A simple model framework for the prediction of controlled release from bulk eroding polymer matrices

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A broadly applicable model for predicting controlled release could eliminate the need for exploratory, *in vitro* experiments during the design of new biodegradable matrix-based therapeutics. We have developed a simple mathematical model that can predict the release of many different types of agents from bulk eroding polymer matrices without regression. New methods for deterministically calculating the magnitude of the initial burst and the duration of the lag phase (time before Fickian release) were developed to enable the model's broad applicability. To complete the model's development, such that predictions can be made from easily measured or commonly known parameters, two correlations were developed by fitting the fundamental equations to published controlled release data. To test the model, predictions were made for several different biodegradable matrix systems. In addition, varying the readily attainable parameters over rational bounds shows that the model predicts a wide range of therapeutically relevant release behaviors.

Introduction

Since polymer matrices were first used to protect and deliver drugs,[1] controlled release technology has expanded considerably. At present, a wide variety of biodegradable polymers, encapsulation techniques, and matrix geometries have been employed to deliver agents ranging from small molecule chemotherapeutics to protein vaccines.[2–4] The wide applicability of polymer matrix-based controlled release technology allows for the development of numerous unique therapeutics, each with the potential to improve patient quality of life through increased patient compliance and more effective administration.[5]

The methods for developing specific therapeutics have, however, changed little since the field of controlled release first began.[1] Although research on controlling the delivery of numerous drugs now abounds, formulating each new therapeutic still requires months of iterative and costly *in vitro* testing to target a suitable drug release profile.[6,7] Studying a broad array of literature on bulk eroding polymer matrices shows that this profile can range from linear to four-phase patterns with (1) an initial burst, (2) a lag phase, (3) a secondary burst and (4) a terminal release phase.[8–21] Further, reports studying these systems debate which, if any one, property, such as the polymer degradation mechanism, matrix crystallinity or others, is the most influential for controlling release.[22]

Spurred by a desire to hasten the development of new therapeutics, many efforts have been made to model degradation-controlled release profiles based on the physical properties of the matrix, drug, and polymer.[22–29] In one of the first models describing release from a biodegradable polymer matrix, Thombre and Himmelstein used finite element mathematics to compute release governed by Fick's second law.[24] In an effort to account for the effect of matrix erosion on release, an effective diffusivity proportional to the extent polymer degradation was incorporated into the model. Later work by Saltzman and Langer used percolation theory and *in vitro* release studies to demonstrate that protein diffusion through non-biodegradable, porous polymer matrices was accurately described by Fick's second law with an effective diffusivity dependent on the matrix porosity.[25]

More recently, stochastic methods have been used to describe a porosity that increases with time in biodegradable systems. Göpferich and Langer employed these methods to calculate the release of a water soluble small molecule from polyanhydride disks that were assumed to degrade solely through surface erosion (the rate of hydrolysis being much faster than the diffusion of water).[26] While varying two parameters produced an accurate description of pore formation, significant deviations were reported during comparisons to release data.[26] Using a similar approach, Siepmann *et al.* described the release of a low molecular weight chemotherapy agent from bulk-eroding PLGA microspheres.[27] To improve the description of drug egress, equations governing porosity dependant diffusion of agent were added to the Monte Carlo simulation. A two parameter regression confirms that fluorouracil release data can be fitted with an R^2 of 0.99.[27] Together, these models show that stochastic simulations can represent pore growth in biodegradable matrices and that the regression of Fick's second law extends this description to small molecule release.

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Taking a different approach, Batycky *et al*. recently developed a model based upon differential equations to describe burst–lag–burst type release from polyester microparticles.[28] This model was validated for the release of several different proteins from 50 : 50 PLGA or PLA microspheres and, in one case, predicted up to 85% of release. While the piecewise functions used in this model can predict release without regression, values for five formulation-specific parameters that can only be acquired through careful observation of release data[28] are required to make these predictions. Furthermore, the initial burst release in this model was attributed to the desorption of agent from the matrix surface,[28] a mechanism which has recently been disputed.[15,30]

Each of the aforementioned models[22–29] takes steps towards enabling the rational design of biodegradable controlled release matrices. In order to supplant the need for exploratory *in vitro* release experiments in the design of controlled release therapeutics, though, a model must satisfy three requirements. 1) The model must apply to a wide range of agents because each new therapeutic must deliver a unique drug.[2,4] 2) The release of such agents must be described entirely from readily attainable design parameters, thereby allowing researchers to acquire specifications for a matrix from a given release profile or dosing schedule.[3] 3) The model must be robust enough to capture the breath of release behaviors that have been documented for the system in question, in this case, bulk eroding polymer matrices.[8–21]

The present work documents the development and implementation of a new controlled release model designed to meet the criteria specified above. This model uses new methods to describe the release of water-soluble agents that are discretely encapsulated in bulk eroding, polymer matrices and that dissolve rapidly, relative to the time scale of release. In addition to new fundamental equations, the model includes two correlations that enable predictions with knowledge of just five parameters, all commonly known or easily measured prior to release. These parameters are microsphere radius R_p, occlusion radius R_{occ}, polymer degradation rate kC_w, polymer initial molecular weight M_{wo}, and agent molecular weight M_{wA}. As a test of the model, regression-free predictions were compared to multiple sets of published experimental data. Furthermore, by varying the matrix-specific parameters, we explored the range of attainable dosing schedules. Finally, regression to a desired dosing schedule will generate a set of matrix design parameters to guide the fabrication of a matching controlled release therapeutic.

