Reliability of a Novel Model for Drug Release from 2D HPMC-Matrices

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Abstract: *A novel model of drug release from 2D-HPMC matrices is considered. Detailed mathematical description of matrix swelling and the effect of the initial drug loading are introduced. A numerical approach to solution of the posed nonlinear 2D problem is used on the basis of finite element domain approximation and time difference method. The reliability of the model is investigated in two steps: numerical evaluation of the water uptake parameters; evaluation of drug release parameters under available experimental data. The proposed numerical procedure for fitting the model is validated performing different numerical examples of drug release in two cases (with and without taking into account initial drug loading). The goodness of fit evaluated by the coefficient of determination is presented to be very good with few exceptions. The obtained results show better model fitting when accounting the effect of initial drug loading (especially for larger values).*

Keywords: *Drug release, Diffusion, Hydroxypropyl methylcellulose swelling, Finite element to modeling, Difference scheme.*

Introduction

Polymeric matrices containing hydroxypropyl methylcellulose (HPMC) are widely used for preparation of sustained-release drug carriers [3]. 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.

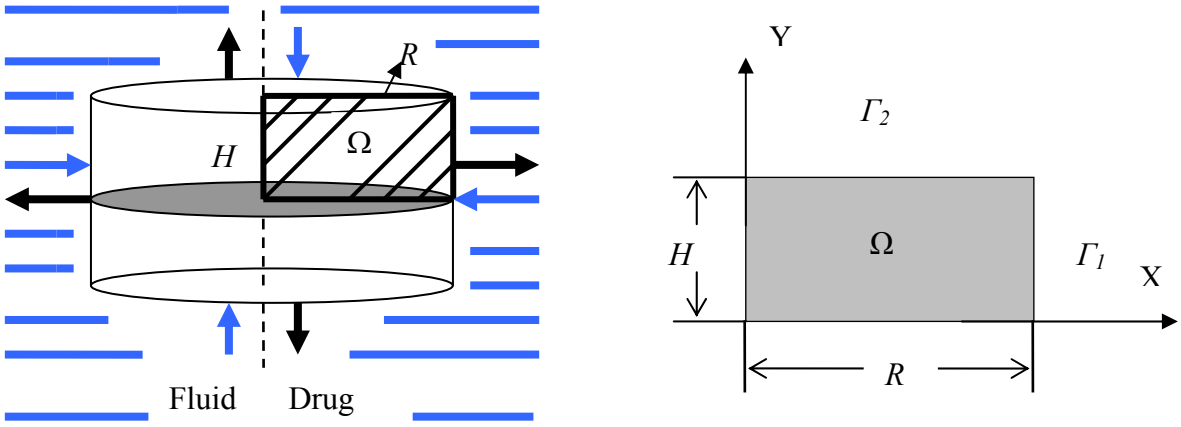
A comprehensive mathematical model (so called "sequential layer" one) describing drug release from HPMC-based matrix tablets has been developed during the last decade [10, 11, 13-15]. This model is implemented by using finite difference method which leads to some limitations when generalizing model equations, initial and boundary conditions. Recently a new variant of the sequential layer model was developed introducing a detailed mathematical description of matrix swelling [6]. A new finite element (FE) approach to modeling drug release from 2D polymeric matrices was also proposed [4, 5]. It is based on FE domain approximation and an appropriate time difference method which allows solving strongly nonlinear model problems of the considered type. This model variant was additionally improved taking into account the effect of the initial drug content [7].

The aim of the present paper is to investigate the reliability of the above model for different drugs accounting the effect of the Initial Drug Loading (IDL) on swelling and drug release kinetics. A numerical procedure for evaluation of the water uptake parameters when fitting the model to available experimental data was developed, as a first step. The numerical evaluation of drug release parameters was performed under the obtained water uptake

parameters, as a second step. Noncommercial software corresponding to the above procedures was created and validated.

Model 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 (schematically presented in Fig. 1a). 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 [13, 14].



