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# Modeling of drug release from bulk-degrading polymers

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ABSTRACT

This paper aims to provide a comprehensive review of the various models or simulations for predicting drug release from bulk-degrading systems. A brief description of bulk degradation processes and factors affecting the degradation rate, and consequently the release kinetics, is presented first. Next, several important classical models, often used as the basis for subsequent model development, are discussed.

Both mathematical models and Monte-Carlo based simulations have been developed for controlled release from bulk-degrading systems. The mathematical models can be further subdivided into two categories. First, the diffusion-based models whose transport mechanism is mainly governed by diffusion, but with degradation-dependent diffusion coefficients. These are generally simpler and easier to use and are sufficient to illustrate *mono-phasic* release. Second, comprehensive models that combine diffusion with other theories such as erosion, drug dissolution and/or pore percolations. These models usually involve more complex equations but provide good matches for *multi-phasic* release profiles.



## 1. Introduction

In the past four decades, research in the field of controlled drug delivery has been critical to the systemic administration of sustained dosages of bioactive molecules for various indications. This research in more recent times has concentrated on injectable and implantable long-term delivery of bioactive molecules with narrow therapeutic window and low bioavailability when administered through conventional routes. The injectable and implantable routes of administration have often focused on the use of biodegradable rather than biostable carriers.

The usefulness of various polymers acting as drug delivery carriers has long been well established (Kost, 1995; Ranade and Hollinger, 1996; Bodmeier and Siepmann, 1999). The use of biodegradable polymers has increased in recent years; as such polymers erode away over time, and eliminate the need for a second retrieval surgery upon drug exhaustion. In addition, degradable polymer carriers have the flexibility to deliver both hydrophilic and hydrophobic drugs (Leong and Langer, 1987; Langer, 1990; Smith et al., 1990; Ron and Langer, 1992; Domb et al., 1993, 2002).

With regard to degradable polymers, the following two terms: *degradation* and *erosion* have been often used interchangeably in literature. To avoid confusion in this review, these two terms are defined as follows. Degradation refers to the actual process of polymer chain cleavage/bond hydrolysis into shorter chains or oligomers, while erosion refers to mass loss from the matrix, which may include the loss of (water-soluble) monomers, oligomers and/or other degradation products.

Along with various reports on the original experimental results on drug release from bulk-degrading systems, many mathematical models have been developed (Siepmann and Göpferich, 2001; Arifin et al., 2006). These models aim to elucidate the governing release mechanisms and provide predictive power on the release behaviour of a particular formulation; hence, minimizing laborious in vitro studies. This review aims to provide an overview of the models developed mainly for predicting the release kinetics of bioactive molecules from bulk-degrading systems.

## 2. Degradable polymers

### 2.1. Bulk degradation of poly (α-hydroxy esters)

Degradable polymers can be categorized into two groups on the basis of degradation mechanisms: bulk-degrading polymers and surface-degrading polymers. Bulk degradation is a homogeneous process in which degradation occurs throughout the polymer matrix. In contrast, surface degradation is a heterogeneous process in which degradation (and subsequent erosion) is confined to a thin surface layer of polymer (see also Fig. 1.)

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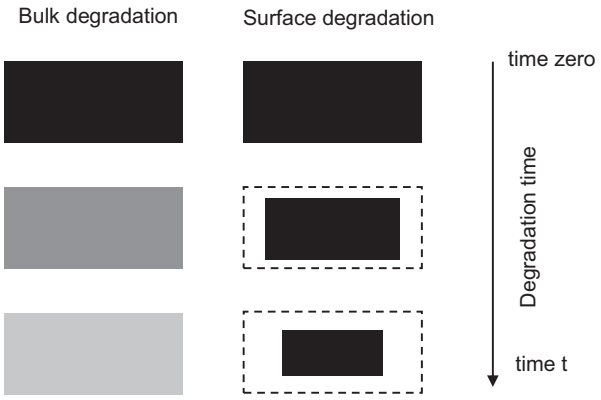


**Fig. 1.** Schematic illustration of surface- and bulk-degradation.

Bulk degradation in poly (α-hydroxy esters), which are the biodegradable polymers most commonly used, can be described as consisting of four consecutive steps (Wu, 1995a; Hasirci, 2000). First, a polymer absorbs water and undergoes some swelling. The water penetrates into the amorphous region and disrupts secondary and tertiary structures stabilized by van der Waal's forces and hydrogen bonds. Second, cleavage of the covalent/ester bonds in the polymer backbone (by hydrolysis) begins. More and more carboxylic end groups are generated which may autocatalyze the hydrolysis. Molecular mass begins to decrease and loss of mechanical strength is observed. Third, massive cleavage of the backbone covalent bonds continues. At some critical value of molecular weight, significant mass loss begins to occur. Loss of physical and mechanical integrity is also observed concurrently. Fourth, the polymer loses substantial mass due to solubilisation of oligomers into the surrounding medium. The polymer breaks down to many small fragments, which will be further hydrolyzed into free acids.

Up to now, the more popular choices of bulk-degrading matrices as drug delivery vehicles are homopolymers or copolymers of lactide/glycolide polymers and poly(ε-caprolactone); both belong to the family of poly (α-hydroxy esters) (Wu, 1995a,b; Amecke et al., 1995; Li and Vert, 1999). Fig. 2 shows the chemical structures of these polyesters.

### 2.2. Factors affecting degradation and release kinetics

In many cases, drug release kinetics is greatly affected by the degradation profiles of the bulk-degrading matrices. Therefore, the release rate, duration of release and overall profiles (*mono-* or *multiphasic* patterns) can be easily modulated by choosing and/or modifying the polymers with suitable degradation behaviour. The factors listed below can be used to control the degradation profiles of bulk-degrading polymers (Zhu et al., 1991; Wu, 1995a; Frank, 2005):

- Polymer composition
  The glycolide group degrades faster than the lactide moiety; therefore, degradation rate of lactide/glycolide copolymers can be adjusted by modifying the ratio of the two moieties. Similarly, degradation rate of poly(ε-caprolactone) can be accelerated by copolymerization with lactide and/or glycolide (Kaetsu et al., 1987; Lewis, 1990; Li, 1999; Wu and Wang, 2001).
- Molecular mass and polydispersity
  Degradation rate increases as the molar mass decreases. The presence of low molar mass species and/or monomers leads to faster degradation rate, in agreement with the presence of more carboxylic acid catalyzing groups (Pitt et al., 1981; Asano et al., 1990; Omelczuk and McGinity, 1992; Park, 1994).
- Polymer crystallinity
  Amorphous regions of a polymer matrix degrade earlier than its crystalline counterparts as water penetration into crystalline structures is more hindered (Chu, 1981; Li et al., 1990c; Vert et al., 1991).
- pH of the release medium
  As chain degradation takes place via hydrolysis of ester bonds, both alkaline and strongly acidic media accelerate degradation rate (Belbella et al., 1996; Holy et al., 1999).
- Physical size of the matrix
  Thicker/bulkier samples are more susceptible to autacatalytic degradation because the degradation products leach out less rapidly from the network (Li et al., 1990a,b).
- Other factors such as nature of drugs incorporated, initial drug loading, additives, sterilization, fluid flow, γ-radiation, and porosity also have been shown to influence the degradation kinetics.

As the kinetics of drug release from bulk-degrading matrices normally involve complex physical and chemical phenomena, it is important to characterize the degradation and erosion of the systems during the period of release. Some of the most common techniques are described here.

Molecular weight reduction is commonly monitored by size-exclusion chromatography (SEC) also called gel permeation chromatography (GPC). The evolution of molecular weight and polydispersity with time are important data to determine the degradation constant, used to estimate the time-dependent diffusion coefficients in many models (discussed in later sections). Measurement of mass loss and water absorption throughout the release study can provide valuable insights onto the mechanisms of release and the types of degradation. Bulk-degrading systems normally experience delayed mass loss as opposed to surface-degrading systems that record (usually linear) mass loss as soon as it is in contact with water. Differential scanning calorimetry (DSC) is a useful technique to determine changes in glass transition temperature ($T_g$) and crystallinity during the course of degradation. On the other hand, scanning electron microscopy (SEM) provides information on surface topography and formation of (micro) pores, if any.

## 3. Classical models for drug release from biostable systems

A brief overview of the important classical equations that are useful for the subsequent model development of more sophisticated delivery systems is presented in this section.

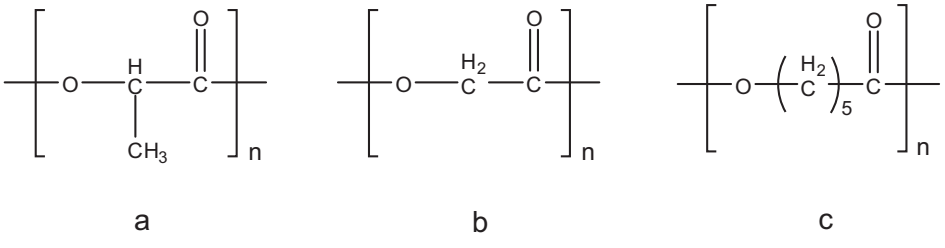


**Fig. 2.** Chemical structures of bulk-degrading polyesters: (a) poly(lactide), (b) poly(glycolide) and (c) poly (ε-caprolactone).

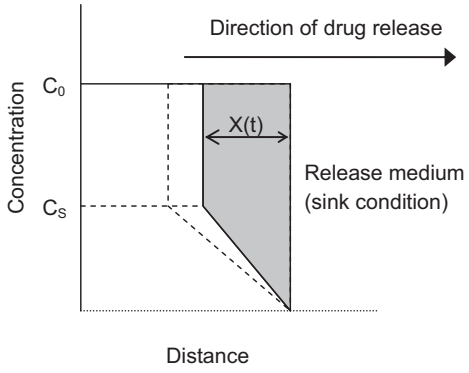


**Fig. 3.** Schematic drawing of monolithic drug release system according to Higuchi model.

### 3.1. Fick's laws of diffusion

Diffusion is the spontaneous net movement of molecules from an area of high concentration to an area of low concentration in a given volume of fluid, down the concentration gradient. Fick (1855, 1995) introduced one of the earliest analyses of this mass transport phenomenon. His work was well recognized through the two fundamental equations, called Fick's laws of diffusion.