Model development

Paradigm

Consider an initially uniform matrix of known geometry comprised of a biodegradable polymer, such as a polyester or polyanhydride, and with randomly distributed entrapped release agent (*e.g.* drug of concentration C_{Ao}), loaded below its percolation threshold (such that agent remains discrete) to ensure matrix mediated release. This agent can either be dispersed as crystals (such as in the case of uniformly loaded systems, *e.g.* single emulsion-based particulates) or housed as a solution in occlusions (*e.g.* double emulsion-based particulates).[3] At time zero, an aqueous reservoir begins to hydrate the matrix, a process which happens quickly for the bulk eroding polymers matrices considered herein.[28,31] As the matrix hydrates, encapsulated agent adjacent to the matrix surface (with a direct pathway for egress) diffuses into the reservoir in a phase typically dubbed "the initial burst" (Fig. 1, phase 1). The relative size of the occlusion (R_{occ}) occupied by the encapsulated agent is proportional to the magnitude of the initial burst as illustrated in Fig. 2.

As the initial burst release commences, degradation of the polymer begins, increasing chain mobility and effectively leading to the formation of pores in the polymer matrix[32] (Fig. 1, phase 2). Although a number of mechanisms have been proposed for this heterogeneous degradation profile, one hypothesis, which has been reinforced by experimental data, is based upon regions of varying amorphicity and crystallinity.[33–35] It is believed that

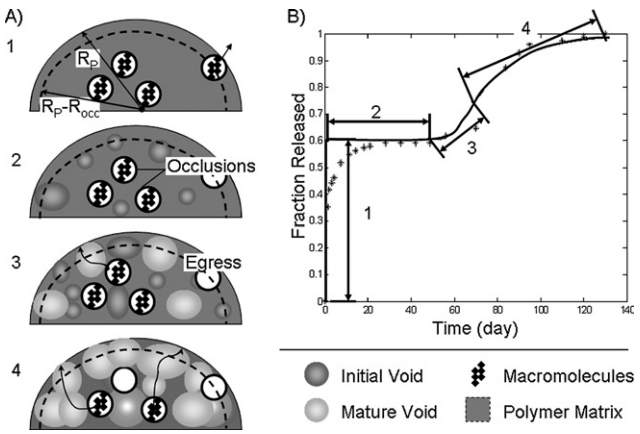

Fig. 1 Schematic depiction of a model paradigm that can account for four-phase release. A) Cross section diagrams depicting the four phases of release for a double emulsion microparticle with agent encapsulated heterogeneously in occlusions. Initially, agent abutting the matrix surface is released (1). The remaining agent requires the growth and coalescence of pores for further egress (2–4). B) Release profile for macromolecular drug encapsulated in biodegradable polymer matrix with four phases of release labeled. The numbers associated with each cross section diagram (A) indicate which phase of the release profile is illustrated. These phases are 1) initial burst, 2) lag phase, 3) secondary burst and 4) final release.

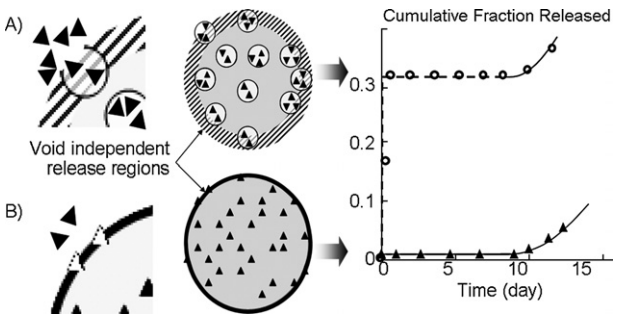

Fig. 2 Schematic depiction of the initial burst as it relates to occlusion size. A) The double emulsion particle contains large occlusions filled with drug solution and produces a significant initial burst. B) The more uniformly loaded (*e.g.* single emulsion particle, melt cast matrix) contains small granules of drug and has minimal initial release.

amorphous regions of polymer erode first, leaving behind pores (as shown using scanning electron microscopy).[32] These pores appear to be essential for subsequent release[36] (Fig. 1, phase 3).

With the cumulative growth and coalescence of these pores, agents are able to diffuse towards the surface of a polymer matrix that would otherwise be too dense to allow their passage[36] (Fig. 1, phase 4). Thus, a pore is defined as a region of polymer matrix with an average molecular weight low enough to allow the release of encapsulated agent. (This is in contrast to the occlusion, which is defined as a region occupied by dissolved or solid agent, marked by the *absence* of polymer matrix.) Further, the molecular weight associated with release may vary for each encapsulated agent type (small molecule, peptide, protein, *etc.*), leading to a size-dependent restriction for agent egress.