(a) (b)

Fig. 1 a) Schematic representation of drug release from a cylindrical tablet;
b) The domain Ω with boundary $\Gamma = \Gamma_1 \cup \Gamma_2$ as a quarter of the axial cross section.

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

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

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

where: $c_1 = C_1 / c_{eq}$, $c_2 = C_2 / c_{in}$, 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.

The Fujita-type exponential dependences of the diffusion coefficients are considered [9]:

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

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:

$$c_1(x,\ y,\ 0) = 0, \quad 0 \le x \le R_0, \quad 0 \le y \le H_0 \tag{4}$$
$$c_2(x,\ y,\ 0) = 1, \quad 0 \le x \le R_0, \quad 0 \le y \le H_0 \tag{5}$$

$$c_1(x,\ y,\ t) = 1, \quad 0 < t \le t_f, \quad x = R_t,\ 0 \le y \le H_t \ \text{ or } \ 0 \le x \le R_t,\ y = H_t \tag{6}$$
$$c_2(x,\ y,\ t) = 0, \quad 0 < t \le t_f, \quad x = R_t,\ 0 \le y \le H_t \ \text{ or } \ 0 \le x \le R_t,\ y = H_t \tag{7}$$

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

The basic equations describing matrix volume changes in time are the following:

$$\rho_1 \frac{d\bar{V}}{dt} = \frac{d\bar{M}_1}{dt} = c_{eq} \frac{d}{dt} \int_{\bar{\Omega}(t)} c_1(t)\, dv, \quad \rho_2 \frac{d\bar{V}}{dt} = \frac{d\bar{M}_2}{dt} = c_{in} \frac{d}{dt} \int_{\bar{\Omega}(t)} c_2(t)\, dv, \tag{8}$$

where $\bar{M}_1$, $\bar{M}_2$ are the masses of water and drug corresponding to the domain under consideration $\bar{\Omega}$ with volume $\bar{V}$ and ρ_1, ρ_2 are the water and drug density, respectively. The first equation of (8) 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:

$$R(t) = 1 - \frac{1}{S_t} \int_{\Omega_t} c_2 dv, \quad U(t) = \frac{1}{S_t} \int_{\Omega_t} c_1 dv, \tag{9}$$

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

FE approach. Formulae of volume changes

FE discretization of the domain Ω_t is performed and the numerical solution of the following initial matrix problem equivalent to (1) – (7) is sought at each time step [6, 7]:

$$\frac{d[\mathbf{CM}\ \mathbf{C}_1]}{dt} + \mathbf{ST1}\ \mathbf{C}_1 = 0 \tag{10}$$
$$\frac{d[\mathbf{CM}\ \mathbf{C}_2]}{dt} + \mathbf{ST2}\ \mathbf{C}_2 = 0 \tag{11}$$
$$\mathbf{C}_1 = 0, \quad \mathbf{C}_2 = \mathbf{I}, \tag{12}$$

where $\mathbf{C}_1$ and $\mathbf{C}_2$ are vectors with elements FE nodal values of $\mathbf{C}_1$ and $\mathbf{C}_2$ and **CM**, **ST1**, **ST2** are FE matrices generated under the current FE mesh. The unit vector is denoted with **I**. An appropriate predictor-corrector hybrid scheme is proposed for solving the above problem.

The matrix volume changes due to the water penetration into the tablet and drug release from it 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 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) and 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 are derived:

$$\Delta\tilde{y}_{n+1}^{k} = \Delta y_{n}^{k}\sqrt{\frac{\rho_1 - c_{eq}\bar{c}_{1,n}^{k}}{\rho_1 - c_{eq}\bar{c}_{1,n+1}^{k}}},\ \Delta y_{n+1}^{k} = \Delta\tilde{y}_{n+1}^{k}\sqrt{\frac{\rho_2 - c_{in}\bar{c}_{2,n}^{k}}{\rho_2 - c_{in}\bar{c}_{2,n+1}^{k}}},\ k = 1, ..., M_1 \tag{13}$$

