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Structural modeling of drug release from biodegradable porous matrices based on a combined diffusion/erosion process

V. Lemaire [a], J. Bélair [b], P. Hildgen [c,*]

[a] *Département de Physique, Centre de Recherches Mathématiques, Université de Montréal, Montréal, Que., Canada*
[b] *Département de Mathématiques et de Statistique, Institut de Génie Biomédical, Centre de Recherches Mathématiques, Université de Montréal, Montréal, Que., Canada*
[c] *Faculté de Pharmacie, Université de Montréal, C.P. 6128, Succursale Centre-Ville, Montréal, Que., Canada H3C 3J7*

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Abstract

Biodegradable, porous microspheres exhibit a wide range of release profiles. We propose in this paper a unifying approach based on the dual action of diffusion and erosion to establish which mechanisms are responsible for the variety of release kinetics observed during in vitro experiments. Our modeling procedure leads to the partitioning of the matrix into multiple, identical elements, thus simplifying significantly the mathematical and numerical treatment of the problem. The model equations cannot be solved analytically, since the domain contains a moving interface, and must therefore be solved numerically, using specific methods designed for that purpose. Our model confirms the major role that the relative dominance between diffusion and erosion plays in the release kinetics. In particular, the velocity of erosion, the effective diffusion coefficient of the drug molecule in the wetted polymer, the average pore length, and the initial pore diameter are sensitive parameters, whereas the porosity and the effective diffusion coefficient of the drug in the solvent-filled pores is seen to have little influence, if any, on the release kinetics. The model is confirmed by using release data from biodegradable microspheres with different ratios of low and high molecular weight PLA. Excellent goodness of fit is achieved by varying two parameters for all types of experimental kinetics: from the typical square root of time profile to zero-order kinetics to concave release curves. We are also able to predict, by interpolation, release curves from microspheres made of intermediate, untested ratios of PLA by using a relation between two model parameters.

Keywords: Mathematical modeling; Release kinetics; Diffusion; Erosion; Biodegradable porous matrices; Microspheres

1. Introduction

Drug delivery controlled by biodegradable microspheric devices has undergone significant expansion in the past 20 years. The popularity of this technique has been enhanced by the excellent intrinsic delivery properties of microspheres, of which we mention three. First, the drug is encapsulated inside a polymeric matrix until it is released from the microsphere, so that the drug is prevented from being degraded by the body during the early stages following administration (Cohen et al., 1991). Second, the small size of microparticles makes them suitable for direct injection without requiring surgical implant

* Corresponding author. Tel.: +1-514-343-6448; fax: +1-514-343-2102.
E-mail addresses: vincent.lemaire@umontreal.ca (V. Lemaire), jacques.belair@umontreal.ca (J. Bélair), patrice.hildgen@umontreal.ca (P. Hildgen).

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(Jalil and Nixon, 1990). Third, microspheres are usually made of biodegradable polymers, which have the advantage of being degraded and eliminated from the body once they achieved their goal (Hanes et al., 1998).

Microspheres, however, would constitute a poor delivery device if the control of the release of the core material were impossible. Many studies have actually shown that, by modifying the microsphere preparation parameters (such as the choice of polymer or the formulation method), it is possible to exert control on the in vitro release profile (Sah et al., 1994; Bain et al., 1999; Capan et al., 1999; Siepmann et al., 1999; Bezemer et al., 2000b; Jain et al., 2000; Ravivarapu et al., 2000; Yang et al., 2000). Although this control may be difficult to obtain or partially achievable, the association of controllability and natural delivery properties makes microspheric systems particularly effective.

Two different approaches may be undertaken to improve the reliability of drug delivery devices, such as microspheric systems. The first approach relies on experimental procedures to determine and adjust the device preparation parameters. The second approach is based on a theoretical investigation of the basic mechanisms of drug release. This latter approach allows for a more detailed understanding of the physical and chemical processes acting during drug release. We are particularly interested in the interaction between the erosion and diffusion processes, and its consequences on the release kinetics. To investigate some of these issues, we present a model based on a simplified representation of the porous network with simultaneous erosion and diffusion actions. Since our interest lies in investigating release mechanisms and local release kinetics, we only rely on in vitro data to compare the model with experiments.

Biodegradable microspheric systems commonly exhibit an initial burst release of variable amplitude, followed by a zero order profile in the release kinetics (Cohen et al., 1991; Sah et al., 1994; McGee et al., 1995; Kissel et al., 1996; Boury et al., 1997; Lacasse et al., 1997; Liu et al., 1997; Hernádez et al., 1998; Veronese et al., 1998). Given the pharmacological importance of the zero-order kinetics, our initial motivation was to determine the sequence of events generating this particular kinetics.

Before presenting the model in details, we review relevant models and their relation to our perspective.

2. Background and motivation

The first release models predicted a square root of time initial release profile for spherical devices (Higuchi, 1963; Baker and Lonsdale, 1974). Explicit analytical solutions of the diffusion equation were used directly in (Baker and Lonsdale, 1974) to represent the release of a drug dissolved (below solubility) in a polymeric matrix. On the other hand, Higuchi (1963) had to assume that the initial drug loading exceeds the drug solubility in the diffusing medium in order to derive (by now) famous expressions for the release of drug from spherical pellets. In the case of a porous matrix, the porous structure slows down the progression of the diffusing agent. In a second equation, Higuchi (1963) simulated the hindering effects of the porous network by lumping these effects in the definition of the diffusion coefficient, using the relation $D_{\text{eff}} = D\varepsilon/\tau$. In the case of a biodegradable polymer, erosion affects the drug release by carrying along drug molecules with the eroded product. In addition, if the matrix is porous, polymer erosion increases the diffusional space by expanding the pore volume, thus accelerating the release of drug by diffusion. A convenient way to simulate the effect of erosion on diffusion is to allow the effective diffusion coefficient to increase with time (Heller and Baker, 1980; Wada et al., 1995; Bezemer et al., 2000a; Charlier et al., 2000). The time-dependency of the diffusion coefficient was either determined empirically in studies by Wada et al. (1995) and Bezemer et al. (2000a), or derived from assumptions relating the polymer molecular weight to the diffusion coefficient in other works by Heller and Baker (1980) and Charlier et al. (2000). The new equation for the time-dependent diffusion coefficient was then directly incorporated into solutions of the diffusion equation (Wada et al., 1995; Bezemer et al., 2000a), or used with Higuchi's relations (Heller and Baker, 1980; Charlier et al., 2000) to obtain a generalized form of these equations.

