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Drug release from matrix systems: analysis by finite element methods

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Abstract In this work some problems in drug delivery from solid systems were described in terms of transient mass balances with diffusion and solved by using FEM. Firstly, the solving codes were compared with known analytical solutions, available for simple problems (simple geometries, constant diffusivities). Then, models were written to describe more realistic systems (complex geometries, variable diffusivities). Eventually, the behaviors of some real drug delivery systems were successfully predicted.

1 Introduction

Several forms of drug administration, like pills, injections, lotions and suppositories are of quite common use. People eat to survive and usually enjoy (or at least tolerate) the act of ingestion. For this reason, oral dosage forms are the more advantageous: they are easy to use, passable for patients (high compliance) and they assure considerable specific area for drug transport after ingestion.

An efficient delivery system for oral assumption must to guarantee a drug concentration, in blood or in target tissues, within the *therapeutic window* (the interval between minimum effective concentration and minimum toxic level) as long as possible, without requiring too frequent administrations. If global elimination kinetics is known, connected to transport and degradation phenomena, the ideal dosage form should be prepared in order to give a release profile (a kinetics of the drug delivery) equal and opposite to total excretion kinetics. By this way, drug concentration remains constant at a predetermined value: this is the goal of the Controlled Release Systems (CRS).

In designing such devices, usually based on polymer matrices and/or enteric coated tablets, a key role is played by the transport phenomena which take place: water uptake, gel swelling, diffusivity increase due to hydration, and drug diffusion through the solid device and polymer erosion. Because of the complexity of the procedures required to set the fundamental parameters involved in the determination of release profiles, it would be very useful to have a mathematical tool able to predict the drug release rate as a function of preparation parameters. By this way, the preparation parameters of the dosage form could be selected a priori, before executing the usual in vitro release tests, extremely onerous in terms of human and material resources and time-consuming. Thus, mathematical modeling has a very important value in CRS optimization. The model can be thought as a "mathematical metaphor of some aspects of reality".

Numerous studies have been reported in the literature investigating the transport mechanisms in solid pharmaceutical forms and trying to quantify the resulting drug release kinetics [1].

The first significant example [2] of a mathematical model aimed to describe drug release from a matrix system is the one proposed by Higuchi in 1961. It was initially conceived for planar systems, but it was then extended to different geometries and porous systems. The Higuchi equation is, in fact, the solution of the transient drug mass balance (Fick's balance equation) obtained under hypothesis of pseudo–stationary conditions, 1-D diffusion, absence of swelling, erosion and dissolution phenomena, constant diffusivity and perfect sink condition in the release medium. It shows a direct proportionality between the drug released fraction and the square root of time, just

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like predicted by the exact solution of Fick's second law of diffusion [3], for thin films in the same conditions of the Higuchi system and for short exposure times. Besides the pure diffusion contribution, also a "second-kind" of transport mechanism, named "dynamic swelling" and relative to the relaxation process of polymer macromolecules after the water uptake, has to be taken into account, as proposed from Peppas to Sahlin [4].

The process of drug liberation from controlled release devices governed by diffusion can be described using the analytical solutions obtained from Crank [3] solving the Fick's second law of diffusion for simple geometries and various boundary conditions. Solutions for more complicated geometries were found by other authors [5–7]. In addition, literature suggests several applications of the finite difference methods and of the finite element methods to the simulation of drug release. For example, Zhou and Wu [8, 9] applied finite element procedures to analyze drug release into a finite and well-stirred volume from matrix devices of complex geometries including a convex tablet, a hollow cylinder, a doughnut-shaped ring, and an inward-release hemisphere.

Siepmann and co-workers [10] developed a model able to describe the water and drug diffusion in HPMC tablets. They took into account the axial and radial transport in a cylindrical device, moving boundaries of the pharmaceutical form due to swelling and erosion phenomena and water concentration-dependent diffusivities. The polymer dissolution was investigated considering a constant dissolution velocity per surface area. The numerical model, solved using finite differences, was then improved adding inhomogeneous swelling, poorly water-soluble drugs and high initial drug loadings. Mathematically, the matrix was structured as a sequence of hydrated layers ("*Sequential layer model*") [11].

In the 2000 Grassi and co-workers [12] presented a new model suitable to describe the drug release from delivery systems constituted by an ensemble of drug loaded cross-linked polymer particles. The model accounts for the main factors affecting the drug release, such as the particle size distribution, the physical state and the concentration profile of the drug inside the polymeric particles, the viscoelastic properties of the polymer–penetrant system and the dissolution–diffusion properties of the loaded drug.

Kiil and Dam-Johansen [13] developed a detailed model for drug release from a swellable HPMC matrix. The code, solved by the method of orthogonal collocation, took into account water-induced swelling, drug dissolution and external and internal mass transport resistances of dissolved drug. Differently from earlier models, explicit equations for the rate of movement of the swelling, diffusion and erosion fronts, with the relevant physical properties of drug and HPMC matrix contained in the equations, were derived. Then, the authors compared the numerical results from simulation with experimental data for three drugs of very different water solubility (buflomedil pyridoxal phosphate, nitrofutantoin, and sodium diclofenac) and a good agreement was found, in spite of several simplifying assumptions and numerous parameters to be estimated.

Other models also considerate the polymer erosion/degradation phenomena during the drug desorption, in terms of both surface and mass erosion. Some of them present a statistical approach, for example using Monte Carlo methods [14, 15].

Aim of this work is to test the applicability of the finite element methods, as implemented in commercial software, to simulate the behavior of several matrices systems. To this purpose, the ability of the software has been validated firstly against known solutions, analytical as well as from literature, and then the software has been used to successfully simulate some real cases, taken from literature.