where $\Delta\tilde{y}_{n+1}^{k}$ and Δy_{n+1}^{k} are the thickness after swelling and the final thickness of the k^{th} layer at $(n + 1)$ time level. The average water and drug concentration for the k^{th} layer at $(n + 1)$ time level is denoted by $\bar{c}_{1,n+1}^{k}$ and $\bar{c}_{2,n+1}^{k}$, respectively. They are calculated in terms of the nodal concentration values obtained from (10) – (12). The half thickness of the tablet is finally evaluated at each time level as follows:

$$H_{n+1} = \sum_{k=1}^{M_1} \Delta y_{n+1}^{k} \tag{14}$$

Integrating Eq. (8) for the whole cylindrical domain the following change in radius is expressed at each time step:

$$\tilde{R}_{n+1} = R_n\sqrt{\frac{H_n\left(\rho_1 - c_{eq}\bar{c}_{1,n}\right)}{\tilde{H}_{n+1}\left(\rho_1 - c_{eq}\bar{c}_{1,n+1}\right)}},\ R_{n+1} = \tilde{R}_{n+1}\sqrt{\frac{\tilde{H}_{n+1}\left(\rho_2 - c_{in}\bar{c}_{2,n}\right)}{H_{n+1}\left(\rho_2 - c_{in}\bar{c}_{2,n+1}\right)}} \tag{15}$$

Reliability of the model

The reliability of the model is investigated consecutively for HPMC matrices as follows:

Step I

Numerical evaluation of the water uptake model parameters D_{1eq} and β_1 on the basis of available experimental data.

Step II

Numerical evaluation of the drug model parameters D_{2eq} and β_2 under determined water uptake parameters and available experimental data for drug release.

The numerical evaluation of the considered couples is performed introducing the objective functions [1, 2]:

$$F_1(D_{1eq}, \beta_1^k) = \sum_{n=1}^{N} (U_{num}^n(D_{1eq}, \beta_1^k) - U_{exp}^n)^2, \quad D_{1eq} \in G_1, \quad k = 1, 2, \ldots, K \tag{16}$$

$$F_2(D_{2eq}, \beta_2^k) = \sum_{n=1}^{N} (R_{num}^n(D_{2eq}, \beta_2^k) - R_{exp}^n)^2, \quad D_{2eq} \in G_2, \quad k = 1, 2, \ldots, K \tag{17}$$

where U_{num}^n, R_{num}^n are the numerical values of water uptake and drug release at the moment under consideration with number n and U_{exp}^n, R_{exp}^n are the corresponding experimental data; G_1, G_2 are the domains of admissible values of D_{1eq}, D_{2eq} and β_1^k, β_2^k are character consistent values of β_1, β_2. A method of consecutive restrictions of the admissible values is used when optimizing the objective functions.

To evaluate the goodness of fit the coefficient of determination was calculated at each step as follows [8, 15]:

$$R^2 = 1 - \frac{\sum_{n=1}^{N} (U_{num}^n - U_{exp}^n)^2}{\sum_{n=1}^{N} (U_{arithm}^n - U_{exp}^n)^2}, \quad R^2 = 1 - \frac{\sum_{n=1}^{N} (R_{num}^n - R_{exp}^n)^2}{\sum_{n=1}^{N} (R_{arithm}^n - R_{exp}^n)^2},$$

where U_{arithm}^n and R_{arithm}^n is the arithmetic mean of the experimental data of the considered water uptake and drug release, respectively.

Numerical evaluation of the water uptake parameters

Numerical evaluation of the water uptake parameters D_{1eq} and β_1 is performed for the tablets with sizes of R = 0.4 cm and H = 0.18 cm on the basis of the available experimental data presented in Fig. 2 [13, 16]. It is shown a very good agreement, especially for the first 8 hours, with the numerical values obtained under $D_{1eq} = 2.3 \times 10^{-6}$ cm$^2 \cdot$s^{-1} and $\beta_1 = 5$. The value of Determination Coefficient (DC) is 0.95.