With a size-dependent restriction on egress established, the degradation controlled release of any encapsulated agent can only occur when the following four conditions are satisfied. 1) The release agent must be present in the polymer matrix. 2) A pore must encompass the release agent. 3) That release agent must be able to diffuse through the encompassing pore. 4) The pore must grow and coalesce with others to create a pathway for diffusion to the surface.

Equations

Agent concentration within a matrix (such a microsphere, rod, or thin film) can be calculated from Fick's second law (Equation 1) for any point in time (t) or space (r), provided that the agent is not generated or consumed in any reactions while within the matrix.[23–25,27]

$$\frac{\partial C_A}{\partial t} = \nabla\left(D_{eff}\nabla C_A\right) \tag{1}$$

where D_{eff} is an effective diffusivity term. Integrating C_A/C_{Ao} over the entire matrix volume yields the cumulative fraction of agent retained in the matrix ($P(t)$) (Equation 2).

$$P(t) = V^{-1}\int C_A/C_{Ao}\mathrm{d}V \tag{2}$$

In turn, the cumulative fraction of agent released ($R(t)$), a metric commonly used to document formulation performance, is simply (Equation 3):

$$R(t) = 1 - P(t) \tag{3}$$

At the center point, line, or plane of the matrix ($r = 0$) symmetry conditions are defined such that $\mathrm{d}C_A/\mathrm{d}r = 0$. At the matrix surface ($r = R_p$) perfect sink conditions are specified. A boundary also exists at a depth of R_{occ} in from the matrix surface ($r = R_p - R_{occ}$) where continuity conditions are defined. In the subdomain from R_p to $R_p - R_{occ}$ (terminating one occlusion radius in from the particle surface), agent is subject to the initial release, such that D_{eff} is simply a constant (D), reflecting the movement of agent through the hydrated occlusions abutting the matrix surface. In the subdomain from 0 to $R_p - R_{occ}$, agent is subject to pore-dependent release, such that $D_{eff} = D\varepsilon$ where D is the diffusivity of the agent through the porous matrix and ε is the matrix porosity.

For a system of like matrices, such as microspheres or sections in a thin film, that degrade randomly and heterogeneously, the accessible matrix porosity is simply a function of time as a discrete pore has, on average, an equal probability of forming at any position in the polymer matrix. Hence, the time until pore formation can be calculated from the degradation of the polymer matrix, as any differential volume containing a pore would have a lower average molecular weight than its initial value. Assuming that the polymer degradation rate is normally distributed,[34] the induction time for pore formation will also follow a normal distribution. As this pore formation is cumulative, the time-dependent matrix porosity ($\varepsilon(t)$) can be described with a cumulative normal distribution function (Equation 4).

$$\varepsilon(t) = \frac{1}{2}\left[erf\left(\frac{t-\bar{\tau}}{\sqrt{2\sigma^2}}\right) + 1\right] \tag{4}$$

In this equation, $\bar{\tau}$ is the mean time for pore formation and σ^2 is the variance in time required to form pores.

Implementation

Calculating $\varepsilon(t)$. Calculating the cumulative normal induction time distribution ($\varepsilon(t)$) requires values for $\bar{\tau}$ and σ^2. For polymers that obey a first order degradation rate expression, the mean time for pore formation ($\bar{\tau}$) can be determined as follows:

$$\bar{\tau} = \frac{-1}{kC_w}\ln\left|\frac{M_{wr}}{M_{wo}}\right| \tag{5}$$

where kC_w is the average pseudo-first order degradation rate constant for the given polymer type, M_{wo} is the initial molecular weight of the polymer, and we define M_{wr} as the average polymer molecular weight in a differential volume of matrix that permits the diffusion of the encapsulated agent. For blended polymer matrices, the value for $\bar{\tau}$ was calculated by averaging the results obtained from equation 5 for each component.

It is reasonable to believe that the matrix molecular weight at release (M_{wr}), which dictates how much degradation is required before release can occur, would vary depending on the size of the encapsulated agent. Macromolecules or larger agents can only diffuse through a section of matrix if it is almost entirely free of insoluble polymer chains. Hence the M_{wr} for such agents is considered the polymer solubility molecular weight (668 Da for 50 : 50 PLGA as provided by Batycky *et al.*).[28] As agent size decreases (as indicated by M_{wA}), however, egress can occur through more intact sections of polymer matrix (higher M_{wr}), as less free space is needed to allow their passage.