Fick's first law is used to describe steady-state diffusion, i.e., when the concentration within the diffusion volume does not change with respect to time. Concentration is dependent only on position. In one (spatial) dimension/planar geometry, it is written as

$$J = -D\frac{\partial C}{\partial x} \tag{1}$$

$J$ is the diffusion flux, i.e. amount of drug particles that passes through a unit area per unit time. $C$ is the position-dependent drug concentration in the matrix. $D$ is the drug diffusion coefficient and $x$ is the position normal to the central plane of the membrane/film. The minus sign shows that diffusion takes place down the concentration gradient.

Fick's second law is used to describe non-steady or continually changing state diffusion, i.e., when the concentration within the diffusion volume changes with respect to time as well as position. In one (spatial) dimension/planar geometry, it is written as

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{2}$$

All the parameters carry the same meanings as in Eq. (1), except that $C$ is the time- and position-dependent drug concentration in the matrix and $t$ is time. The main difference between the two equations lies in the fact that concentration is only a function of position in the first law while concentration is a function of both position and time in the second law. Both equations have formed the foundation of various theoretical and empirical drug release models developed in the past decades.

### 3.2. Higuchi model

The Higuchi model is one of the most successful theories at predicting drug release from a non-degradable monolithic system whereby drug particles are dispersed uniformly throughout the matrix (Higuchi, 1961, 1963). It is assumed that steady-state/pseudo-steady-state diffusion exists such that Fick's first law can be applied (see Fig. 3 for the schematic representation of Higuchi model). The Fick's first law, Eq. (1), can be rewritten as follows

$$R_t = -SD\frac{\partial C}{\partial x} \tag{3}$$

$R_t$ is the rate of diffusion; $S$ is the cross-sectional diffusion area; $D$ is the diffusion coefficient in the matrix; $C$ is the concentration of drug in polymer and $x$ is the distance measured from solvent–matrix interface.

The boundary conditions are:

$$C = C_bK \quad \text{at } x = 0 \tag{4}$$

$$C = C_s \quad \text{at } x = X(t) \tag{5}$$

$C_b$ is drug concentration in the release medium and $C_s$ is the saturation concentration in the matrix. $K$ is the matrix-to-medium partition coefficient.

It is also assumed that the concentration profile in the diffusion region is linear at any time. Therefore, upon integrating Eq. (3):

$$R_t = SD\frac{(C_s - C_bK)}{X(t)} \tag{6}$$

To solve Eq. (6), the following mass balance equation in the diffusion region is applied

$$R_t = \frac{dM_t}{dt} = \frac{d}{dt}\left\{\left[C_0 - \frac{1}{2}(C_s + C_bK)\right]SX(t)\right\} \tag{7}$$

After substituting $R_t$ in Eq. (7) with Eq. (6) and then followed by a series of integrations, the final equation is written as

$$M_t = S[D(C_s - C_bK)(2C_0 - C_s - C_bK)t]^{1/2} \tag{8}$$

In the sink condition, $C_b$ is maintained at very low concentration, close to zero. If the drug loading is much higher than its solubility limit in the matrix ($C_0 \gg C_s$), Eq. (8) can be simplified to:

$$M_t = S[2DC_sC_0t]^{1/2} \tag{9}$$

This solution is a good approximation for monolithic system with $C_0 \gg C_s$ under pseudo-steady state condition. Exact solutions to this diffusion problem were developed by Paul and McSpadden (1976) which improved the accuracy up to 11.3% if $C_0 \to C_s$. Further, Lee (1980) developed another model for monolithic system that can be applied at all ($C_0/C_s$) ratios.

### 3.3. Power law

The exact solution to the Fick's second law of one-dimensional diffusion for thin films of thickness $\delta$ under perfect sink conditions where its initial drug concentration is lower than its solubility limit ($C_0 < C_s$, monolithic solutions) and assuming a constant diffusion coefficient is:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\delta^2}\right)^{1/2}\left\{\pi^{-1/2} + 2\sum_{n=1}^{\infty}(-1)^n \, ierfc\frac{n\delta}{2\sqrt{Dt}}\right\} \tag{10}$$

As the second term in the second bracket vanishes at short times, Eq. (10) for $M_t/M_\infty \leq 0.6$ can be approximated as follows:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi\delta^2}\right)^{1/2} \tag{11}$$

Eq. (11) shows an initial $t^{1/2}$ time dependence of drug release by Fickian diffusion from a thin film.

In 1983, Peppas and co-workers introduced a much simpler yet more comprehensive semi-empirical model to describe drug release from polymeric systems, widely known as the power law model (Korsmeyer et al., 1983; Ritger and Peppas, 1987a,b; Peppas and Sahlin, 1989).

$$\frac{M_t}{M_\infty} = at^n \tag{12}$$

**Table 1**
Exponent $n$ of power law (applicable to the first 60% of the fractional release) and drug release mechanism from polymeric delivery systems of different geometries.[a]

| Exponent $n$ | | | Drug release mechanism |
|---|---|---|---|
| Thin film | Cylinder | Sphere | |
| 0.5 | 0.45 | 0.43 | Fickian diffusion |
| $0.5 < n < 1.0$ | $0.45 < n < 1.0$ | $0.43 < n < 1.0$ | Anomalous (non-Fickian) transport |
| 1.0 | 1.0 | 1.0 | Zero-order release |

[a] *Source*: Ritger and Peppas (1987a).

where $M_t$ and $M_\infty$ are the amounts of drug released at time $t$ and as time approaches infinity, respectively; $a$ is a constant incorporating geometrical and structural characteristics of the macromolecular network system and the drug; $n$ is the release exponent, indicative of the transport mechanism. This equation is valid for the first 60% of the fractional release.

The power law can be seen as a general equation that is useful to describe various mechanisms of transport including the Fickian diffusion, non-Fickian transport as well as zero-order (constant-rate) release behaviour. For thin films, Fickian diffusion is the dominating transport mechanism when $n = 0.5$, while anomalous non-Fickian transport is described by $0.5 < n < 1$. When $n = 1$, zero-order release is obtained. The values of $n$ for spheres and cylinders are listed in Table 1.

A special case of the power law arises when $n = 0.5$ for thin films as Eq. (12) is reduced to a general expression ($M_t/M_\infty = kt^{1/2}$) that encompasses drug release from both monolithic dispersions (the classical Higuchi model, Eq. (9)), and monolithic solutions at short times, Eq. (11). Hence, proportionality between the amount of drug released and the square root of time is commonly accepted as an indicator for diffusion-controlled release.

Power law has also been applied to solute release from swellable devices (Ritger and Peppas, 1987b; Peppas and Sahlin, 1989). The same equation may be used to describe the Fickian diffusion and case-II transport (as a result of chain relaxation of an initially glassy polymer undergoing dynamic swelling) and the superposition of the two. Again, exponent $n$ is an important indicator of the operative mechanism. Different sets of values of exponent $n$ were derived for thin films, cylinders and spheres of swellable systems.

Power law was further modified to accommodate the lag time ($l$) in the beginning of the drug release (Ford et al., 1991; Kim and Fassihi, 1997; Pillay and Fassihi, 1999)

$$\frac{M_t}{M_\infty} = a(t-l)^n \tag{13}$$

and to accommodate the possibility of a burst effect, $b$ (Lindner and Lippold, 1995; Kim and Fassihi, 1997)

$$\frac{M_t}{M_\infty} = at^n + b \tag{14}$$

## 4. Modeling of drug release from bulk-degrading systems

This section presents specific models developed for the controlled release from bulk-degrading systems. In fact, the majority of them have used the classical models in the previous section as the basis for degradable systems. Reviews of models developed for other types of delivery systems are available in the literature (Narasimhan et al., 1999; Costa and Lobo, 2001; Siepmann and Peppas, 2001). In this review, the models of drug release from bulk-degrading polymers are organized according to Fig. 4 and are discussed in the same order in the sections that follow next.

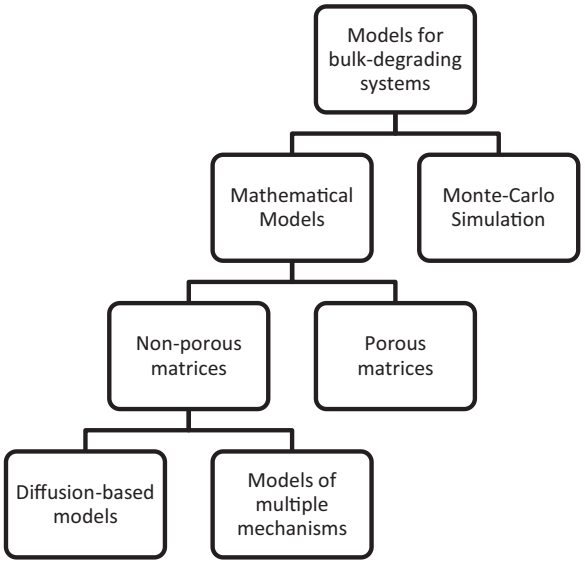


**Fig. 4.** Organization of various models of drug release from bulk-degrading polymers.

### 4.1. Mathematical models

Numerous drug release models of *surface-eroding* and *bulk-eroding* degradable systems have been reported in the literature (Siepmann and Göpferich, 2001; Arifin et al., 2006). In general, it is easier to model drug release from surface-eroding systems because the drug is released concurrently with the layer-by-layer erosion from the outermost surface of the matrix. As the theme of this review is mainly on the bulk-degrading polymers, the focus will be on the mathematical models developed for such systems.

For easy reference, the models of drug release from bulk-degrading systems are categorized according to the initial states of the drug carriers: (1) non-porous and (2) porous matrices.