In 1980, Lee proposed an improved version of Higuchi's relations in planar geometry by adding a

moving erosion front to the dissolution front. Again, the derivation assumed that the initial drug loading exceeds the drug solubility in the matrix. More detailed representations of the degradation and erosion processes have still been developed (Joshi and Himmelstein, 1991; Pitt and Schindler, 1995; Batycky et al., 1997). Batycky et al. (1997) proposed a theoretical model for predicting the time evolution of polymer erosion and macromolecular release. This model is based on the mechanics of polymer chain breaking leading to pore coalescence. We will make use of this model for its results on the rate of pore erosion. Joshi and Himmelstein (1991) represented the degradation process and the ensuing drug release as a reaction-diffusion problem. The effects of erosion are simulated by allowing the diffusion coefficient to increase as the concentration of undegraded polymer decreases. The problem as a whole is solved numerically. A similar numerical procedure is applied by Siepmann and Peppas (2000) to solve a system of equations representing drug release from hydrophilic matrices. Processes such as diffusion, changes in matrix volume, swelling of the system, drug dissolution and polymer erosion are taken into account in the equations. A general dissolution/diffusion model for the release of drug from porous non-swelling transdermal devices is proposed by Lee et al. (1998). In this model, the polymer is not supposed to be biodegradable and the hindering effects of the porous network on diffusion are again lumped in the definition of the diffusion coefficient. Analytical solutions are derived in some specific cases and the general problem is solved numerically. Recently, Tzafriri (2000) proposed a model in which drug release is supplied by two sources, or pools: one pool of a freely diffusing agent, and another composed of an agent which can only diffuse after matrix degradation. A major assumption in this model is the uncoupling of the diffusion processes in both pools.

In all the above models, a system of equations is developed from basic principles of physics and chemistry, and the solutions are either extracted by mathematical analysis, numerical methods, or a combination thereof. Recently, other avenues have been explored: mainly, cellular automata-based methods and percolation-based methods (Zygourakis, 1990; Göpferich and Langer, 1995; Göpferich, 1996; Mohanty et al., 1982; Ottino and Shah, 1984; Siegel et al., 1989; Ehtezazi and Washington, 2000). We mention the existence of these methods for completeness purpose, however, being based on computer modeling techniques, these methods differ essentially from our own approach.

The dissolution of a solid agent provides a continuous supply of drug, acting as a reservoir, as long as the drug is diffusing. Conveniently, this reservoir allows the introduction of pseudo-steady state assumptions in the derivation of the release equations. In our case, the use of this hypothesis cannot be justified because most microsphere preparation techniques, like the spray drying method, lead to a molecular dispersion of the active agent within the matrix, with no solid aggregate of drug. Models based on drug dissolution (e.g. Higuchi, 1963; Heller and Baker, 1980; Lee, 1980; Charlier et al., 2000) should therefore not be used to describe the release of drug from such microspheric devices. We believe that most release profiles from porous degradable matrices are generated by the interaction of three components: polymer erosion, drug diffusion, and the structure of the porous microenvironment. Our goal is to create a model which incorporates these three components, and determine the contribution of each to the release kinetics. Although the general mechanisms of release are well-known (dissolution, diffusion, erosion, etc.), the exact scenario of the release is not clearly established, and this paper aims to provide clarifications on that point. We thus adopt a modeling procedure which takes into account the contribution of the porous network on the diffusion rates, and represents *directly* the effect of erosion on the release kinetics. We propose a structural modeling approach based on the partitioning of the porous matrix into identical subsystems which allows both a clearer visualization of the release behaviors and an easier mathematical treatment.

3. Model derivation

3.1. Hypothesis and representation

We consider a porous, biodegradable polymeric medium in which a drug is uniformly distributed. The drug molecules are either trapped within the polymer, or deposited inside the pores. In the model, the

pores are represented as hollow cylinders of constant cross-sectional area. We suppose that the drug is not chemically bond to the polymer. The drug is simply physically entrapped into the matrix. Thus, polymer degradation is not required before any drug diffusion takes place. At all times, the drug concentration is below its solubility C_s in the solvent, so that there is no solid aggregate of drug. Once the matrix is dipped into the solvent, the latter invades the pores and permeates the polymer more deeply by traveling through a network of pores considerably smaller, the micropores, which are connected to the main pores. These micropores are extremely small cavities, comparable in size with the drug molecule, and generally composed of the empty space located between the chains of polymer. The permeation of the solvent in the matrix may lead to some limited swelling, depending on the type of polymer used. In the model, we suppose that, initially, the matrix is perfectly hydrated and swollen. This implies that the initiatory phenomena, such as the hydration of the matrix, as well as the resultant drug release, the burst, are not accounted for by the model. The mechanisms of release operate differently during the initiatory phase and would require a completely different model. However, the hydration and swelling occur over short, transitory periods which generally represent only a tiny fraction of the total release time (between 1 and 5%).

During the release phase, a drug molecule located inside a pore will naturally diffuse towards one of the endpoints of the pore, and eventually reach the outside. A drug molecule located within the network of micropores will first diffuse toward the closest pore. At the same time, the internal surface of the pores erodes slowly by its contact with the solvent, thereby bringing parcels of polymer and additional material to the outside. The movement of the drug's molecules in the micropore network is highly limited due to the cramped space available, and so diffusion is extremely slow. For the same reasons, we suppose that polymer erosion with loss of material is unlikely to take place in micropores, although a local weakening of the matrix by polymer degradation is still possible.

Suppose that a drug molecule is located in the network of micropores. As just described, this molecule will diffuse towards one pore or another. Every pore is thus surrounded by a domain of attraction, inside which all molecules diffuse towards the said pore. Any molecule located outside this domain will join with another pore. It is therefore possible to divide space along these boundaries, each of which defining a zone in which resides a single pore, and these zones together compose the entire sphere. Thus we have a partitioning of the microsphere into more or less identical regions, each one playing the role of a pore drainage basin collecting the drug molecules to the pore (Fig. 1A). We call these regions basic microsphere elements. These elements are independent of each other, and the surfaces of division between them, while only conceptual, are nonetheless impermeable barriers. A drug molecule in a given basin thus remains in its basin until it is released outside of the microsphere. While the length, diameter, and shape of the basic microsphere elements are certainly variable, we may nonetheless consider, for simplification purpose, each element idealized as a cylinder of constant radius, as indicated in Fig. 1B. Since each element will release its drug molecules outside the sphere independently of the other elements, the release characteristics of the microsphere as a whole are identical to the release characteristics of each element considered individually. The geometric model derived in this section leads us to postulate that the drug release can be represented by a typical basic microsphere element, an element of average length L and radius R, as shown in Fig. 1B, without losing the essential features of the release process.