The distribution of polymer degradation rates ($kC_w(n)$) attributed to matrix crystallinity is needed to calculate the variance (σ^2) in the induction time distribution for pore formation ($\varepsilon(t)$).[33] To determine $kC_w(n)$, the first order degradation rate equation $M_w = M_{wo}e^{-kC_w t}$ was linearly fitted at three different time periods to published degradation data for the desired hydrolysable polymer. Fitting the initial slope of the degradation profile provides the degradation rate constant of amorphous polymer as degradation occurs faster in amorphous regions of the matrix.[33] Fitting data from the final weeks of degradation produces a rate constant for the crystalline material, as amorphous regions are largely eroded by this point. Finally,

a fit of the entire degradation profile yielded a rate constant indicative of the overall morphology.

With values for $kC_w(n)$ defined, a distribution of induction times ($\tau(n)$) was calculated using equation 5. For blended polymer matrices this $\tau(n)$ includes values calculated at all component $kC_w(n)$ and M_{wo}. The standard deviation was taken for $\tau(n)$, then divided by a crystallinity-based factor and squared, yielding an adjusted variance (σ^2), which conforms with lamellar size data.

This crystallinity-based factor adjusts the probability of finding pores formed from the fastest degradation rate in $kC_w(n)$ to match the probability of finding a differential volume of matrix containing purely amorphous polymer. For all modeled cases, this differential volume is defined as a region large enough to allow the passage of a small virus or protein complex (20 nm diameter). As multiple lamellar stacks can fit into this differential volume, the probability that such a volume is purely amorphous can be calculated from of the number of stacks per differential volume and the average crystallinity of the matrix. From crystallinity data on 50 : 50 PLGA matrices,[33,34] the probability of finding a purely amorphous differential volume is calculated as 0.05%. Thus, to ensure that the probability of finding a pore formed from the fastest degradation rate in $kC_w(n)$ also equals 0.05%, the standard deviation in the induction time distribution for pore formation was adjusted by a factor of 5. Similarly, factors of 4 and 2 were calculated from crystallinity data for 75 : 25 PLGA and polyanhydride matrices, respectively.[34,37,38]

Solution and regression

With values for $\bar{\tau}$ and σ^2 selected (defining $\varepsilon(t)$), a finite element solution to equation 1 was calculated (Comsol®, v3.3) for the given matrix geometry, using default solver settings. (To decrease computation time, the matrix geometry was simplified to one dimension based on symmetry, for a sphere, or high aspect ratio, for a thin film.) The resulting concentration profiles were numerically integrated to calculate the cumulative fraction of agent released (equations 2 and 3). For validation, the numerical solutions of the model were fit to experimental data sets by varying M_{wr} and D. (It should be noted that data points charting the kinetics of the initial burst were omitted from these regressions, as the model only predicts the magnitude of this phase.) Each fit was optimized (Matlab®, R2007a) based on a minimized sum-squared error (SSE) or weighted sum-squared error (wSSE) when error bars were provided.

Validation

As derived above, values for D and M_{wr}, while not easily quantifiable, are needed to solve the fundamental model equations 1–5. Hence, to further develop the model, regressions to multiple data sets[8–21] were conducted to relate these parameters to more readily attainable system properties. For these regressions, values for the readily attainable model parameters, M_{wo} and R_p, were taken from the published data sets.[8–21] $kC_w(n)$ was calculated and averaged from several different sources[28,39–42] as described above. Data points documenting the kinetics of the initial burst were not included for fitting, as the model, in its current form, only predicts the magnitude of this phase. (This current limitation is described further in the Discussion section.) Properties for the experimental systems described by these regressions are listed in Table 1.

Predictions

To test the model, regression-free predictions were made for a variety of biodegradable matrix systems, each with published controlled release data.[16–18] Values for the parameters needed to make these predictions were all taken from the literature[16–18,21,35,39–42] and, where applicable, translated through the correlations described above. The occlusion radius (R_{occ}) was found by averaging the sizes of 10 occlusions, randomly selected from scanning-electron or fluorescence microscopy images of the microspheres.

The model's predictive capabilities were explored by specifying *a priori* conditions such as occlusion (R_{occ}) and matrix (R_p) sizes as well as the mean polymer molecular initial weight (M_{wo}) and its distribution. Specifically, occlusion size was varied from that of a matrix with a homogeneously loaded, small molecule ($R_{occ} < 1$ nm) to a larger occlusion containing drug (800 nm), as could be found in double emulsion formulation, R_p was set between 8 and 150 μm and M_{wo} was varied from 7.4 to 100 kDa. In addition, blends of common polyesters were considered such as a 2:1 ratio of 7.4 kDa 50:50 PLGA and 60 kDa PLA or a 1:1 ratio of 10 kDa and 100 kDa PLGA. To provide continuity all predictions were generated for a short peptide (900 Da) encapsulated in a spherical matrix.

