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Analytical review

Monolithic Controlled Delivery Systems: Part II. Basic Mathematical Models

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Abstract: *The article presents a brief but comprehensive review of the large variety of mathematical models of drug controlled release from polymeric monoliths in the last 25 years. The models are considered systematically, from the first simple empirical models up to the most comprehensive theoretical ones taking into account the main release mechanisms (diffusion, swelling, dissolution or erosion) simultaneously. Their advantages and limitations are briefly discussed and some applications are outlined. The present review shows the choice of appropriate mathematical model for a particular controlled system design mainly depends on the desired predictive ability and accuracy of the model. This aspect is connected with the necessity the main factors influencing the concrete release kinetics, especially the basic controlling mechanisms, to be identified in advance.*

Keywords: *Controlled delivery, Drug release, Monolithic systems, Mathematical models, Diffusion, Swelling, Dissolution, Erosion.*

Introduction

Controlled-release systems (CRS) are common in a number of product areas including food, medicine, cosmetics, pesticides and paper. Controlled Release (CR) is the field of scientific activity concerned with the control in time and space of the biological effects of therapeutic agents in human and animal health, and of other active agents in environmental, consumer and industrial applications.

CRS for drug delivery first appears in the 1960's and 1970's [21]. Their variety has increased dramatically in the last three decades. The design of new CRS necessitates the creation of appropriate mathematical models to predict the desired drug release kinetics.

Basic characteristics and mechanisms of monolithic drug delivery systems were recently presented in a review [3] from the point of view of mathematical modelling the controlled drug release (CDR). The present paper is a continuation of this review and aims to analyze and systemize the existing mathematical models of monolithic (matrix) CRS for drug delivery.

Mathematical modelling

Empirical and semi-empirical approaches

The first mathematical model describing drug release from monolithic systems was proposed by Higuchi [21]. Created for planar systems it was later extended to different geometries and porous systems [37]. This basic model assumes that: (1) initial active agent (drug) concentration in the monolith is much higher than drug solubility; (2) drug diffusion takes place only in one dimension (edge effects must be negligible); (3) drug particles are much smaller than system thickness; (4) monolith swelling and dissolution is negligible; (5) drug diffusivity is constant; (6) perfect sink conditions are always attained in the release environment. The Higuchi model equation is the following:

$$M_t = A\sqrt{D(2C_0 - C_s)C_s t} \qquad C_0 > C_s, \tag{1}$$

where M_t is the amount of drug released until time t, A is the release area, D is the drug diffusion coefficient, C_0 is the initial drug concentration in the monolith, while C_s is drug solubility. This model shows a M_t square rate dependence on time corresponding to Fick's solution when the amount released is less than 60% according to Crank [11]. The Higuchi model is still widely used due to its extreme simplicity [37], although its high degree of approximation. The researchers continue to apply the above equation to interpret their experimental drug release data even in the case of systems based on HPMC (hydroxypropyl methylcellulose) [44, 45] characterized by high matrix swellability.

Another simple and useful empirical model is the so-called power low [30, 31, 35, 36]:

$$M_t / M_\infty = Kt^n, \tag{2}$$

where M_∞ is the amount of drug released after an infinite time, K is a constant incorporating structural and geometric characteristics of the system and n is the exponent characterizing the release process. Peppas and coworkers were the first to give an introduction to the use and the limitations of these equations [37]. It is clear that when the exponent n takes the value of 1.0, the drug release rate is independent of time (the case of the so called zero-order release kinetics) [37]. For slabs, the mechanism that creates the zero-order release is known among polymer scientists as case-II transport. Equation (2) has two distinct realistic meanings in two special cases: diffusion controlled drug release ($n = 0.5$) and swelling controlled drug release ($n = 1.0$). Values of n between 0.5 and 1.0 can be regarded as superposition of both phenomena. The two extreme values for the exponent n (0.5, 1.0) are only valid for slab geometry. For spheres and cylinders different values have been derive [35, 36], as listed in Table 1.

