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Numerical Modelling of Drug Release from 2D HPMC-Matrices

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Abstract: *The article considers numerical modelling of drug release from HPMC-matrices assuming the main controlling processes are diffusion of water and drug and swelling of the matrix. A detailed mathematical description of matrix swelling, connected with the free boundary conditions of the arisen model problem, is introduced. A numerical approach to solution of the posed nonlinear 2D problem is developed on the basis of finite element domain approximation and time difference method. It is implemented in noncommercial software which is used for numerical simulation of fractional drug release under various shapes and sizes of the tablets. This investigation of the effect of aspect ratio (radius/height) and sizes of HPMC tablets on drug release is an inexpensive and effective tool to modify the release kinetics. The proposed numerical approach enables further generalization of the model and performing more profound investigations of the effect of the initial drug loading, matrix erosion and type of release medium.*

Keywords: *Drug release, Diffusion, HPMC Swelling, FEM, Difference scheme.*

Introduction

Hydrophilic polymers are widely used for preparation of oral controlled drug delivery systems [1]. From commercial point of view, hydroxypropyl methylcellulose (HPMC) is one of the most often used carrier materials in pharmaceutical applications. An important characteristic property of HPMC is that upon contact with biological fluid (e.g. gastrointestinal fluid) it swells significantly changing its micro- and macrostructure.

A comprehensive mathematical model describing drug release from HPMC-based matrix tablets has been developed during the last decade [6-10]. It takes into account diffusion of water and drug, non constant diffusivities, swelling of the system and polymer drug dissolution in radial and axial directions (cylindrical geometry).The so called "sequential layer" model is implemented by using finite difference method which leads to some limitations when generalizing model equations, initial and boundary conditions.

Recently a new finite element (FE) approach to modelling drug release from 2D polymeric matrices was proposed [2-4]. This approach based on FE domain approximation and appropriate time difference method allows direct solving of the corresponding strongly nonlinear model problem.

The aim of the present paper is to offer a similar model to the "sequential layer" one following the above approach from the point of view of further model generalization. The review of the papers of Siepmann et al. [7-10] shows there is a lack of mathematical details when describing the swelling process in time. Obviously, depending on the chosen

approximation technique there will be some differences in the solution of the coupled partial differential equations [6]. That is why our purpose is to introduce a strict mathematical description of the mass balance of the fluid penetration into the matrix which governs its swelling. The increase of the matrix dimensions and volume will be evaluated and a new FE discretization will be performed at each time step. Numerical simulations of drug release of propranolol hydrochloride for different sizes and aspect ratio (radius/height) of the tablet will be investigated.

Statement of the problem

We consider drug release from a cylindrical matrix of radius R and height $2H$ completely surrounded by a fluid (water) schematically presented in Fig. 1a. It is assumed that: (1) main controlling mechanisms of drug kinetics are water penetration into the matrix, drug diffusion and matrix swelling; (2) drug dissolution is neglected (very rapid in respect to the other processes); (3) matrix swelling is ideal and isotropic throughout the system; (4) the water concentration at the tablet surface is at its equilibrium value; (5) perfect sink conditions are maintained; (6) water imbibing in axial/radial direction leads to a volume increase in axial/radial direction that is proportional to the relative surface area in this direction [7].

The model equations describing the main controlling processes in a cylindrical matrix occupying the domain $\Omega \subset R^2$ (Fig. 1b) are as follows:

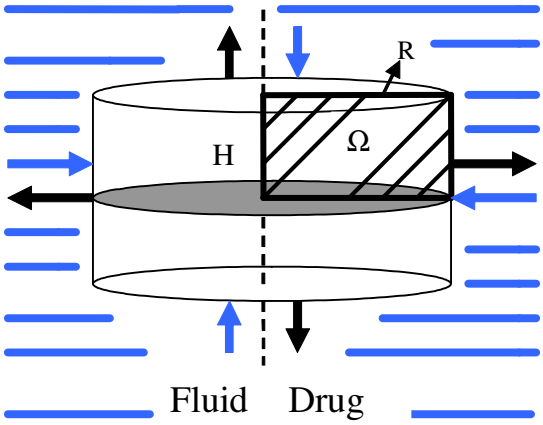

Fig. 1a Schematic representation of drug release from a cylindrical tablet

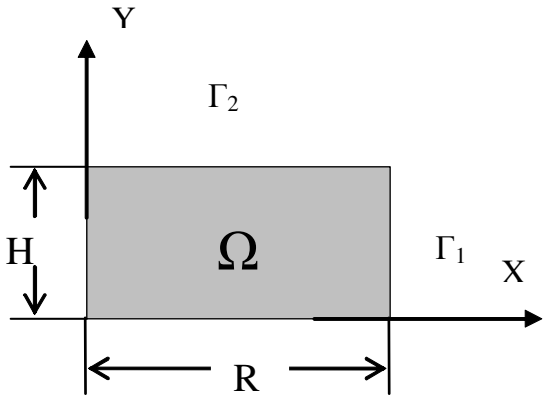

Fig. 1b The domain Ω with boundary $\Gamma = \Gamma_1 \cup \Gamma_2$ as a quarter of the axial cross section