Results

Validation

Solving the fundamental model equations requires values for D and M_{wr}, which are difficult to directly measure. Fitting the

Table 1 List of experimental systems used for model validation

Agent	M_{wA}/Da	Polymer	M_{wo}/kDa	R_p/μm	Ref.
Metoclopramide	297	50:50 PLGA	98	75	20
Ethacrynic ccid	303	50:50 PLGA	110	35 (film)	21
Betamethasone	392	50:50 PLGA	41.8	19.5	19
Gentamicin	477	50:50 PLGA	13.5, 36.2	133, 276	16
Leuprolide	1 209	50:50 PLGA	18, 30	20	14
Melittin	2 860	50:50 PLGA	9.5	2.15, 3.5	17
SPf66	4 700	50:50 PLGA	100	0.6	13
Insulin	5 808	50:50 PLGA	6.6, 8	1.5	10
Neurotrophic factor	12 000	50:50 PLGA	9.3	8.85	15
BSA	69 000	PSA	37	10	18

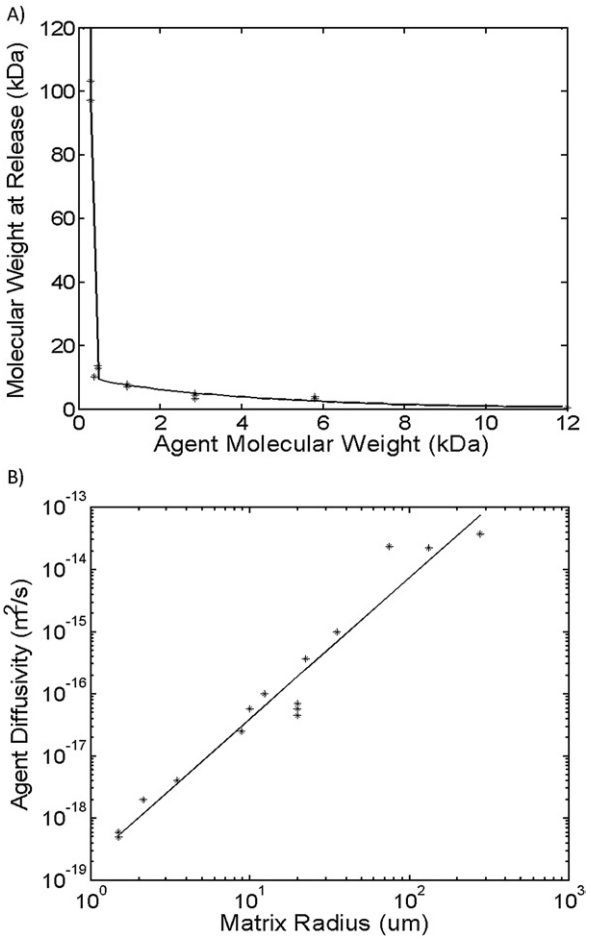

Fig. 3 Correlations for D and M_{wr} developed from regressions to experimental data as referenced in Table 1. A) Plot of polymer molecular weight at the onset of drug release (M_{wr}) *vs.* release agent molecular weight (M_{wA}). The data used to form this correlation comes from 50:50 PLGA systems. B) Plot of D *versus* R_p. The line indicates the power expression, $D = 2.071 \times 10^{-19} R_p^{2.275}$ which fits the estimations with an $R^2 = 0.95$.

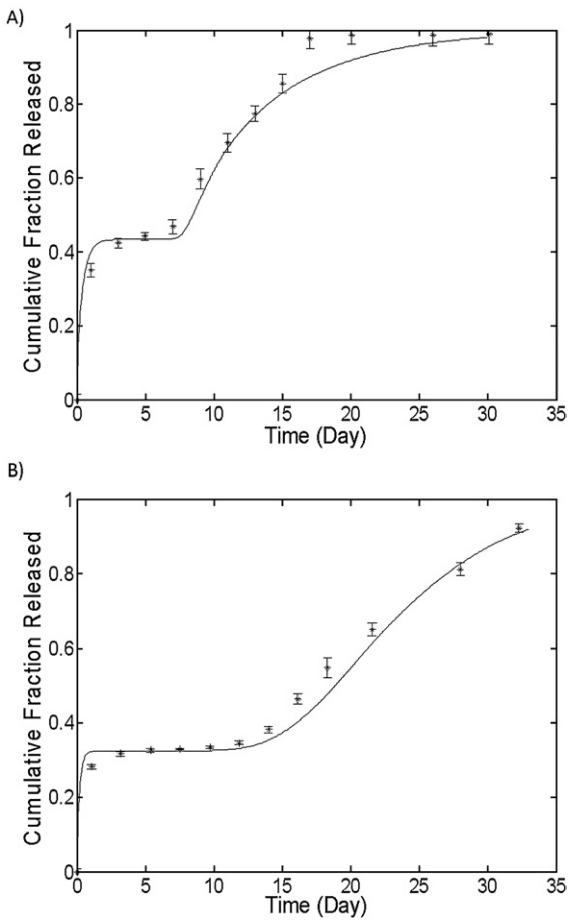

Fig. 4 Regression-free prediction for peptide release from PLGA microspheres.[17] The M_{wr} for melittin ($M_{wA} = 2.86$ kDa) was calculated at 4.68 kDa from the correlation in Fig. 3A. A) For the 9.5 kDa 50:50 PLGA microsphere ($R_p = 3.7$ μm, $R_{occ} = 0.52$ μm) D was correlated at 4.06×10^{-18} m²/s. B) The diffusivity (D) for 9.3 kDa 75:25 microspheres ($R_p = 4.5$ μm, $R_{occ} = 0.54$ μm) was calculated at 6.34×10^{-18} m²/s.