Table 1. Exponent *n* of the power law and drug release mechanism from polymeric controlled delivery systems of different geometry

Exponent n slab	**Cylinder**	**Sphere**	**DR mechanism**
0.5	0.45	0.43	Fickian diffusion
$0.5 < n < 1.0$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Anomalous transport
1.0	0.89	0.85	Case-II transport

The power low was applied to experimental drug release data obtained for different CRS including HPMC-based ones [9, 10, 34]. Different values for the exponent were obtained corresponding to the dominating drug release mechanism.

Peppas and Sahlin [32] incorporate both the Fickian diffusional contribution and the non Fickian one (case-II relaxational contribution) as follows:

$$M_t / M_\infty = k_1 t^n + k_2 t^{2n}, \quad (3)$$

where m, k_1 and k_2 are constants related to the Fickian and non Fickian diffusional contribution, respectively.

Betini et al. [2] applied this equation to investigate the effect of molecular weight of the HPMC type used and the addition of partial impermeable coating to HPMC matrix tablets. The authors concluded that the importance of the relaxational contribution for drug release is more significant in the case of partially coated HPMC matrix tablets.

Grassi et al. [17], studding drug release from partially and non coated HPMC tablets, developed mathematical model based on the assumption that a release resistance exists due to drug dissolution and diffusion through the developing gel layer surrounding the dry glassy core. Following the usual equation of solid drug dissolution [1] and supposing that the diffusion front moves inward under sink conditions, it results:

$$C_r^+ = C_r /(M_0 / V_r) = 1 - \left(1 - \frac{2(1+K)x_d}{3M_0^{1/3}} \left(\frac{\pi}{K^2 C_0^2}\right)^{1/3} F(t)\right)^3, \quad (4)$$

$$F(t) = C_s \left[\frac{t}{B + 1/\ fk_d} + \frac{\ln(1 + Rfk_d)}{(B + 1/\ fk_d)b}\right], \quad R = B(1 - \exp^{-bt}) \quad (5)$$

where C_r is drug concentration in the release environment, V_r is the release environment volume, M_0 is the total drug amount contained in the tablet, C_0 is the initial drug concentration in the tablet, R is the resistance contribution, B and b are two adjustable parameters, x_d is the drug mass fraction at the swelling front, k_d is drug dissolution constant and f is a parameter accounting the gel presence. The ratio K between the penetration depth in the axial and in the radial directions is assumed to be equal to that of the tablet height and radius.

Theoretical approaches

Let us suppose that: (1) drug dissolution is very fast compared to drug diffusion; (2) the swelling process does not occur or it takes place instantaneously; (3) no matrix erosion occurs and (4) drug diffusion takes place only in one dimension. Under these assumptions drug release is controlled only by diffusion with a constant drug diffusion coefficient in case of both uniform and non-uniform initial drug distribution in the matrix as described in Crank [11, 17]. Fu and co-workers [14] obtained an analytical solution of Fick's law for cylindrical geometry considering mass transfer in three dimensions:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{h^2 r^2} \sum_{m=1}^{\infty} \alpha_m^{-2} \exp\left(-D\alpha_m^2 t\right) * \sum_{m=1}^{\infty} \beta_n^{-2} \exp\left(-D\beta_n^2 t\right), \quad (6)$$

$J_o(r\alpha) = 0$, $\beta_n = \frac{(2n+1)\pi}{2h}$,

where M_t and M_∞ are the amount of drug released at time t and infinite time respectively; h denotes the half length and r the radius of the cylinder; D is the constant diffusivity; α and β are defined by the above given equations, such that J_o a zero order Bessel function and m and n are integers. This model is applicable to tablets that range from the shape of a flat disk (radius > thickness) to that of a cylindrical rod (radius < thickness). Especially for porous systems the effective drug diffusivity depending on matrix porosity ε, tortuosity τ and drug diffusivity in the solvent (filling the pores) is used as follows $D_e = \frac{D_w}{\tau}\varepsilon$. This model doesn't consider the matrix volume swelling and also assumes constant diffusion coefficient. Nevertheless these disadvantages it can be applied successfully for some special CRS. For example Grassi et al. [18] consider paracetamol release from a poly dispersed stearic acid/lactose spheres and assume that upon contact with the release environment lactose instantaneously dissolves so that release kinetics is diffusion controlled. A good model prediction is obtained under the effective diffusivity calculated by model fitting on release experimental data referring to approximately mono disperse systems.