$$\frac{\partial c_1}{\partial t} = div(D_1(c_1) grad\, c_1) \quad \text{in} \quad \Omega_t \times (0, t_f] \tag{1}$$

$$\frac{\partial c_2}{\partial t} = div(D_2(c_1) grad\, c_2) \quad \text{in} \quad \Omega_t \times (0, t_f] \tag{2}$$

where: $c_1 = C_1 / c_{1eq}$, $c_2 = C_2 / c_{in}$, c_{1eq}, c_{in}, $D_1(c_1), D_2(c_1)$, t and t_f are the dimensionless concentration of the penetrating water and drug, the equilibrium water concentration, the initial drug concentration, the concentration dependent water and drug diffusivity, the time and the final moment under consideration, respectively.

Following the free volume theory a Fujita-type exponential dependence of the diffusion coefficients are considered [5]:

$$D_i(c_1) = D_{ieq}\exp\left(-\beta_i(1-c_1)\right),\ i=1,2 \tag{3}$$

where D_{1eq}, D_{2eq} are the diffusion coefficients in the equilibrium swollen state of the system and β_1, β_2 are dimensionless constants characterizing the concentration dependence.

The model problem is posed under the following initial and boundary conditions:

$$c_1(x,y,0)=0,\ 0\le x\le R_0,\quad 0\le y\le H_0 \tag{4}$$

$$c_2(x,y,0)=1,\ 0\le x\le R_0,\quad 0\le y\le H_0 \tag{5}$$

$$c_1(x,y,t)=1,\ 0<t\le t_f,\ x=R_t,\ 0\le y\le H_t \ \text{ or } \ 0\le x\le R_t,\ y=H_t \tag{6}$$

$$c_2(x,y,t)=0,\ 0<t\le t_f,\ x=R_t,\ 0\le y\le H_t \ \text{ or } \ 0\le x\le R_t,\ y=H_t \tag{7}$$

where R_0, H_0 are the initial dimensions of the tablet and R_t, H_t are the current ones.

The basic equation describing matrix swelling is the following:

$$\frac{d\overline{V}}{dt}=\frac{1}{\rho_1}\frac{d\overline{M}_1}{dt}=\frac{c_{1eq}}{\rho_1}\frac{d}{dt}\int_{\overline{\Omega}(t)}c_1(t)dv \tag{8}$$

where $\overline{M}_1$ is the mass of the water corresponding to the domain under consideration $\overline{\Omega}$ with volume $\overline{V}$ and ρ_1 is the water density.

The fractional drug release and water uptake are expressed as follows:

$$R(t)=1-\frac{1}{S_t}\int_{\Omega_t}c_2dv,\qquad U(t)=\frac{1}{S_t}\int_{\Omega_t}c_1dv \tag{9}$$

where S_t is the area of the current cross-sectional domain Ω_t.

Finite element statement

The numerical solution of the initial boundary value problem (1-7) is sought in the finite element (FE) form:

$$\overline{c}_1(x,y,t)=\sum_{p=1}^{M}N_p(x,y)c_{1p}(t),\ \overline{c}_2(x,y,t)=\sum_{p=1}^{M}N_p(x,y)c_{2p}(t) \tag{10}$$

or $\overline{c}_1(x,y,t)=\mathbf{C}_1^T(t)\mathbf{N}(x,y),\ \overline{c}_2(x,y,t)=\mathbf{C}_2^T(t)\mathbf{N}(x,y)$

where $N_p, p=1,...,M$ are the shape interpolation functions corresponding to the current FE discretization of the domain Ω_t and $c_{1p}, c_{2p}, p=1,....M$ are the nodal values of the water and drug concentrations, respectively; $\mathbf{C}_1, \mathbf{C}_2, \mathbf{N}$ are vectors with elements c_{1p}, c_{2p}, N_p. The upper notation $(\cdot)^T$ means a vector transposition.