3.2. Modeling equations

We now derive the equations translating the geometric representation of the previous section. The basic microsphere element, denoted Ω, is composed of two embedded parts (Fig. 1B): the first one, labeled domain (1), is a cylinder with axis z, length L and radius $r(t)$. This domain represents a pore filled with solvent containing a drug at concentration $C_0 < C_s$. The second part, labeled domain (2), lies between two coaxial cylinders with axis z, length L, internal radius $r(t)$ and external radius R. This domain, which corresponds to the network of micropores of the previous section, contains the same drug at concentration C_0. The external surface of the domain Ω does not allow flow of the drug molecules, as discussed in the last section. The internal surface of domain (2), which is also the external surface of domain (1), grows in

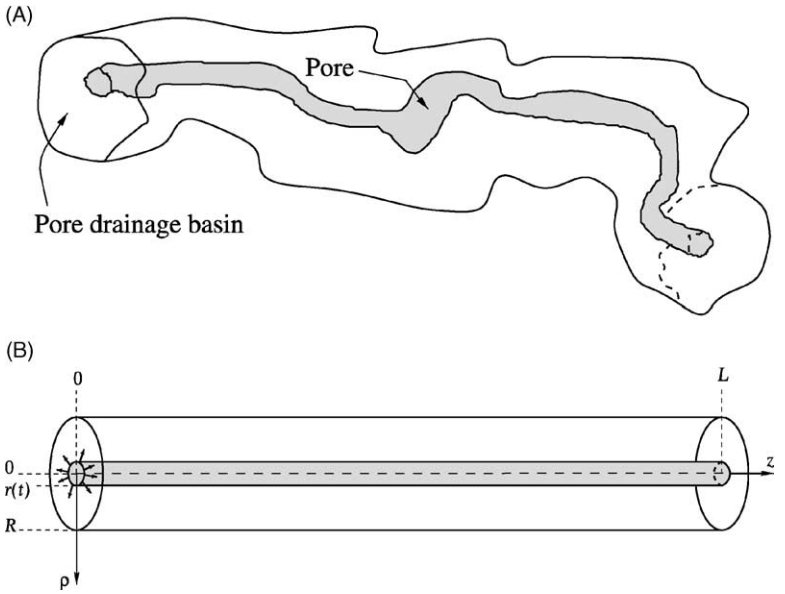

Fig. 1. (A) Isolated pore and its drainage basin. (B) Symbolic representation of the pores and basins in the model.

time as the polymer erodes in contact with the solvent contained in the pore. As mentioned in Section 2, a theoretical model of erosion in this context has been developed by Batycky et al. (1997). The authors give an expression for the growth of the mean pore radius due to polymer erosion. To a good approximation, this radius is shown to be a linear function of time:

$$r(t) = kt + r_0, \tag{1}$$

in which k is a velocity of erosion (here, a constant) and r_0 is the initial pore radius. There may be a delay before any polymer weight loss occurs by erosion (Shah et al., 1992), in which case, relation (1) has to be modified accordingly.

We let σ denote the diffusion coefficient of the drug in the solvent. We suppose that the diffusion is Fickian in domain Ω, and that the diffusion coefficients in each of the domains (1) and (2), respectively denoted σ_1 and σ_2, are constant. Siegel (1989) calls σ_1 the effective diffusion coefficient of the drug in the porous network. In fact, σ_1 is related to σ through the relation $\sigma_1 = \sigma/\mathcal{R}$, where $\mathcal{R}$ is called the retardation factor to reflect how the porous structure (pore geometry and topology) affects the time scale of the drug diffusion. A similar relationship can be established for σ_2, namely $\sigma_2 = K_r\sigma_1$, where K_r is called the restriction factor to account for the interactions between the drug and the polymer. The diffusion coefficients in the domain Ω follow the ordering $\sigma_2 \ll \sigma_1 \ll \sigma$ (Siegel, 1989).

Cylindrical coordinates are clearly most appropriate for our problem. The system is symmetrical about the z axis, with no azimuthal contribution, and thus our problem reduces to a two-dimensional diffusion problem in the (ρ, z) plane. In addition, the symmetry about to the midpoint $z = L/2$ allows us to consider only half $(0 \le z \le L/2)$ of the domain Ω, denoted $\Omega_{1/2}$, in the calculations. The equation describing the evolution of the concentration $C(\rho, z, t)$ under Fickian diffusion, in both space and time, in the domain $\Omega_{1/2}$ is given (Crank, 1975) by

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial \rho^2} + \frac{1}{\rho}\frac{\partial C}{\partial \rho} + \frac{\partial^2 C}{\partial z^2}\right) \tag{2}$$

for $(\rho, z) \in \Omega_{1/2}$ and $t \ge 0$, where $D = \sigma_1$ in domain (1), and $D = \sigma_2$ in domain (2). The initial condition applicable to Eq. (2) is

$$C(\rho, z, 0) = C_0, \tag{3}$$

for all $(\rho, z) \in \Omega_{1/2}$. The boundary conditions are: a perfect sink condition at the endpoint $z = 0$ of the cylinder (common for in vitro experiments),

$$C(\rho, 0, t) = 0, \tag{4}$$

for all $0 \leq \rho \leq R$ and for all $t > 0$, a no flux condition at the external, lateral surface of $\Omega_{1/2}$,

$$\frac{\partial C}{\partial \rho}(0, z, t) = \frac{\partial C}{\partial \rho}(R, z, t) = 0, \tag{5}$$

for all $0 \leq z \leq L/2$ and for all $t > 0$, and the additional no flux condition at the midpoint $z = L/2$ (due to the symmetry),

$$\frac{\partial C}{\partial z}(\rho, L/2, t) = 0, \tag{6}$$

for all $0 \leq \rho \leq R$ and for all $t > 0$.

Once diffusion has started, the amount of drug still inside Ω at time t is given by

$$m_t = 2 \int_{z=0}^{L/2} \int_{\rho=0}^{R} 2\pi\rho C(\rho, z, t)\, \mathrm{d}\rho\, \mathrm{d}z,$$

and the proportion of drug that has left Ω at the same time t is given by

$$Q_t = \frac{m_0 - m_t}{m_0} = \frac{M_t}{M_\infty},$$

where $M_t = m_0 - m_t$ corresponds to the amount of drug that has left Ω at time t (of course, we have $m_0 = M_\infty$). We want to determine Q_t for all time t, but there is no analytical expression for Q_t, since the problem given by Eqs. (2)–(6) includes a moving interface. We must therefore perform numerical computation of Q_t.