Modelling the drug release from a swellable matrix implies introduction of the relevant mass balance and the flux constitutive equation of both the swelling fluid entering the matrix (penetrant or solvent) and the drug leaving it [17]. One of the first models aimed to describe CDR from a swellable matrix is this one of Peppas et al. [33] considering drug diffusion from a single surface for the case of countercurrent diffusion of a solvent which is compatible with the polymer. The considerable volume extension due to matrix swelling is accounted for by introducing a moving boundary diffusion problem. It is obtained a good agreement of the results for drug concentration profiles within the polymer with experimental data for the system of KCl distributed in HPMC matrix tablets.

Singh and Fan [42] developed a comprehensive model for simultaneous diffusion of a drug and a solvent in a planar glassy polymer matrix. The matrix undergoes macromolecular chain relaxation and volume expansion due to solvent absorption into the matrix. The swelling behavior of the polymer is characterized by a stress-induced drift velocity term. The volume change due to the relaxation phenomena is assumed instantaneous. The model implies convective transport (induced by volume expansion and by stress gradient) of the two species.

Cohen and Erneux [7] modeled swelling controlled release using free boundary problems. Drug release is achieved by countercurrent diffusion through a penetrating solvent. The drug release rate is determined by the rate of the solvent diffusion into the polymer. This model was developed also for thin films and not for cylindrical tablets.

Korsmeyer et al. [25, 26] proposed a model, describing two-component diffusion in a polymer slab with moving diffusional front. A Fujita type exponential dependence of diffusion coefficients on penetrant concentration was chosen. Dimensional changes of the sample are predicted by allowing each spatial increment to expend according to the amount of penetrant sorbed.

Ju and co-workers [23, 24] developed a comprehensive model to describe the swelling/dissolution behaviors and drug release from HPMC matrices. An important feature of this model is defining the polymer disentanglement concentration $\rho_{p,dis}$ below which chains' detach from swollen network occurs. The authors found the following relation between $\rho_{p,dis}$ and the polymer molecular weigh *M*:

$$\rho_{p,dis} = 0.05 * (M / 96000)^{-0.8} \tag{7}$$

The mathematical analysis is based on the following equation:

$$\left(\frac{\partial \rho_i}{\partial t}\right) = -\frac{\partial \rho_i}{\partial r}\frac{\partial r}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}\left(rD_i\rho_t\frac{\partial w_i}{\partial r}\right) - \rho_i\frac{dV/V}{dt}, \tag{8}$$

where $\rho_i, D_i, w_i, r, t, V$ are the mass concentration, the diffusivity of the species *i,* the restrictive weight fraction, radial position, time and matrix volume, respectively. The first term on the right hand side in (8) is a convection term, arising from the moving boundary. The second term accounts for the Fickian diffusion of the species *i*, where ρ_t is the local overall mass concentration. The presence of the second term corresponds to the assumption that the drug diffusion is the controlled mechanism. This assumption is only valid for water-soluble drugs. In the case of poorly water-soluble drugs (the rate of dissolution is much slowly than diffusion one) a dissolution term needs to be included into the governing equation. The last term is the source one which considers concentration changes resulting from the matrix volume changes. Based on the measurements of Gao and Fagerness [15] reasonable concentration dependences of the diffusivities are proposed. A good agreement between the model predictions for drug release and experimental data was found (within 15% error). However, the application of the model is restricted to radial processes only, ignoring axial transport.

