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Review

Mathematical modeling of polymer erosion: Consequences for drug delivery

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ABSTRACT

Bioerodible polymers have been extensively used as carriers for drug delivery and as scaffolds for tissue engineering. The ability to model and predict erosion behavior can enable the rational design and optimization of biomaterials for various biomedical applications *in vivo*. This review examines critically the current approaches in mathematical modeling of the erosion of synthetic polymers. The models are classified broadly based on whether they use phenomenological, probabilistic, or empirical approaches. An analysis of the various physical, chemical, and biological factors affecting polymer erosion and the classes of bioerodible polymers to which these analyses have been applied are discussed. The key features and assumptions associated with each of the models are described, and information is provided on the limitations of the models and the various approaches. The review concludes with several directions for future models of polymer erosion.

Contents

1. Introduction

Bioerodible polymers are a class of biomaterials with a backbone that can be broken by hydrolysis to form biocompatible degradation products. These polymers are well suited for applications such as drug delivery, which require the gradual release of a drug over time; or for tissue scaffolds, which must gradually break down over time, as they are replaced by cells and tissue. Devices based on these materials (e.g., implants and particles) have the advantage of degrading over time, thus obviating the need for surgical removal.

While a variety of polymer chemistries, geometries, and applications using bioerodible polymers have been investigated, it is beneficial to have the ability to quantitatively model and predict the erosion behavior of the system. If erosion behavior can be predicted, then appropriate materials, conditions, dimensions, and geometries can be chosen for the specific application. In drug delivery, it is important to know the rate at which the drug will be released from the polymer in order to keep the delivery above the mini-

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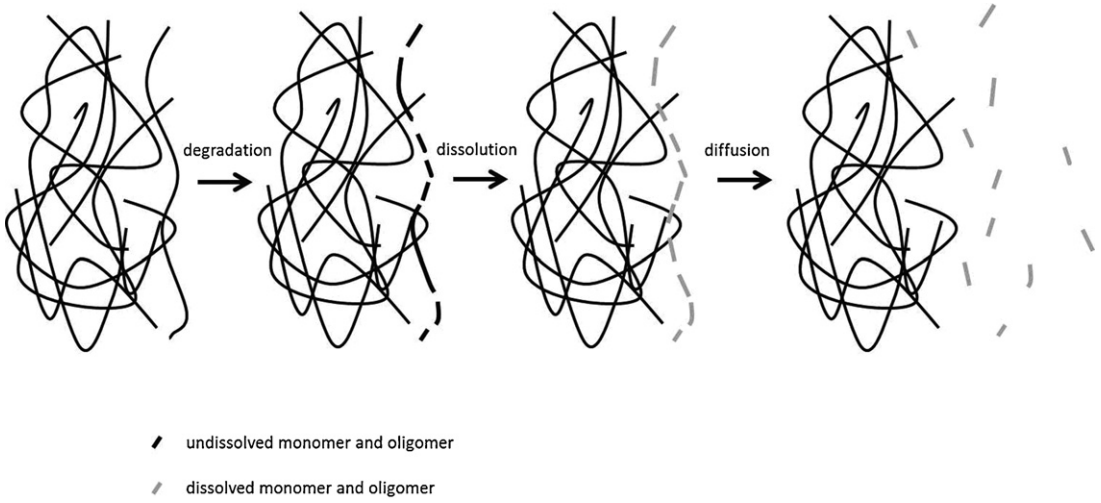

Fig. 1. The process of polymer erosion, which is a combination of degradation, dissolution, and diffusion.

mum level of efficacy but below the level of toxicity. By knowing *a priori* the characteristics of polymer degradation and erosion, drug release profiles can be predicted. In tissue engineering applications, the extent of polymer erosion from the device will determine the mechanical stability of the remaining polymer. The knowledge of the timescale of these events is an important consideration when designing such a device.

Polymer erosion has been defined elsewhere as a combination of degradation, dissolution, and diffusion processes (Fig. 1); in this review we will use similar definitions (Kipper and Narasimhan, 2005; Siepmann and Gopferich, 2001). Degradation refers to the chain scission events, which in the case of bioerodible polymers is nearly always due to hydrolysis. In most cases, degradation appears to be the controlling step of erosion. The oligomers and monomers resulting from degradation are often more water-soluble than the original polymer chains. The dissolved degradation products, along with released drug, finally diffuse away from the device.

This picture of polymer erosion is oversimplified, as many other factors can alter the erosion behavior. Before degradation via hydrolysis can occur, water must come into contact with the polymer. Depending on the hydrophobicity of the polymer and its thickness, water ingress into the device may occur at different rates. Also, many bioerodible systems are based on copolymers that exhibit some degree of phase (or microphase) separation, making some regions of the polymer more accessible than others (Shen et al., 2001, 2002). Once the water does reach the polymer, its bonds may not all cleave at the same rate: for example, bonds between different monomers in a copolymer may have different hydrolysis rates (Larobina et al., 2002). In semicrystalline polymers, bonds in the amorphous region are more easily broken than those in the crystalline region, and increased mobility of shorter chains in the amorphous region may cause them to crystallize during the course of the degradation (Han and Pan, 2009). There are some cases in which the degradation products of polymer hydrolysis are acidic monomers, which catalyze the hydrolysis reaction, complicating the rate equations (Antheunis et al., 2009, 2010).

The polymers that bioerodible devices are based upon are usually polydisperse, which means that their degradation products of oligomers and monomers will have a time-dependent molecular weight distribution. Also, the bond scission rates at different locations along the polymer chain can vary, further complicating the picture as a number of different hydrolysis reactions could occur along the length of the polymer chain. Chain length is also important in the dissolution and diffusion steps, as both solubility and diffusivity in polymers can be molecular weight dependent. Solubility, diffusivity, and reaction rates can also be dependent on temperature and pH.

Furthermore, polymer erosion can be affected by polymer swelling, pore formation, and many other factors. In any case, it is clear that erosion is a combination of coupled and simultaneously occurring molecular-scale and micro-scale processes. The erosion rate and behavior of a particular system may be controlled by one or more of these processes, and as erosion progresses, the controlling phenomenon may change.

The goal of this review is to summarize the various approaches for modeling the erosion behavior of synthetic polymers, as well as to highlight the features of the models based on the controlling phenomena they describe. First, we describe briefly the classes of bioerodible polymers that have been widely used in drug delivery applications. Next, we discuss and analyze the various approaches that have been taken to model polymer erosion and finally, we point out some observations for future research in this area.

2. Classes of synthetic bioerodible polymers

The main classes of synthetic bioerodible polymers are shown in Fig. 2. The three types of polymers that have been widely studied as drug carriers and that have motivated the most specific degradation models are polyesters, poly(orthoesters), and polyanhydrides.

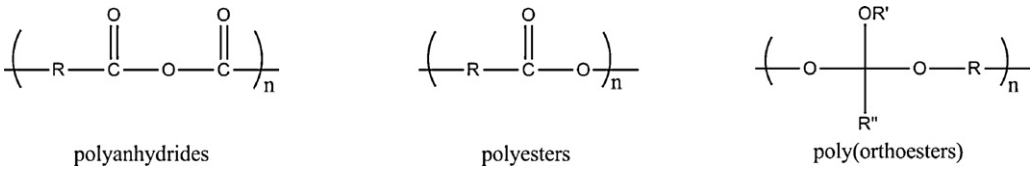

Fig. 2. Chemical structures of the most well studied synthetic bioerodible polymers.

Table 1
Summary of approaches and physics of models of polymer erosion.