#### 4.1.1. Non-porous matrices

It is generally accepted that the degradation of bulk-degrading polymers follows first order kinetics as follows:

$$\frac{dM_w}{dt} = -kM_w \tag{15}$$

$$M_{w,t} = M_{w,0}\exp(-kt) \tag{16}$$

$M_{w,t}$ is the polymer molecular weight at time $t$, $M_{w,0}$ is the initial polymer molecular weight and $k$ is the degradation rate constant.

Many different drug release patterns have been obtained from bulk-degrading systems, mainly as a result of several factors such as polymer type, drug interactions with polymer, device geometry and size. Therefore, in the development of suitable models, various approaches have been taken. In the next two sub-sections, these approaches are sub-grouped according to the release mechanisms considered during the derivation of the models: (1) diffusion-based models, modified with time-dependent diffusivities, usually sufficient to predict *mono-phasic* release and (2) models that combine diffusion with erosion and/or drug dissolution and/or percolation theory, etc., usually required to describe *multi-phasic* release.

*4.1.1.1. Diffusion-based models.* The majority of the approaches examined in this sub-section have based their models on the popular Higuchi model for non-degrading systems. The constant diffusion coefficient in the Higuchi model was modified to take into account the time-dependent matrix degradation.

Heller and Baker (1980) used the classical Higuchi equation as the starting point to develop a mathematical model to describe

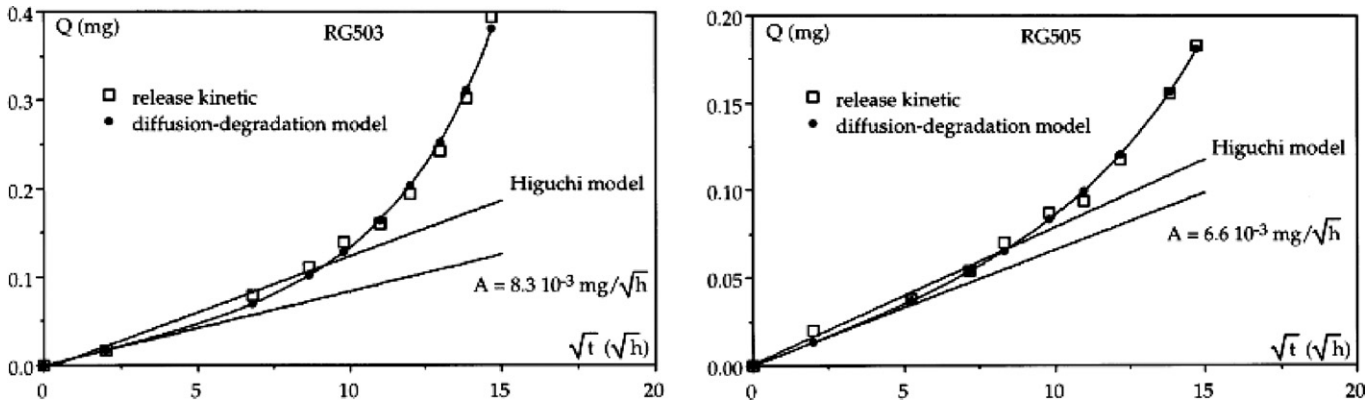


**Fig. 5.** Comparison of diffusion-degradation model by Charlier et al., Higuchi model and experimental data of mifepristone release from bulk-degrading PLGA films (molecular masses of RG503 and RG505 are 30,000 and 60,000, respectively, and term $A = S(2C_0C_sD_0)^{1/2}$).
(reprinted from Charlier et al., 2000 with permission from Elsevier).

drug release from polymer films that undergo hydrolytic backbone cleavage. The following modified Higuchi model was used

$$\frac{dM_t}{dt} = \frac{S}{2}\left(\frac{2PC_0}{t}\right)^{1/2} \tag{17}$$

$S$ is the surface area of both sides of the film, $P$ is the (time-dependent) permeability of the drug within the matrix, $C_0$ is the initial drug concentration (above the solubility limit) in the matrix and $M_t$ is the cumulative amount of drug released at time $t$.

Permeability is not constant but increases with time as degradation proceeds, given by the following expression

$$\frac{P_t}{P_0} = \frac{\text{initial number of bonds}}{\text{remaining number of bonds}} = \frac{N}{N-Z} \tag{18}$$

$P_t$ is the drug permeability at time $t$, $P_0$ is the initial drug permeability, $N$ is the number of initial bonds, $Z$ is the number of bond cleavages during the time interval $[0;t]$. It was further assumed that the polymer bonds are cleaved according to first-order kinetics:

$$\frac{dZ}{dt} = K(N-Z) \tag{19}$$

where $K$ is the first order rate constant.

Following integration and rearrangement, the final equation for the rate of drug released can be written as

$$\frac{dM_t}{dt} = \frac{S}{2}\left[\frac{2P_0\exp(Kt)C_0}{t}\right]^{1/2} \tag{20}$$

In another approach, Charlier et al. (2000) postulated that the time-dependent diffusion coefficient ($D_t$) depends on the polymer molecular weight ($M_{w,t}$) and varies in inverse ratio to it. Their model was developed for drug release from a degradable matrix with initial loading above saturation, under similar drug transport conditions as with the Higuchi model.

It assumes that the system degrades by first order kinetics and the diffusion coefficient is inversely proportional to the polymer molecular weight as follows

$$\frac{D_t}{D_0} = \frac{M_{w,0}}{M_{w,t}} \tag{21}$$

Substituting Eq. (16) into Eq. (21),

$$D_t = D_0\exp(kt) \tag{22}$$

Following the same principle as the Higuchi model, the final expression for $M_t$, the cumulative amount of drug released at time $t$, was derived

$$M_t = S\left\{\frac{2C_0C_sD_0[\exp(kt)-1]}{k}\right\}^{1/2} \tag{23}$$

where $S$ is the surface area of the film, $C_0$ and $C_s$ are the initial drug concentration and solubility limit of the drug in the system, respectively, $D_0$ is the initial diffusion coefficient and k is the first-order degradation constant determined by Eq. (16). Fig. 5 shows good agreement between Charlier et al. model with the experimental release data while the classical Higuchi model is only applicable at early times prior to substantial degradation.

Siepmann and co-workers (Faisant et al., 2002, 2006; Siepmann et al., 2004) also took a similar approach for the drug release from bulk-degrading microspheres. Their theory is derived based on the assumption that a linear, pseudo-steady state drug concentration gradient was established within the microspheres upon water imbibition as $C_0 \gg C_s$. Solutions to similar conditions have been derived by Higuchi (1961, 1963) for the case of planar devices and other geometries. Further, Koizumi and Panomsuk (1995) derived an (approximate) explicit solution that is easier to handle than the respective equation derived by Higuchi for release from non-degradable spheres:

$$M_t = 4\pi r^2\left\{[2(C_0-C_s)C_sDt]^{1/2} + \frac{4C_sDt}{9r}\left(\frac{C_s}{2C_0-C_s}-3\right)\right\} \tag{24}$$

Here, $M_t$ is the cumulative amount of drug released at time $t$, $r$ is the radius of the sphere, $D$ is the constant diffusion coefficient while $C_0$ and $C_s$ are the initial drug concentration and solubility limit of the drug in the system, respectively.

When the polymer carrier is degradable, the constant diffusion coefficient $D$ in Eq. (24) is changed into a time-dependent diffusion coefficient $D_t$, described by the following equation:

$$D_t = D_0 + \frac{c}{M_{w,t}} \tag{25}$$

where $D_t$ and $D_0$ are the diffusion coefficients at time $t$ and time zero, respectively, and $c$ is a constant. $M_{w,t}$ is the molecular weight of the degradable polymers at time $t$ calculated according to Eq. (16). Subsequently, mathematical programming language C++ (Borland C++ 6.0) was used to fit Eqs. (16), (24) and (25) to the experimentally derived release data, as shown in Fig. 6.

Next, Siepmann et al. (2005) demonstrated the importance of autocatalysis to predict lidocaine release from PLGA-based microspheres. The drug release was assumed to be diffusion controlled; however, the effective diffusivity ($D_{eff}$) was observed to be a function of microsphere diameters. Higher $D_{eff}$ values were obtained for larger spheres due to autocatalysis effect, which in turn led to increasing polymer degradation rate and higher mobility of the drug to be released into the medium. For example, $D_{eff}$ values were found to vary from $4.6 \times 10^{-14}$ cm$^2$/s to $2.0 \times 10^{-12}$ cm$^2$/s when the radii of PLGA50/50 microspheres increase from 7.2 μm to 53 μm.

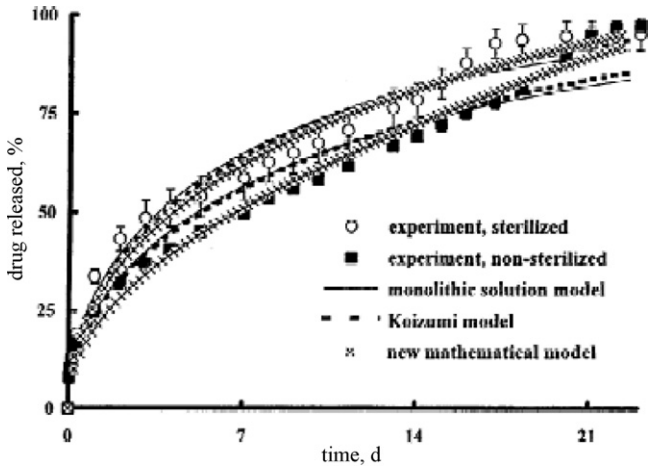


**Fig. 6.** Comparison of Siepmann et al. model, Fickian diffusion (monolithic solution) model, Koizumi model and experimental data of 5-FU release from bulk-degrading PLGA microparticles.
(reprinted from Faisant et al., 2002 with permission from Elsevier).

Similarly, Raman et al. (2005) used a common diffusion equation for spherical geometry, but with different diffusivity dependence on molecular weight.

$$\frac{\partial C}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D(M_w)\frac{\partial C}{\partial r}\right) \tag{26}$$

$C$ is the drug concentration, $r$ is the radial position, $t$ is time and $D(M_w)$ is the molecular weight dependent drug diffusivity. Boundary conditions include: at $r=0$, $\partial C/\partial r=0$ and at $r=R$, $C=0$, where $R$ is the radius of the sphere. The initial condition is given by $C(r)=f(r)$, i.e. the initial drug distribution is not uniform but determined by confocal microscopy.