3.3. Numerical method

The moving interface $r(t)$ makes the numerical solution delicate to compute. The motion of this interface is essentially determined by the physicochemical properties of the polymer, which are captured in the value of k. The meshes of integration can be determined a priori, since the location of the interface does not depend on the drug concentration in its surrounding. It is nevertheless necessary to set rules to manage the flow of drug around the interface in the numerical scheme, namely how diffusion takes place around it, and how the interface is laced in with the meshes. We based our numerical scheme, including the calculation of the stability criterion, on previous investigations of the diffusion equation in cylindrical coordinates (Albasiny, 1960; Iyengar and Mittal, 1978; Ben-Zarty, 1985). We used a modified Crank–Nicholson scheme, based on finite difference formulas of order 2 on a non-uniform mesh (Hirsch, 1998). Standard techniques of numerical evaluation of integrals were used to compute M_t.

4. Simulation results

We computed numerically the solutions of the modeling Eqs. (2)–(6) to compare the results to experimental data, and to test the predictive capabilities of our model.

The parameters listed in Table 1 provide the physicochemical characteristics of the medium. They have been divided in two subsets: those in (a) can only be determined indirectly, whereas those in (b) can be directly estimated by a proper experimental procedure. For example, the value of σ_2 can only be determined by indirect methods (by using our model, for example), and σ_1 is even less accessible. The length L of the basic element depends not only on the size of the matrix, which is readily available, but also on the

Table 1
Physicochemical parameters of the model and their characteristics

Parameter	Value of reference	Domain of validity	Description
(a)			
σ_1	5×10^5 (nm^2 per day)	$\sigma_1 \gg \sigma_2$	Effective diffusion coefficient in the pore network
σ_2	5000 (nm^2 per day)	$\sigma_2 \geq \bar{\sigma}_2(\mu) \approx 4150$	Effective diffusion coefficient in the micropore network
L	1000 (nm)	$0 < L \leq \bar{L}(\mu) \approx 1100$	Average pore length in the matrix
(b)			
k	0.3 (nm per day)	$0 \leq k \leq \bar{k}(\mu) \approx 0.36$	Velocity of erosion of the polymer
ε_0	0.2	$0 < \varepsilon_0 \leq 0.5$	Initial porosity of the matrix
r_0	4.47 (nm)	$r_0 \geq \bar{r}_0(\mu) \approx 3.57$	Initial pore radius
C_0	Arbitrary	$C_0 < C_s$	Initial drug concentration in the matrix

distribution (orientation, concentration) of the pores in the medium, which is much harder to evaluate. The last parameter in the table, C_0, corresponds to the initial drug loading, and is under explicit control of the experimentalist. Furthermore, its role on the release kinetics is rather limited.

A value of reference was assigned to each parameter, to be able to carry out numerical simulations. The unit of length is the nanometer and the unit of time is the day. All the model parameters have a domain of validity, outside of which the model solutions become unrealistic. The parameters σ_2 and r_0 must be assigned values greater than the minimal values $\bar{\sigma}_2$ and $\bar{r}_0$, whereas k and L have to be smaller than the maximal values $\bar{k}$ and $\bar{L}$. Each of these minimal and maximal values depends on the values of the other parameters, and this dependence is denoted as μ in Table 1. These limits on the parameters describe that domain (2) of Ω should never be completely eroded before all drug has left Ω. Otherwise the porous structure of the matrix would be destroyed before all drug is released, rendering the model invalid. We have also set a maximum limit to ε_0 to preserve some of the model hypothesis: for example, cylindrical pores are unlikely in a matrix with $\varepsilon_0 > 0.5$. The porosity ε is usually defined as the fraction of matrix that exists as pores and channels into which liquid can penetrate: it may depend on time if erosion occurs. Within the framework of our model, the initial porosity is given by $\varepsilon_0 = r_0^2/R^2$.

We explored the range of release curves that can be generated by the model as parameters are varied. In Fig. 2, we show release curves for different values of the erosion velocity k defined in Eq. (1), keeping all other parameters fixed at their value of reference. To better compare the global aspects of all release curves, they are all displayed again in the right graph with uniform time scaling so that $t = 1$ when $M_t/M_\infty = 0.99$. The time rescaling is thus different for each curve, and amounts to a time stretching. This type of representation allows for a direct visualization of the release kinetics, and facilitates comparison between curves. In the left graph, the value of k is 0 for the rightmost curve (the leftmost curve in the right graph). This curve exhibits a typical square root of time profile, which is characteristic of a release entirely controlled by diffusion. The drug molecules originally contained in domain (2) can reach domain (1) in two ways: they can either diffuse in domain (2) with diffusion coefficient σ_2, or be released with eroded material at the frontier between the two domains where erosion takes place. As k increases, erosion is taking more importance in the release process, the curves monotonically shift to the left (to the right in the right graph), and the release profiles flatten. When the value of k is around 0.3, the quantity of drug transferred by diffusion from domain (2) to domain (1) approximately equals the quantity of drug transferred by erosion. We then observe an almost perfectly linear release curve indicating a quasi zero-order kinetics. When $0.3 < k \leq \bar{k}(\mu)$, erosion slightly dominates diffusion and the release curve gently bends down below, taking a concave shape.

In Fig. 3, release curves are shown for a range of values of σ_2, the other parameters being fixed at their

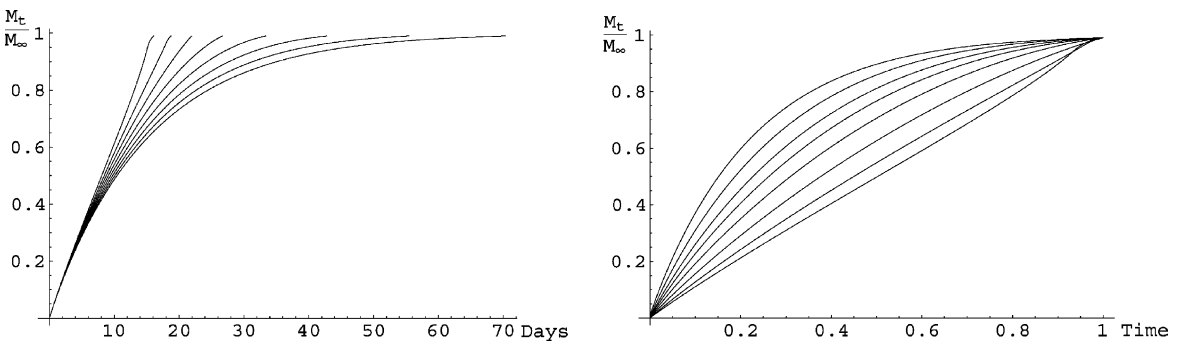

Fig. 2. Release curves generated by the model when k varies over a range of values, namely, 0, 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.36, and the other parameters are kept fixed at their value of reference (listed in Table 1). In the left graph, k is 0 for the rightmost curve and 0.36 for the leftmost curve (the curves positions are reversed in the right graph). The right graph displays the same curves under different time scaling.