Modeling approach	Method	Physics accounted for by model	Degradable polymers applied to	References
Probabilistic	CA	Bulk erosion	Polyesters	Bertrand et al. (2007)
Probabilistic	CA	Crystallinity, surface erosion	Polyanhydrides	Yu et al. (2008)
Probabilistic	MC	Crystallinity, bulk erosion	Polyesters	Siepmann et al. (2002) and Faisant et al. (2003)
Probabilistic	MC	Surface erosion, porosity, monomer solubility	Polyanhydrides	Zygourakis and Markenscoff (1996)
Probabilistic	MC	Monomer solubility and diffusion, porosity	Polyanhydrides	Gopferich and Langer (1995a,b)
Phenomenological	RD	Copolymer microstructure and scission rate differences, crystallinity, surface erosion	Polyanhydrides	Kipper and Narasimhan (2005) and Larobina et al. (2002)
Phenomenological	RD	Polydispersity, chain length dependent diffusivity	Polyesters	Soares and Zunino (2010)
Phenomenological	RD	Catalyzed hydrolysis, polydispersity, fraction of crystallinity and differences in copolymer scission rate (through degradation rate constants)	Polyesters	Antheunis et al. (2009, 2010)
Phenomenological	RD	Crystallinity (through water partition coefficient), diffusivity dependent on extent of polymer hydrolysis, catalyzed hydrolysis, oligomer formation	Polyesters	Prabhu and Hossainy (2007)
Phenomenological	RD	Bulk erosion ("shrinking core"), polydispersity, catalyzed hydrolysis	Polyesters	Arosio et al. (2008) and Perale et al. (2009)
Phenomenological	RD	Time-dependent crystallinity, catalyzed hydrolysis	Polyesters	Han and Pan (2009) and Wang et al. (2008)
Phenomenological	RD	Surface erosion, catalyzed hydrolysis	Poly(orthoesters)	Thombre and Himmelstein (1984, 1985)
Phenomenological	RD	Bulk erosion, time-dependent average molecular weight	Poly(orthoesters)	Batycky et al. (1997)
Phenomenological	RD	Surface and bulk erosion, time-dependent average molecular weight	Polyanhydrides, poly(orthoesters), and polyesters	Rothstein et al. (2009) and Lyu et al. (2005)

2.1. Polyesters

Polyesters are bulk-eroding polymers with acid-catalyzed degradation. Given the fact that their degradation products are acid monomers, they are prone to autocatalysis effects. The three most common polyesters are poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and poly(ε-caprolactone) (PCL). PGA is the least hydrophobic and the most rapidly hydrolyzed (Gunatillake and Adhikari, 2003). It also has a high degree of crystallinity. In addition to acid-catalyzed hydrolysis, PGA can also undergo enzymatic hydrolysis (Gunatillake and Adhikari, 2003). Often, copolymers of PGA and PLA are used for tuning degradation since PLA and PGA degrade at different rates (Gopferich, 1996). PCL degrades much slower than PGA and PLA, on a timescale of years (Gunatillake and Adhikari, 2003).

2.2. Poly(orthoesters)

Poly(orthoesters), like polyesters, degrade via acid-catalyzed hydrolysis. Depending on the relative rates of water intrusion into the polymer and polymer degradation, poly(orthoesters) can undergo either bulk or surface erosion (Heller et al., 2000). Under some conditions, poly(orthoesters) can also exhibit autocatalytic degradation behavior (Heller et al., 2000).

2.3. Polyanhydrides

Polyanhydrides, in contrast to polyesters, are surface eroding. This is mainly due to their hydrophobicity, which prevents the intrusion of water into the bulk of the material until the surface has eroded to expose the interior (Domb and Langer, 1987; Leong et al., 1986; Tamada and Langer, 1992; Torres et al., 2006). Polyanhydrides undergo base-catalyzed hydrolysis. Some examples of monomers for polyanhydrides used as biomaterials include those containing aliphatic groups such as sebacic acid (SA) and those containing aromatic groups such as 1,3-bis(*p*-carboxyphenoxy)propane (CPP), 1,6-bis(*p*-carboxyphenoxy)hexane (CPH), 1,8-bis(*p*-carboxyphenoxy)-3,6-dioxaoctane (CPTEG), as well as various copolymers thereof. Monomer solubility is pH-dependent and greatly influences the erosion behavior of polyanhydrides (Determan et al., 2004, 2006a,b; Lopac et al., 2009; Torres et al., 2006).

2.4. Other bioerodible polymers

While there are a variety of other bioerodible polymers, such as poly(phosphazenes) and polyamides, very few degradation models have been directly applied to them, perhaps because of their slower hydrolysis (Siepmann and Gopferich, 2001). One exception is a simple phenomenological model for polyamides that assumes a first-order degradation reaction (Mahadevan and Smith, 2007).

3. Modeling approaches

There is a large body of work on the modeling of polymer erosion. In the broadest terms, these models could be classified into three major approaches: phenomenological, probabilistic, and empirical. Table 1 summarizes these approaches and the physics described by the models. Next, a critical analysis of the underlying physics, assumptions, and limitations of these approaches is presented.

3.1. Phenomenological models

Most models that seek to characterize polymer erosion based on mechanistic phenomena are based on the equations governing species reaction, diffusion, and dissolution. Since this type of model is based on the governing equations, they are applicable to a wide variety of polymer types, device geometries, and conditions. They are general enough that they could be easily applied or extended broadly. However, they are specific enough to accurately

take into account the phenomena specific to a certain system. Since they often include the consideration of such phenomena, they are often complicated. In many cases, it is non-trivial to find analytical solutions to the equations and may even be difficult to apply the equations.

In general, this approach has been used to model bulk eroding systems, which demonstrate more complex reaction behavior. This is the case for two early models by Thombre and Himmelstein (1984, 1985), which are based on reaction-diffusion (RD) phenomena, of which the latter accounted for autocatalysis effects. The same approach has been used in more recent models to characterize autocatalytic behavior (Antheunis et al., 2009, 2010) and the effects of crystallization (Han and Pan, 2009; Wang et al., 2008). The RD models are not limited to bulk-eroding systems; this approach was used by Larobina et al. (2002) and Kipper and Narasimhan (2005) to model the effects of microstructure on the surface erosion of polyanhydride copolymers.

A phenomenological model for polymer erosion was developed by Lee (1980), where the effect of drug solubility and loading on release from an eroding planar polymer matrix was modeled with moving diffusion and erosion fronts. When the velocities of these fronts were synchronized, a near zero-order drug release was observed. A similar approach was proposed by Charlier et al. (2000), where first order polymer degradation kinetics were coupled with pseudo steady state assumptions. This model is comparable to the classic Higuchi model for release from a non-degradable polymer matrix, to which it is similar at early time points (Charlier et al., 2000; Higuchi, 1963).

3.1.1. Bulk vs. surface erosion

The majority of models that describe polymer erosion assume that erosion occurs via one of two macroscopic mechanisms: bulk erosion or surface erosion. Bulk erosion takes place when water ingress into the polymer matrix is faster than polymer degradation. As a result, the polymer degrades at roughly the same rate everywhere in the system. However, if polymer degradation occurs faster than water diffuses into the polymer bulk, then erosion occurs only at the section of the polymer closest to the surface.

As discussed before, polyesters are a class of commonly studied bulk eroding polymers, and most of the models that describe bulk erosion are based on polyesters. In the models for bulk erosion, either a simple parameterized model is used or a more complicated RD approach from the governing equations is employed. The second approach was used by Batycky et al. (1997) in modeling drug release from PLGA microspheres. A combined random- and end-chain scission mechanism that allows for a distribution of molecular weights was employed. Drug release was modeled as an initial burst caused by drug desorption followed by an induction time after which continuous drug release by diffusion occurred. However, it has been observed that several input parameters to this model can only be obtained from release data (Rothstein et al., 2008). The results from this model were used to characterize pore erosion in a subsequent model that combined both erosion and diffusion effects on drug release from porous polymer matrices (Lemaire et al., 2003).

Another model based on the RD approach to bulk erosion was developed by Charlier et al. (2000), who derived a simple model of drug release from PLGA films by assuming first order degradation and molecular weight dependent polymer diffusion. Several others have used this approach to model bulk erosion using a variety of assumptions, and these earlier works are thoroughly reviewed elsewhere (Arifin et al., 2006; Siepmann and Gopferich, 2001).

