ABSTRACT. Numerical modeling of swelling and drug release from HPMC (Hydroxypropyl Methylcellulose) matrices is considered. It is assumed the main controlling processes are diffusion of water and drug, and swelling of the matrix. The recently proposed by the authors mathematical model (a new version of “sequential layer” one) is used for simulation of drug release. The description of matrix swelling due to the water penetration is improved taking into account the initial drug loading and matrix contraction. A numerical approach to solving the arisen nonlinear 2D initial boundary value problem is developed on the basis of finite element domain approximation at each time step and time difference method. The created noncommercial software is used for analyzing the effect of release media and initial drug loading of the considered type of cylindrical tablet (HPMC Methocel K15M, 1% MgSt) on drug release kinetics. The presented numerical approach enables further generalization of the model taking into account matrix erosion.

KEY WORDS: drug release, swelling, initial drug loading, numerical approach

1. Introduction
Polymeric matrices containing hypromellose (HPMC) are widely used for preparation of oral sustained-release drug delivery systems [1]. An important characteristic property of HPMC is that upon contact with biological fluid (e.g. gastrointestinal fluid or water) it swells significantly changing its micro- and macrostructure.

A comprehensive mathematical model (so called “sequential layer” one) describing drug release from HPMC-based matrix tablets has been developed during the last decade [2-4]. 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. This model is implemented by using finite difference method which leads
to some limitations when generalizing model equations, initial and boundary conditions.

Recently a modification of the sequential layer model was developed and a new finite element (FE) approach to modeling drug release from 2D polymeric matrices was proposed [5]. This approach based on FE domain approximation and an appropriate time difference method allows solving strongly nonlinear model problems of the considered type [5, 6]. A detailed mathematical description of matrix swelling, connected with the free boundary conditions, was introduced.

The aim of the present paper is to improve the above model in order to account the effect of the initial drug loading (IDL) on swelling and drug release kinetics. That is why our intent is to introduce a strict mathematical description of the mass balance of the fluid penetration into the matrix simultaneously with drug loss from it. The increase (or/and decrease) of the matrix dimensions and volume change is evaluated and a new FE discretization is performed at each time step. Numerical simulations of drug release kinetics under various initial drug loading are performed and comparison with available experimental data for different drugs is presented.

2. Statement of the problem

Drug release from a cylindrical matrix of radius $R_0$ and height $2H_0$ is considered completely surrounded by a biological fluid or water. It is assumed: (1) main controlling mechanisms of drug kinetics are water penetration into the matrix, drug diffusion and matrix swelling; (2) drug dissolution is neglected as very rapid in respect to the other processes; (3) matrix swelling is ideal throughout the system - the sum of the volumes of water, drug and polymer are always equal to the total system volume and there is no volume contraction upon mixing; (4) the water concentration at the tablet surface is at its equilibrium value; (5) perfect sink conditions are maintained; (6) water imbibing as well as drug loss in axial and radial direction leads to a volume increase/decrease in axial and radial direction that is proportional to the relative surface area in the considered direction; (7) polymer dissolution is slower in comparison with the considered controlling mechanisms [2, 5].

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

\[
\frac{\partial c_1}{\partial t} = \text{div}(D_1(c_1) \text{grad} c_1) \quad \text{in} \quad \Omega \times (0, t_f],
\]

\[
\frac{\partial c_2}{\partial t} = \text{div}(D_2(c_1) \text{grad} c_2) \quad \text{in} \quad \Omega \times (0, t_f],
\]

where: $c_1 = C_1 / c_{eq}$, $c_2 = C_2 / c_{eq}$, $c_{eq}$, $c_{in}$, $D_1(c_1)$, $D_2(c_1)$, $t$ 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 is considered [2]: $D_i(c_1) = D_{eq} \exp(-\beta_i(1-c_1))$, $i = 1, 2$, 

\[
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\]
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where \( D_{1eq}, D_{2eq} \) are the diffusion coefficients in the equilibrium swollen state of the system and \( \beta_1, \beta_2 \) are dimensionless constants characterizing the concentration dependence.