2 Methods

The Fick's second law of diffusion (1), on which the problem of the drug release from a solid matrix is based, is a non linear partial differential equation (PDE), in time and space; it admits analytical solutions only in few simple cases. For more complex problems, constituted by a certain number of PDEs to be solved simultaneously, which include a parameter variability with time and/or position, space- dependent initial conditions, time-variant boundary conditions or moving boundaries, the way to follow is to introduce hypotheses and idealizations necessary to simplify the problem, but still able to provide approximated enough solutions and satisfactory results. The link between the complex physical system and the mathematical solution is supplied by the mathematical model of the idealized system, that includes all the significant hypotheses for the real system's simulation. Nowadays, one class of the best methods to solve sets of PDEs is the class of *Finite Element Methods* (FEM) [16]. The FEM software used in this work to implement the simulations is *COMSOL Multiphysics*® *3.4* (Copyright © 1994–2007 by COMSOL AB, Tegnérgatan 23 SE-111 40 Stockholm). It is a powerful interactive environment for modeling and solving all kind of scientific and engineering problems based on PDEs; this software allows transforming conventional models for each kind of physical model into multi-physics models, which solve coupled physics phenomena simultaneously [17]. The development and implementation of the simulations have been carried out with the help of a workstation based on the processor Intel® Core™2 Duo E8500, with a clock rate of 3.16 GHz and a RAM of 3 Gb, 800 MHz.

3 Preliminary validation

As first step, models were implemented concerning matrices with simple shape (slab, cylinder, and sphere) and with a complex shape (convex tablet), uniformly loaded with drug and for which the release is controlled by the pure diffusion through the device's polymeric network. Drug delivery from such devices are ruled by the Fick's second law of diffusion (1), which correlates the temporal evolution of the concentration in every point of the system with the variation of the concentration gradient with position:

$$\frac{\partial C_k}{\partial t} = \overrightarrow{\nabla} \cdot \left(D_k \overrightarrow{\nabla} C_k \right) \tag{1}$$

where C_k is the concentration of the diffusion compound k ($k = 1$ for water and 2 for drug), D_k is the diffusion coefficient of the k-species and $\overrightarrow{\nabla}$ is the gradient operator. For simple-shaped matrices, drug release could take place in an undefined extent medium, in which one can assume *perfect sink* conditions; for both simple-shaped and complex-shaped devices, drug release could take place in a finite medium, where drug concentration increases with time during the delivery process. Assuming constant system's density and constant diffusion coefficient of the diffusing species (drug and water), and neglecting polymer swelling and erosion phenomena, in literature [3] analytical solutions of the Fick's second law of diffusion are available (Tables 1, 2) for some geometries. Numerical release profiles have been compared with these solutions (Sects. 3.1, 3.2). In the case of the convex tablet, FEM procedures validation has been accomplished by comparison with the FEM code built by Zhou and Wu [8] (Sect. 3.3). For all the cases considered here, the default options of the code for meshing, the so-called "Normal" density was used. Larger meshes (option "Coarse") gave less accurate simulations (when compared with analytical solutions); finer meshes (option "Fine") requires more computational time without any improvement in simulation results.

3.1 Perfect sink condition in the release medium, simple-shaped matrices

In the above-mentioned hypotheses, the diffusion equations (1) for the drug and the water are completely decoupled and, therefore, solvable separately, once assigned initial and boundary conditions. So it's enough to verify the agreement between the numerical result and the analytical one in terms of concentration profiles of only a diffusing species (the drug), or in terms of drug release (ratio between the active principle's mass released until the time t and the mass initially loaded). The remaining drug mass $[M_r(t)]$ is the volume integral of the drug concentration (C) present in the matrix device (2):

$$M_r(t) = \int_{\Omega} C(\vec{x}, t) \mathrm{d}V \tag{2}$$

where $\vec{x}$ is the position vector. Therefore, fractional release can be evaluated as (3):

$$R(t) = \frac{M(t)}{M_0} = \frac{M_0 - M_r(t)}{M_0} = 1 - \frac{M_r(t)}{M_0}. \tag{3}$$

Second Fick's law of diffusion for the drug was numerically solved using the following initial condition (4), valid for all the matrix-systems considered in this work:

$$@t = 0 \quad \forall \vec{x} \in \Omega \quad C = C_0 \tag{4}$$

where Ω is the matrix volume and C_0 is the initial drug concentration. The boundary condition (5) states that at the matrix surfaces, through which the drug liberation occurs, the drug concentration is negligible (*perfect sink* condition):

$$@\vec{x} \in \Gamma \quad \forall t > 0 \quad C = C^* = 0 \tag{5}$$

Here Γ denotes the boundary of the region Ω.

The 1-D drug release from a plane sheet, a cylinder and a sphere was evaluated by means of FEM procedures, using a C_0 value of 1 mg cm^{-3}, a drug diffusivity (D) within the matrix of 3×10^{-6} cm^2 s^{-1}, a slab half-thickness of 1 mm and a cylinder and a sphere radius of 6.5 mm. All of them are reasonable values, already chosen in the previous validation process of the finite difference code. In the case of slab and cylinder, edge effect was neglected assuming an infinite cylinder length and an infinite extent of the slab base surfaces: in doing so, the plane sheet releases only in thickness direction and the cylinder releases only in radial direction. If the height and the radius of the cylinder are comparable, the axial transport cannot be neglected. In this case, drug delivery becomes a 3-D problem that, thanks to

Table 1 Analytical solutions [3], in terms of fractional release of the k-th component, for several geometries, under the hypotheses of constant diffusivity and surface concentration of the k-th species, uniform initial concentration of the k-th species and constant density of the system