More recently, Arosio et al. suggested a model for a cylindrical bulk-eroding polymer with a "shrinking core" of degrading polymer surrounded by an uneroded shell (Arosio et al., 2008). The model has two parts: a simplified degradation model (accounting only for monomer formation) as well as a more detailed option which

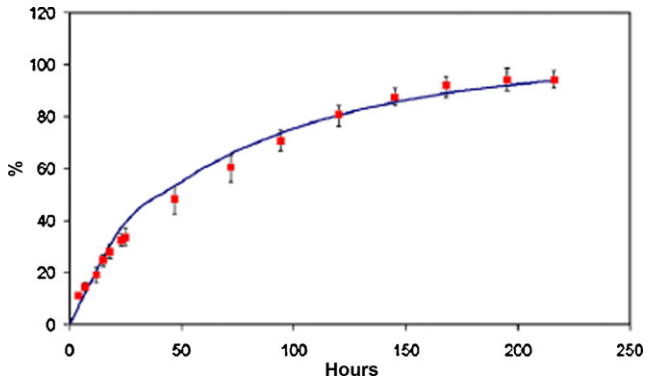

Fig. 3. Comparison of model prediction and experimental drug release from PGA threads (from Perale et al., 2009). Reproduced with permission.

accounts for the changing molecular weight of the polymer chains. This information was summarized by mass balances on the zero, first, and second order moments of the molecular weight distribution function. The degradation model was used to show changes in both mechanical strength (based on polymer average molecular weight) and drug release. Drug release was modeled as dependent on drug solubility, diffusivity, molecular weight, and density. The ideas from this model were expanded by the same group in a more detailed one dimensional model which seeks to make it more applicable to the transition between reaction-controlled and diffusion-controlled states (Perale et al., 2009). Thus, the equations governing polymer degradation are essentially the same as the previous model, and the drug release equations are more detailed. The model was validated by comparison with experimental results for release of several different drugs from various polymers, including PGA threads (Fig. 3).

While much attention has been given to bulk erosion, several models have also been proposed to describe surface erosion. The surface erosion phenomenon in a drug device with a barrier membrane was described by Thombre and Himmelstein (1984) using the concept of an erosion front, which follows the water diffusion front through the polymer matrix. An updated version of this model also considered catalysis and degradation product diffusion (Thombre and Himmelstein, 1985). While Thombre and Himmelstein used a phenomenological approach, many statistically based models have been proposed to describe the surface erosion of polymers. These models assign a lifetime to each small element of the polymer matrix, and the important phenomena are accounted for in the probability of these cells eroding (Gopferich and Langer, 1993, 1995a; Zygourakis, 1990; Zygourakis and Markenscoff, 1996). This modeling approach is discussed in Section 3.2.

Polyanhydrides are a class of bioerodible polymers that exhibit surface erosion due to their hydrophobic exclusion of water from the bulk of the polymer. The surface erosion of polyanhydrides has been described in a model suggested by Larobina et al. (2002) and later modified by Kipper and Narasimhan (2005). The model proposed by Kipper and Narasimhan, which takes into account the phase behavior of a copolymer system, assumes that only the polymer at the surface of the device and its pores erodes.

While most of these models assume that polymers undergo strictly one of the two erosion mechanisms, it has long been known that this is an idealized picture of the actual physical processes. Early on, the importance of both erosion mechanisms was recognized and models have been proposed with two parts: one for the bulk erosion regime and one for the surface erosion regime (Zhang et al., 2003). Although this model acknowledged the need to bridge the two concepts, it was still disjointed in that it had two different sets of equations. A model suggested by von Burkersroda et al. (2002) presented a dimensionless parameter that related the

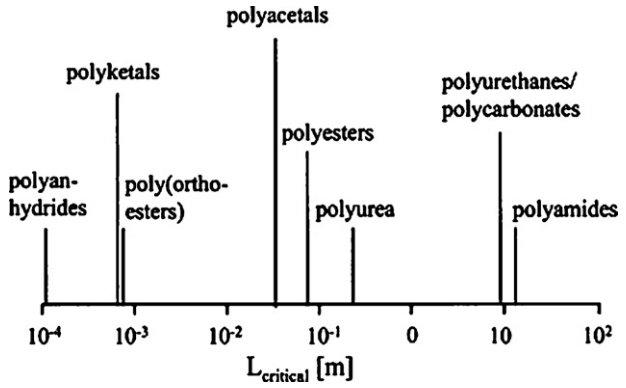

Fig. 4. Critical thicknesses for surface erosion for a variety of classes of bioerodible polymers (from von Burkersroda et al., 2002). Reproduced with permission.

tendency of a polymer to undergo surface or bulk erosions under certain conditions:

$$\varepsilon = \frac{\langle x\rangle^2 \lambda \pi}{4D_{eff}\ln[\langle x\rangle] - \ln[\sqrt[3]{\bar{M}_n/N_A(N-1)\rho}]} \tag{1}$$

Here D_{eff} is the effective water diffusivity, M_n is the number average molecular weight of the polymer, N_A is Avogadro's number, N is the average degree of polymerization, ρ is polymer density, λ is a degradation rate constant based on backbone functionality, and $\langle x\rangle$ is a mean travel distance of water. The model took into account polymer density, backbone reactivity (but not catalysis), polymer molecular weight, and water diffusion in the polymer. With the knowledge of this erosion parameter, a critical thickness above which surface erosion occurs could be calculated and was determined for several polymer types (Fig. 4) (von Burkersroda et al., 2002).

A few others have built on the results of von Burkersroda et al. by creating models that yield a critical length scale for surface erosion, but which are based on the governing RD equations. Lyu et al. proposed a model with moving boundaries (Lyu et al., 2005). Another approach to a unified model was proposed by Rothstein et al., who also considered the release of drug from the matrix (Rothstein et al., 2009). The model results were compared to experimental data for erosion-controlled drug release from polyanhydrides (Fig. 5) and for dissolution-controlled drug release from polyorthoesters.

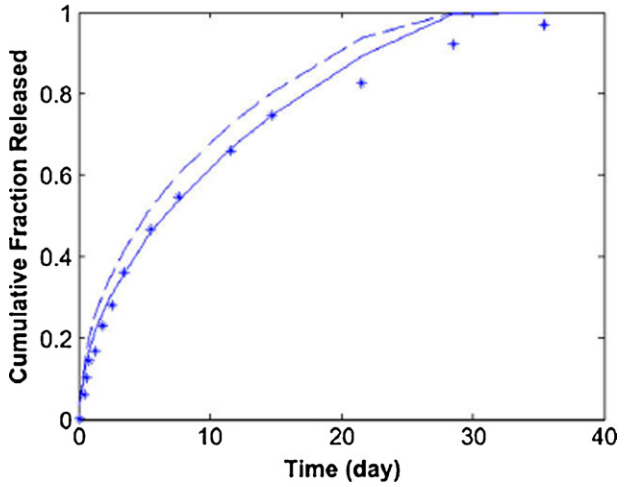

Fig. 5. Comparison of model prediction and experimental data for erosion-controlled release of bupivacaine from polyanhydride disks (from Rothstein et al., 2009). Reproduced with permission.

A recent model that addressed the multi-scale issues in polymer erosion was proposed by Soares and Zunino (2010). Along with the others mentioned above, this model recognized that while surface and bulk erosion have the same basis on a microscopic scale, macroscopic diffusion differs between the two. The model proposes $i-1$ possible degradation reactions for a polymer chain of average length j (and therefore average degree of polymerization $\bar{x}_j$) (Soares and Zunino, 2010):

$$\bar{x}_i \xrightarrow{k_{ij}} \bar{x}_j + \bar{x}_{i-j}, \quad \text{for} \quad j = 1, \ldots, i-1 \tag{2}$$

This one-dimensional multi-scale approach for stent coating applications takes into account the effect of polydispersity on the microscale process of chain scission, but also recognizes the effect that chain size has on polymer diffusivity (Soares and Zunino, 2010). The non-dimensionalized governing equations for water w, encapsulated drug d, and polymer chain with i repeating units were respectively given by:

$$\dot{\rho}_w = \Lambda\,\mathrm{div}(D\,\mathrm{grad}\,\rho_w) - K\sum_{i=1}^{N}\frac{(i-1)}{i}\rho_w\rho_i \tag{3}$$

$$\dot{\rho}_d = \Lambda\,\mathrm{div}\left(\frac{D}{n^k}\,\mathrm{grad}\,\rho_d\right) \tag{4}$$

$$\dot{\rho}_i = \Lambda\,\mathrm{div}\left(\frac{D}{n^i}\,\mathrm{grad}\,\rho_i\right) + \rho_w\bar{x}_1\left[-(i-1)\rho_i + 2\sum_{j=i+1}^{N}\frac{i}{j}\rho_j\right], \quad \text{for} \quad i = 1, \ldots, N \tag{5}$$

Here $\dot{\rho}$ is the non-dimensional partial density of the species, D is the constitutively specified diffusivity, n is a factor that relates diffusivity to polymer chain length, K is the ratio between molar water volume and dry monomer chains, and Λ is the Thiele modulus, which is defined as:

$$\Lambda = \frac{D^\infty}{L^2\tilde{k}\rho_w^\infty} \tag{6}$$

Here ρ_w^∞ is the density of the surrounding water, $\tilde{k}$ is the hydrolysis rate constant, L is the stent coating thickness, and D^∞ is the diffusivity of water into an intact, dry polymer (Soares and Zunino, 2010). The Thiele modulus is the key parameter that determines whether the polymer erodes via a surface or bulk mechanism. The numerical solution to this system reflected the expected sigmoidal mass loss for a bulk eroding system (high Thiele modulus) and the zero-order mass loss for a surface eroding system (low Thiele modulus).