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

\[
\begin{align*}
(2.3) \quad & c_1(x, y, 0) = 0, \quad 0 \leq x \leq R_0, \quad 0 \leq y \leq H_0 \\
(2.4) \quad & c_2(x, y, 0) = 1, \quad 0 \leq x \leq R_0, \quad 0 \leq y \leq H_0 \\
(2.5) \quad & c_1(x, y, t) = 1, \quad 0 < t \leq t_f, \quad x = R_1, \quad 0 \leq y \leq H_t \quad \text{or} \quad 0 \leq x \leq R_1, \quad y = H_t \\
(2.6) \quad & c_2(x, y, t) = 0, \quad 0 < t \leq t_f, \quad x = R_1, \quad 0 \leq y \leq H_t \quad \text{or} \quad 0 \leq x \leq R_1, \quad y = H_t
\end{align*}
\]

where \( R_0, H_0 \) are the initial dimensions of the tablet and \( R_1, H_t \) are the current ones.

The basic equations describing matrix volume changes in time are:

\[
\begin{align*}
(2.7) \quad & \rho_1 \frac{d\overline{M}_1}{dt} = c_{eq} \frac{d}{dt} \int_{\Omega(t)} c_1(t)dv, \quad \rho_2 \frac{d\overline{M}_2}{dt} = c_{in} \frac{d}{dt} \int_{\Omega(t)} c_2(t)dv,
\end{align*}
\]

where \( \overline{M}_1, \overline{M}_2 \) are the masses of water and drug corresponding to the domain under consideration \( \Omega \) with volume \( \overline{V} \) and \( \rho_1, \rho_2 \) are the water and drug density, respectively. The first equation describes the increase in matrix volume (swelling due to water penetration) while the second equation describes the decrease in matrix volume corresponding to the decrease of drug concentration in the tablet.

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

\[
(2.8) \quad R(t) = 1 - \frac{1}{S_t} \int_{\Omega_t} c_2 dv, \quad U(t) = \frac{1}{S_t} \int_{\Omega_t} c_1 dv,
\]

where \( S_t \) is the area of the current cross-sectional domain \( \Omega_t \).

3. Numerical approach. Formulas of volume changes

FE discretization of the domain \( \Omega_t \) is performed and the numerical solution of the initial boundary value problem (2.1-2.6) is sought in the FE form:

\[
(3.1) \quad \overline{c}_1(x, y, t) = C_1^T(t)N(x, y) , \quad \overline{c}_2(x, y, t) = C_2^T(t)N(x, y),
\]

where \( C_1 \) and \( C_2 \) are vectors with elements nodal values of \( c_1 \) and \( c_2 \) and \( N \) is the vector of the shape interpolation functions.

Applying the numerical approach derived in [5] an appropriate time difference method is used for solving the matrix problem [5, 6]:

\[
(3.2) \quad \frac{d[CMC_1]}{dt} + ST1 C_1 = 0
\]
(3.3) \[ \frac{d}{dt} \left[ CM C_2 \right] + ST2 C_2 = 0 \]

(3.4) \[ C_1 = 0, \quad C_2 = \mathbf{I}, \]

where \( CM, \ ST1, \ ST2 \) are FE matrices. The unit vector is denoted with \( \mathbf{I} \).

The matrix volume changes are considered in two main directions – radial and axial. We assume these volume changes realize in two steps in each time interval: tablet swelling caused by the water uptake first and tablet volume decrease caused by drug release. Integrating equations (2.7) 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 formulas are obtained:

\[
\Delta \tilde{y}_{n+1} \tilde{S}_{n+1} - \Delta y_n S_n = \frac{c_{eq}}{\rho_1} \tilde{c}_{1,n+1} \Delta \tilde{y}_{n+1}^{k} \tilde{S}_{n+1} - \frac{c_{eq}}{\rho_1} \tilde{c}_{1,n} \Delta y_n^{k} S_n, \quad k = 1, \ldots, M_1,
\]

(3.5)

\[
\Delta y_{n+1} S_{n+1} - \Delta \tilde{y}_{n+1} \tilde{S}_{n+1} = \frac{c_{in}}{\rho_2} \tilde{c}_{2,n+1} \Delta \tilde{y}_{n+1}^{k} \tilde{S}_{n+1} - \frac{c_{in}}{\rho_2} \tilde{c}_{2,n} \Delta y_{n+1}^{k} \tilde{S}_{n+1}, \quad k = 1, \ldots, M_1,
\]

(3.6)

where \( \Delta y_n^{k} \) and \( S_n \) are the final thickness of the \( k \)th layer and area of the radial cross-section at \((n+1)\) time level. The average water and drug concentration for the \( k \)th layer at \((n+1)\) time level is denoted by \( \tilde{c}_{1,n+1} \) and \( \tilde{c}_{2,n+1} \), respectively. They are calculated in terms of the nodal concentration values obtained from (3.2)-(3.4).