Numerical evaluation of the drug release parameters

Release of three different drugs from HPMC tablets is investigated under the obtained values of the water uptake parameters. The parameters of drug release D_{2eq} and β_2 are evaluated in two cases: with and without taking into account the IDL, i.e. under different formulas for tablets volume change corresponding to our two variants of the model presented in [7] and [6], respectively.

Example 1

Both variants of the model are fitted to the experimental data for propranolol hydrochloride release from tablets of sizes R = 0.65 cm and H = 0.069 cm at c_{in} = 0.109 g$\cdot$cm^{-3} [13]. The following values for the drug parameters are obtained: $D_{2eq} = 5.7 \times 10^{-7}$ cm$^2 \cdot$s^{-1}, $\beta_2 = 15$ (with IDL = 10%) and $D_{2eq} = 6.9 \times 10^{-7}$ cm$^2 \cdot$s^{-1}, $\beta_2 = 15$ (without taking into account IDL). A very good agreement between the numerical and experimental results in both cases is shown in Fig. 3 (DC = 0.992, DC = 0.986).

Example 2

The release of chlorpheniramine maleate from tablets with sizes of R = 0.6 cm and H = 0.23 cm is presented in Fig. 4 in comparison with available experimental data [14] under the obtained values: $D_{2eq} = 5.9\times10^{-7}\,\mathrm{cm^2\cdot s^{-1}}$, $\beta_2 = 3$ (with IDL = 60% and $c_{in} = 0.58\,\mathrm{g\cdot cm^{-3}}$); $D_{2eq} = 9.7\times10^{-7}\,\mathrm{cm^2\cdot s^{-1}}$, $\beta_2 = 1$ (without taking into account IDL). Obviously, accounting higher IDL is essential for more accurate simulation of the considered drug release (DC is 0.96 against 0.89 without accounting IDL).

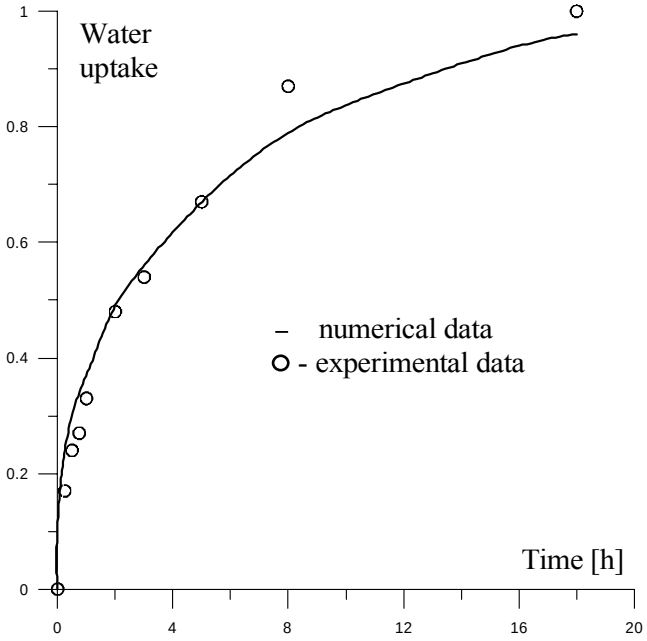


Fig. 2 Comparison of the water uptake numerical results with the corresponding experimental ones under the evaluated parameters D_{1eq} and β_1