Slab	$R_{slab}(t) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\left[-\frac{(2n+1)^2\pi^2}{4} \frac{D_k t}{L^2} \right]$
Infinite cylinder	$R_{cyl}(t) = 1 - \sum_{n=1}^{\infty} \frac{4}{R^2 \alpha_n^2} \exp\left(-D_k \alpha_n^2 t\right)$
	α_n are the positive roots of the equation $J_0(R\alpha_n) = 0$;
	J_0 is the Bessel function of the first kind of order zero
Finite cylinder	$R_{fin\_cyl}(t) = 1 - [1 - R_{slab}(t)] \cdot [1 - R_{cyl}(t)]$
Sphere	$R_{sphere}(t) = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-n^2\pi^2 \frac{D_k t}{a^2}\right)$

Table 2 $M(t)/M_\infty$ in the case of simple geometries, loaded with an uniform concentration of the k-th component (the drug) and releasing into a well-stirred solution of limited volume, under the hypotheses of constant diffusivity and system density [3]

Slab	$\frac{M(t)}{M_\infty}\Big\|_{slab} = 1 - \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2(q_n)^2} \exp\left[-D_k\left((q_n)^2 \frac{t}{L^2}\right)\right]$	$M_\infty = \frac{2LC_{k0}}{1+1/\alpha}$ $\alpha = \frac{a}{KL}$
	q_n are the non-zero positive roots of the equation $\tan q_n = -\alpha q_n$	
Infinite cylinder	$\frac{M(t)}{M_\infty}\Big\|_{cyl} = 1 - \sum_{n=1}^{\infty} \frac{4\alpha(1+\alpha)}{4+4\alpha+\alpha^2(q_n)^2} \exp\left[-D_k\left((q_n)^2 \frac{t}{R^2}\right)\right]$	$M_\infty = \frac{\pi R^2 C_{k0}}{1+1/\alpha}$ $\alpha = \frac{A}{\pi R^2 K}$
	q_n are the non-zero positive roots of the equation $\alpha q_n J_0(q_n) + 2\, J_1(q_n) = 0$; J_0 is the Bessel function of the first kind of order zero; J_1 is the Bessel function of the first kind of the first order	A is the cross-section of the release medium in which the cylinder is immersed
Sphere	$\frac{M(t)}{M_\infty}\Big\|_{sphere} = 1 - \sum_{n=1}^{\infty} \frac{6\alpha(1+\alpha)}{9+9\alpha+\alpha^2(q_n)^2} \exp\left[-D_k\left((q_n)^2 \frac{t}{R^2}\right)\right]$	$M_\infty = \frac{4/3\pi R^3 C_{k0}}{1+1/\alpha}$ $\alpha = \frac{V_{ext}}{4/3\pi R^3 K}$
	q_n are the non-zero roots of the equation $\tan q_n = 3q_n/(3 + \alpha\, q_n^2)$	V_{ext} is the volume occupied by the release medium

the axial symmetry of the device, can be reduced to a 2-D problem. In the simulations, a cylinder with a radius of 6.5 mm and a height to diameter ratio of 1 was implemented. Initial drug concentration and diffusion coefficient are the same of the 1D-case. Numerical and analytical results in terms of fractional release are reported in Fig. 1 versus the dimensionless time τ (so, the analysis can be generalized to similar devices, but with different dimensions) (6):

$$\tau = \sqrt{\frac{Dt}{a^2}} \tag{6}$$

in which a represents the cylinder and sphere radius, or the slab's half-thickness. It can be seen that the numerical solutions match the exact solutions very well for all the investigated cases. The geometry of the device strongly influences the release rate: at the same dimensionless time, a spherical matrix releases faster than a plane or cylindrical (of infinite height) device.

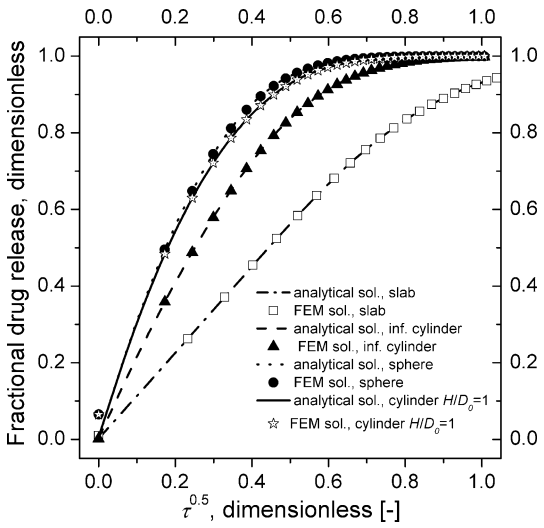

Fig. 1 Fractional drug release versus the square root of dimensionless time, τ (constant ρ and D, perfect sink condition). Comparison of release profile calculated by FEM with analytical solution [3] for four types of geometry ($a = 0.65$ cm, $D = 3 \times 10^{-6}$ cm^2 s^{-1}). *Symbols*, FEM solutions (*open square* slab, *filled triangle* infinite cylinder, *star symbol* finite cylinder, *filled circle* sphere); curves, analytical solutions (*dash dotted* slab, *dashed* infinite cylinder, *continuous* finite cylinder, *dotted* sphere)

3.2 Release into a well-stirred finite volume, simple-shaped matrices

If drug release occurs in a well-stirred finite volume, it is not possible to adopt a *perfect sink* condition in the release medium, since the active principle concentration in the solution will rise with time. Therefore, on the surface Γ it is necessary to use the following condition for the drug (7):

$$@\vec{x} \in \Gamma\, \forall t\, \frac{V_{ext}}{K} \frac{\partial C}{\partial t} = \vec{\Gamma} \cdot \left(-D\, \vec{\nabla}\, C\right) \tag{7}$$

where K is the partition factor between the drug into the release medium (of volume V_{ext}) and the one on the matrix surface, i.e. (8):

$$K = \frac{C|_{\vec{x} \in \Gamma}}{C_{ext}} \tag{8}$$

Here C_{ext} is the drug concentration in the release medium.