Diffusivity dependence on $M_w$ can also be measured experimentally and is given by an empirical cubic polynomial equation that relates $\ln(D)$ to $\ln(M_w)$ as follows

$$\ln(D) = -0.347[\ln(M_w)]^3 + 10.394[\ln(M_w)]^2 - 104.950[\ln(M_w)] + 316.950 \tag{27}$$

$$M_w = \begin{cases} M_{w,o} & \text{when } t < t_{lag} \\ M_{w,o}e^{-k(t-t_{lag})} & \text{when } t \geq t_{lag} \end{cases} \tag{28}$$

$k$ is first-order degradation constant while $t_{lag}$ is the lag time before the polymer degradation begins.

All models reviewed in this sub-section have focused mainly on diffusional mass transport, controlled by a time-dependent diffusion coefficient. As a result, these models demonstrated good agreement with experimental data of mostly *mono-phasic* drug release patterns. In the next section, models that combine diffusion and other modes of transport mechanisms to illustrate *multi-phasic* drug release patterns are examined.

*4.1.1.2. Models of multiple release mechanisms.* Himmelstein and co-workers (Thombre and Himmelstein, 1985; Joshi and Himmelstein, 1991) developed a comprehensive theory for the degradation and release from poly(ortho ester) slab. This model takes into account the acid generation, its role in accelerating matrix hydrolysis and the accompanying chemical reactions as shown in Fig. 7a. In the beginning, water ($A$) penetrates into the matrix and activates the acid generator such as acid anhydride ($B$). The generated acid ($C$) then catalyzes hydrolysis of ester linkages in the polymer ($D$) forming unstable intermediate ester ($D^*$). Further reaction with water leads to final degradation products that are released together with the drug ($E$) into the surrounding medium.

These chemical reactions were then coupled with diffusion-controlled mass transfer processes as follows

$$\frac{\partial C_i}{\partial t} = \frac{\partial}{\partial x}\left[D_i(x,t)\frac{\partial C_i}{\partial x}\right] + \upsilon_i \quad i = A, B, C, E \tag{29}$$

$C_i$ and $D_i$ are the concentration and diffusion coefficient of species $i$, while $A$, $B$, $C$ and $E$ represent water, acid generator (for e.g. acid anhydride), acid and drug, respectively, $\upsilon_i$ is the net sum of synthesis and degradation rate of species $i$, and $x$ is the space variable.

To account for the effect of degradation, the diffusion coefficient of all species is related to the local extent of polymer hydrolysis and is given by the following expression

$$D_i = D_{i,0}\exp\left[\frac{\mu(C_{D,0}-C_D)}{C_{D,0}}\right], \quad i = A, B, C, E \tag{30}$$

$D_{i,0}$ is the diffusion coefficient of species $i$ when the polymer is not hydrolyzed, $C_{D,0}$ and $C_D$ are the concentrations of species $D$ (ester

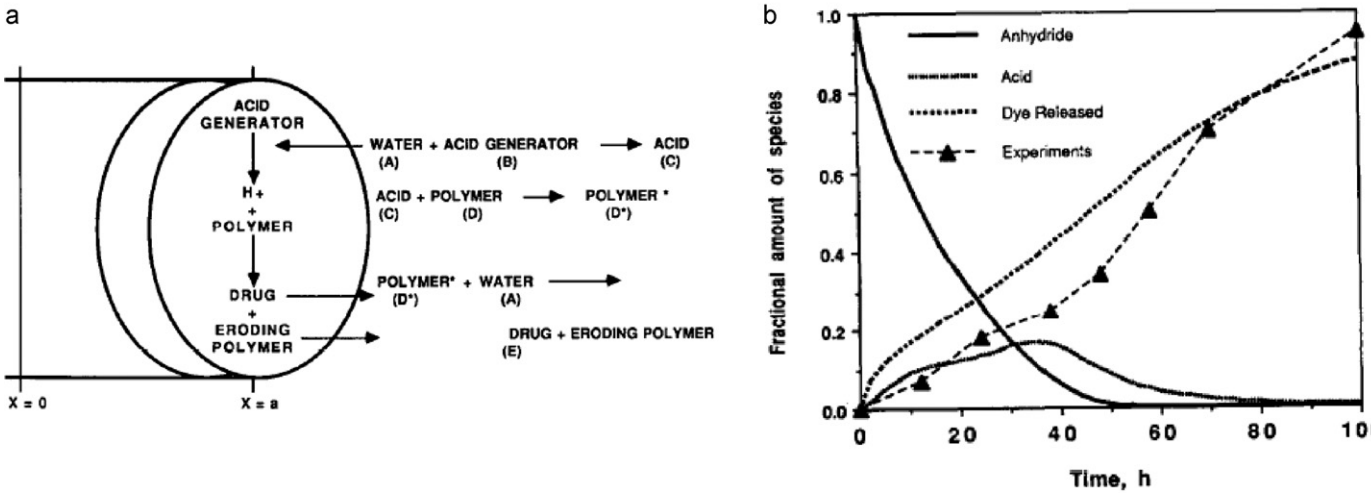


**Fig. 7.** (a) Schematic illustration of mathematical model developed by Himmelstein et al. (b) comparison of model predictions with actual cumulative release of amaranth red dye (initial loading = 0.5%) from poly(ortho ester) disc.
(reprinted from Joshi and Himmelstein, 1991 with permission from Elsevier).

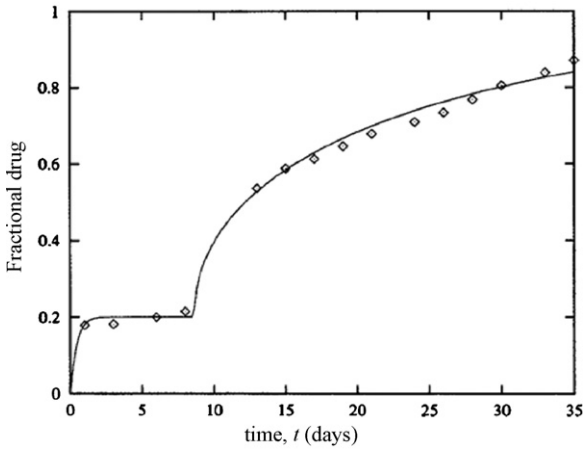


**Fig. 8.** Comparison of Batycky et al. model and experimental data of glycoprotein 120 (gp 120) release from bulk-degrading PLGA 50/50 microspheres. (reprinted from Batycky et al., 1997 with permission from Wiley Inc.).

linkages in the polymer) at time zero and time $t$, respectively, and $\mu$ is a constant. Fig. 7b shows the experimental release data of a dye from poly(ortho ester) and good agreement with Himmelstein model.

A bi-phasic profile of macromolecular (glycoprotein) release from poly(lactide-co-glycolide) 50/50 microspheres was described in the work of Batycky et al. (1997). A theoretical model is outlined for predicting microsphere hydration, polymer erosion, mass loss and drug release. Its drug release model took into account the presence of initial burst due to drug desorption from the surface of microspheres and surfaces of existing mesopores. Continuous diffusional release was postulated to take place after sufficient amount of pores developed and interconnected. Their proposed equation to predict the fraction of drug released at time $t$ is given by

$$\frac{M_t}{M_\infty} = 1 - \phi_b[1 - \exp(-k_d t)] - (1-\phi_b)\left[1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left\{-n^2\pi^2\frac{D(t-t_d)}{r^2}\right\}\right] \quad (31)$$

where $M_t$ is the cumulative amount of drug released at time $t$, $M_0$ is the initial amount of drug loaded in the microsphere, $\phi_b$ is the fraction of burst release, $k_d$ is the drug desorption constant, $D$ is the drug diffusion coefficient ($D = 0$ at $t \le t_d$), $t_d$ is the induction phase time, and $r$ is the radius of the microsphere.

An estimation of the induction time, $t_d$, can be calculated from the following equation

$$t_d = \frac{4r^2[\epsilon_{M,0} + \epsilon_{\mu,0}]a_d}{R_{M,0}^3 k_{coal}} \quad (32)$$

where $\epsilon_{M,0}$ and $\epsilon_{\mu,0}$ are the initial mesoporosity and microporosity, respectively, $a_d$ is the Stokes–Einstein radius of the drug, $R_{M,0}$ is the initial mesopore radius and $k_{coal}$ is the rate of mesopore formation to be determined from visual observation of pore coalescence on the surface of microspheres.

Good agreement between the model and experimental data was obtained, as seen in Fig. 8. In addition, models to predict the time evolution of total mass loss and mean molecular weight were derived by combining both mechanisms of random chain scission and end scission.

Zhang et al. (2003) developed another mathematical model whereby the overall release process is jointly governed by three mechanisms: drug diffusion, drug dissolution and polymer erosion. Model development involves the introduction of the concept of three phases: (1) liquid phase, (2) virtual solid phase; and (3) effective solid phase.

In this model, there is a virtual solid phase of constant volume $V_0$ (initial volume before erosion) in which erosion and dissolution decrease the drug concentration, $C_s$. The drug that is lost ends up in the liquid phase, whose volume is also kept constant at $V_0$. In this liquid phase, the drug is free to diffuse. Lastly, the effective solid phase simulates the actual changes in the solid phase. It has variable volume $V_1$ and the change pattern is related to the different erosion patterns.

The drug concentration in virtual solid phase, $C_S$, is related to the drug concentration in effective solid phase, $C_{SE}$, by the following expression

$$C_S = \left(\frac{V_1}{V_0}\right) C_{SE} \quad (33)$$

In the effective solid phase, concentration decreases only due to the drug dissolution process. When the liquid phase concentration is higher than the saturation concentration, the drug will deposit back to the solid phase. In addition, the effective diffusivity ($D_{eff}$) varies with the changes of polymer porosity and tortuosity. Here, the porosity and tortuosity changes are assumed to be proportional to the volume change of the effective solid phase.