3.1.2. Reaction kinetics (autocatalytic reactions)

The autocatalytic effect of acid degradation products is one reason that many polymers undergo bulk erosion. For example, polyesters degrade into carboxylic acid monomers, but their degradation is acid-catalyzed. The local concentration of monomer, which is affected by device thickness and diffusion and degradation rates, will affect how quickly the polymer degrades. It has been observed that due to monomer entrapment, thicker devices actually degrade more quickly than thinner ones when they are made of polymers that have acid-catalyzed degradation. As shown in Fig. 6, the interior of such a device tends to degrade before the exterior (Antheunis et al., 2009). Thus, although bulk erosion has been termed "homogeneous" because water diffuses equally to all parts of the matrix, degradation throughout the device often is dependent on pH. Autocatalytic effects make local pH another important factor to consider when modeling polymer erosion. However, this factor is often ignored due to the complications it introduces into the relevant rate equations.

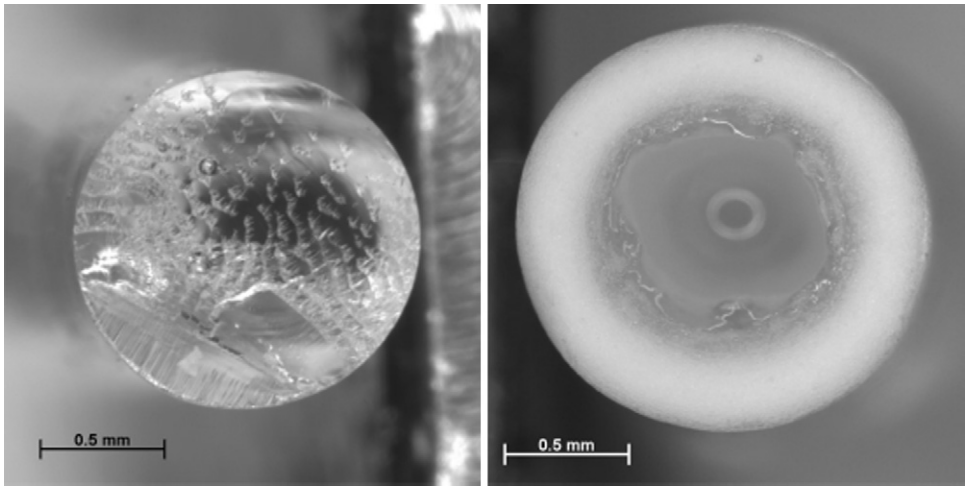

Fig. 6. PLA rod initially (left) and after 70 days of autocatalyzed degradation (right) (from Antheunis et al., 2009). Reproduced with permission.

This phenomenon was described by Thombre and Himmelstein (1985) in poly(orthoesters) and expanded upon by Prabhu and Hossainy (2007) in their model for drug release from stents, by considering the acid-catalyzed polymer degradation to occur in three steps: polymer, oligomer, and acid monomer. Antheunis et al. proposed a more comprehensive model for polyesters (Antheunis et al., 2009, 2010). As shown by the series of conservation equations below, the reaction rate was assumed to be second order and dependent on acid concentration. For a polymer P_i of chain length n and containing i ester bonds, the rate of change of polymer concentration was given by:

$$\frac{d[P_i]}{dt} = 2\sum_{m=i+1}^{n} k[P_m][A] - ik[P_i][A] \tag{7}$$

Here $[A]$ is the acid concentration and k is the hydrolysis rate constant. The equation governing monomer concentration $[P_0]$ was:

$$\frac{d[P_0]}{dt} = 2\sum_{i=1}^{n} k[P_i][A] \tag{8}$$

The hydrolysis rate constant in this case took into account the fact that in a copolymer of A and B, the different types of bonds (A–A, B–B, and A–B) have different hydrolysis rates. The resulting coupled differential equations are adaptable to polymer chains with non-carboxylic end groups and were solved numerically (Antheunis et al., 2009). The results for a 53:47 PLGA copolymer demonstrated that the predicted degradation profile matches the sigmoidal curve observed experimentally (Fig. 7).

Antheunis et al. also proposed a simpler model, which assumed constant mass and volume and a uniform molecular weight calculated using the number average rather than the weight average (Antheunis et al., 2010). This final assumption, while prone to more error from sensitivities in experimental error, allows for a single differential equation with an analytical solution. The resulting expression for number average molecular weight was given by:

$$M_n(t) = \left(\frac{[A]_0}{\rho}\frac{e^{c_1 t}-1}{1+c_2 e^{c_1 t}} + \frac{1}{M_n(0)}\right)^{-1} \tag{9}$$

Here ρ is the polymer density, c_1 is a constant of integration that accounts for hydrolysis rate and crystallinity, and c_2 is a constant of integration that is a ratio between the initial concentrations of acid and ester bonds.

Prabhu and Hossainy (2007) considered drug release from a PLA stent coating. They used unsteady mass balances containing

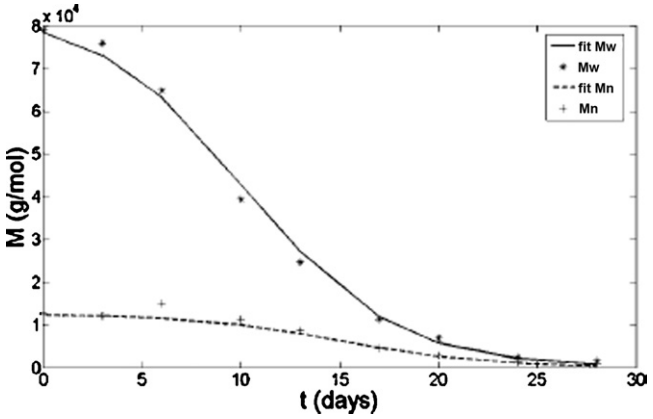

Fig. 7. Comparison of model prediction and experimental degradation profiles for PLGA 53:47 based on number and weight average molecular weights (from Antheunis et al., 2009). Reproduced with permission.

rate expressions that assumed an autocatalytic role of the lactic acid monomer in degradation. They also assumed an exponential dependence of diffusivity on extent of polymer hydrolysis. It was also noted that enzymatic degradation and diffusivity of non-hydrolyzed PLA were neglected in the model. A partitioning coefficient present in the boundary conditions for the water balances accounted for effects such as crystallinity and porosity on degradation rates. The model coefficients were obtained through fitting to experimental data.

3.1.3. *Phase effects: crystallinity, copolymers, and blends*

Yet another complication in the erosion process is the crystallization of polymers as they undergo degradation. In semicrystalline polymers, the degree of crystallinity is always changing due to the preferential hydrolysis of polymer in the amorphous phase (Han and Pan, 2009). To add to this effect, the polymer molecules that have been cleaved from the amorphous region can crystallize due to the increased mobility of short chains (Han and Pan, 2009). The degree of crystallinity in a degrading polymeric biomaterial is important as it can affect not only degradation rate, but also mechanical stability. However, this effect is usually neglected in mathematical modeling of polymer degradation because it adds another time-dependent variable.

