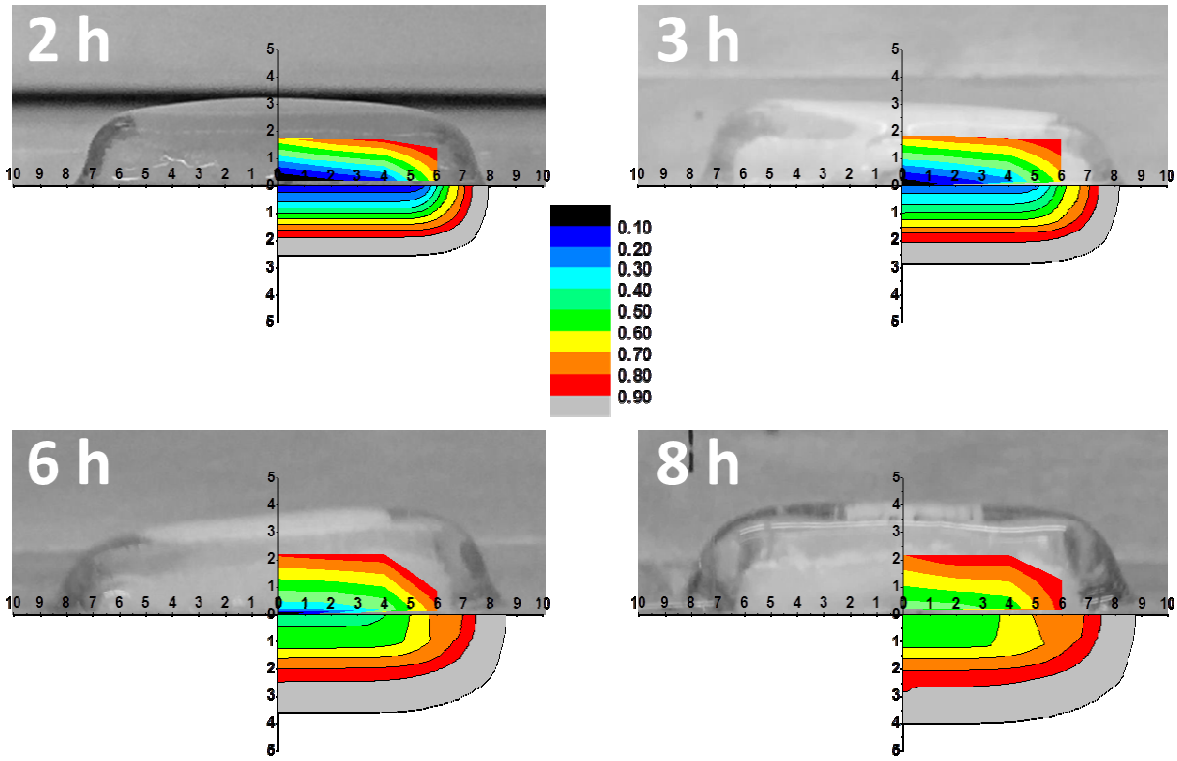

Figure 5. Semi-overall dissolution: comparison between experimental and modeling results in terms of tablets pictures (top part of the graphs), experimental water mass fraction from texture analysis (top right part of the graphs) and modeling water mass fraction (bottom right part of the graphs). All the spatial dimensions are in mm; color scale is referred to water content mass fraction (black = dry matrix; light gray = fully hydrated matrix).