Three types of erosion patterns were modeled, namely linear, "S-shape" and hyperbolic erosions. For the case of "S" erosion, water diffusion is slower than degradation at the very beginning. After a period of degradation, the water diffusion rate is increased because the porosity increase makes the transport much faster and hence degradation is accelerated. Finally, when the easily degradable part of polymer is completely eroded, degradation will be slowed down.

The following equations are solved together to investigate the drug release pattern under "S" erosion mechanism.

For liquid phase:

$$\frac{\partial C_L}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(Dr^2\frac{\partial C_L}{\partial r}\right) - \frac{\partial C_{SE}}{\partial t}\left(1 - \frac{1}{1 + b\exp(-tK_{ero})}\right) + \frac{C_{SE}bK_{ero}\exp(-tK_{ero})}{[1 + b\exp(-tK_{ero})]^2} \quad (34)$$

For virtual solid phase:

$$\frac{\partial C_S}{\partial t} = \frac{\partial C_{SE}}{\partial t}\left(1 - \frac{1}{1 + b\exp(-tK_{ero})}\right) - \frac{C_{SE}bK_{ero}\exp(-tK_{ero})}{[1 + b\exp(-tK_{ero})]^2} \quad (35)$$

For effective solid phase:

$$\frac{\partial C_{SE}}{\partial t} = -k_{dis}(\varepsilon C_{sat} - C_L) \quad (36)$$

In Eq. (34), diffusion, dissolution and erosion are represented by the first, second and third terms on the right-hand side, respectively. The dissolution term is $k_{dis}(\varepsilon C_{sat} - C_L)$ because the rate of drug dissolution is proportional to its driving force, namely the difference between the actual and saturation concentrations.

From the numerical solution of these three equations, the mass remaining in the liquid and virtual solid phases can be calculated. Drug release is then equal to the initial drug loading substracting the sum of masses remaining in liquid phase and virtual solid phase.

He et al. (2005) proposed a model that described drug release kinetics as a combined contribution from drug diffusion and matrix erosion. For spherical geometry, the fraction of drug released at time $t$, $M_t/M_\infty$, can be written as

$$\frac{M_t}{M_\infty} = 6\sqrt{\frac{D_t t}{\pi r^2}} - 3\frac{D_t t}{r^2} + F_E\left[\frac{\exp(k_e t - k_e t_{max})}{1 + \exp(k_e t - k_e t_{max})}\right] \quad (37)$$

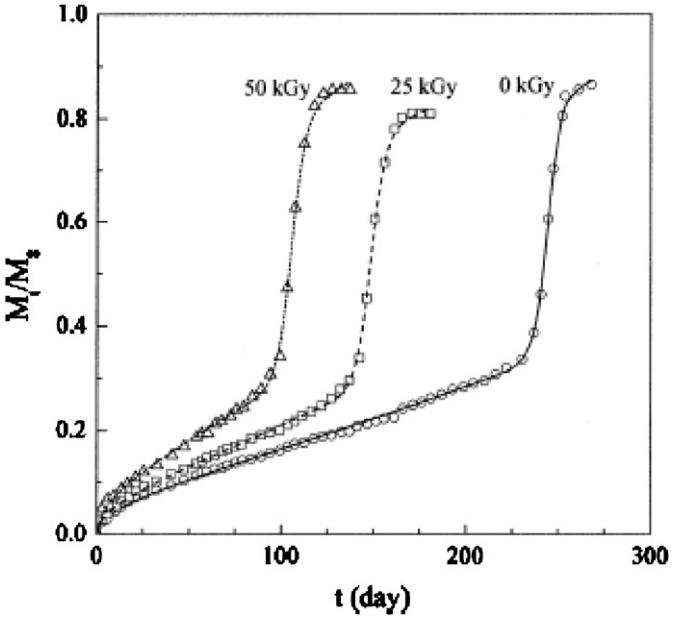


**Fig. 9.** Comparison of He et al. model and experimental data of progesterone release from poly (DL-lactide) microspheres under different γ-irradiation doses. (reprinted from He et al., 2005 with permission from Taylor & Francis).

The first two terms on the right-hand side is derived from Baker and Lonsdale (1974), but with time-dependent diffusivity $\{D_t = D_0 \exp(kt)$, see also Eq. (22)$\}$. The last term is the fraction of drug release due to pure matrix erosion by Fitzgferald and Corrigan (1993). $F_E$ is a factor counting the contribution of matrix erosion to drug release, $k_e$ is the acceleratory coefficient describing matrix erosion and $t_{max}$ is the time to maximum matrix erosion rate.

This model is able to describe a triphasic drug release process, including (1) an initial burst; (2) the intermediate phase, an approximately zero-order drug release, as a result of drug diffusion and polymer degradation; and (3) the second rapid drug release phase caused by the matrix erosion. It is important to note that this model works by assuming complete matrix erosion (mass loss) at the end of drug release process. It was also demonstrated that the model parameters can be correlated to various factors such as γ-irradiation dose (see Fig. 9), copolymer composition and initial drug loading.

Recently, Rothstein et al. (2008, 2009) reported a different approach to predict the release of a water soluble agent that is loaded discretely (initial agent concentration $C_{A,0}$), below its percolation threshold, in a bulk eroding polymer matrix. Their model is able to determine the magnitude of the initial burst and the duration of the lag phase followed by a secondary burst and a terminal release phase.

Schematic representation of the proposed mechanism is shown in Fig. 10a. It is postulated that the initial burst is caused by diffusion of encapsulated agent (occlusion) adjacent to the matrix surface. The relative size of the occlusion ($R_{occ}$) is proportional to the magnitude of the initial burst. Following this initial burst, degradation begins and leads to formation of pores that continue to grow and coalesce with others to create a pathway for drug diffusion.

Agent concentration within a matrix can be calculated from Fick's second law for any point in time ($t$) or space ($r$) as follows

$$\frac{\partial C_A}{\partial t} = \nabla(D_{eff}\,\nabla C_A) \tag{38}$$

where $C_A$ is the concentration of agent in polymer matrix and $D_{eff}$ is an effective diffusivity term. At the center point ($r = 0$), $dC_A/dr = 0$ and perfect sink conditions are assigned at the surface ($r = R_p$).

Further, $D_{eff}$ is defined as

$$D_{eff} = \begin{cases} D; & R_p - R_{occ} \le r \le R_p \\ D\varepsilon(t); & 0 \le r \le R_p - R_{occ} \end{cases} \tag{39}$$

$R_p$ is matrix dimension across which diffusional release occurs (e.g. particle radius or film thickness) and $R_{occ}$ is the radius of agent occlusion near the surface. $D$ is a constant diffusivity of agent through porous matrix and $\varepsilon(t)$ is the time-dependent matrix porosity, described with a cumulative normal distribution function

$$\varepsilon(t) = \frac{1}{2}\left[erf\left(\frac{t - \tau_{mean}}{\sqrt{2\sigma^2}}\right) + 1\right] \tag{40}$$

$$\tau_{mean} = \frac{-1}{kC_w} \ln\left|\frac{M_{w,r}}{M_{w,o}}\right| \tag{41}$$

$\tau_{mean}$ is the mean time for pore formation, determined by Eq. (41), and $\sigma^2$ is the variance in time required to form pores. $kC_w$ is the average pseudo-first order degradation rate constant, $M_{w,0}$ is the initial polymer molecular weight and $M_{w,r}$ is the average polymer molecular weight low enough to allow release of encapsulated agents.

A finite element solution to Eq. (38) was calculated (using Comsol®, v3.3) for the given matrix geometry. The resulting con-

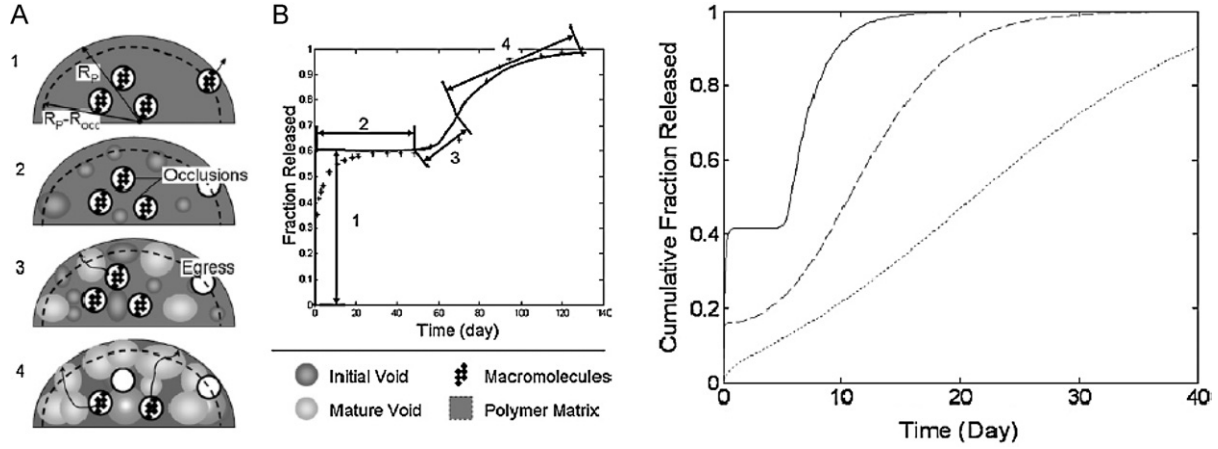


**Fig. 10.** (a) Schematic representation of Rothstein et al. model; (b) the theoretical release profiles obtained from: 13 kDa PLGA 50/50 (solid), 1:1 blend of 10 kDa:100 kDa PLGA 50/50 (dashed line), and 2:1 blend of 7.4 kDa PLGA 50/50 and 60 kDa PLA (dotted line). (reprinted from Rothstein et al., 2008 with permission from the Royal Society of Chemistry).