However, an interesting model proposed by Han and Pan (2009) expands on their previous phenomenological model which used the exponential Avrami equation to account for a time-dependent

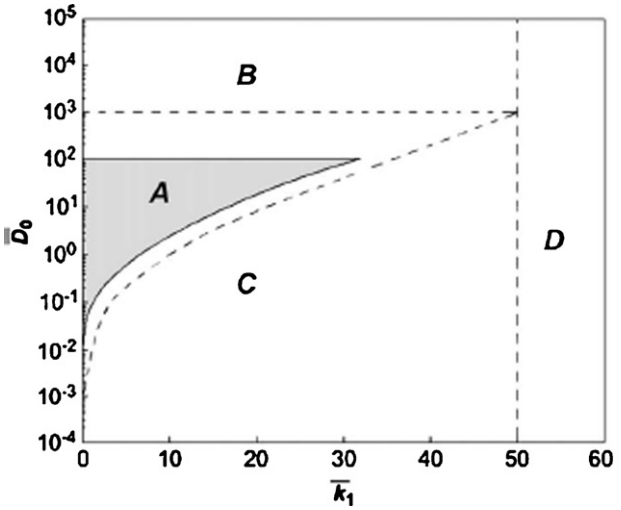

Fig. 8. Biodegradation map for an infinitely large plate. $\bar{D}_0$ is the ratio of diffusion and catalyzed degradation rates and $\bar{k}_1$ is the ratio of uncatalyzed and catalyzed hydrolysis reactions. Dashed lines are for amorphous polymers, while the shaded area is for semi-crystalline polymers. Zone A is the region where both diffusion and hydrolysis control the erosion rate, Zone B is the non-catalyzed hydrolysis controlled (fast diffusion zone), Zone C is slow diffusion, and in Zone D hydrolysis is fast and non-catalyzed (from Han and Pan, 2009). Reproduced with permission.

crystallinity that accounts for phase changes within the polymer during degradation (Wang et al., 2008). The time dependent degree of crystallinity X_c was expressed using Avrami's theory modified to account for the short incubation time for bioerodible polymers:

$$\frac{dX_c}{dX_{ext}} = [1 - X_c]^{\lambda} \tag{10}$$

Here X_{ext} is the crystalline phase extended volume fraction and λ is an impingement parameter (Han and Pan, 2009). Avrami's theory also accounts for a number of crystallization nuclei, N, whose modified governing equation was given by

$$dN = -\xi N\, dt - \frac{N}{1 - X_c} dX_c + \frac{N_0}{C_{e0}} dR \tag{11}$$

Here ξ represents the probability of a nuclei becoming active during time dt, R is the moles of monomer produced per volume of semicrystalline polymer, and C_{e0} is the initial ester bond concentration (Han and Pan, 2009). Among the non-dimensional governing equations was that for ester bond concentration:

$$\frac{d\bar{C}_e}{d\bar{t}} = -\frac{d\bar{R}}{d\bar{t}} - \frac{1}{1 - X_c}\frac{dX_c}{d\bar{t}} \tag{12}$$

The final term couples crystallization to biodegradation.

The model has good agreement with experimental data for PLGA erosion for both weight loss and degree of crystallinity for varying initial degrees of crystallinity. Fig. 8 shows a biodegradation map that emphasizes the phenomena which control biodegradation for different values of the dimensionless parameters $\bar{D}_0$ and $\bar{k}_1$, where $\bar{D}_0$ is the ratio of diffusion and catalyzed degradation rates and $\bar{k}_1$ is the ratio of uncatalyzed and catalyzed hydrolysis reactions (Han and Pan, 2009). The authors point out that a limitation of this model is that during the latter part of the degradation the crystalline fraction of the polymer is essentially one, and thus some of the governing equations may be invalid. The model also does not account for polymer weight loss and greatly simplifies the treatment of polymer chain length.

Copolymers are frequently used as biomaterials, especially in degradable drug delivery devices, because their degradation rates can easily be tuned by varying copolymer composition. Since copolymer composition is a design parameter for such devices, it is important to have an erosion model which accurately predicts its effect on the degradation and erosion processes. When two different monomers, *A* and *B*, are used in bioerodible copolymers, there are three different types of bonds: *A*–*A*, *A*–*B*, and *B*–*B*. All three of these may have different scission rates, and depending on the polymer type may be present in different ratios. Also, if *A* and *B* are different enough from each other, the presence of microstructure caused by phase separation may influence the polymer device make up and thus its erosion behavior. Finally, if the device is being used as a drug delivery vehicle, that drug may preferentially partition to regions with high concentrations of one of the monomer types (Shen et al., 2002). This drug partitioning, even though it may or may not affect the actual degradation rates, will certainly affect the apparent drug release kinetics.

Kipper and Narasimhan (2005) proposed an erosion model that takes into account the effect of copolymer microstructure on the overall erosion process. The model assumed that the polymer degrades at the surface of the polymer's pores, which is composed of four fractions: crystalline and amorphous regions of either type 1 or type 2 monomers (Fig. 9). This model is an expansion of an earlier model by Larobina et al. (2002), which accounted for copolymer microphase separation. Both models were developed for surface eroding polyanhydrides.

One key feature of this model is that it takes into account the fact that semicrystalline polymer degrades at different rates in its amorphous and crystalline regions, thus making crystallinity time-dependent. In addition, it accounts for the separation of the two monomers in the copolymer, which also degrade at different rates. Thus, there were essentially four different types of degradation occurring simultaneously, which were expressed by four coupled partial differential equations. For example, for amorphous polymer 1:

$$\frac{\partial f_{a1}}{\partial \tau} = -f_{a1} + [(p_{aa}f_{ma1} + p_{ca}f_{mc1})\kappa_1 + (p_{aa}f_{ma2} + p_{ca}f_{mc2})\kappa_2]\phi_{a1} \tag{13}$$

Here f_{a1} is the surface area fraction of polymer type 1, p_{ij} is the probability of polymer in phase i dissolving to expose polymer in phase j, f_{mij} is the surface area fraction of monomer formed from polymer of type j in phase i, K_i is the dissolution rate for monomer i, φ_{a1} is the fraction of amorphous polymer of type 1, and τ is dimensionless time (Kipper and Narasimhan, 2005). This equation demonstrated that a polymer of a certain type (in this case amorphous polymer type 1) can be degraded into monomer but also can be exposed by the degradation of other polymers at the surface above it. Analogous expressions were presented for the other three surface fractions.

The remaining equations in the model account for monomer formation and monomer dissolution, as well as the changing pore size and porosity. Monomer is formed via polymer degradation, which was assumed to be a first order process dependent on the polymer type but not on polymer chain length. Monomer is assumed to dissolve within the pore and then diffuse out, allowing for saturation to occur under some conditions. The authors showed that an important factor that needed to be considered was that the acidic degradation products affected the local pH. One aspect that the model does not account for is the effect of acidity on degradation rate. A logical extension of this model would be to account for drug partitioning in the two polymer types, which was the case in the earlier and simpler model (Larobina et al., 2002).

Lao et al. proposed a model that characterized drug release from polymer blends (Lao et al., 2008). Although the model does not directly characterize polymer degradation, it uses information about the degradation characteristics of the two polymers in the blend (PLGA and PCL) in order to predict drug release. A heuristic approach is taken which combines effects of drug release caused by

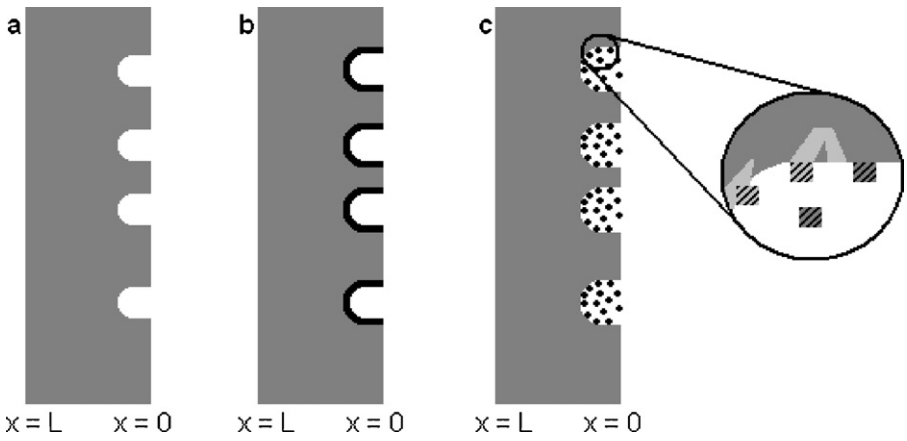

Fig. 9. Surface erosion of a tablet. Part (c) shows that monomer of one type can dissolve and diffuse away to reveal polymer of another type (shown in grey) (from Kipper and Narasimhan, 2005). Reproduced with permission.

the initial burst, diffusion, and degradation-controlled relaxation from each part of the blend.