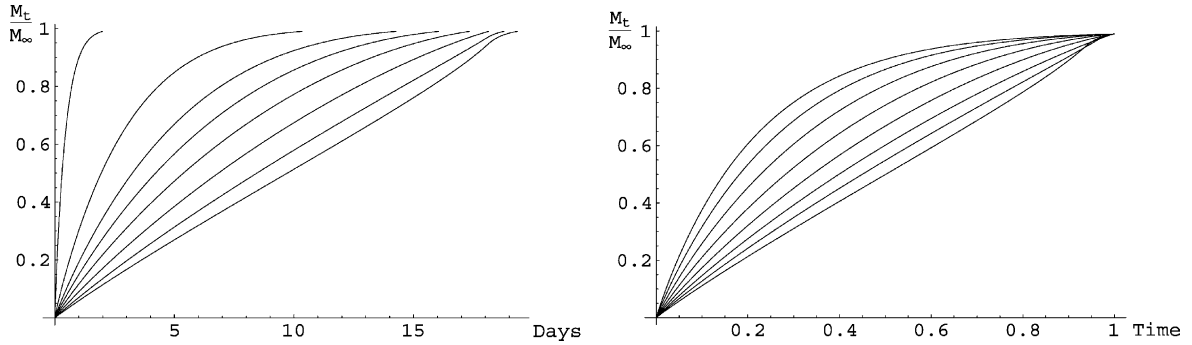

Fig. 3. Release curves generated by the model for different values of σ_2, namely, 4150, 5000, 6500, 8600, 11,300, 15,000, 25,700, 170,000. The other parameters are kept fixed at their value of reference, except σ_1 which varies according to the relation $\sigma_1 \gg \sigma_2$. In both graphs, σ_2 is 4150 for the rightmost curve and 170,000 for the leftmost curve. The right graph displays the same curves as in the left graph but under different time scaling.

value of reference, except σ_1 to keep its relative value with respect to σ_2 ($\sigma_1 \gg \sigma_2$). The same curves are showed again in the right graph using the same representation scheme as before ($M_t/M_\infty = 0.99$ when $t = 1$). The action of erosion is constant since k is fixed. However, the balance between erosion and diffusion varies with σ_2. For large values of σ_2 (here, $\sigma_2 >$ 150,000), diffusion markedly dominates erosion and the release profiles display typical diffusion-controlled release curves. For smaller values of σ_2, the action of erosion is no longer negligible, the curve profiles flatten and the duration of release increases.

When the initial pore radius r_0 is allowed to vary in its domain of validity, the model produces release curves similar to that of Fig. 2. On the other hand, release curves obtained for different values of the average pore length L are similar to those displayed in Fig. 3. In addition, the parameters ε_0 and σ_1 are shown to have little influence (if any, in the case of σ_1) on the release kinetics. Variations of ε_0, however, modify the total duration of release.

The results of these simulations lead us to believe that the release properties of the matrix are essentially determined by the relative dominance between diffusion in domain (2) and erosion. These properties are modulated by variations of the parameters k and σ_2 (or equivalently, r_0 and L), whereas ε_0 and σ_1 are seen to have limited influence on the release kinetics.

We now put the model to the test by evaluating its power to represent experimental release profiles, using data previously published by one of the authors (Lacasse et al., 1997). These data are release profiles of spray-dried biodegradable microspheres having different poly(D,L-lactide) blend formulations and containing an antihypertensive drug. The microspheres are made of various blends of high (PLA 82,000 $\bar{M}_w$) and low (PLA 10,000 $\bar{M}_w$) molecular weight polymers. Five batches of microspheres (numbered from 1 to 5) were prepared by using the following ratios of PLA 82,000/10,000 (in percentage): 100/0, 90/10, 80/20, 70/30 and 60/40. The release curves 1–5 are displayed in Fig. 4, where the dots represent data points, and the solid lines are the corresponding release curves computed from the model. The rightmost curve corresponds to batch 1, the leftmost curve to batch 5. The average microsphere diameter is measured to about 900 nm in all five sets. Based on the pore geometry and topology of these microspheres, we estimate the value of the average pore length L to 1 μm. Based on the same morphological characteristics, the radius of the pore drainage basin R is estimated to 10 nm. The average initial porosity of the microspheres is measured by using a gas absorption porosimeter. Values of 0.1, 0.13, 0.17, 0.2 and 0.23, are found for, respectively, batches 1–5. Most of these experimental measurements appear in Lacasse (1999). The parameters k and σ_2 are the fitting parameters: they are left totally free to vary during the fitting procedure (an optimization algorithm). In the fitting algorithm, σ_1 is subject, as before, to the relation $\sigma_1 \gg \sigma_2$ (which we interpret as $\sigma_1 \approx 1000 \times \sigma_2$) to maintain the difference between the fast diffusion in domain (1) and the slow diffusion in domain (2) imposed by the structure of the model.

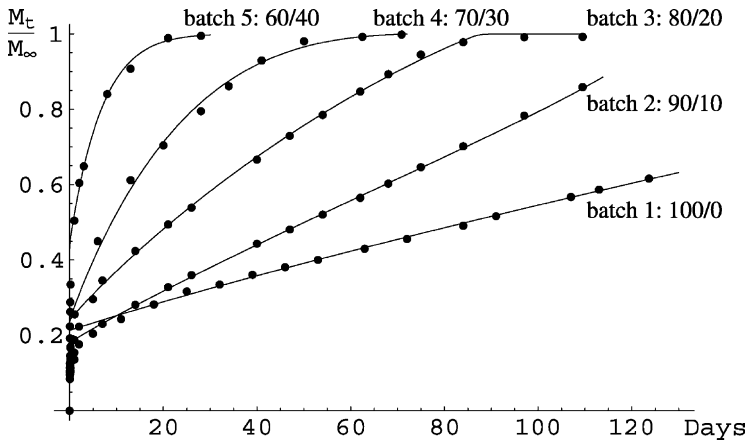

Fig. 4. Cumulative release of an antihypertensive drug from PLA microspheres with the indicated ratios (in percentage) of high/low molecular weight PLA. Solid lines are best fits from the model for each data set.