Applying the semi-discrete Galerkin method to equations (1), (2) (as in [2-4]) the following initial matrix problem for the vector functions $\mathbf{C}_1, \mathbf{C}_2$ is obtained:

$$\frac{d[\mathbf{CM}\ \mathbf{C}_1]}{dt} + \mathbf{ST1}\ \mathbf{C}_1 = \mathbf{0} \tag{11}$$

$$\frac{d[\mathbf{CM}\ \mathbf{C}_2]}{dt} + \mathbf{ST2}\ \mathbf{C}_2 = \mathbf{0} \tag{12}$$

$$\mathbf{C}_1 = \mathbf{0}, \quad \mathbf{C}_2 = \mathbf{I} \tag{13}$$

where $\mathbf{CM} = \int_{\Omega_t} \mathbf{N}\mathbf{N} dv$, $\mathbf{ST1} = \int_{\Omega_t} \overline{D}_1(c_1) \nabla \mathbf{N} \nabla \mathbf{N} dv$, $\mathbf{ST2} = \int_{\Omega_t} \overline{D}_2(c_1) \nabla \mathbf{N} \nabla \mathbf{N} dv$. The unit vector is denoted with **I**.

Time difference scheme

The following nonlinear matrix equations are obtained after integration of (11), (12) by using a two-point time difference scheme:

$$\begin{aligned} &\mathbf{A1}_{n+1}\ \mathbf{C}_1^{n+1} = \mathbf{B1}_n\ \mathbf{C}_1^n \\ &\mathbf{A2}_{n+1}\ \mathbf{C}_2^{n+1} = \mathbf{B2}_n\ \mathbf{C}_2^n \end{aligned} \tag{14}$$

where

$$\mathbf{A1}_{n+1} = \mathbf{CM} + 0.5\Delta_{n+1}\mathbf{ST1}_{n+1}$$

$$\mathbf{B1}_n = \mathbf{CM} - 0.5\Delta_{n+1}\mathbf{ST1}_n$$

The lower index of the FE matrices corresponds to the considered time level under introduced time difference mesh. Matrix **CM** is assumed to be unchanged within the considered time step as FE remeshing is performed at the next time step.

In order to avoid equations nonlinearity the next predictor-corrector scheme is proposed:

$$\begin{aligned} &\mathbf{A1}_n\ \tilde{\mathbf{C}}_1^{n+1} = \mathbf{B1}_n\ \mathbf{C}_1^n + \mathbf{O}(\Delta_{n+1}^2) \\ &\mathbf{A2}_n\ \tilde{\mathbf{C}}_2^{n+1} = \mathbf{B2}_n\ \mathbf{C}_2^n + \mathbf{O}(\Delta_{n+1}^2) \end{aligned} \tag{15}$$

$$\begin{aligned} &\mathbf{A1}_{n+1}^*\ \mathbf{C}_1^{n+1} = \mathbf{B1}_n\ \mathbf{C}_1^n + \mathbf{O}(\Delta_{n+1}^3) \\ &\mathbf{A2}_{n+1}^*\ \mathbf{C}_2^{n+1} = \mathbf{B2}_n\ \mathbf{C}_2^n + \mathbf{O}(\Delta_{n+1}^3) \end{aligned} \tag{16}$$

where $\mathbf{A1}_{n+1}^*$, $\mathbf{A2}_{n+1}^*$ are evaluated at the obtained from (15) predictor solutions $\tilde{\mathbf{C}}_1^{n+1}$, $\tilde{\mathbf{C}}_2^{n+1}$. The notation $\mathbf{O}(\Delta_{n+1}^3)$ means a second order accuracy of the numerical scheme.

The scheme correctness is investigated and the following sufficient condition for its initial stability is derived:

$$\tilde{\Delta}_{n+1} \le \min\left(\frac{1}{\beta_1}; \frac{1}{D_{2eq}\beta_2}\right) \tag{17}$$

where $\tilde{\Delta}_{n+1}$ is the dimensionless time step under the introduced dimensionless variables $T = \frac{tD_{1eq}}{R_0^2}$, $X = \frac{x}{R_0}$, $Y = \frac{y}{R_0}$.