Recently Siepman et al. [38-40] developed a new comprehensive mathematical model describing drug release from HPMC-based matrix tablets, taking into account the diffusion of water and drug, non-constant diffusivities, the swelling of the system, polymer drug dissolution and radial and axial mass transfer in cylindrical geometries. The model is valid for various kinds of HPMC types, freely and poorly water-soluble drugs and a wide range of drug loading. This model can be considered as an extension of Ju's work which is valid for freely water-soluble drugs. One of the most important differences with Ju's work consists in the fact that polymer dissolution is accounted for using the reptation theory [28]. When water concentration exceeds a critical threshold, c_{1crit}, surface polymer chains start to disentangle and diffuse through unstirred layer into the bulk fluid. The loss of the polymer mass per unit area is expressed by the following equation:

$$M_{\rho t} = M_{\rho 0} - k_{diss}A_t t \tag{9}$$

where A_t is the surface area of the device at time *t*, k_{diss} is the dissolution rate constant while M_{pt} and M_{p0} are the dry polymer mass at time *t* and $t = 0$, respectively. Water and drug diffusion are described using Fick's second law of diffusion for cylindrical geometry, taking into account axial and radial mass transport and concentration-dependent diffusivities [11]:

$$\frac{\partial c_k}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD_k\frac{\partial c_k}{\partial r}\right)+\frac{\partial}{\partial \theta}\left(\frac{D_k}{r}\frac{\partial c_k}{\partial \theta}\right)+\frac{\partial}{\partial z}\left(rD_k\frac{\partial c_k}{\partial z}\right)\right\} \tag{10}$$

where c_k and D_k represent concentration and diffusion coefficient of the diffusing species (k = 1, water; k = 2, drug), respectively, while r and z are respectively the radial and axial coordinate. The authors in the light of the Fudjita theory [38] choose the following equation for the diffusion coefficient dependence on the local water concentration:

$$D_k = D_{kcrit}\exp\left\{-\beta_k\left(1-\frac{c_1}{c_{1crit}}\right)\right\} \tag{11}$$

where β_1 and β_2 are the dimensionless constants characterizing this concentration dependence. The constants D_{1crit} and D_{2crit} denote the water and drug diffusivity at the interface matrix/release medium, where the polymer chain disentanglement occurs [38-40]. If ideal mixing conditions are supposed (no volume variations occur upon drug, polymer and water mixing) the total matrix volume at any instant is given by the sum of each component volume. The equation (10) is numerically solved imposing that at $t = 0$ the matrix is completely dry and drug concentration is uniform. The critical concentration c_{1crit} is calculated from the polymer disentanglement concentration and drug concentration is assumed to be zero in the release environment (perfect sink conditions). This model has been successfully tested on theophyline release from HPMC matrices [37].

Another comprehensive model for drug release from a swellable matrix is this one of Grassi et al. [20]. Among several approaches proposed to describe the swelling fluid (penetrant) in a glassy polymer matrix Grassi and Lapasin have choused the model of Camera-Roda and Sarti [6] for mass transport with relaxation which can account for the complex phenomena governing the penetrant flux and particularly the viscoelastic properties of the swellable matrix. This approach allows avoiding a great number of experimental information normally requested by other, more general models [17]. It is assumed that drug diffusivity is dependent on the penetrant concentration using Mackie and Meares equation. Anisotropic as well as isotropic matrix swelling is considered and formulas for local volume changes are derived in [20].

The corresponding problem of drug release from a polymeric matrix occupying the domain (matrix) $\Omega \subset R^N$, $N = 1, 2, 3$ was posed by Blagoeva in [4] as follows:

$$\frac{\partial c_d}{\partial t} = div(D_d(c_p)gradc_d) \text{ in } \Omega\times(0, t_f] \tag{12}$$

$$c_d = c_{do}, \quad t = 0 \tag{13}$$

$$c_d(\mathbf{x}, t) = \frac{V^m c_{do} - M_d(t)}{V_r} \quad \text{for } \mathbf{x}\in\partial\Omega,\ 0\le t\le t_f \tag{14}$$

$$D_d(c_p) = D_{do}\left(\frac{c_p}{2\rho_s - c_p}\right)^2, \quad M_d(t) = \int_{\Omega(t)} c_d(t)dv \tag{15}$$

where c_d, c_{do}, c_p, ρ_s, D_d, D_{do}, V^m, V_r, M_d are correspondingly: the drug concentration, the initial drug concentration, the penetrant concentration, the penetrant density, the drug diffusivity in the matrix and in the pure penetrant, the initial matrix volume, the release environment volume coinciding with the external penetrant volume and the amount of the drug in the matrix. The boundary of the domain is denoted by $\partial\Omega$ and the time when the process is in equilibrium – by t_f .The above equations are coupled with the model equations for the penetrant uptake [5, 20]:

$$\frac{\partial c_p}{\partial t} = -\nabla \mathbf{j},\ \mathbf{j} = \mathbf{j}_f + \mathbf{j}_r,\ \text{in}\ \Omega \times (0, t_f] \tag{16}$$

$$\mathbf{j}_f = -D_f \nabla c,\ \mathbf{j}_r = -D_r \nabla c_p - \tau \frac{\partial \mathbf{j}_r}{\partial t}, \tag{17}$$

$$D_f(c_p) = D_o = const,\ D_r(c_p) = D_{eq}\, exp\left[g(c_p - c_{eq})\right] - D_o, \tag{18}$$

$$\tau(c_p) = \tau_{eq}\, exp\left[r(c_{\text{eq}} - c_p)\right] \tag{19}$$

under the initial and boundary conditions:

$$\mathbf{j}_f = 0, \quad \mathbf{j}_r = 0, \quad c = 0, \text{ for } t = 0 \text{ in } \Omega; \tag{20}$$

$$c_p = 0.8 c_{eq}, \text{ for } t = 0 \text{ on } \partial\Omega; \tag{21}$$

$$\tau \frac{dc_p}{dt} = c_{eq} - c_p \ \text{in}\ \partial\Omega_t \times (0,\ t_f] \tag{22}$$

where $\mathbf{j}$ is the total penetrant diffusive flux; $\mathbf{j}_f$, $\mathbf{j}_r$ are the classical (Fickian) and non-classical (non-Fickian) part of the total diffusive flux; c_{eq} is the penetrant concentration at equilibrium; D_f, D_r, D_o are the diffusivities connected with $\mathbf{j}_f$, $\mathbf{j}_r$, respectively and the penetrant diffusivity in the dry matrix; τ is the concentration dependent relaxation time for the polymer/penetrant system and $\partial\Omega_t$ is the boundary of the domain at the moment *t*.

This complex problem was numerically solved in the 2-D case for cylindrical tablets using finite element domain discretization and a time differencing scheme [4, 5].

The drug dissolution phenomena taking place inside the matrix may be accounted for by resorting to the following equation [17]:

$$\frac{\partial c_{dd}}{\partial t} = -K(c_s - c_d), \qquad K = K^I S, \tag{23}$$

where K is the dissolution constant, K^I is the dissolution constant per unit area, S is the dissolution area, c_{dd} is the solid drug concentration, c_s is the drug solubility in the swelling fluid. A phase transition upon dissolution may be considered as it is done by Nogami et al. [17]. The dissolution can be taken into account adding a source term, based on (23), in the drug balance equation (12).

Another possible factor for drug release behavior (as it was concluded in [3]) is physicochemical polymer-drug interactions. Singh and co-workers assumed a drug sorption-

desorption phenomenon occurring on polymer chains during diffusion and proposed the following equation using a Langmuir isotherm [17, 43]:

$$c_p \frac{\partial M_b}{\partial t} = r_{ads} - r_{des}, \quad r_{ads} = k_a c(M_b^{max} - M_b), \quad r_{des} = k_d M_b c_p (c_s - c), \tag{24}$$

where M_b is the amount of drug bound per unit mass of polymer; M_b^{max} is its maximum value; c and c_s are the drug concentration and solubility in the swelling fluid, respectively; k_a and k_d are the adsorption and desorption constants, respectively. Thus, the mass balance equation describing (in one dimension) the drug concentration in the matrix is given as follows:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial X^2} - c_p \frac{\partial M_b}{\partial t} \tag{25}$$

An additional process which can take place because of chemical or physical reasons is matrix erosion related to some extent with polymer-drug interactions and dissolution. It can develop according to two different mechanisms [17, 41]: surface or heterogeneous; bulk or homogeneous. There exist several models describing these erosion processes using: (1) direct Monte Carlo approach [16, 48]; (2) classical 1-D diffusion equation under moving boundaries for both diffusion and erosion (with constant rate) leading to a Stefan problem [8]; (3) diffusion equations including appropriate source terms and time, space or concentration dependent diffusivities [22, 27, 29].