The release process by diffusion from a slab, an infinite-height cylinder and a sphere with dimensions analogous to the previous case was analyzed, referring to the same initial condition (4). Release profiles in Fig. 2 are obtained using $K = 1$ and $\alpha = 1$ (α represents a measure of the ratio between the external volume and the matrix volume, as reported in Table 2), and compared with the exact solutions in Table 2. The computed results are in good agreement with these solutions. In the case of release into a finite volume, not all the drug present in the device can diffuse out to the release medium, because of both its limited capacity and of the active principle's partition between the two phases. So the mass M_∞ released in the finite volume is the amount of drug released after an infinite time, rather

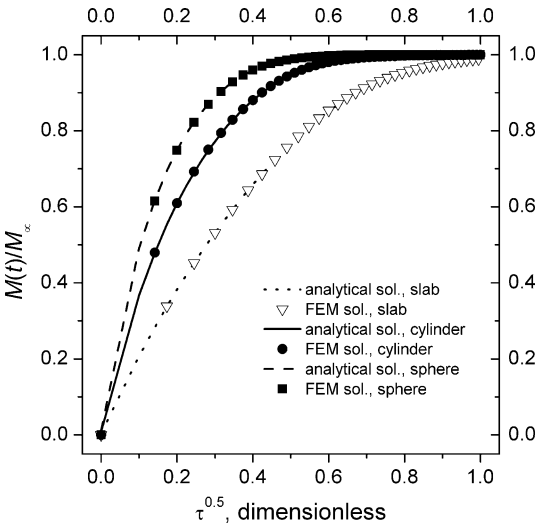

Fig. 2 $M(t)/M_\infty$ versus the square root of dimensionless time, τ (constant ρ and D, well-stirred finite outer volume). Comparison of release profile calculated by FEM with analytical solution [3] for three types of geometry ($a = 0.65$ cm, $D = 3 \times 10^{-6}$ cm^2 s^{-1}, $K = 1$, $\alpha = 1$). *Symbols*, FEM solutions (*open inverted triangle* slab, *filled circle* infinite cylinder, *filled rectangle* sphere), *curves* analytical solutions (*dotted* slab, *continuous* cylinder, *dashed* sphere)

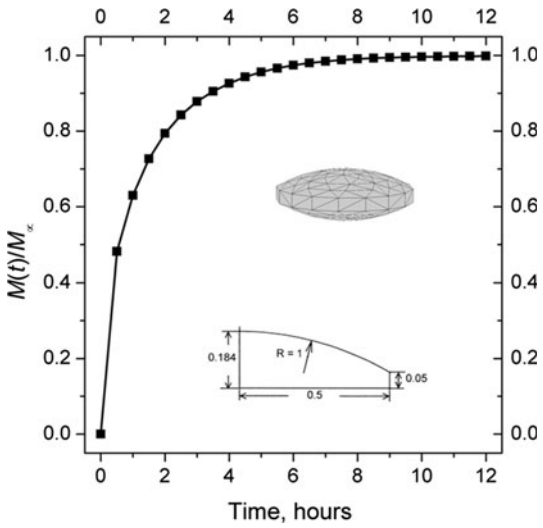

Fig. 3 $M(t)/M_\infty$ versus time (constant ρ and D, well-stirred finite outer volume). Comparison of release profile calculated by FEM with another FEM solution drawn from literature [8] for a convex tablet whose dimensions are reported down, in a bi-dimensional outline ($D = 1 \times 10^{-6}$ cm^2 s^{-1}, $\alpha = 10$, $K = 1$). *Filled square* FEM solution from this work, *straight line* FEM solution from literature

than the amount initially loaded, and results smaller than the M_∞ released into a *perfect sink*.

3.3 Release into a well-stirred finite volume, convex tablet

Many matrix devices intended for controlled drug release have complex geometries. For such systems it is necessary to study a 3-D diffusive process and, normally, derivation of analytical solutions for the Fick's second law of diffusion is very difficult, even impossible. The situation gets worse if the release takes place with time-variant boundary conditions, as occurs in the case of finite release volume. In this work the release from a convex tablet (whose dimensions, in centimeters, are reported in Fig. 3) was investigated, and the solution, in terms of evolution of fractional release with time, was compared with the profile obtained by Zhou and Wu [8]. The values assigned to the model parameters are the same used by the above-mentioned researchers: $C_0 = 0.15$ mg cm^{-3} (initial drug concentration) and $D = 1 \times 10^{-6} \times$ cm^2 s^{-1} (drug diffusivity) (also in this case, as in Sect. 3.1, the parameters choice was dictated by previous selection made by the Authors of the first work); the release occurs from all the device's surfaces, to a dissolution medium with a volume equal to 10 times the matrix' one ($\alpha = 10$, $K = 1$). As it can be seen from the Fig. 3, the two codes' predictions perfectly agree.

3.4 Concentration-dependent diffusion coefficients, simple-shaped matrices

If the diffusivity of both the drug and the water is somewhat influenced by the concentration of one of the species present in the system, it is evident that diffusion equations of water and drug are coupled and their solution must occur simultaneously. For example, the pseudo-diffusion coefficients D_k ($k = 1$ for water and 2 for drug) in matrix systems strongly depend on hydration level achieved by the device during the release process, and can be modeled according to the following equation (9):

$$D_k(\omega_1) = D_k^* \exp\left[-\beta_k\left(1 - \frac{\omega_1}{\omega_{1,eq}}\right)\right] \tag{9}$$

where $D_k^*/\exp(\beta_k)$ is the value of the pseudo-diffusion coefficient in the dry matrix ($\omega_1 = 0$), and D_k^* is the value of the pseudo-diffusion coefficient in the fully swollen matrix ($\omega_1 = \omega_{1,\,eq}$). At this point, diffusion equations for water and drug in terms of mass fraction of the diffusing species (ω_k) were implemented and solved with the following initial (10) and boundary conditions (11):

$$@\, t = 0 \quad \forall \vec{x} \in \Omega \quad \begin{cases} \omega_1 = \omega_{10} = 0 \\ \omega_2 = \omega_{20} = 0.3 \end{cases} \tag{10}$$

$$@\, \vec{x} \in \Gamma \quad \forall t > 0 \quad \begin{cases} \omega_1 = \omega_{1eq} = 0.8 \\ \omega_2 = \omega_{20} = 0^* \quad {}^*\text{perfect sink} \end{cases} \tag{11}$$