Swelling formulas

The matrix swelling due to the water penetration into the tablet is assumed in two main directions – radial and axial. Integrating eq. (8) for each volume element (cylindrical domain), corresponding to the k^{th} layer in y-direction with one and the same radial cross-section, the following formula is obtained:

$$\Delta y_{n+1}^{k} S_{n+1} - \Delta y_{n}^{k} S_{n} = \frac{c_{1eq}}{\rho_1} \bar{c}_{1,n+1}^{k} \Delta y_{n+1}^{k} S_{n+1} - \frac{c_{1eq}}{\rho_1} \bar{c}_{1,n}^{k} \Delta y_{n}^{k} S_{n}, \quad k = 1,...,M_1 \tag{18}$$

where Δy_{n+1}^{k} and S_{n+1} are the thickness of the k^{th} layer (the distance between 2 FE nodes in y-direction) at (n+1) time level and the area of the radial cross-section at the same time level. The average water concentration for the k^{th} layer at (n+1) time level is denoted by $\bar{c}_{1,n+1}^{k}$. It is calculated in terms of the nodal concentration values within each k^{th} layer obtained from (15), (16).

Taking into account the assumption (6) when posing the model problem the following formula for matrix swelling of each volume element in y-direction is derived:

$$\Delta y_{n+1}^{k} = \Delta y_{n}^{k} \sqrt{\frac{\rho_1 - c_{1eq} \bar{c}_{1,n}^{k}}{\rho_1 - c_{1eq} \bar{c}_{1,n+1}^{k}}}, \quad k = 1,...,M_1 \tag{19}$$

Then we can evaluate the half thickness of the tablet at each time level and in the equilibrium state as follows:

$$H_{n+1} = \sum_{k=1}^{M_1} \Delta y_{n+1}^{k}, \quad H_{eq} = H_0 \sqrt{\frac{\rho_1}{\rho_1 - c_{1eq}}} \tag{20}$$

Integrating eq. (8) for the whole cylindrical domain we can express the increase of radius at each time step as follows:

$$R_{n+1} = R_n \sqrt{\frac{H_n}{H_{n+1}} \frac{(\rho_1 - c_{1eq} \bar{c}_{1,n})}{(\rho_1 - c_{1eq} \bar{c}_{1,n+1})}} \tag{21}$$

From (20) and (21) the next expression for the tablet radius in the equilibrium state is derived:

$$R_{eq} = R_0 \sqrt[4]{\frac{\rho_1}{\rho_1 - c_{1eq}}} \tag{22}$$

Numerical results

A numerical procedure created on the basis of the proposed numerical scheme under FE domain approximation (using 2D simplex elements) is implemented in noncommercial software. It is used for obtaining numerical results of fractional release of propranolol hydrochloride in 0.1 M phosphate buffer (pH = 7.4) under the following model parameters $D_{1eq} = 5.6 \times 10^{-6} \text{cm}^2 \cdot \text{s}^{-1}$, $D_{2eq} = 6.3 \times 10^{-7} \text{cm}^2 \cdot \text{s}^{-1}$, $\beta_1 = 2.5$, $\beta_2 = 9.5$, $c_{1eq} = 0.76 \text{g} \cdot \text{cm}^{-3}$ and $\rho_1 = 1 \text{ g} \cdot \text{cm}^{-3}$ [7].

Case 1. Comparison between FEM results of fractional drug release for tablet dimensions of $R_0 = 0.65$ cm, $H_0 = 0.069$ cm and the corresponding experimental and numerical ones obtained by Siepmann et al. [7] is given in Fig. 2.

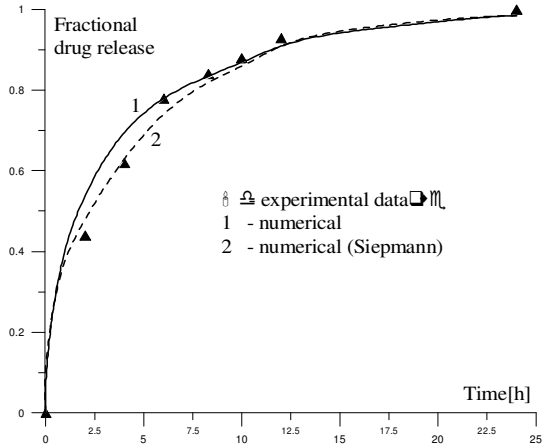

Fig. 2 Numerical results of drug release compared with these ones of Siepmann et al.

A rather good agreement with experimental results for drug release is obtained with exception of the time range (2h, 4h). The established deviations from the results of Siepmann et al. could be explained with the application of a different numerical method and the lack of clear mathematical description of swelling kinetics in [7].

Numerical results for the radius, height and volume increase in respect to the corresponding initial one due to the water penetration are also presented in Fig. 3. It is obvious the swelling process is much faster than the drug release. Swelling steady state is established within the first 2-3 hours (under considered HPMC and release medium).