Additionally, hydrolyzable and/or ionizable functional groups such as maleic anhydrides can be grafted onto non-degradable polymers or other degradable polymers in order to control drug release rates or to modify polymer properties (Cerbai et al., 2008; Ladaviere et al., 1999; Pan et al., 2005; Pompe et al., 2005). The phenomenological models discussed herein could be directly applied or adjusted in order to account for the erosion behavior observed in these systems.

3.2. Probabilistic models

Probability distributions can be used to model mechanistic changes in a system without an equation that accurately describes that phenomenon. This seems especially appropriate in the case of polymer erosion, because polymers are composed of a distribution of molecular weights and their linear degradation into monomers can be modeled probabilistically (Bose and Git, 2004; Grancher, 1992). These approaches to modeling erosion usually involve dividing the two- or three-dimensional system into discrete volume units or "cells" representing different species which change properties based on randomly distributed "lifetimes". Also, probabilistic models are ideal for situations where polydispersity and polymer chain length are important considerations.

It has been noted that probabilistic approaches such as the cellular automata (CA) method have traditionally been used to model surface-eroding polymers (Arifin et al., 2006). This was the case in most of the models by both Göpferich and Zygourakis from the 1990s, although bulk erosion was also modeled (Gopferich, 1997; Gopferich et al., 1995; Gopferich and Langer, 1993, 1995a,b; Zygourakis, 1989, 1990; Zygourakis and Markenscoff, 1996). Zygourakis used the Monte Carlo (MC) approach to model erosion, but did not take into account the effects of diffusion. Göpferich combined the probabilistic MC approach for degradation with a phenomenological model for diffusion, and was able to combine these and account for a variety of phenomena.

Siepmann et al. modeled polymer degradation using a MC technique similar to that used by Göpferich with the intent to model drug release from polymer microspheres (Siepmann et al., 2002). Taking advantage of the planes of symmetry within the spherical geometry, they divided the sphere into cells (Fig. 10) with random "lifetimes" given by:

$$t_{lifetime} = t_{average} + \frac{(-1)^{\varepsilon}}{\lambda} \ln\left(1 - \frac{\varepsilon}{100}\right) \quad (14)$$

Here $t_{average}$ is the average lifetime of the pixels, λ is a constant specific to the polymer, and ε is a random integer between 0 and 99 (Siepmann et al., 2002). Polymer crystallinity was accounted for by the characteristic constant in the MC equation. Drug diffusion based on resulting polymer porosity was modeled using Fick's second law and varying rates of drug dissolution were accounted for (Siepmann et al., 2002).

This model also considered the effect of γ-irradiation on drug release, updating the model for a variety of geometries (Faisant et al., 2003). The authors also proposed a simplified model based on polymer degradation kinetics of pseudo-first order and linear drug concentration gradients.

Bertrand et al. (2007) proposed a model using the CA method to predict drug diffusion from bioerodible polymer microspheres. Five "states" of the cells were identified: polymer, solvent, pores, and solid and dissolved drug. In their model, the "life expectancy" of the polymer cell as well as how many neighboring solvent cells it had were considered to compute its non-erosion probability. However, this model does not adequately match experimental results in cases where bulk detachment and surface erosion are present.

Yu et al. (2008) proposed a three dimensional extension of the CA models of polymer erosion by Zygourakis (Zygourakis, 1989; Zygourakis and Markenscoff, 1996). The model was applied to a multi-layer device for drug delivery, extending the 3D MC simulations from Gopferich and Langer (1995b) to a more complex geometry. In this model, cells were considered to either be drug, solvent, or polymer. Polymer cells were either in the crystalline or amorphous status, which accounted for the fact that crystalline polymer degraded more slowly than amorphous polymer. Crystallinity of the polymer cell was determined probabilistically based on the degree of crystallinity as an input parameter. Drug release from the cells was determined based on the number of drug cells containing dissolved drug. While this model is a useful extension of the other CA models, it does not account for the diffusional aspects of drug release.

It is worth noting the probabilistic approach to porosity used by Rothstein et al. (2008), who accounted for observed drug release kinetics from polymer matrices by the growth of pores in the bulk. The growing porosity in the polymer was modeled as a cumulative normal distribution function, so that the porosity, ε, is a function of time, t:

$$\varepsilon(t) = \frac{1}{2}\left[erf\left(\frac{t-\bar{\tau}}{\sqrt{2\sigma^2}}\right) + 1\right] \quad (15)$$

Here $\bar{\tau}$ and σ^2 are the mean and variance, respectively, of time for pore formation (Rothstein et al., 2008). This model demonstrated the strong relationship between the initial burst and the

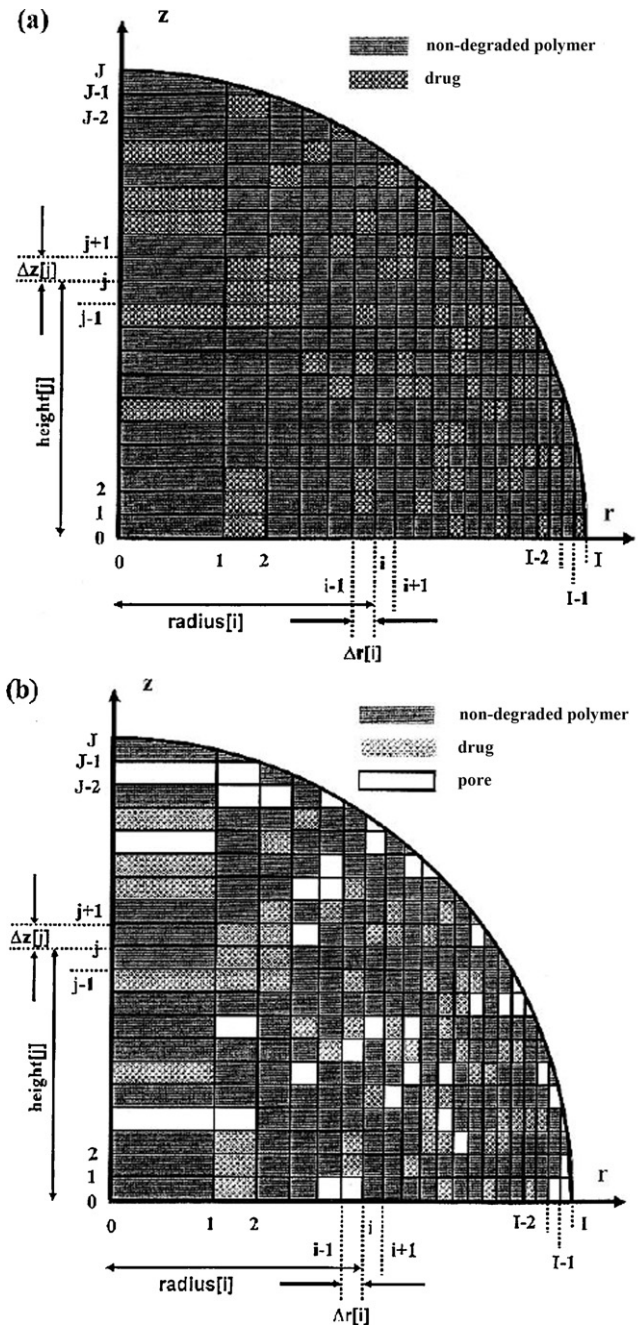

Fig. 10. Monte Carlo approach to modeling polymer erosion: (a) before and (b) during drug release (from Siepmann et al., 2002). Reproduced with permission.

drug located just inside the device surface (Rothstein et al., 2008). However, this model is limited in that it requires the specification of pore formation and release characteristics that must be determined experimentally.