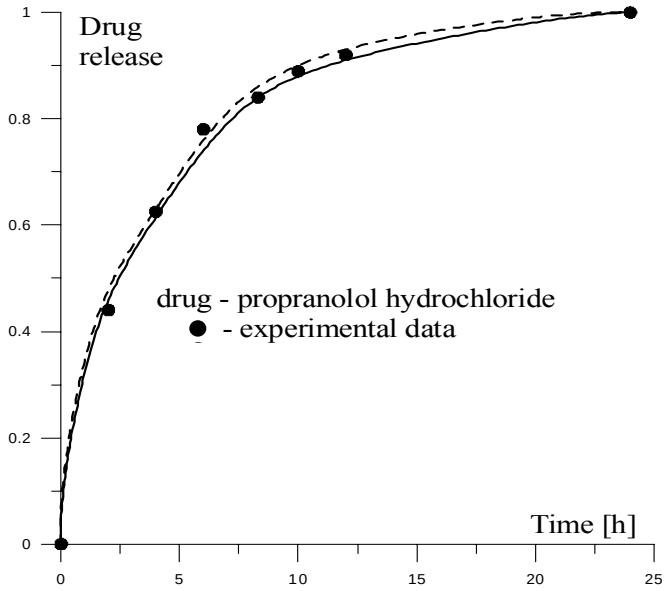


Fig. 3 Fit of the both model variants to experimental data for propranolol hydrochloride release: with IDL = 10% (continuous curve); without taking into account IDL (dashed curve).

The experimental results for the release of the same drug but at IDL = 10% (corresponding to $c_{in} = 0.109\ \mathrm{g \cdot cm^{-3}}$) presented in Fig. 5 show approximately a linear behavior after the first hour [14]. The considered model is not enough reliable in this case under the obtained values $D_{2eq} = 3.45 \times 10^{-7}\ \mathrm{cm^2 \cdot s^{-1}}$, $\beta_2 = 2$ (DC = 0.84).

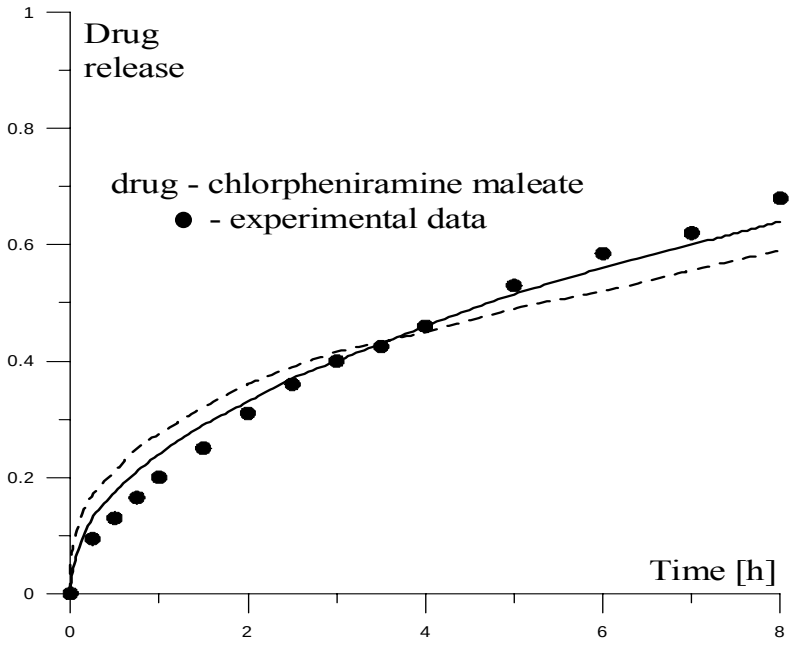


Fig. 4 Fit of the both model variants to experimental data for chlorpheniramine maleate release: with IDL = 60% (continuous curve); without taking into account IDL (dashed curve).