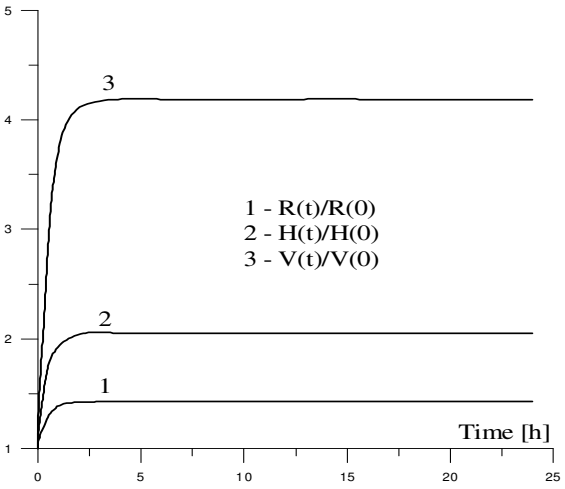

Fig. 3 Increase in radius, height and volume of the HPMC tablet (swelling kinetics)

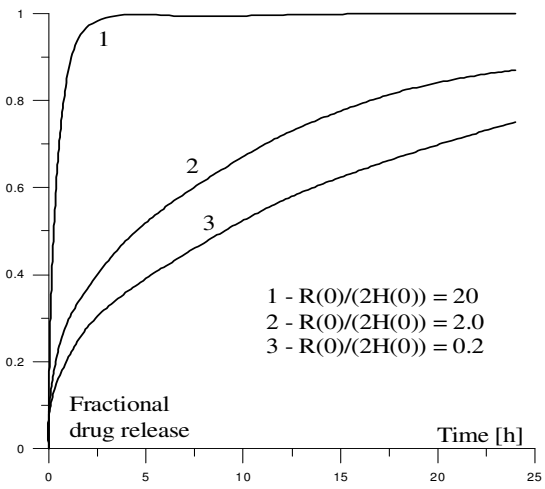

Fig. 4 Effect of the aspect ratio (radius / height) of the tablet on the release kinetics

Case 2. The numerical results for the release of propranolol hydrochloride (phosphate buffer (pH = 7.4)) from tablets with different aspect ratio (R/2H) and constant volume (0.18 cm^3) are

presented in Fig. 4. It is appropriate to use the flat tablets ($R/2H$ = 20) in the case of desired fast drug release (within 4 hours) whether the regular ($R/2H$ = 2) and rod-shaped tablets ($R/2H$ = 0.2) can be designed for very slow drug release. Obviously, the investigation of the effect of aspect ratio is a very easy, inexpensive and effective tool to modify the release kinetics of the system.

Case 3. Influence of the size of the tablets on the release kinetics of propranolol hydrochloride at constant aspect ratio ($R/2H$ = 1.25) is shown in Fig. 5. The full drug release from the smallest tablets is achieved within approximately 24 hours, whether it is significantly slower (66% and 40% within 24 hours, respectively) in the other two cases.

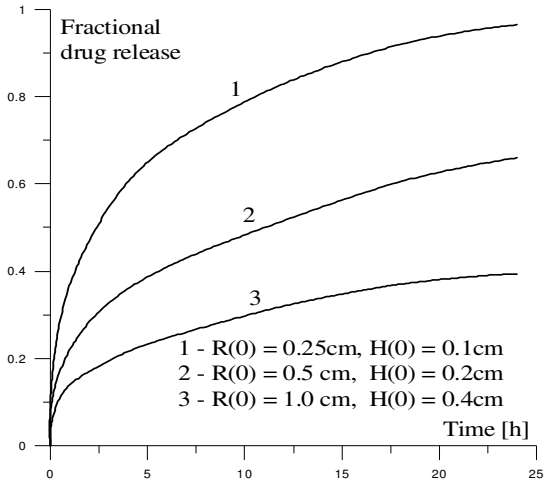

Fig. 5 Effect of the size of the tablets on the release kinetics

Conclusion

A new version of the so called "sequential layer" model for drug release from HPMC matrices [7] is developed. A detailed mathematical description of matrix swelling (one of the main controlling processes), connected with the free boundary conditions of the arisen model problem, is introduced at each time step.

A new FE approach to solution of the posed nonlinear 2D problem is proposed on the basis of FE domain approximation and appropriate time difference scheme. The created noncommercial software is used for numerical investigation of the effect of aspect ratio (radius/height) and sizes of HPMC tablets on drug release profile.

The developed version of "sequential layer" model is an inexpensive and effective tool to predict the drug release kinetics. The proposed numerical approach enables further generalization of the model equations and performing more profound investigations of the effect of the initial drug loading, matrix erosion and type of release medium.

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