The 1-D diffusion problem relative to the same geometries of the previous cases (a slab, a cylinder and a sphere) was investigated. Besides, fixed boundaries of the devices were assumed: that means system density is an invariant, i.e. matrices do not swell because of the water up-take and do not erode because of the polymer dissolution in the release medium. This approximation is quite strong, as water penetration (with the subsequent increase in diffusivities) and matrix swelling is concomitant phenomena.

The simulations were performed using the following diffusion parameters: $D_1^* = 5.6 \times 10^{-10}$ m^2 s^{-1}, $D_2^* = 8 \times 10^{-11}$ m^2 s^{-1}, $\beta_1 = 2.5$, $\beta_2 = 8.3$. Then the FEM results were compared with the profiles obtained by Barba et al. [18], by means of a Finite Differences (FD) code, elsewhere validated. In Fig. 4 evolution versus the square root of the dimensionless time (τ) of the fractional drug release (FEM results and FD results) is reported; the pseudo-diffusion coefficient taken as reference in the definition of τ is D_2^*. Because of the low initial D_2 value (due to the dehydration of the matrix), the delivery rate is quite low for short times, though the drug concentration gradient which causes the diffusive transport is initially on its maximum value. The match between the FEM code and the FD one is satisfactory, confirming the accuracy of the implemented models.

Both the techniques require similar computational time, even if the FD scheme was implemented by an high-level mathematical programming language (Mathcad 14, Mathsoft Engineering and Education, Inc.) whereas the FEM scheme was implemented using a commercial code (Comsol 3.4, see Sect. 2). The FD scheme was 1-D, the FEM scheme was one- (slab), two- (cylinder) or 3-D (sphere), therefore a comparison of the mesh size is not straightforward. It is worth noticing that, even the computational time requirements are similar, the FD scheme cannot be easily extended to complex geometries, then the use of FEM schemes are preferred.

4 Case histories

After the validation stages, two case histories from literature were analyzed and modeled, both confirming effective results achieved with the FEM procedures adopted and pointing out the possibility to simulate more complex systems, with a good level of detail. In the first case, a model able to predict the drug release kinetics from a porous system was worked out. In order to validate such a code, release data coming from a work of Horcajada et al. [19] were used; they studied the influence of pore dimensions of mesoporous materials (bio-ceramics MCM-41) on the release rate of Ibuprofen, a common use analgesic and anti-inflammatory (Sect. 4.1). In the second case a work by

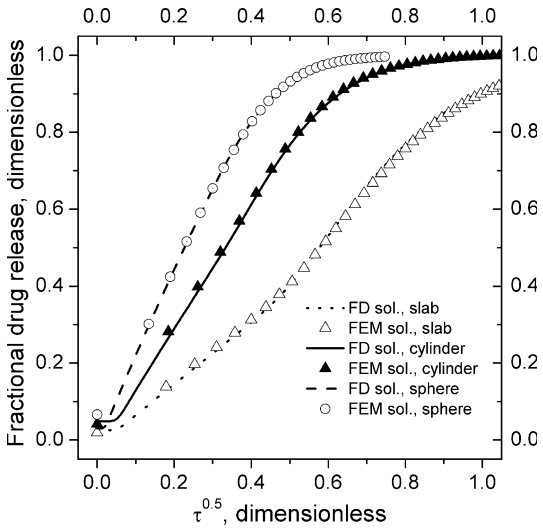

Fig. 4 Fractional drug release versus the square root of dimensionless time, τ (constant ρ, water concentration-dependent D, perfect sink condition). Comparison of release profile calculated by FEM with FD code by Barba et al. [18] for three types of geometry ($a = 0.65$ cm, $D_1^* = 5.6 \times 10^{-6}$ cm^2 s^{-1}, $D_2^* = 8 \times 10^{-7}$ cm^2 s^{-1}, $\beta_1 = 2.5$, $\beta_2 = 8.3$). *Symbols*, FEM solutions (*open triangle* slab, *filled triangle* infinite cylinder, *open circle* sphere), *curves* FD solutions (*dotted* slab, *continuous* cylinder, *dashed* sphere)

Grassi et al. [20], concerning the macro- and microscopic characterization of a scleroglucan-borax gel system loaded with active principles, inspired a model capable to identify the thickness of the aqueous interfacial layer, which surrounds the cylindrical gel and exerts an additional resistance to diffusive phenomena, reducing drug delivery rate (Sect. 3.2).

4.1 Ibuprofen release from MCM-41 matrices

During the release process of a drug loaded into a porous matrix, the system can be schematized as a biphasic medium, constituted by the matrix where the active principle is dispersed and a fluid phase (initially solute-free) that penetrates porous structure's cavities and dissolves the drug, making it capable to diffuse out to the external medium. Between the two phases, equilibrium and mass transfer phenomena establish, whose modeling can be described through thermodynamic equilibrium relations, obtained considering matrix and solvent characteristics, mass transfer equations and material balances, implemented with reference to the transferring component (the drug), on differential volumes of the system (the nanoporous bio-ceramic particle). The object of modeling is the determination of both the concentration of the drug in the dissolution medium which infiltrates into the pores (C, mg_{drug}/mg_{fluid}) (12) and the concentration of the drug immobilized in the solid matrix (Q, mg_{drug}/mg_{matrix}) (13).