Table 2
Computed parameters of the model resulting from the fitting procedure on each data set

Parameters	Data set 1	Data set 2	Data set 3	Data set 4	Data set 5
σ_1 (nm^2 per day)	4×10^5	6.5×10^5	14×10^5	32×10^5	110×10^5
σ_2 (nm^2 per day)	400	680	1340	3300	10,600
k (nm per day)	0.027	0.051	0.067	0.070	0.072
ε_0	0.10	0.13	0.17	0.20	0.23

The model curves resulting from the fitting procedure are shown in Fig. 4, and the computed values of the fitting parameters are presented in Table 2. Clearly, the model provides excellent goodness of fit. Indeed, for all curves, the errors (difference between the model curve and the data points) are always less than 0.025 except for the first 2.7% of the total release time (corresponding to the burst, which is not described by the model). For the remaining 97.3% of the total release time, the errors are mostly less than 0.01. The model curves of Fig. 4 are displayed again in Fig. 5, using the same time rescaling procedure as

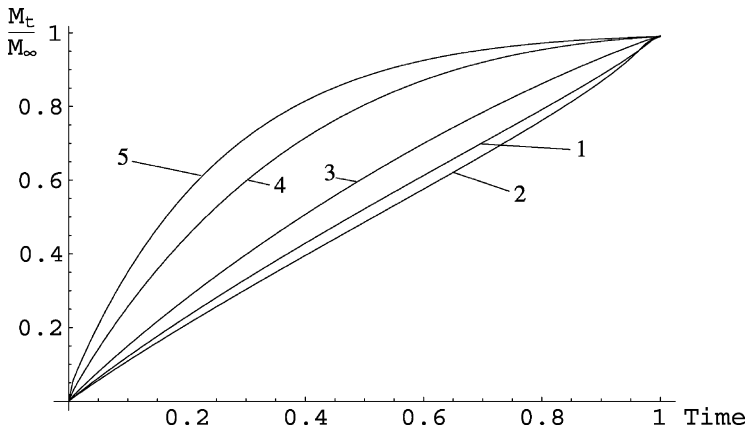

Fig. 5. Same curves as in Fig. 4, but time is now scaled, differently for each curve. As indicated, the curves, from right to left, correspond to the following data sets: 2, 1, 3, 4 and 5.

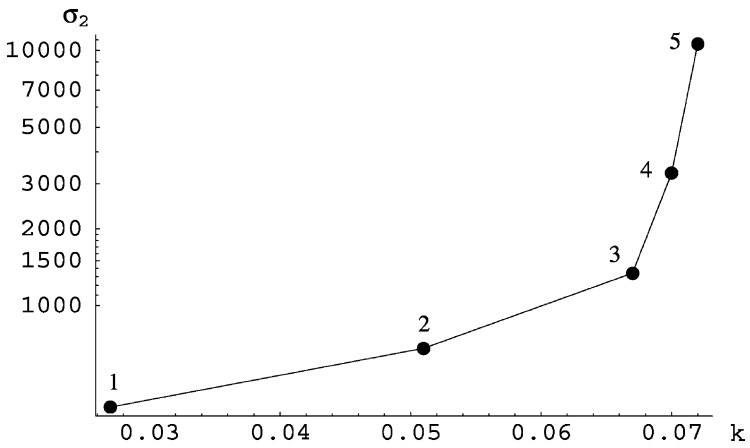

Fig. 6. Computed values of parameters k and σ_2 transfered on plane (k, σ_2). As indicated, the points, from bottom up, correspond to fits of data sets 1–5.

before ($M_t/M_\infty = 0.99$ when $t = 1$). The typical convex form of curve 5 suggests a diffusion-controlled release kinetics, whereas the linearity of curve 1 indicates a quasi zero-order kinetics. The intermediate profiles of curves 3 and 4 imply intermediate kinetics. On the other hand, curve 2 (the rightmost curve) displays a slight concave curvature, indicating that the balance between diffusion and erosion is tilted towards erosion.

The values of the parameters k and σ_2 from Table 2 are displayed in Fig. 6, where the points (k, σ_2) (one for each data set) obviously follow a regular curve. There seems to be a relation between changes in the physicochemical properties of the microspheres generated by various polymer blend proportions and the resultant release kinetics. It is remarkable that the model renders this relation apparent in the form of a relation between the parameters k and σ_2. The curve in Fig. 6 allows us to make some predictions based on interpolation. For example, a new polymer blend with proportions 75/25 would generate a release profile associated to a point in the plane (k, σ_2) between point 3 and point 4, corresponding to values of k around 0.069, and σ_2 around 2100. The corresponding predicted release curve could then be generated by a run of the model. It thus becomes possible to appreciate the shape of a release curve from a polymeric matrix that is not even formulated. This use of the model would confer an unquestionable advantage for the preparation of these microspheres.

5. Discussion

The model proposed in Section 3.1 is based on the hypothesis that the release of a basic element represents the release of the entire system. Although this assumption significantly simplifies the problem, it also implies that the release kinetics depends only on internal properties, and not on the external geometry of the system. Release profiles from planar, cylindrical, and spherical systems are certainly different (Crank, 1975), but the role of the external geometry of bulky systems for the release kinetics is limited. For comparison, the variations of the model parameters k and σ_2 offer a much larger variability in the release profiles as the figures of the last section illustrate. The shape of release curves is mostly determined by the lengthening of the diffusional path, and by internal matrix properties that may influence the drug release during diffusion. Nevertheless, it is possible to simulate the effect of different external geometries with the model by considering a distribution of the pore lengths. If we assume that the pores are randomly distributed in space, then a slab, for example, has a narrower pore length distribution than a sphere.

The initial burst release observed in experiments is sometimes attributed to the rapid release by diffusion of dissolved drug initially deposited inside the pores. Our results do not support this view: we observe that domain (2) continuously supplies domain

(1) in drug (by diffusion and erosion) as soon as domain (1) releases its drug content outside, preventing the concentration gradient at the interface between the two domains from increasing immoderately. This behavior is even observed when σ_1 is significantly greater than σ_2. Our model precisely suggests that the interaction between domain (1) and domain (2) is essential to the outcome of the release kinetics. Tzafriri (2000) assumed that total drug release is supplied by two uncoupled pools, one pool of fast diffusing drug (responsible for the burst), and another pool of slow diffusing drug controlled by polymer degradation. Our results are consistent with Tzafriri's hypothesis provided that his two pools do not take up the same physical space (otherwise, they would not be uncoupled). This would be the case if we suppose that the burst originates from the release of insufficiently incorporated drug located at the surface of microspheres (as well as at the entry of big cavities). For example, some drug particles could have migrated at the surface during the drying of microspheres (Lacasse, 1999). This explanation for the burst is the most commonly supported hypothesis (Cohen et al., 1991; Shah et al., 1992; Niwa et al., 1993; Boury et al., 1997).