model to release data for a wide range of agents generated values for molecular weight of release (M_{wr}) that display a strong correlation with agent molecular weight (M_{wA}) as shown in Fig. 3A. Fitting a power expression ($y = ax^b$) to the plot of the regressed diffusivity values *versus* particle size data (R_p), as suggested by Sieppman *et al.*,[32] resulted in $a = 2.071 \times 10^{-19}$ and $b = 2.275$ ($R^2 = 0.95$) (Fig. 3B). These correlations compile data from multiple agents, polymer molecular weights and matrix sizes (Table 1).

Predictions

Predictions of release data. Regression-free model predictions for experimental data capture the magnitude of the initial burst, the duration of the lag phase, the onset of the secondary burst and the final release phase. Fig. 4 displays one set of predictions for peptide release from various PLGA copolymer microspheres.[17] These predictions appear to extend to polymer matrices other than PLGA, such as polyanhydride microspheres (which, if sized less than 75 μm, are theorized to be entirely hydrated for the duration of release).[31] The prediction for BSA release from 20:80 CPH:SA polyanhydride microspheres ($R_p =$ 10 μm)[18] illustrates this broader applicability (Fig. 5). In addition, release predictions have also been made for matrices formulated from a blend of two different polymers[16] (Fig. 6). All of these predictions serve to confirm that the model can describe: 1) the magnitude (but not the kinetics) of the initial burst from known occlusion size; 2) the duration of the lag phase from known polymer initial molecular weight, degradation rate and release agent molecular weight; 3) the onset of the initial burst from the matrix crystallinity derived rate distribution; and 4) the rate of subsequent release from the agent diffusivity (D) correlated to the matrix size.

Theoretical predictions. By varying the readily attainable model parameters within logical bounds for controlled release formulations, it was possible to predict behaviors ranging from a four phase release profile to zero order release (Fig. 7). Changing the ratio of occlusion size (R_{occ}) to particle size (R_p) (representing the fraction of matrix volume defined as "near the surface") affected the magnitude of the initial burst (Fig. 2). The ratio of the polymer molecular weight at release

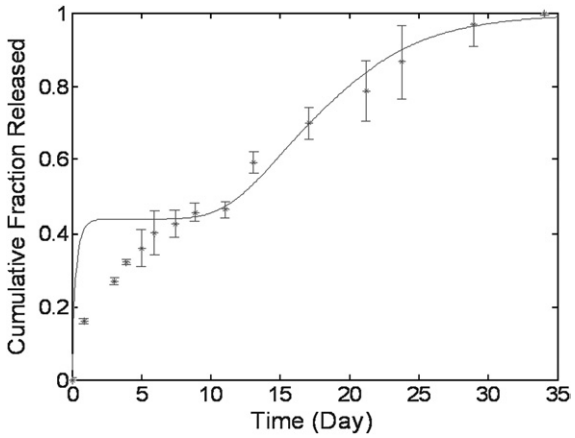

Fig. 5 Regression-free prediction for polyanhydride based microparticle release of BSA. System is composed of 20:80 CPH:SA polyanhydride (M_{wo} = 18 kDa, R_p = 10 μm and R_{occ} = 1.54 μm).[18] As the M_{wr} values presented in Fig. 3A are specific to PLGA copolymers, the M_{wr} for this prediction (940 Da) was acquired by fitting the model to data from microparticles fabricated in an identical manner using polysebacic acid (data not shown).[18] In accordance with the correlation in Fig. 3B, D was set at 3.67×10^{-17} m^2/s.

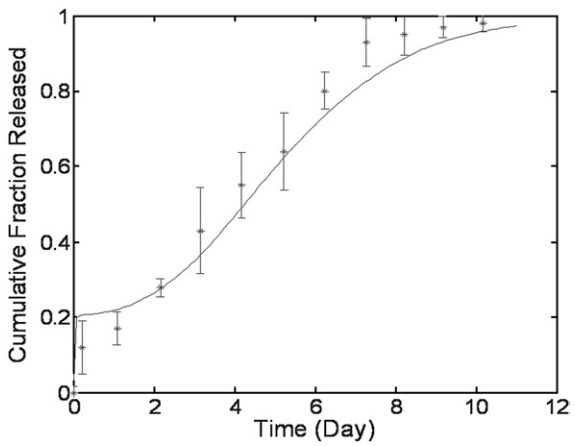

Fig. 6 Regression-free predictions compared to small molecule release data from blended polymer microspheres. Gentamicin (M_{wA} = 477 Da) was release from microspheres (R_p = 374.6 μm and R_{occ} = 24.7 μm) composed of a 1:1 blend of 13.5 and 36.2 kDa 50:50 PLGA (asterisks).[16] As the R_{occ} could not be determined from the published SEM images, the value of 24.7 μm was acquired from different sized gentamicin-loaded microspheres fabricated under like conditions.[16] The M_{wr} and D were correlated at 13.3 kDa and 1.48×10^{-13} m^2/s, respectively.