$$C = C(t, \vec{x}, \Lambda) \tag{12}$$

$$Q = Q(t, \vec{x}, \Lambda). \tag{13}$$

Both the concentrations are functions of independent temporal (t) and spatial ($\vec{x}$) variables, and of the system's physical parameters vector (Λ). The system under consideration can be modeled by two partial differential equations (PDEs), a transient mass balance equation for the drug in the fluid phase (14) and a transient mass balance equation for the drug in the solid phase (15):

$$\rho_f \varepsilon \frac{\partial C}{\partial t} = \rho_f \varepsilon \overrightarrow{\nabla} \cdot (D_L \overrightarrow{\nabla} C) + J(Q, C, \Lambda) \tag{14}$$

$$\rho_s (1 - \varepsilon) \frac{\partial Q}{\partial t} = -J(Q, C, \Lambda). \tag{15}$$

Here ρ_s is the density of the bio-ceramic matrix (mg_{matrix}/cm^3), ρ_f is the density of the dissolution medium (mg_{fluid}/cm^3), $(1 - \varepsilon)$ is the volume fraction occupied by solids (ε is the porosity, i.e. the volume fraction occupied by pores), $J(Q, C, \Lambda)$ is the mass flowrate, per unit of volume, of the active principle leaving the solid phase to the fluid one into pores (mg_{drug}/cm^3 s), D_L is the apparent diffusivity of the drug in the fluid bounded in the pores. The system of PDEs can be written as follows (16):

$$\begin{cases} \dfrac{\partial C}{\partial t} = \overrightarrow{\nabla} \cdot (D_L \overrightarrow{\nabla} C) - \dfrac{(1 - \varepsilon)}{\varepsilon} \dfrac{\rho_s}{\rho_f} \dfrac{\partial Q}{\partial t} \\ \dfrac{\partial Q}{\partial t} = -f(Q, C, \Lambda) \end{cases} \tag{16}$$

where $f(Q, C, \Lambda) = \frac{J(Q,C,\Lambda)}{\rho_s(1-\varepsilon)}$. To be solved, it calls for the definition of appropriate initial and boundary conditions, the selection of an expression for the forcing term f, on the basis of equilibrium and transport phenomena, the knowledge of the system's parameters (geometry, ε, ρ_s, ρ_f) and the determination of equilibrium and transport parameters. The spherical particles, of radius $R_S = 500$ nm, are initially loaded with a homogeneous drug concentration, Q_0; the fluid phase is initially pure ($C_0 = 0$). On the surface a *perfect sink* condition is assumed. Particles' radius, in absence of erosion and swelling phenomena, results constant. Every moment, the overall drug mass contained into the matrix (m_F) can be calculated as sum of the mass contained into the solid phase and the mass contained into the liquid, i.e. (17):

$$m_F(t) = \int_V \rho_s (1 - \varepsilon) Q \mathrm{d}V + \int_V \rho_f \varepsilon C \mathrm{d}V \tag{17}$$

where V is the particle volume. So, the fractional release can be calculated as (18):

$$R(t) = 1 - m_F(t)/m_{F0} \tag{18}$$

where m_{F0} is the initial drug mass loaded in the device. In the course of modeling, the equilibrium between the Ibuprofen on the particle surface and the drug solubilized in the fluid and the drug transport from the solid surface to the liquid have been taken into account as steps controlling the rate of the entire process. In these hypotheses, the forcing term f assumes the following form (19):

$$f(Q, C, \Lambda) = k_c (C^* - C) \tag{19}$$

where k_c is the Ibuprofen transfer coefficient from the pore surface to the fluid phase (s^{-1}): the greater its value, the smaller the resistance to the transport encountered by the drug. C^* represents the drug concentration at solid–fluid interface (fluid-side), in equilibrium with the solid-side concentration Q^* (supposed as uniform on the whole internal channels' surface, i.e. $Q = Q^*$). Any equilibrium formula can be chosen to describe the relationship between the two concentrations, Q and. The simplest is a partition relation, with a single material parameter, the partition factor K, and it was selected here to avoid the introduction of other model parameters.

$$Q^* = KC^*. \tag{20}$$

Therefore, the system of PDEs to solve becomes (21):

$$\begin{cases} \dfrac{\partial C}{\partial t} = \overrightarrow{\nabla} \cdot \left(D_L \overrightarrow{\nabla} C \right) - \dfrac{(1 - \varepsilon)}{\varepsilon} \dfrac{\rho_s}{\rho_f} \dfrac{\partial Q}{\partial t} \\ \dfrac{\partial Q}{\partial t} = -k_c (C^* - C) \\ Q = KC^* \end{cases} \tag{21}$$

equipped with the initial and boundary condition previously described. At this point, known the densities of the two phases ($\rho_s = 2{,}600$ mg cm^{-3}, $\rho_f = 1{,}000$ mg cm^{-3}) and the porosity of the different MCM-41 samples, and assuming a partition factor equal to 1 (the error in this approximation will be offset by the parameter optimization procedure), it is possible to numerically solve the system, optimizing the parameters D_L and k_c on the basis of a comparison with the experimental Ibuprofen delivery data collected by Horcajada et al. [19]. In the Table 3 the principal characteristics of the four MCM-41 samples calcined and loaded with Ibuprofen are reported [19]. More details about the formulation and the preparation of the bio-ceramic samples and about the drug incorporation's procedures can be found in [19].

Since k_c represents a local transfer coefficient and it is not correlated to the pore dimensions, in order to reproduce the behavior of all the analyzed bio-ceramic materials, it is possible to optimize the k_c value for a single mesoporous matrix and then adopt the same value for the other samples, so performing just the optimization of the apparent diffusivities. In particular a value of the mass transfer coefficient equal to 1×10^{-4} s^{-1} was found.