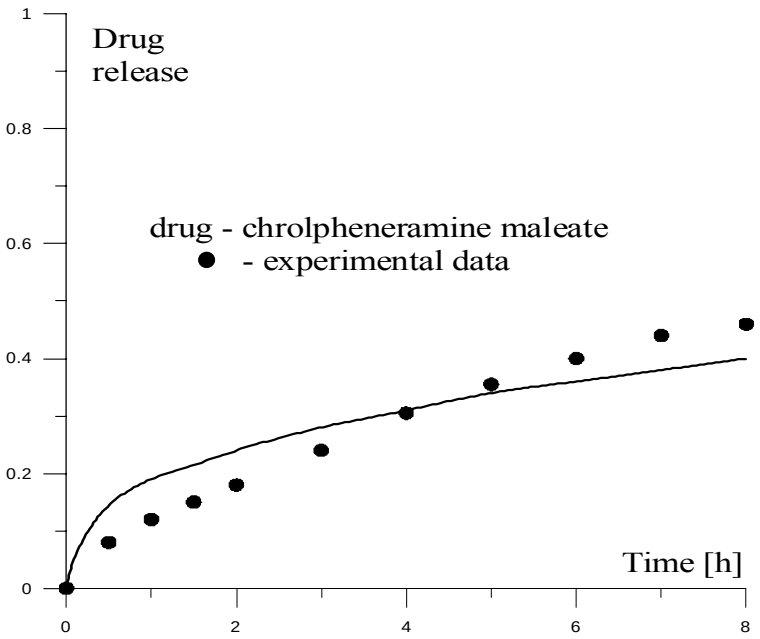


Fig. 5 Fit of the new model [7] to experimental data for chlorpheniramine maleate release with IDL = 10% (continuous curve)

Example 3

Molsidomin drug release from tablets with sizes of $R = 0.4$ cm and $H = 0.15$ cm at IDL = 4% is presented in Fig. 6 under the drug release parameters obtained from the fit of the new model [7] to experimental data [12]. An approximately good correspondence is obtained for the determined values $D_{2eq} = 5.75 \times 10^{-7}\,\mathrm{cm^2 \cdot s^{-1}}$, $\beta_2 = 4$ at $c_{in} = 0.05\,\mathrm{g \cdot cm^{-3}}$ (DC = 0.89).

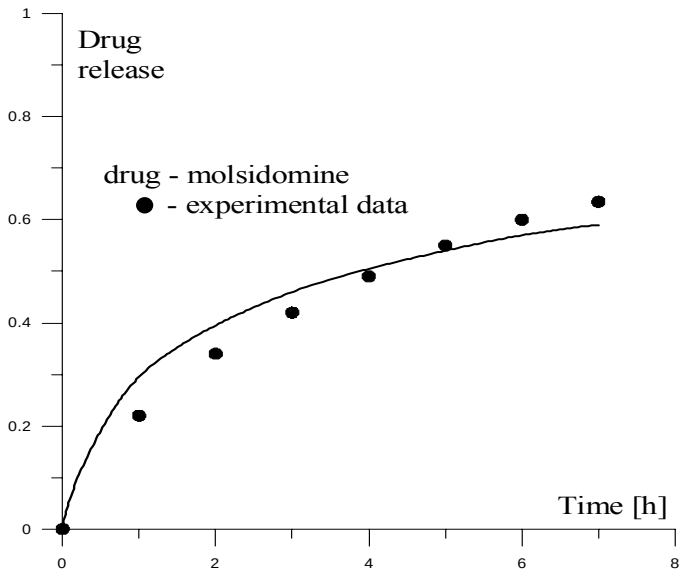


Fig. 6 Fit of the new model [7] to experimental data for molsidomine release with IDL = 4% (continuous curve)

Conclusion

The reliability of the recently developed novel model (an improved version of the "sequential layer" one) for drug release from 2D-HPMC matrices [6, 7] is investigated. This model proposes a detailed mathematical description of tablet swelling and contraction due to water uptake and drug release. Its improved version takes into account the effect of the initial drug loading on swelling and drug release kinetics.

A numerical procedure for evaluation of two water uptake parameters when fitting the model to available experimental data is developed, as a first step. As a second step, a procedure for evaluation of drug release parameters is introduced under the evaluated water uptake parameters. Noncommercial software corresponding to the above procedures is created.

In order to validate the whole procedure for fitting the model, numerical examples of drug release for three different drugs (propranolol hydrochloride, chlorpheniramine maleate and molsidomine) in two cases (with and without taking into account initial drug loading) are performed. The obtained results show better model fitting when taking into account the effect of IDL (especially for larger values). The values of determination coefficient corresponding to goodness of fit are in the range $0.99 \div 0.84$. The worst result can be explained with approximately linear behavior of the corresponding experimental data.

The investigated novel model can be used as a cheap and effective simulation tool when designing new pharmaceutical products with HPMC carriers.

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