(associated with the molecular weight of the release agent) to its initial molecular weight (M_{wr}/M_{wo}) and the mean reaction rate (associated with polymer type) were collectively found to be responsible for the duration of the lag phase. Lastly, modifying the distribution of degradation rates ($kC_w(n)$) or incorporating an M_{wo} distribution (used to calculate the induction time distribution for pore growth) influenced the rate of onset for the secondary without affecting the initial burst. Tuning these parameters in combination can minimize the magnitude of the initial burst and the duration of the lag phase, while

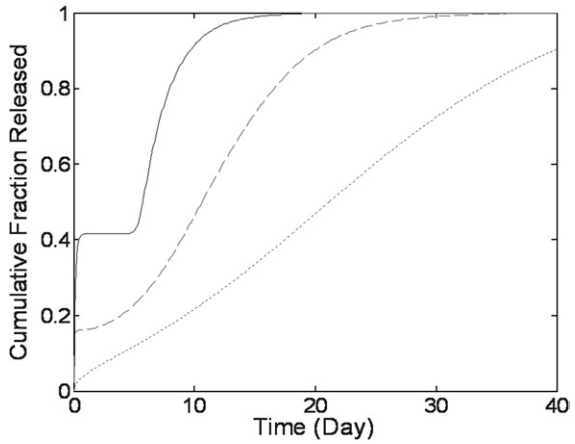

Fig. 7 Theoretical release profiles for obtained by varying model parameters: R_p, R_{occ}, M_{wo}, and $kC_w(n)$. The profiles progress from a typical four phase release pattern (solid) to zero order release (dotted). For the solid line a 13 kDa 50:50 PLGA matrix was considered with R_p = 150 μm, and R_{occ} = 23.5 μm. The dashed line was generated based on a 1:1 blend of 10 kDa and 100 kDa 50:50 PLGA (R_p = 20 μm, R_{occ} = 1 μm) For the dotted line a 2:1 ratio of 7.4 kDa 50:50 PLGA and 60 kDa PLA was considered in a single emulsion matrix with R_p = 8 μm.

simultaneously slowing the rate of onset of the second burst, leading to a more linear release profile.

Discussion

In the effort to hasten the development of biodegradable matrix-based, controlled release therapeutics, many models have been developed to describe the release of specific classes of agents, such as small molecules or proteins.[22,24–29] In general, these models require parameters that can only be obtained by fitting controlled release data,[26,27] or otherwise by carefully observing controlled release experiments.[28] In order to eliminate the need for exploratory *in vitro* experiments, which investigate the drug dosing schedules supplied by potential controlled release therapeutics, a model must be able to predict, without regression, a broad range of release behaviors for a wide array of agents, entirely from tunable matrix properties. To meet this goal, we developed new methods of calculating the magnitude of the initial burst release and the duration of the subsequent lag phase, which allow these features to be predicted with commonly known parameters regardless of the encapsulated agent type, be it small molecule, peptide or protein. We also applied this model to numerous sets of published data to generate values for two correlations. These correlations complete a set of readily attainable parameters for making regression-free predictions of drug release from uniformly hydrated biodegradable matrices. Finally, by varying the tunable parameters over rational bounds, the range of potential release behaviors attainable with such systems were explored.

The comparison of model predictions and experimental data strongly suggests that the magnitude of the initial burst is directly proportional to the amount of agent localized to occlusions residing just *inside* the matrix surface. This region is defined over the entire surface of the matrix to a depth of $R_p - R_{occ}$, such that any occlusion localized to this region would abut the

matrix–reservoir interface. Prior models attributing the initial burst to the amount of agent adsorbed to the matrix surface required the fitting of empirical parameters for each new absorption/desorption drug type.[22,28] Further, results from several studies examining release from particles of uniform size and surface morphology, but varying occlusion size (based on the formulation method), suggest that it is unlikely that desorption from the surface (with surface area being proportional to the magnitude of the initial burst) is responsible for the initial burst phase of release.[14,15]

Regression-free predictions of published experimental data also suggest that the model consistently calculates the duration of the lag phase for release agents ranging from small molecules to proteins. Prior models have only accurately predicted the duration of the lag phase for either small molecules[26,27,29] or proteins.[28] The current model establishes a polymer molecular weight associated with release (M_{wr}) and inversely correlates it to agent molecular weight (M_{wA}) (Fig. 3A). The concept that small molecules can diffuse more readily through a higher molecular weight polymer matrix than larger molecules is supported by both diffusion flow cell studies[36] and careful analysis of release data.[8–21] In addition, scanning electron microscopy[32,43] and other morphological[44] studies have shown that with degradation, PLGA matrices become increasingly porous solids. The current model attributes this heterogeneous degradation to matrix crystallinity, a mechanism also supported by previous models.[26,45]