The applicability of the model depends, of course, on the validity of its hypothesis. Most of the modeling hypothesis presented in Section 3.1 were verified in the case of the microspheres used for the validation of the model. For example, the molecular dispersion of the drug's molecules in the matrix has been shown in Lacasse et al. (1998). The porous structure of polymeric matrices is so diverse that no model is likely to represent all pore geometries and topologies. In our model, the pores are represented as cylinders (as was verified for the microspheres we used for the model validation; Lacasse, 1999). If the pores were rather spherical, the model would be inadequate, and attempts could be made to transpose the same modeling framework to represent drug release from bubble-connected pores using a spherical basic element and drainage basin. Also, the pores have to be isolated from one another, at least initially. The matrix should not look like a foam with high porosity because, for the same geometrical reasons, the release kinetics may not be well-represented by our model. On the other hand, some polymeric matrices exhibit a porous structure almost identical to our modeling representation. The microspheres prepared by Kissel et al. (1996), Bezemer et al. (2000c) and Bain et al. (1999), for example, are made from porous, biodegradable polymer, which creates a matrix structure similar to what we defined as the micropore network. The in vitro release kinetics presented in these papers show striking resemblance with our modeling curves, with zero-order kinetics, square root of time kinetics, and concave profiles.

6. Conclusion

We have presented a model to describe the release of a drug immersed in a biodegradable, porous, polymeric matrix. The modeling framework is general and applicable to a wide class of porous systems, not uniquely to microspheric devices, which are of particular interest to us. The numerical results confirm that the relative dominance between diffusion and erosion plays a major role in the release kinetics. In particular, the velocity of erosion, the effective diffusion coefficient of the drug molecule in the wetted polymer, the average pore length, and the initial pore diameter are sensitive parameters, whereas the porosity and the effective diffusion coefficient of the drug in the solvent-filled pores are seen to have little influence, if any, on the release kinetics. The model produces a wide range of observed release kinetics, from the typical square root of time profile to zero-order kinetics to concave release curves, by varying one modeling parameter. The model was validated on release data from biodegradable microspheres with different ratios of low molecular weight PLA. Excellent goodness of fit for all types of experimental kinetics was achieved. A relation between the model parameters and the type of polymer used was even brought to light, allowing us to predict the shape of release curve from microspheres made of any ratios of low and high PLA. We believe that the model offers a unifying explanation for the diversity of release kinetics from biodegradable, porous polymeric matrices. In the future, the model could be used as a tool to provide access to a wide range of physical and chemical parameter configurations, allowing its predictive capacities to help to identify those providing the most interesting release characteristics.

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References

Albasiny, E.L., 1960. On the numerical solution of a cylindrical heat-conduction problem. Quart. J. Mech. Appl. Math. 13, 374–384.

Bain, D.F., Munday, D.L., Smith, A., 1999. Solvent influence on spray-dried biodegradable microspheres. J. Microencapsul. 16, 453–474.

Baker, R.W., Lonsdale, H.K., 1974. Controlled release: mechanisms and rates. In: Tanquarry, A.C., Lacey, R.E. (Eds.), Controlled Release of Biologically Active Agents. Plenum Press, New York, pp. 15–71.

Batycky, R.P., Hanes, J., Langer, R., Edwards, D.A., 1997. A theoretical model of erosion and macromolecular drug release from biodegrading microspheres. J. Pharm. Sci. 86, 1464–1477.

Ben-Zarty, O., 1985. On numerical schemes of the Crank–Nicolson type for the cylindrical diffusion equation. Utilitas Math. 28, 151–157.

Bezemer, J.M., Radersma, R., Grijpma, D.W., Dijkstra, P.J., Feijen, J., van Blitterswijk, C.A., 2000a. Zero-order release of lysozyme from poly(ethylene glycol)/poly(butylene terephthalate) matrices. J. Control. Release 64, 179–192.

Bezemer, J.M., Radersma, R., Grijpma, D.W., Dijkstra, P.J., van Blitterswijk, C.A., Feijen, J., 2000b. Microspheres for protein delivery prepared from amphiphilic multiblock copolymers. 1. Influence of preparation techniques on particle characteristics and protein delivery. J. Control. Release 67, 233–248.

Bezemer, J.M., Radersma, R., Grijpma, D.W., Dijkstra, P.J., van Blitterswijk, C.A., Feijen, J., 2000c. Microspheres for protein delivery prepared from amphiphilic multiblock copolymers. 2. Modulation of release rate. J. Control. Release 67, 248–260.

Boury, F., Marchais, H., Proust, J.E., Benoit, J.P., 1997. Bovine serum albumin release from poly(α-hydroxy acid) microspheres: effect of polymer molecular weight and surface properties. J. Control. Release 45, 75–86.

Capan, Y., Woo, B.H., Gebrekidan, S., Ahmed, S., DeLuca, P.P., 1999. Influence of formulation parameters on the characteristics of poly(D,L-lactide-co-glycolide) microspheres containing poly(L-lysine) complexed plasmid DNA. J. Control. Release 60, 279–286.

Charlier, A., Leclerc, B., Couarraze, G., 2000. Release of mifepristone from biodegradable matrices: experimental and theoretical evaluations. Int. J. Pharm. 200, 115–120.

Cohen, S., Yoshioka, T., Lucarelli, M., Hwang, L.H., Langer, R., 1991. Controlled delivery systems for proteins based on poly(lactic/glycolic acid) microspheres. Pharm. Res. 8, 713–720.

Crank, J., 1975. The Mathematics of Diffusion, 2nd ed. Oxford University Press, Oxford.

Ehtezazi, T., Washington, C., 2000. Controlled release of macromolecules from PLA microspheres: using porous structure topology. J. Control. Release 68, 361–372.

Göpferich, A., 1996. Mechanisms of polymer degradation and erosion. Biomaterials 17, 103–114.

Göpferich, A., Langer, R., 1995. Modeling monomer release from bioerodible polymers. J. Control. Release 33, 55–69.

Hanes, J., Chiba, M., Langer, R., 1998. Degradation of porous poly(anhydride-co-imide) microspheres and implications for controlled macromolecule delivery. Biomaterials 19, 163–172.

Heller, J., Baker, R.W., 1980. Theory and practice from controlled drug delivery from bioerodible polymers. In: Baker, R.W. (Ed.), Controlled Release of Bioactive Materials. Academic Press, New York, pp. 1–18.