Taking into account the assumption (6) when posing the model problem the following formulas for change of the thickness of each volume element in y-direction, the half thickness and radius at the considered moment are derived:

\[
\tilde{y}_{n+1} = \tilde{y}_{n} \sqrt{\frac{\rho_1 - c_{eq} \tilde{c}_{1,n+1}}{\rho_1 - c_{eq} \tilde{c}_{1,n}}} \quad \text{and} \quad \tilde{y}_{n+1} = \tilde{y}_{n+1} \sqrt{\frac{\rho_2 - c_{in} \tilde{c}_{2,n+1}}{\rho_2 - c_{in} \tilde{c}_{2,n+1}}}, \quad k = 1, \ldots, M_1.
\]

\[
H_{n+1} = \sum_{k=1}^{M_1} \Delta \tilde{y}_{n+1}.
\]

(3.7)

\[
H_{n} \left( \frac{H_{n-1}}{(\rho_1 - c_{eq} \tilde{c}_{1,n})} \right), \quad R_{n+1} = H_{n+1} \left( \frac{H_{n+1}}{(\rho_2 - c_{in} \tilde{c}_{2,n})} \right).
\]

(3.8)

5. Numerical results

A numerical procedure created on the basis of the proposed numerical approach under FE domain approximation (using 2D simplex elements) is implemented in noncommercial software. It is used for simulation of fractional release of different drugs for different release media under the water uptake parameters \( D_{eq} = 5.6 \times 10^{-8} \text{ cm}^2 / \text{s}, \beta_1 = 2.5, \rho_1 = 1 \text{g/cm}^3, \ c_{eq} = 0.76 \text{g/cm}^3 \) and drug parameters used in [2].
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**Case 1.** Comparison between FEM results of drug release from tablet (200mg) with dimensions of $R_o = 0.65\, \text{cm}, H_o = 0.069\, \text{cm}$ at $c_{in} = 0.109\, \text{g/cm}^3$ and the corresponding available experimental results [2] is given in Figs.1, 2. The obtained numerical results for diclofenac sodium (DS) at two different release media (phosphate buffer pH=7.4 and deionized water) are presented in Fig.1. They show a very good agreement for deionized water, whether a deviation less than 8% between 6 and 12 hours for phosphate buffer pH=7.4 is obtained. A very good agreement of the experimental results for chlorpheniramine maleate (CHM) release with the numerical ones is observed in Fig.2.

![Fig.1 Numerical results of DS release](image1.png)

![Fig.2 Numerical results of CHM release](image2.png)

**Case 2.** Simulation results of diclofenac sodium release from tablet with dimensions of $R_o = 0.6\, \text{cm}$ and $H_o = 0.21\, \text{cm}$ are presented in Figs.3, 4 for different IDL at $D_{2eq} = 4.9 \times 10^{-7}\, \text{cm}^2/\text{s}, \beta_2 = 8.1$ [2] and $\rho_2 = 0.7\, \text{g/cm}^3$ [7]. The effect of IDL on the

![Fig.3 Relative volume change of DS tablet for different initial drug loading](image3.png)

![Fig.4 Effect of initial drug loading on DS release](image4.png)
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relative tablet volume values is shown in Fig.3. The matrix swelling is predominant in the first ten hour period (especially in case of low IDL), while a slow volume contraction due to drug loss is observed in the consecutive period (especially in case of the highest IDL). The effect of initial drug loading on DS release is presented in Fig.4. The obtained results are natural consequence of the tablet volume changes shown in Fig.2.

6. Conclusion

The recently proposed numerical approach to analyzing swelling and drug release from 2D HPMC matrices [5] was improved introducing the effect of initial drug loading. A detailed mathematical description of matrix volume change (tablet swelling and/or contraction) connected with the free boundary conditions of the arisen model problem is introduced at each time step.

The created noncommercial software is used for numerical simulation of drug release kinetics under different release media. A very good agreement with available experimental data is obtained. The effect of initial drug loading on the tablet volume change and drug release profile is investigated for diclofenac sodium.

The improved 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 taking into account matrix erosion and drug dissolution.

REFERENCES