In Fig. 5 the predictions of the model presented in this work, in terms of fractional release of Ibuprofen, were reported as curves, the experimental data as symbols. It can be observed that the implemented code guarantees a good reproduction of the experimental data, for all the investigated bio-ceramics. The delivering rate strongly decrease as the pore sizes varies from 3.6 to 2.5 nm: this is caused by the reduction of the apparent diffusivity, due to the larger specific hindrance of the Ibuprofen molecules inside smaller channels. The narrower are the pores, the more difficult is the diffusive phenomenon. Between the apparent drug diffusivity and the pore diameter a linear dependence was discovered (Fig. 6) that, from the engineering point of view, expresses the chance to use the transport model just described as a predictive tool to reconstruct the release kinetics from similar porous materials, with any pore dimension.

4.2 Vitamin B12 and myoglobin release from hydrogels

Grassi et al. [20] prepared pharmaceutical formulations for oral assumption constituted by Scleroglucan (a water-soluble polysaccharide produced by fungi of genus *Sclerotium*), borax (a ligand suitable for polymers containing hydroxyl groups) and molecules of pharmaceutical interest, like Theophylline, Vitamin B12 and Myoglobin. Tablets were produced with consistency of a high-stability hydrogel, suitable for controlling and modifying host molecules' release. In particular, the gel has been structured in the form of cylindrical tablets, of radius R_c equal to 1.1 cm and of height $H = 1$ cm. During drug release tests (the initial drug concentration, C_0, is 5 mg cm^{-3}), carried out in 200 cm^3 of distilled water (V_{rel}, pH = 5.5), the gel was kept at a certain height from the bottom of the container by a thin web, while the dissolution medium was magnetically stirred. The erosion of the gel, in terms of polymer dissolution, was quantitatively determined by a colorimetric method, using phenol in the presence of sulphuric acid. In the first 8 h, the researchers found negligible erosion ($\leq$4%). Besides, the experimental evidence has explained

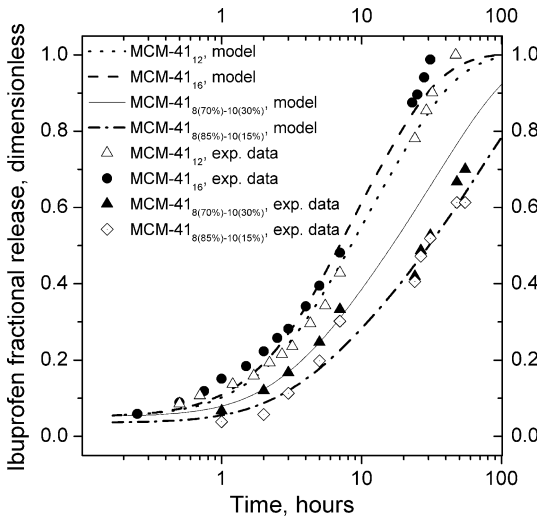

Fig. 5 Ibuprofen delivery from different pore-sized MCM-41. *Symbols*, experimental data [*open triangle* MCM-41$_{12}$, *filled circle* MCM-41$_{16}$, *filled triangle* MCM-41$_{8(70\%)-10(30\%)}$, *open diamond* MCM-41$_{8(85\%)-10(15\%)}$], *curves* model predictions [*dotted* MCM-41$_{12}$, *dashed* MCM-41$_{16}$, *continuous* MCM-41$_{8(70\%)-10(30\%)}$, *dash dotted* MCM-41$_{8(85\%)-10(15\%)}$]

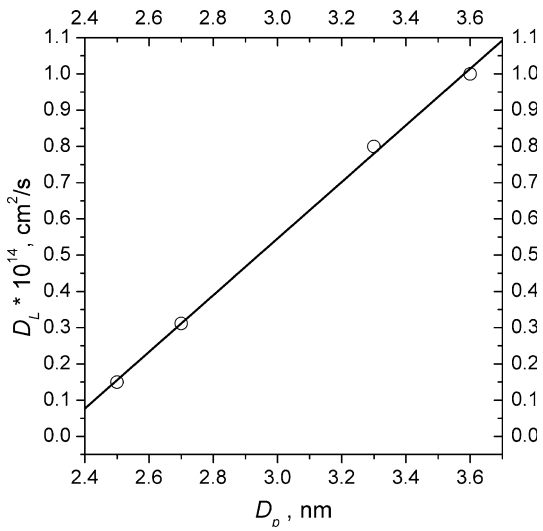

Fig. 6 Apparent diffusivity of the drug molecules into the liquid phase penetrated the pores versus pore diameter. *Open circle* optimized D_L, *straight line* fitting straight line

Table 3 Characterization and results of Ibuprofen content of MCM-41 samples [4]

	MCM-41$_{16}$	MCM-41$_{12}$	MCM-41$_{8(70\%)-10(30\%)}$	MCM-41$_{8(85\%)-10(15\%)}$
d (nm), Network spacing	3.9	3.65	3.4	3.4
a_0 (nm), Unit cell size	4.42	3.84	3.9	3.9
D_p (nm), Pore diameter	3.6	3.3	2.7	2.5
v_p (cm^3/g), Pore specific volume	0.98	0.85	0.95	1.012
ε, Porosity	0.718	0.688	0.712	0.725
mg$_{IBU}$/g, Ibuprofen content	337	233	150	106
Q_0	0.34	0.23	0.19	0.11

that the formulated hydrogels don't further swell when introduced in the release environment [20]. Inevitably the presence of a web around the device represents a resistance to the drug diffusion towards the external medium: it lightly reduces the mass transfer surface area and promotes the boundary layer formation (of thickness δ) at the interface between the gel and the surroundings. To model the diffusive process, two diffusion coefficients have been introduced by Grassi and co-workers: an interfacial diffusion coefficient (D_i) in the aqueous level and a bulk diffusion coefficient (D_b) in the gel network ($D_i < D_b$). Fick's second law of diffusion (22) has been numerically solved in cylindrical coordinates according to the control volume method, satisfying the following initial (23) and boundary conditions (24):

$$\frac{\partial C}{\partial t} = \frac{D}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C}{\partial r}\right) + D\frac{\partial^2 C}{\partial z^2} \tag{22}$$

$$@\, t = 0, \forall (r,z) \in \Omega \quad C = C_0 \quad C_{rel} = 0 \tag{23}$$

$$@ (r,z) \in \Gamma, \forall t \quad C(r,z,t) = KC_{rel}(t) \tag{24}$$

$$V_{rel}C_{rel}(t) = \pi R_c^2 HC_0 - \int_0^H \int_0^{R_c} C(r,z,t) 2\pi r \mathrm{d}r\mathrm{d}z \tag{25}$$