Hernádez, R.M., Igartua, M., Gascón, A.R., Calvo, M.B., Pedraz, J.L., 1998. Influence of shaking and surfactants on the release of BSA from PLGA microspheres. Eur. J. Drug Metab. Pharmacokinet. 23, 92–96.

Higuchi, T., 1963. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.

Hirsch, C., 1988. Numerical computation of internal and external flows. Volume 1: Fundamentals of numerical discretization. Wiley Series in Numerical Methods in Engineering. Wiley/Interscience, Chichester, UK.

Iyengar, S.R.K., Mittal, R.C., 1978. High accuracy difference schemes for the cylindrical heat conduction equation. J. Inst. Math. Appl. 22, 321–330.

Jain, R.A., Rhodes, C.T., Railkar, A.M., Waseem Malick, A., Shah, N.H., 2000. Controlled release of drugs from injectable in situ formed biodegradable PLGA microspheres: effect of various formulation variables. Eur. J. Pharm. Biopharm. 50, 257–262.

Jalil, R., Nixon, J.R., 1990. Biodegradable poly(lactic acid) and poly(lactide-co-glycolide) microcapsules: problems associated with preparative techniques and release properties. J. Microencapsul. 7, 297–325.

Joshi, A., Himmelstein, K.J., 1991. Dynamics of controlled release from bioerodible matrices. J. Control. Release 15, 95–104.

Kissel, T., Li, Y.X., Volland, C., Görich, R., Koneberg, R., 1996. Parental protein delivery systems using biodegradable polyester of ABA block structure, containing hydrophobic poly(lactide-co-glycolide) A blocks and hydrophilic poly(ethylene oxide) B blocks. J. Control. Release 39, 315–326.

Lacasse, F.-X., 1999. Développement et mise au point d'un système microparticulaire pour implantation vasculaire et périvasculaire. Ph.D. thesis, Université de Montréal.

Lacasse, F.-X., Hildgen, P., Pérodin, J., Escher, E., Phillips, N.C., McMullen, J.N., 1997. Improved activity of a new angiotensin receptor antagonist by an injectable spray-dried polymer microsphere preparation. Pharm. Res. 14, 887–891.

Lacasse, F.X., Fillion, M.C., Phillips, N.C., Escher, E., McMullen, J.N., Hildgen, P., 1998. Influence of surface properties at biodegradable microsphere surfaces: effects on plasma protein adsorption and phagocytosis. Pharm. Res. 15, 312–317.

Lee, P.I., 1980. Diffusional release of a solute from a polymeric matrix—approximate analytical solutions. J. Membr. Sci. 7, 255–275.

Lee, A.J., King, J.R., Hibberd, S., 1998. Mathematical modelling of the release of drug from porous, nonswelling transdermal drug-delivery devices. IMA J. Math. Appl. Med. Biol. 15, 135–163.

Liu, L.S., Liu, S.-Q., Ng, S.Y., Froix, M., Ohno, T., Heller, J., 1997. Controlled release of interleukin-2 for tumour immunotherapy using alginate/chitosan porous microspheres. J. Control. Release 43, 65–74.

McGee, J.P., Davis, S.S., O'Hagan, D.T., 1995. Zero order release of protein from poly(D,L-lactide-co-glycolide) microparticles prepared using a modified phase separation technique. J. Control. Release 34, 77–86.

Mohanty, K.K., Ottino, J.M., Davis, H.T., 1982. Reaction transport in disordered composite media: introduction of percolation concepts. Chem. Eng. Sci. 37, 905–924.

Niwa, T., Takeuchi, H., Hino, T., Kunou, N., Kawashima, Y., 1993. Preparations of biodegradable nanospheres of water-soluble and insoluble drugs with D,L-lactide/glycolide copolymer by a novel spontaneous emulsification solvent diffusion method and drug release behavior. J. Control. Release 25, 89–98.

Ottino, J.M., Shah, N., 1984. Analysis of transient sorption and permeation of small molecules in multiphase polymer systems. Polym. Eng. Sci. 24, 153–162.

Pitt, C.G., Schindler, A., 1995. The kinetics of drug cleavage and release from matrices containing covalent polymer–drug conjugates. J. Control. Release 33, 391–395.

Ravivarapu, H.B., Burton, K., DeLuca, P.P., 2000. Polymer and microsphere blending to alter the release of a peptide from PLGA microspheres. Eur. J. Pharm. Biopharm. 50, 263–270.

Sah, H.K., Toddywala, R., Chien, Y.W., 1994. The influence of biodegradable microcapsule formulations on the controlled release of a protein. J. Control. Release 30, 201–211.

Shah, S.S., Cha, Y., Pitt, C.G., 1992. Poly(glycolic acid-co-D,L-lactic acid): diffusion or degradation controlled delivery? J. Control. Release 18, 261–270.

Siegel, R.A., 1989. Modeling of drug release from porous polymers. In: Rosoff, M. (Ed.), Controlled Release of Drugs: Polymers and Aggregate Systems. VCH Publishers, Weinheim, Chapter 1, pp. 1–51.

Siegel, R.A., Kost, J., Langer, R., 1989. Mechanistic studies of macromolecular drug release from macroporous polymers. I. Experiments and preliminary theory concerning comleteness of drug release. J. Control. Release 8, 223–236.

Siepmann, J., Peppas, N.A., 2000. Hydrophilic matrices for controlled drug delivery: an improved mathematical model to predict the resulting drug release kinetics (the "sequential layer" model). Pharm. Res. 17, 1290–1298.

Siepmann, J., Lecomte, F., Bodmeier, R., 1999. Diffusion-controlled drug delivery systems: calculation of the required composition to achieve desired release profiles. J. Control. Release 60, 379–389.

Tzafriri, A.R., 2000. Mathematical modeling of diffusion-mediated release from bulk degrading matrices. J. Control. Release 63, 69–79.

Veronese, F.M., Marsilio, F., Caliceti, P., De Filippis, P., Giunchedi, P., Lora, S., 1998. Polyorganophosphazene microspheres for drug release: polymer synthesis, microsphere preparation, in vitro and in vivo naproxen. J. Control. Release 52, 227–237.

Wada, R., Hyon, S.-H., Ikada, Y., 1995. Kinetics of diffusion-mediated drug release enhanced by matrix degradation. J. Control. Release 37, 151–160.

Yang, Y.-Y., Chia, H.-H., Chung, T.-S., 2000. Effect of preparation temperature on the characteristics and release profiles of PLGA microspheres containing protein fabricated by double-emulsion solvent extraction/evaporation method. J. Control. Release 69, 81–96.

Zygourakis, K., 1990. Development and temporal evolution of erosion fronts in bioerodible controlled release devices. Chem. Eng. Sci. 45, 2359–2366.