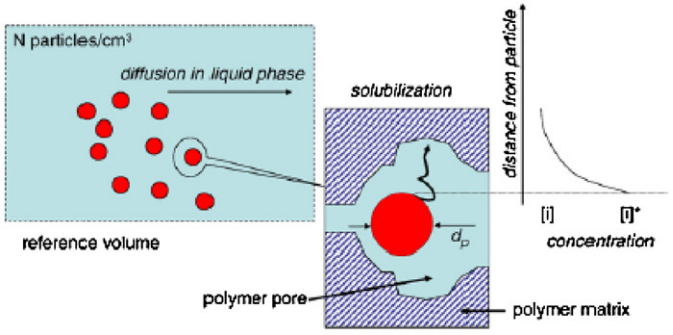


**Fig. 11.** Schematic representation of the solubilisation of solid drug particles embedded in the polymer matrix according to Masi et al. model. (reprinted from Perale et al., 2009 with permission from Elsevier).

centration profiles were numerically integrated over the entire matrix volume ($V$) to determine the cumulative fraction of agent released, $R(t)$ as follows

$$P(t) = V^{-1} \int \frac{C_A}{C_{A,0}} dV \tag{42}$$

$$R(t) = 1 - P(t) \tag{43}$$

$P(t)$ is the cumulative fraction of agent retained in the matrix at time $t$ and $C_{A,0}$ is the initial agent concentration in the polymer matrix. Fig. 10b shows various release profiles obtained by varying the model parameters and blending PLGA 50/50 of different initial molecular weights or blending PLGA50/50 with PLA.

This model was further enhanced so that it could predict drug release not only from bulk-eroding systems, but also from surface-eroding matrices and those that transition from surface- to bulk-eroding scheme during the course of degradation (Rothstein et al., 2009).

Recently, Masi and co-workers (Arosio et al., 2008; Perale et al., 2009, 2010) proposed models to illustrate polymer degradation and drug release from degradable systems. Drug release was described as the combined effect of (1) solubilisation of entrapped solid drug particles and (2) diffusion of solubilised drugs, as can be seen from the schematic drawing in Fig. 11.

The solubilisation of a solid drug particle, made up of $n$ moles, in a generic location within the device can be expressed by the following equation

$$\frac{\partial n}{\partial t} = -k_C(C_S - C)\pi d^2 \tag{44}$$

$k_C$ is the mass transport coefficient for the drug within a stagnant fluid layer, $C_S$ is the maximum drug molar solubility in water, $C$ is the drug molar concentration in the liquid phase surrounding drug solid particle and $d$ is the drug solid particle diameter. Assuming solid drug particles are of spherical shape ($n = \rho\pi d^3/6$; $\rho$ is the molar density of the solid drug) and of mono-disperse size system, the overall drug dissolution rate referred to the device volume, $\Delta$, can be written as

$$\Delta = N\rho k_C(C_S - C)\pi\left(\frac{6n}{\pi\rho}\right)^{2/3} \tag{45}$$

where $N$ is the number of solid drug particles per unit polymer volume.

Therefore, the equation expressing the mass balance for the drug in the liquid phase is

$$\varepsilon\frac{\partial C}{\partial t} = D_{eff}\nabla^2 C + \Delta \tag{46}$$

$$D_{eff} = \frac{\varepsilon D_L}{\tau} \tag{47}$$

where $\varepsilon$ is the polymer porosity after the polymer swelling and $D_{eff}$ is the drug effective diffusion coefficient within the swollen polymer matrix, dependent on the porosity ($\varepsilon$) and tortuosity ($\tau$) of the system. $D_L$ is the drug diffusion coefficient in the liquid phase.

Thus, the final conservation equations for the dispersed drug are expressed by the teamed combinations of Eqs. (44) and (46). This release model represents significant improvement over the standard models based mainly on the Fick's second law of diffusion, i.e. Eq. (46) neglecting the $\Delta$ term, whose application is limited to the release of very soluble compounds. When drug solubility is lower, this simpler approach fails to provide a good prediction as it is unable to include the drug solubilisation dynamics. This case is especially highlighted in the study of the release of an extremely water-insoluble agent from biodegradable polymers (Lao and Venkatraman, 2008).

Lao et al. (2008, 2009) developed a novel model that postulated that the total fraction of drug release from bulk-degrading polymer is a summation of three mechanisms/steps that occur in sequence: (1) burst release, (2) relaxation-induced drug dissolution controlled release, and (3) diffusional release.

At any time, the step with the lowest rate becomes *the rate limiting step* and ultimately controls the overall drug release rate. Of these three steps, the second step is greatly affected by the aqueous solubility/hydrophobicity of the drugs being released. For the case of hydrophobic drugs, all three steps are important as step 2 is very slow when polymer degradation has not made enough progress such that the amount of water available is insufficient to dissolve the practically insoluble drug. However, for hydrophilic drugs, burst and diffusional release steps are sufficient to account for the whole release process as the second step usually occurs very fast and hence it is not a limiting step. The proposed model is given by a summation of these three steps.

$$\frac{M_t}{M_\infty} = \Phi_b\{1 - \exp(-k_b t)\} + \Phi_r\{\exp[k_r(t - t_b)] - 1\} + \Phi_d\left\{1 - \sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\left[\frac{-D(2n+1)^2\pi^2(t - t_r)}{4l^2}\right]\right\} \tag{48}$$

Here, $M_t/M_\infty$ is the fraction of drug released at time $t$ ($M_t/M_\infty = 0$ at $t = 0$ and $M_t/M_\infty = 1$ at $t = \infty$).

The first term on the right-hand side of Eq. (48) describes the fraction of drug released through initial burst, $\phi_b$ due to immediate desorption of drug particles located at or near the surface of a film. Its kinetics follows an exponential relationship, as pointed out by Batycky et al. (1997), see Eq. (31). The burst constant, $k_b$ denotes the rate of drug desorption while the end of burst release is given by $t_b$.

The second term on the right-hand side of Eq. (48) describes the relaxation-induced drug dissolution release where $\phi_r$ is the coefficient of relaxation-induced release, $k_r$ is the degradative relaxation constant and $t_r$ is the end of relaxation-induced release. As degradation proceeds, some short chains (oligomers) "dissolve out" of the matrix and the degree of chain entanglement decreases, leading to a more "open" network. This phenomenon is called relaxation of the polymer matrix and its release kinetics is represented using an exponential expression with degradative relaxation constant $k_r$. As relaxation depends heavily on the rate of production of shorter polymer chains, i.e. on the polymer's degradation rate, as a first approximation, the value of $k_r$ was taken to be of the order of the polymer's degradation constant $k$ as determined by Eq. (16).

The third term on the right-hand side of Eq. (48) describes the diffusional release, adapted from the exact solution by Crank (1975) for Fick's second law of one-dimensional diffusion for thin films of thickness $2l$ under perfect sink conditions where its initial drug

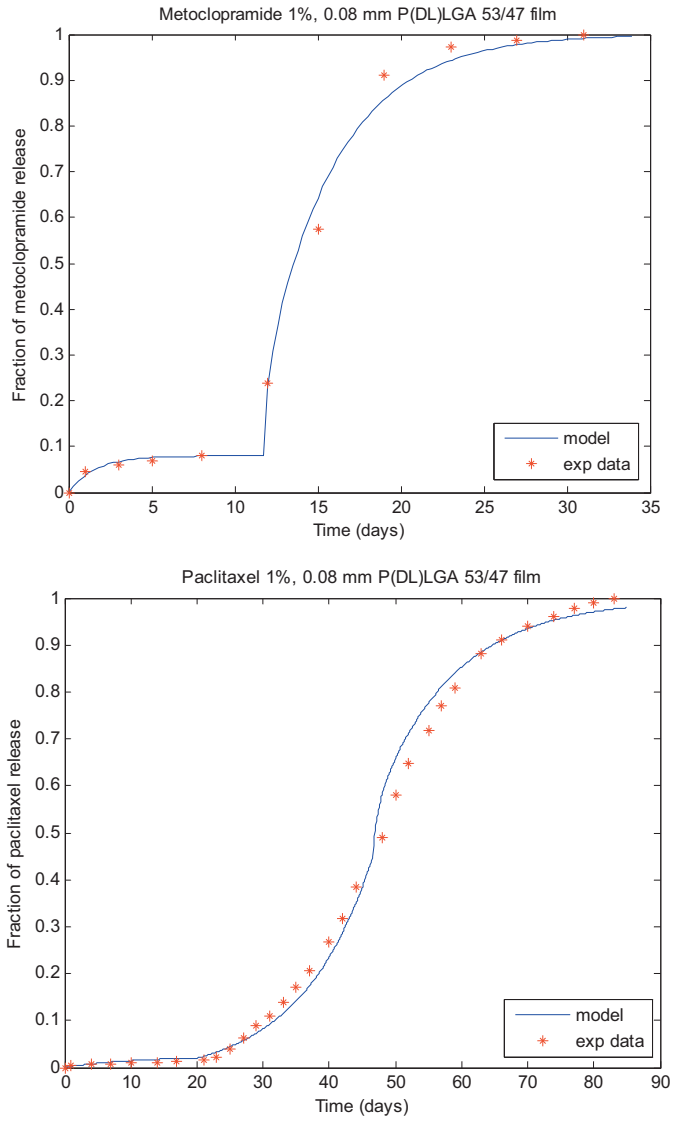


**Fig. 12.** Comparison of Lao et al. model and experimental data of hydrophilic metoclopramide (*top*) and hydrophobic paclitaxel (*bottom*) release from bulk-degrading PLGA 53/47 films.
(reprinted from Lao et al., 2009 with permission from Wiley Inc.).

concentration is lower than its solubility limit ($C_0 < C_s$, monolithic solutions). The fraction of drug released by diffusion is given by $\phi_d$ and the diffusion coefficient is denoted by $D$.

MATLAB, a programming software, was used to fit Eq. (48) to the experimental data of in vitro release of hydrophilic (metoclopramide salt) and hydrophobic (paclitaxel) drugs from P(DL)LGA 53/47 thin films. Good correlation coefficients ($R^2 = 0.99$) were obtained for both cases, as seen in Fig. 12.