A class of CRS for which the analysis becomes much more complicated is the polydisperesed swellable spherical matrices. The first attempt for drug release modelling accounting for particle polydispersity is that of Crassi and co-workes [19] based on the above Eqs. (12) - (23). The obtained predictions for Temazepan release from PVP under Weibull particles distribution variation show that when particles size increases, drug release becomes slower, and the desired observation effects tend to disappear [17]. This is due to the fact that diffusion becomes too slow in comparison with recrystallisation, because of particles dimensions.

An important factor for dug release kinetics is the degree of anisotropy [3]. Zhou and co-workers numerically solved problems for drug release for polymer matrix tablets taking into account the material anisotropy [46]. Recently they analyzed diffusional drug release from 2-D matrix tablets with consideration of two separate diffusion coefficients in two directions [47]. The model was experimentally verified and various factors influencing release kinetics were analyzed including the ratio of initial solute loading to solubility, the matrix anisotropy and ratio of tablet radius to the half-thickness.

Frenning and co-workers developed a more generalized model for anisotropic drug transport, which takes the effects of final dissolution rates into account [12]. It combines the following diffusion and Noyes-Whitney equations [13]:

$$\frac{\partial c}{\partial t} = D_r \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right) + D_z \frac{\partial^2 c}{\partial z^2} + k\left\langle s^{2/3}(c_s - c)\right\rangle, \tag{26}$$

$$\frac{\partial s}{\partial t} = -k\left\langle s^{2/3}(c_s - c)\right\rangle, \text{ where the Macaulay bracket } \langle x\rangle = \frac{x + |x|}{2} = \begin{cases} x & if \quad x \geq 0 \\ 0 & if \quad x < 0 \end{cases} \tag{27}$$

may be seen as the integral of the Heaviside function. In these equations D_r, D_z are the diffusion coefficients in the radial and axial directions, respectively:

$c = C / C_{tot}$, $s = S / C_{tot}$, $c_s = C_s / C_{tot}$, $k = k_d A_w C_{tot}$,

where C is the concentration of dissolved drug within the matrix, S is the concentration of solid drug, C_{tot} is initial total concentration of the drug, C_s is drug solubility in the matrix, k_d is the dissolution rate constant, and A_w the weight-specific surface area of the solid drug before dissolution. It is assumed that all drug is present in solid form in the initial state or that the matrix initially contains a saturated drug solution. The fraction of released drug may be expressed as

$$Q(t) = 1 - \frac{1}{V}\int_{\Omega}(c + s)d\Omega, \tag{28}$$

where V is the matrix volume.

The numerical analysis performed by using finite element method shows that a finite dissolution rate may affect the release profile significantly, producing an initial delay. It is demonstrated the proposed model describes experimental drug (acetylsalicylic acid and ethyl cellulose) release data well.

Conclusions

A brief review of the current state of the art of mathematical modelling drug release from polymeric monoliths is performed. The most important models are presented with their advantages and limitations in two main groups: empirical and semi-empirical models and theoretical comprehensive ones.

The first class of simple models can be adopted as an initial step of approximation of the real experimental data. It is mentioned that in many cases (even in the case of swellable matrices) they are fully sufficient. On the other hand their application gives limited insight into the exact release mechanisms. When more detailed information is required models from the second class must be applied.

The present study can serve as a useful guide for the discussed models consumers. The best strategy for choosing an appropriate model consists of careful identification of the main controlling mechanisms (diffusion, swelling, erosion or dissolution, or a combination of some of them) and other important factors (as initial drug distribution, particles drug distribution, degree of matrix porosity and anisotropy, matrix geometry), followed by neglecting the other processes and dependences. In such a way the application of overly complex models can be avoided.

Even though very profound theoretical models for CRS have been proposed, further development of some of them is desirable. This process is going on simultaneously with appearance of new experimental evidence for the existing drug delivery systems and with the design of new more contemporary ones.

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