K is the partition factor of the drug between the gel and the environmental release fluid, C_{rel} is the drug concentration in the release medium. The equation 25 is the drug mass balance for the gel/release fluid system and states the relation between C_{rel} and $C(r, z, t)$. Set $K = 1$, the proposed model has two parameters (D_i and D_b), adjusted by comparison with experimental data. For Vitamin B12 the researchers have found $D_b = (3.67 \pm 0.22) \times 10^{-6}$ cm^2 s^{-1} and $D_i = (4.0 \pm 0.4) \times 10^{-7}$ cm^2 s^{-1}; for Myglobin $D_b = (1.21 \pm 0.21) \times 10^{-6}$ cm^2 s^{-1} and $D_i = (1.6 \pm 0.3) \times 10^{-7}$ cm^2 s^{-1}. Since D_i is about one order of magnitude lower than D_b for both the host molecules, the web around the device really exerts an additional resistance. At this point, known the two drugs' diffusion coefficients in water, Grassi et al. were able to determine the average polymeric network mesh. In this work, the results drawn from literature in terms of diffusion coefficients (without further optimization) have been used to work out a FEM model analogous to literature one, but also able to provide in output the thickness of the aqueous level, just implementing, with a Boolean expression (26), the following drug diffusion coefficient (D):

$$D = D_i \cdot (-\delta < z < 0 \text{ or } H < z < H + \delta \text{ or } R_c < r < R_c + \delta) + D_b \cdot (0 < z < H \text{ and } r < R_c). \tag{26}$$

The coordinate system (r, z) has been fixed so that the origin coincides with the centre of the hydrogel base surface. So, inside the bulk of the tablet, $D = D_b$, in the aqueous layer $D = D_i$. Varying from time to time the thickness of the interfacial layer, the value of δ that guarantees the best agreement with the release experimental data has been obtained. The results of the simulations in terms of time evolution of the ratio $C_{rel}/C_{rel,\infty}$ were compared with experimental data and shown in Fig. 7.

The best comparison can be found for $\delta = 180$ μm in the case of Vitamin B12 and for $\delta = 100$ μm in the case of Myoglobin.

5 Conclusions

The modeling of drug release from solid systems is an interesting goal for the pharmaceutical sciences. At the same time, it is a hard task, because of the large number of concurrent phenomena which take place (solvent and drug diffusion in presence of variable diffusivity, matrix swelling and/or erosion which lead to moving fronts, different boundary conditions). The model equations, aiming to describe complex transient phenomena in the space, are at least PDEs with variable coefficients and often with changing boundary conditions and moving boundaries. Such complex behaviors ask for numerical solutions, such as Finite Difference or Finite Element methods.

In this work, the diffusion equation was solved in transient using a commercial FEM code, accounting for different geometries, for two distinct boundary conditions (the so-called perfect sink, i.e. the negligible drug concentration in the dissolution medium, or the presence of a

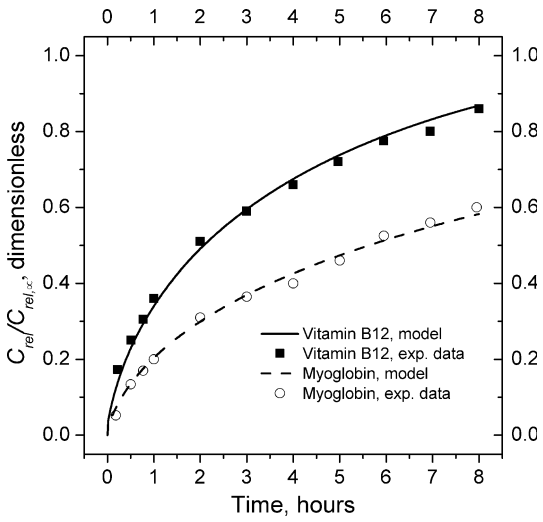

Fig. 7 Time evolution of the ratio $C_{rel}/C_{rel,\infty}$ for the two guest drugs, Vitamin B12 and Myoglobin, released from a cylindrical SCLG-borax hydrogel. *Symbols*, experimental data (*filled square* Vitamin B12, *open circle* Myoglobin), *curves* model predictions (*continuous* Vitamin B12, *dashed* Myoglobin)

well-mixed finite external volume). For these problems the numerical solution is successfully compared with the analytical solutions, available from literature. Then, the FEM code was tested in predicting the behavior in presence of variable diffusivity, giving the same results of a FD code from literature. The validation section was completed by the simulation of a complex shape matrix system, the results obtained being in agreement with results taken from literature, also obtained by a Finite Element Method.

Afterwards, codes based on FEM were purposely pointed out, to solve two problems, the desorption of a drug from some bio-ceramics and the release of two drugs from a matrix system, whose experimental data were taken from literature. Both the cases were successfully described by suitable models, confirming the ability of code based on Finite Element Method in the description of the drug release problems.

Therefore, the FEM approach was proven useful in the analysis of drug release phenomena. A further step, currently under consideration by our research group, is the analysis of the phenomena which cause the movement of the matrices boundary, i.e. the swelling and the erosion of the matrices.

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