The tri-phasic release model was further enhanced to describe drug release from blends of PCL and P(DL)LGA 53/47 films (Lao et al., 2008). Given low (or non-) miscibility of PCL and P(DL)LGA, the blend system consists of PCL rich and PLGA rich phases. Therefore, a "heuristic" approach was taken whereby it is postulated that drug partitions into either phase and remains in that particular phase until it is released. Further, the release from each phase follows the same mechanism of its respective unblended state. The overall fraction of drug release is a summation of drug released from PCL phase and PLGA phase:

$$\left[\frac{M_t}{M_\infty}\right]_{blend} = f_{PCL}\left[\frac{M_t}{M_\infty}\right]_{PCL} + f_{PLGA}\left[\frac{M_t}{M_\infty}\right]_{PLGA} \tag{49}$$

Here, $f_{PCL}$ and $f_{PLGA}$ are the fractions of drug that partition into and are released from PCL and P(DL)LGA phases, respectively. The sum of the two fractions is equal to 1 ($f_{PLGA} + f_{PCL} = 1$).

Substituting Eq. (48) into Eq. (49) led to the expanded Eq. (50). Drug release from PCL phase was sufficiently represented by 2 steps while release from P(DL)LGA phase was represented by 3 steps.

$$\begin{aligned}\left[\frac{M_t}{M_\infty}\right]_{blend} &= f_{PCL}\left(\Phi_{b,PCL}\{1-\exp(-k_{b,PCL}t)\} + \Phi_{d,PCL}\right.\\ &\left.\times\left\{1-\sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\left[\frac{-D_{PCL}(2n+1)^2\pi^2(t-t_{b,PCL})}{4l^2}\right]\right\}\right)\\ &+ f_{PLGA}\left(\Phi_{b,PLGA}\{1-\exp(-k_{b,PLGA}t)\} + \Phi_{r,PLGA}\{\exp\right.\\ &\times[k_{r,PLGA}(t-t_{b,PLGA})]-1\} + \Phi_{d,PLGA}\left\{1-\sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\right.\\ &\left.\left.\times\left[\frac{-D_{PLGA}(2n+1)^2\pi^2(t-t_{r,PLGA})}{4l^2}\right]\right\}\right)\end{aligned} \tag{50}$$

The blend model works by the assumption that drug from each phase is released through interconnected paths of its own phase across the film. As such, good agreement between the model and the experimental data was obtained so long as the weight fraction of the minor phase does not fall below 0.25, in agreement with the percolation theory reported in literature (Siegel, 1989). When the weight fraction of one component is reduced considerably, it is expected that the minor component will assume the forms of isolated islets within the major phase, thus the interconnectivity of the minor phase is lost.

### 4.1.2. Porous matrices

Ehtezazi and Washington (2000) developed a drug release model from porous microspheres by combining percolation theory and diffusional mass transport processes. The pores are classified into conducting (accessible) and discrete (isolated) regions. The accessible pores are connected to the exterior surface and allow mass transport to the surrounding medium whereas the isolated pores are disconnected. The percolation threshold, $\rho^C$, is a critical value below which the accessible porosity vanishes. According to the Bethe lattice theory, $\rho^C$ is related to coordination number, $z$, as follows

$$\rho^C = \frac{1}{Z-1} \tag{51}$$

After the Bethe lattice coordination number, $z$, is determined, the effective diffusion coefficient, $D_{eff}$, is given by

$$D_{eff} = D_L\varepsilon^E \tag{52}$$

where $D_L$ is the drug diffusion coefficient in the release medium and $\varepsilon^E$ is the transport coefficient of the porous structure, calculated from

$$\varepsilon^E = -\left(\frac{Z-1}{Z-2}\right)\frac{C'(0)}{D_L} \tag{53}$$

$C'(x)$ is the first derivative of a non-linear integral equation defined by Ehtezazi and Washington (2000).

The fraction of drug released from a microsphere, with size $r$, at time $t$ is calculated by the following equation, adapted from Crank

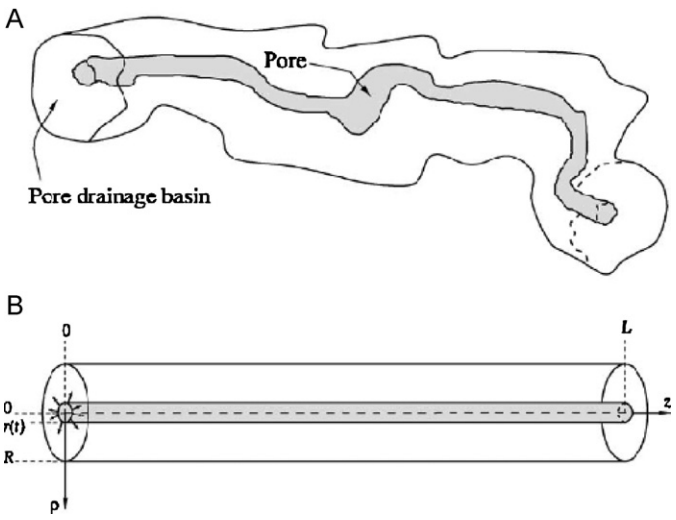


**Fig. 13.** Schematic drawing of Lemaire et al. model. (a) Isolated pore and its drainage basin; (b) symbolic representation of the pores and basins in the model. (reprinted from Lemaire et al., 2003 with permission from Elsevier).

(1975)

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-n^2\pi^2\frac{D_{eff}t}{r^2}\right) \tag{54}$$

In the case of microspheres with non-uniform sizes, the equation was modified by introducing size distribution for the microspheres.

Lemaire et al. (2003) presented another model to describe drug release from porous biodegradable matrices by partitioning the matrix into multiple, identical elements. Each element is idealized as a cylinder of length $L$ and radius $R$ with a pore embedded coaxially in the center with radius $r$ ($r<R$) and length $L$ (see Fig. 13 for the schematic drawing). As such there are two domains per element: domain (1) is a pore filled with solvent containing a drug at concentration $C_0 < C_S$ ($C_S$ = solubility limit) and domain (2), lying between the two coaxial cylinders, corresponds to the network of micropores (empty space between polymer chains) and contains the same drug at concentration $C_0$. Growth of the mean pore radius due to polymer erosion is approximated to be a linear function of time

$$r(t) = at + r_0 \tag{55}$$

$a$ is a velocity of erosion (of a constant value) and $r_0$ is the initial pore radius.

The symmetry about the midpoint $z = L/2$ means the problem can be simplified by considering only half ($0 < z < L/2$) of the element. Thus, the equation describing the evolution of the concentration $C(\rho,z,t)$ under Fickian diffusion is given by

$$\frac{\partial C}{\partial t} = D\left[\frac{\partial^2 C}{\partial \rho^2} + \frac{1}{\rho}\frac{\partial C}{\partial \rho} + \frac{\partial^2 C}{\partial z^2}\right] \tag{56}$$

where $\rho$ and $z$ are the radial and axial axes, respectively, and the diffusion coefficient $D = D_1$ in domain (1) and $D = D_2$ in domain (2):

$$D_1 = \frac{D_L}{\xi} \tag{57}$$

$$D_2 = K_r D_1 \tag{58}$$

$D_L$ is the drug diffusion coefficient in the solvent/liquid, $\xi$ is the retardation factor that reflects how the pore geometry and topology affects the diffusion and $K_r$ is the restriction factor to account for the interactions between the drug and the polymer ($D_2 \ll D_1 \ll D_L$).

Once diffusion has started, the amount of drug remaining in the element at time $t$, $m_t$, is given by

$$m_t = 2\int_{Z=0}^{L/2}\int_{\rho=0}^{R} 2\pi\rho C(\rho, z, t)\, d\rho\, dz \tag{59}$$

Thus, the fraction of drug release at time $t$, $M_t/M_\infty$, is given by

$$\frac{M_t}{M_\infty} = \frac{m_0 - m_t}{m_0} \tag{60}$$

As the problems involve a moving interface, the equations were solved by numerical computation.

### 4.2. Monte Carlo simulations

The first Monte Carlo-based model/simulation of drug release from surface-eroding systems was reported in late 1980s (Zygourakis, 1989, 1990; Zygourakis and Markenscoff, 1996). Similar approach was later developed by Göpferich (1997a) to study the degradation (molecular weight reduction) and erosion (mass loss) of bulk-degrading polymers, P(DL)LGA 50/50. The model works on the assumption that degradation is a necessary condition for the erosion of water insoluble polymers and that degraded polymer can only erode after the degraded polymer connects to a pore or the matrix surface.

Polymer cross-sections are represented by a two-dimensional ($n \times n$) rectangular grid, that is made of many pixels, i.e. small polymer pieces. Each pixel, $P_{i,j}$, where $1 \le i \le n$, $1 \le i \le n$, was assigned an individual lifetime as follows

$$t_{i,j} = \frac{1}{\lambda \ln(n^2)}\ln(1-\epsilon) \tag{61}$$

$t_{i,j}$ is the time at which pixel $P_{i,j}$ degrades; $\lambda$ is the degradation rate constant; $\epsilon$ is a random variable equally distributed in the interval [0,1], generated by the computer.

The pixels are then degraded in the sequence of their lifetimes. When the lifetime of a pixel $P_{i,j}$ expires, it is assumed to be degraded. However, the erosion of the corresponding grid site can only takes place when at least one of the eight neighbouring pixels is already eroded. Therefore, the states of individual pixels ($x_{i,j}$) are assigned one of the three possible properties

$$\begin{aligned} x_{i,j} &= 1 \quad \text{nondegraded} \\ x_{i,j} &= 0 \quad \text{degraded} \\ x_{i,j} &= -1 \quad \text{eroded} \end{aligned} \tag{62}$$

The degree of polymer degradation, $degr(t)$, can be followed by determining the relative number of nondegraded pixels

$$degr(t) = \frac{1}{n^2}\sum_{i=1}^{i=n}\sum_{j=1}^{j=n} s(x_{i,j}); \qquad s(x_{i,j}) = \begin{cases} 1; & x_{i,j} = 1 \\ 0; & \text{else} \end{cases} \tag{63}$$

while erosion (mass loss) is gauged in terms of relative mass of noneroded polymer, $mass(t)$, by the following equation

$$mass(t) = \frac{1}{n^2}\sum_{i=1}^{i=n}\sum_{j=1}^{j=n} s(x_{i,j}); \quad s(x_{i,j}) = \begin{cases} 0; & x_{i,j} = -1 \\ 1; & \text{else} \end{cases} \tag{64}$$

These simulations explain the absence of noticeable mass loss in the early degradation times and reveal significant involvement of the percolation phenomena in the degradation and erosion of bulk-degrading polymers.