3.3. Empirical models

Several empirical approaches have been employed to model polymer erosion, and often they are the first step toward a model (Hopfenberg, 1976). For example, a fit based on empirical data has demonstrated correlations for critical length scales for bulk erosion (von Burkersroda et al., 2002). Also, a heuristic approach to using empirical data was used to model drug release from polymer blends (Lao et al., 2008). One critical aspect of empirical models is their ability to discern which factors are most important. For example, drug release data from polyanhydride copolymers were fitted with two exponential functions that contained five parameters (Li et al., 2011). It was determined that the most important parameters controlling drug release in this case were the frequency of non-conjugated backbone ester groups, aromatic rings, and CH_2 bonds in the polymers.

While empirical models are in general reliable within a system that has been studied experimentally and are easy to apply, they are not applicable to all systems and conditions. Additionally, accurate empirical models usually require an input of a large number of parameters and as a result contain little information about the actual underlying mechanisms.

4. Conclusions and future outlook

There are numerous polymer erosion models with varying degrees of sophistication that have been used to accurately predict the degradation of synthetic polymers commonly used as drug carriers. This knowledge aids in the efficient and rational design of biomaterials, as it reduces the need for some initial experimental testing and can provide key directions in choosing an appropriate material for a specific application.

In this review, these models have been broadly classified as phenomenological, probabilistic, or empirical. These modeling approaches have been applied to characterize the erosion behavior of degradable polymers of various geometries (tablets, films, and particles), and many of them are coupled with drug release. While many of the modeling approaches are becoming increasingly detailed as our understanding of polymer erosion evolves, there is also the need for simpler models that are more easily solved and applied to systems. This conflicting need has been expressed in several models which contain two closely related models, one of which is a simplification of a more involved approach. Even as attempts are made to account for all of the phenomena occurring within an eroding polymer device, the models can only focus on a finite number of mechanistic aspects of the system in order to be solvable and for the parameters to have physical significance.

While mathematical modeling of polymer erosion has advanced in the past decades, there are several directions for possible future progress. Most of the models described herein were motivated for use in biological applications. Thus, it would be important to take into account the effects of biological conditions on degradation and erosion. For example, erosion in the presence of a buffered solution like blood would change the rate of polymer degradation for acid- and base-catalyzed hydrolysis (Zolnik and Burgess, 2007), and could also change monomer solubility. The presence of enzymatically catalyzed degradation reactions (Gan et al., 1999) could also be incorporated.

In most cases, the motivation for modeling polymer erosion is to predict drug release kinetics in a biological environment. While there are many models described in this review that already consider drug release, this process is complicated enough that it could be modeled much more robustly. For example, many current drugs are proteins or polypeptides (Determan et al., 2004). The conformational stability of a protein or polypeptide during release is related to the efficacy and functionality of the drug, and it would be important to model conformational changes upon release from an eroding polymer. Accounting for all of the factors involved in this process such as pH, solubility, and temperature would be a challenging yet valuable addition to the current models for drug release.

Due to the wide variety of factors involved in the process of polymer erosion that occur on vastly different scales, there is a need to integrate microstructure and transport effects more rigorously. Currently, most models examine closely only one of those two types

of phenomena. Combining two models that account for different phenomena would be one way to overcome this gap.

With many complex models available, there is a strong need for more direct experimental validation. Most models are validated only by comparisons with erosion or release kinetics, which are the summation of a number of detailed phenomena that need to be validated individually. The use of data from techniques such as electron paramagnetic resonance imaging, small-angle X-ray scattering, and solid state NMR would be helpful for determining dynamic polymer microstructure during erosion (Kipper et al., 2004, 2005a,b; Mader et al., 1997). Such data need to be utilized to compare model predictions, even if the predictions are qualitative to begin with.

Finally, these models can be extended to polymers that undergo degradation mechanisms other than backbone hydrolysis. For example, in tissue engineering scaffolds, polymers with biodegradable crosslinks are used to add mechanical strength during erosion and to control the rate of erosion (Weiner et al., 2007). This can motivate the development of models to study the effect of polymer crosslinking on degradation kinetics.

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References

Antheunis, H., van der Meer, J.C., de Geus, M., Heise, A., Koning, C.E., 2010. Autocatalytic equation describing the change in molecular weight during hydrolytic degradation of aliphatic polyesters. Biomacromolecules 11, 1118–1124.

Antheunis, H., van der Meer, J.C., de Geus, M., Kingma, W., Koning, C.E., 2009. Improved mathematical model for the hydrolytic degradation of aliphatic polyesters. Macromolecules 42, 2462–2471.

Arifin, D.Y., Lee, L.Y., Wang, C.H., 2006. Mathematical modeling and simulation of drug release from microspheres: implications to drug delivery systems. Adv. Drug Deliv. Rev. 58, 1274–1325.

Arosio, P., Busini, V., Perale, G., Moscatelli, D., Masi, M., 2008. A new model of resorbable device degradation and drug release—Part I: Zero order model. Polym. Int. 57, 912–920.

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.

Bertrand, N., Leclair, G., Hildgen, P., 2007. Modeling drug release from bioerodible microspheres using a cellular automaton. Int. J. Pharm. 343, 196–207.

Bose, S.M., Git, Y., 2004. Mathematical modelling and computer simulation of linear polymer degradation: simple scissions. Macromol. Theory Simul. 13, 453–473.

Cerbai, B., Solaro, R., Chiellini, E., 2008. Synthesis and characterization of functional polyesters tailored for biomedical applications. J. Polym. Sci. Part A: Polym. Chem. 46, 2459–2476.

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

Determan, A.S., Graham, J.R., Pfeiffer, K.A., Narasimhan, B., 2006a. The role of microsphere fabrication methods on the stability and release kinetics of ovalbumin encapsulated in polyanhydride microspheres. J. Microencapsul. 23, 832–843.

Determan, A.S., Trewyn, B.G., Lin, V.S.Y., Nilsen-Hamilton, M., Narasimhan, B., 2004. Encapsulation, stabilization, and release of BSA-FITC from polyanhydride microspheres. J. Control. Release 100, 97–109.

Determan, A.S., Wilson, J.H., Kpper, M.J., Wannemuehler, M.J., Narasimhan, B., 2006b. Protein stability in the presence of polymer degradation products: consequences for controlled release formulations. Biomaterials 27, 3312–3320.

Domb, A.J., Langer, R., 1987. Polyanhydrides. 1. Preparation of high molecular weight polyanhydrides. J. Polym. Sci. Part A: Polym. Chem. 25, 3373–3386.

Faisant, N., Siepmann, J., Richard, J., Benoit, J.P., 2003. Mathematical modeling of drug release from bioerodible microparticles: effect of gamma-irradiation. Eur. J. Pharm. Biopharm. 56, 271–279.

Gan, Z., Yu, D., Zhong, Z., Liang, Q., Jing, X., 1999. Enzymatic degradation of poly(ε-caprolactone)/poly(DL-lactide) blends in phosphate buffer solution. Polymer 40, 2859–2862.

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

Gopferich, A., 1997. Polymer bulk erosion. Macromolecules 30, 2598–2604.

Gopferich, A., Langer, R., 1993. Modeling of polymer erosion. Macromolecules 26, 4105–4112.

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

Gopferich, A., Langer, R., 1995b. Modeling of polymer erosion in 3 dimensions—rotationally symmetrical devices. AIChE J. 41, 2292–2299.

Gopferich, A., Shieh, L., Langer, R., 1995. Aspects of polymer erosion. Polym. Med. Pharm. 394, 155–160.

Grancher, G., 1992. A stochastic model for oligomers produced by degradation of linear polymers. In: Vert, M., Feijen, J., Albertsoon, A., Scott, G., Chiellini, E. (Eds.), Biodegradable Polymers and Plastics. The Royal Society of Chemistry, Cambridge, England, pp. 191–199.

Gunatillake, P.A., Adhikari, R., 2003. Biodegradable synthetic polymers for tissue engineering. Eur. Cells Mater. 5, 1–16.

Han, X.X., Pan, J.Z., 2009. A model for simultaneous crystallisation and biodegradation of biodegradable polymers. Biomaterials 30, 423–430.

Heller, J., Barr, J., Ng, S.Y., Shen, H.R., Schwach-Abdellaoui, K., Emmahl, S., Rothen-Weinhold, A., Gurny, R., 2000. Poly(ortho esters)—their development and some recent applications. Eur. J. Pharm. Biopharm. 50, 121–128.