Siepmann et al. (2002) combined the Monte Carlo simulation with mathematical equations to model polymer degradation and drug release from bulk-degrading microspheres. Due to symmetry, the mathematical analysis can be reduced to a quarter of the sphere,

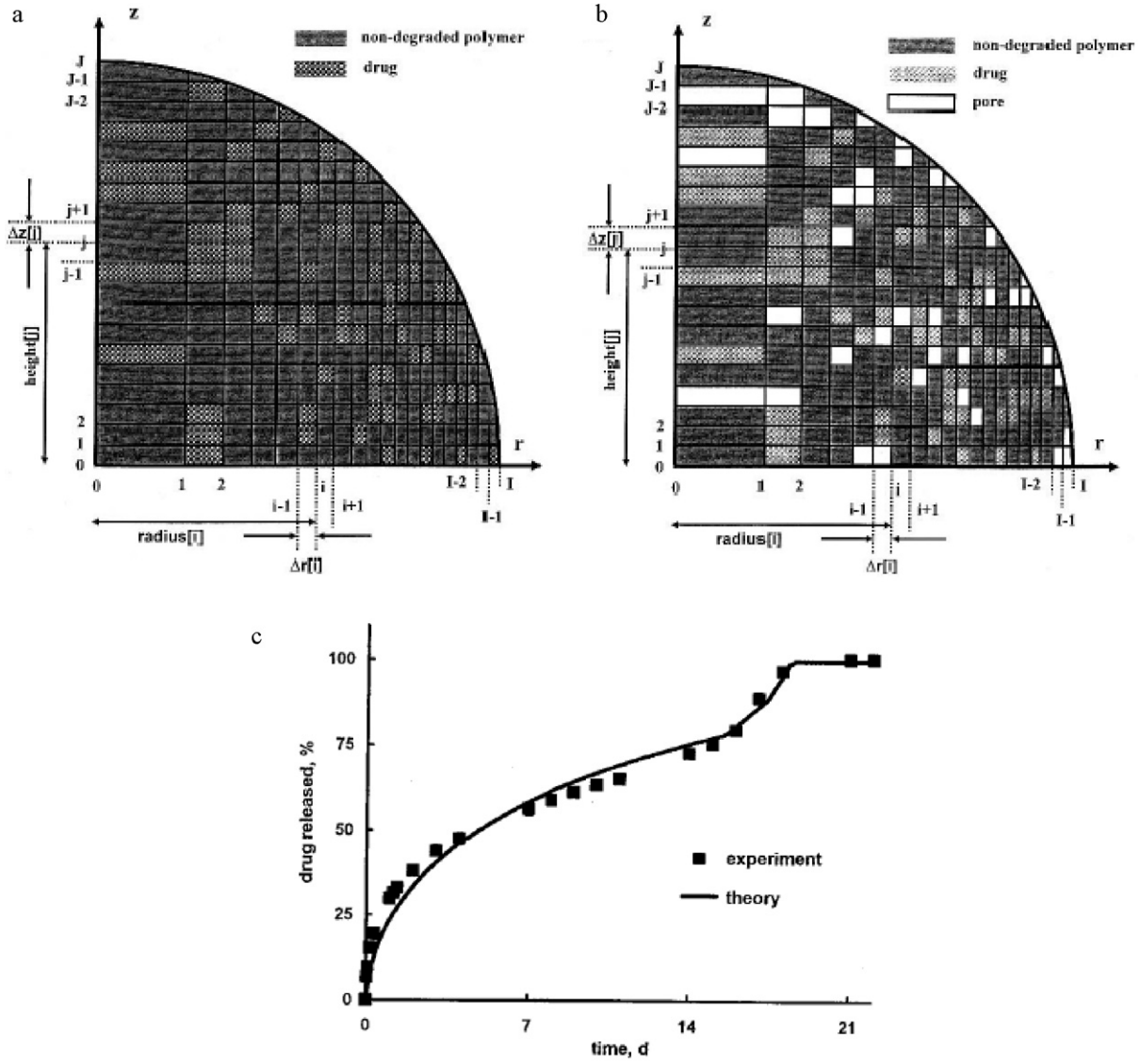


**Fig. 14.** Principle of Monte Carlo-based model according to Siepmann et al. to simulate matrix degradation and drug release (a) at time $t = 0$ and (b) at time $t$. Comparison of the model and experimental data of 5-FU release from PLGA microparticles (c).
(reprinted from Siepmann et al., 2002 with permission from Springer).

represented by a two-dimensional pixel grid (see Fig. 14a and b). The origin of the coordinate system is placed at the center of the sphere and the microsphere is rotational symmetric to the angle $\theta$ along the $z$-axis. The coordinates are chosen in such a way that the volumes of the cylindrical rings, which are described by the rectangular pixels upon rotation around the $z$-axis, are all equal. Each pixel represents either polymer or drug (before exposure to the release medium).

As polymer degradation is a random process, not all pixels degrade exactly at the same time point; instead, they possess individual, randomly distributed "lifetimes". The "lifetime", $t_{lifetime}$, of a pixel is calculated as a function of the random variable $\upsilon$ (integer between 0 and 99)

$$t_{lifetime} = t_{average} + \frac{(-1)^{\upsilon}}{\lambda} \ln\left(1 - \frac{\upsilon}{100}\right) \tag{65}$$

$t_{average}$ is the average "lifetime" of the pixels and $\lambda$ is a constant, being characteristic for the type and physical state of the polymer.

Because there is no concentration gradient in $\theta$-coordinate, the drug diffusion is described by the following Fick's second law of diffusion for cylindrical devices

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial r}\left(D\frac{\partial C}{\partial r}\right) + \frac{D}{r}\frac{\partial C}{\partial r} + \frac{\partial}{\partial r}\left(D\frac{\partial C}{\partial z}\right) \tag{66}$$

$C$ and $D$ are the concentration and diffusion coefficient of the drug; $r$ and $z$ denote the radial and axial coordinate; $t$ is time.

The status of pixel $x_{i,j}$ is updated at each time step by Monte Carlo simulations as follows

$$s(i,j,t) = \begin{cases} 1; & \text{for non-eroded polymer} \\ 0; & \text{for pores} \end{cases} \tag{67}$$

Next, the porosities in radial and axial direction, $\varepsilon(z,t)$ and $\varepsilon(r,t)$ can be calculated as follows

$$\varepsilon(r,t) = 1 - \frac{1}{n_z}\sum_{j=1}^{j=n_z} s(i(r),j,t) \tag{68}$$

$$\varepsilon(z,t) = 1 - \frac{1}{n_r}\sum_{i=1}^{i=n_r} s(i,j(z),t) \tag{69}$$

where $n_z$ and $n_r$ represent the number of pixels in the axial and radial direction at $r$ and $z$, respectively.

Based on the porosity values, the diffusivities of the drug, $D$, in axial and radial direction can be calculated as follows

$$D(r, t) = D_{crit}\varepsilon(r, t) \quad (70)$$

$$D(z, t) = D_{crit}\varepsilon(z, t) \quad (71)$$

where $D_{crit}$ represents a critical diffusion coefficient, being characteristic for a specific drug-polymer combination.

The equations were solved numerically with the help of programming language C++ to determine the actual drug concentration at each grid point at each time step. Fig. 14c shows the comparison between simulation and experimentally derived release data. Only the amount of drug that is soluble is considered to be available for diffusion; the excess is considered to be nondissolved and hence, not available for diffusion. In conclusion, this model takes into account the effect of limited drug solubilities such that in the case of poorly water-soluble drugs, dissolved and undissolved drug coexist within the system.

Bertrand et al. (2007) reported another attempt to model drug release from bioerodible microspheres using a cellular automaton technique that is based on a virtual matrix defined in a cubic space of side dimension equals to 200 (corresponding to 8 million cells). Five states that represent different physical components during release are possible for each cell: polymer (P), solvent (S), porosity (E), solid drug (D) or drug in its solubilised form (SD). Throughout the simulation, the matrix follows successive iterations during which the state of each cell evolves. After every iteration the number of cells in each state is counted and thus the cumulative amount of drug release can be followed from the amount of drug cells remaining in the matrix.

Monte Carlo simulations have also been reported to describe polymer degradation and mass transport processes of surface-eroding polymers and composites matrices made of bulk and surface eroding polymers (Göpferich and Langer, 1993, 1995; Göpferich, 1997b,c).

## 5. Conclusion

This review has summarized various mathematical and Monte Carlo based-models developed to describe controlled release from bulk-degrading systems. Proper characterizations of the systems studied are necessary to provide input values to the model parameters so that accurate matches can be obtained.

Models based solely on diffusion with time/degradation-dependent diffusion coefficient (diffusional-based models) are generally simpler and easier to use. However, their applications may be limited to predict release from systems whose release mechanism is indeed governed mainly by diffusion, for e.g. *monophasic* release of water-soluble agents.

More comprehensive models that combine diffusion with erosion and/or dissolution and/or percolation theories usually provide better match for more complex, *multi-phasic* release. However, these equations/models are more cumbersome to use and almost always require the aid of computer/programming languages.

Monte-Carlo based model/simulation is another interesting approach that describes polymer degradation as a truly random chain scission process and predicts the corresponding drug release rather well.

As all these models have own advantages and limitations, readers are advised to carefully select the appropriate model that can represent the systems under study. Of course, it may also be necessary to perform slight modifications/corrections to suit the geometries of interest.

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