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.

Hopfenberg, H.B., 1976. Controlled release from bioerodible slabs, cylinders, and spheres. In: ACS Symp. Ser., pp. 26–32.

Kipper, M.J., Hou, S.S., Seifert, S., Thiyagarajan, P., Schmidt-Rohr, K., Narasimhan, B., 2005a. Nanoscale morphology of polyanhydride copolymers. Macromolecules 38, 8468–8472.

Kipper, M.J., Narasimhan, B., 2005. Molecular description of erosion phenomena in biodegradable polymers. Macromolecules 38, 1989–1999.

Kipper, M.J., Seifert, S., Thiyagarajan, P., Narasimhan, B., 2004. Understanding polyanhydride blend phase behavior using scattering, microscopy, and molecular simulations. Polymer 45, 3329–3340.

Kipper, M.J., Seifert, S., Thiyagarajan, P., Narasimhan, B., 2005b. Morphology of polyanhydride copolymers: time-resolved small-angle X-ray scattering studies of crystallization. J. Polym. Sci. Part B: Polym. Phys. 43, 463–477.

Lao, L.L., Venkatraman, S.S., Peppas, N.A., 2008. Modeling of drug release from biodegradable polymer blends. Eur. J. Pharm. Biopharm. 70, 796–803.

Ladaviere, C., Delair, T., Domard, A., Pichot, C., Mandrand, B., 1999. Covalent immobilization of biological molecules to maleic anhydride and methyl vinyl ether copolymers—a physico-chemical approach. J. Appl. Polym. Sci. 71, 927–936.

Larobina, D., Mensitieri, G., Kipper, M.J., Narasimhan, B., 2002. Mechanistic understanding of degradation in bioerodible polymers for drug delivery. AIChE J. 48, 2960–2970.

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

Lemaire, V., Belair, J., Hildgen, P., 2003. Structural modeling of drug release from biodegradable porous matrices based on a combined diffusion/erosion process. Int. J. Pharm. 258, 95–107.

Leong, K.W., Kost, J., Mathiowitz, E., Langer, R., 1986. Polyanhydrides for controlled release of bioactive agents. Biomaterials 7, 364–371.

Li, X., Petersen, L., Broderick, S., Narasimhan, B., Rajan, K., 2011. Identifying factors controlling protein release from combinatorial biomaterial libraries via hybrid data mining methods. ACS Comb. Sci., doi:10.1021/co10019d.

Lopac, S.K., Torres, M.P., Wilson-Welder, J.H., Wannemuehler, M.J., Narasimhan, B., 2009. Effect of polymer chemistry and fabrication method on protein release and stability from polyanhydride microspheres. J. Biomed. Mater. Res. Part B 91B, 938–947.

Lyu, S., Sparer, R., Untereker, D., 2005. Analytical solutions to mathematical models of the surface and bulk erosion of solid polymers. J. Polym. Sci. Part B: Polym. Phys. 43, 383–397.

Mader, K., Bacic, G., Domb, A., Elmalak, O., Langer, R., Swartz, H.M., 1997. Noninvasive in vivo monitoring of drug release and polymer erosion from biodegradable polymers by EPR spectroscopy and NMR imaging. J. Pharm. Sci. 86, 126–134.

Mahadevan, R., Smith, L., 2007. A mechanistic model describing the degradation of polymers. J. Polym. Environ. 15, 75–80.

Pan, J., Wang, Y.L., Qin, S.H., Zhang, B.B., Luo, Y.F., 2005. Grafting reaction of poly(D,L)lactic acid with maleic anhydride and hexanediamine to indroduce more reactive groups in bulk. J. Biomed. Mater. Res. Part B 74B, 476–480.

Perale, G., Arosio, P., Moscatelli, D., Barri, V., Muller, M., Maccagnan, S., Masi, M., 2009. A new model of resorbable device degradation and drug release: transient 1-dimension diffusional model. J. Control. Release 136, 196–205.

Pompe, T., Renner, L., Grimmer, M., Herold, N., Werner, C., 2005. Functional films of maleic anhydride copolymers under physiological conditions. Macromol. Biosci. 5, 890–895.

Prabhu, S., Hossainy, S., 2007. Modeling of degradation and drug release from a biodegradable stent coating. J. Biomed. Mater. Res. Part A 80A, 732–741.

Rothstein, S.N., Federspiel, W.J., Little, S.R., 2008. A simple model framework for the prediction of controlled release from bulk eroding polymer matrices. J. Mater. Chem. 18, 1873–1880.

Rothstein, S.N., Federspiel, W.J., Little, S.R., 2009. A unified mathematical model for the prediction of controlled release from surface and bulk eroding polymer matrices. Biomaterials 30, 1657–1664.

Shen, E., Kipper, M.J., Dziadul, B., Lim, M.K., Narasimhan, B., 2002. Mechanistic relationships between polymer microstructure and drug release kinetics in bioerodible polyanhydrides. J. Control. Release 82, 115–125.

Shen, E., Pizsczek, R., Dziadul, B., Narasimhan, B., 2001. Microphase separation in bioerodible copolymers for drug delivery. Biomaterials 22, 201–210.
Siepmann, J., Faisant, N., Benoit, J.P., 2002. A new mathematical model quantifying drug release from bioerodible microparticles using Monte Carlo simulations. Pharm. Res. 19, 1885–1893.
Siepmann, J., Gopferich, A., 2001. Mathematical modeling of bioerodible, polymeric drug delivery systems. Adv. Drug Deliv. Rev. 48, 229–247.
Soares, J.S., Zunino, P., 2010. A mixture model for water uptake, degradation, erosion and drug release from polydisperse polymeric networks. Biomaterials 31, 3032–3042.
Tamada, J., Langer, R., 1992. The development of polyanhydrides for drug delivery applications. J. Biomater. Sci. Polym. Ed. 3, 315–353.
Thombre, A.G., Himmelstein, K.J., 1984. Modeling of drug release kinetics from a laminated device having an erodible drug reservoir. Biomaterials 5, 250–254.
Thombre, A.G., Himmelstein, K.J., 1985. A simultaneous transport-reaction model for controlled drug delivery from catalyzed bioerodible polymer matrices. AIChE J. 31, 759–766.
Torres, M.P., Determan, A., Mallapragada, S.K., Narasimhan, B., 2006. Polyanhydrides. In: Lee, S. (Ed.), Encyclopedia of Chemical Processing. Marcel Dekker, New York, pp. 2247–2257.
von Burkersroda, F., Schedl, L., Gopferich, A., 2002. Why degradable polymers undergo surface erosion or bulk erosion. Biomaterials 23, 4221–4231.
Wang, Y., Pan, J.Z., Han, X.X., Sinka, C., Ding, L.F., 2008. A phenomenological model for the degradation of biodegradable polymers. Biomaterials 29, 3393–3401.
Weiner, A.A., Shuck, D.M., Bush, J.R., Shastri, V.P., 2007. In vitro degradation characteristics of photocrosslinked anhydride systems for bone augmentation applications. Biomaterials 28, 5259–5270.
Yu, R.X., Chen, H.L., Chen, T.N., Zhou, X.Y., 2008. Modeling and simulation of drug release from multi-layer biodegradable polymer microstructure, in three dimensions. Simul. Model. Pract. Theory 16, 15–25.
Zhang, M.P., Yang, Z.C., Chow, L.L., Wang, C.H., 2003. Simulation of drug release from biodegradable polymeric microspheres with bulk and surface erosions. J. Pharm. Sci. 92, 2040–2056.
Zolnik, B.S., Burgess, D.J., 2007. Effect of acidic pH on PLGA microsphere degradation and release. J. Control. Release 122, 338–344.
Zygourakis, K., 1989. Discrete simulations and bioerodible controlled release systems. Polym. Prep. ACS 30, 456–457.
Zygourakis, K., 1990. Development and temporal evolution of erosion fronts in bioerodible controlled release devices. Chem. Eng. Sci. 45, 2359–2366.
Zygourakis, K., Markenscoff, P.A., 1996. Computer-aided design of bioerodible devices with optimal release characteristics: a cellular automata approach. Biomaterials 17, 125–135.