The model predicts the onset of the secondary burst (Fig. 1) using expressions that have both similarities and fundamental differences with those presented in the literature.[25,28,31,36,45,46] Like prior models, the current work employs Fick's second law with an D_{eff} dependent on matrix porosity. Saltzman and Langer first derived this expression to predict protein release from non-degradable porous polymers.[25] Their lattice-based percolation calculations yield an accessible porosity that fits a cumulative normal distribution, a feature that our model is able to implement without estimated parameters. Recent controlled release models based on stochastic methods have also successfully employed a version of this equation to describe the egress of small molecules from regressed degradation rate constants.[26,27] The current work is, however, fundamentally different from these prior models[26,27] as it describes pore formation in biodegradable matrices entirely from known parameters and applies to a broad range of agents, including small molecules, peptides, and proteins.

As mentioned in the Results section, the diffusivity values calculated for Fig. 3B are consistent with those found in the literature.[27,28,32,36] These diffusivities display a power dependence on the size of the encapsulating matrix, where $D = aR_p^b$. This expression was originally developed by Siepmann *et al.*[32] to compensate for the size-dependent increase in degradation rate that occurs in autocatalytic polymers such as PLGA.[47] Further, even though this power expression was only validated for lidocane release from 45 kDa PLGA microspheres,[32] we demonstrate that it applies nearly as well to the much broader range of matrix sizes, polymer molecular weights, and agent types examined herein (Fig. 3B, Table 1). The diffusivity coefficients ranging from 10^{-14} to 10^{-16} m^2/s calculated in prior models also support this finding.[25,27] Our regression-free predictions (Fig. 4–6) help to confirm that this power expression will relate D to matrix size for many different polymers with an acid-based, autocatalytic, first-order rate expressions, including both polyesters[48] and polyanhydrides.[41]

Even though the mathematical framework presented herein provides broader applicability than prior models,[22,24–29] it still requires several assumptions. Specifically, the model considers a water soluble agent that dissolves rapidly, relative to the duration of release, and that is loaded discretely in a bulk eroding, biodegradable polymer matrix. Efforts are currently under way to relax these assumptions in order to describe more complicated systems. For instance, we speculate that systems exhibiting slower kinetics during the initial burst may be subject to dissolution effects. Other efforts will focus on replacing the correlation of D to R_p with a physically relevant degradation rate expression that inherently accounts for size dependent autocatalysis to provide greater accuracy when examining matrices with extreme sizes (<100 nm or >1 mm). Furthermore, simple diffusion reaction equations can be added to the current model framework, extending its predictive capabilities to slowly hydrating or surface eroding systems, such as large polyanhydride implants. However, even prior to these additions, the model still predicts published data on agent egress from bulk eroding biodegradable matrices (Fig. 4–6), which can provide a range of release profiles (Fig. 7).

Finally, having confirmed the model's predictive capabilities, the range of release behaviors that can potentially be attained from bulk eroding matrices were explored. Predictions for such matrices cover a continuum of behaviors ranging from abrupt burst–lag–burst profiles to sustained linear release (Fig. 7). These profiles satisfy the dosing schedules for numerous therapeutic applications, such as the constant delivery of a chemotherapy agent or the replication of multiple vaccine doses with a single injection.[4,5] Along with (1) the model's applicability to a wide array of agents and (2) its use of physically relevant parameters, its ability to capture a broad range of release behaviors (3) completes the set of three specifications required for any framework that supports a rational design methodology.

Conclusions

In conclusion, we have demonstrated that a simple, deterministic model can predict release for an extremely wide array of agents encapsulated in bulk eroding biodegradable polymer matrices. Two new correlations have been developed, allowing release from the popular copolymer, PLGA, to be predicted entirely from readily attainable parameters, representing tunable matrix properties. Further, regression-free predictions from this model provide strong support for the alternative explanations developed to account for the magnitude of the initial burst and the duration of the lag phase. Future work will expand upon the current model framework allowing for more accurate predictions using an expanded set of polymer types and matrix geometries including those that transition from surface to bulk erosion.

Glossary

Variables

C_A = Concentration of agent in the polymer matrix
C_{Ao} = Initial concentration of agent in the polymer matrix

D = Diffusivity of agent leaving the matrix *via* pores
$\varepsilon(t)$ = Time dependent matrix porosity
$kC_w(n)$ = Pseudo-first order degradation rate distribution
M_{wA} = Release agent molecular weight
M_{wo} = Average polymer initial molecular weight
M_{wr} = Molecular weight of release
$P(t)$ = Cumulative fraction of agent retained in the matrix by time t
$R(t)$ = Cumulative fraction of agent released from the matrix by time t
R_{occ} = Occlusion radius
R_p = Matrix dimension(s) across which diffusive release occurs, *e.g.* particle radius, or film thickness
t = Time
$\tau(n)$ = Distribution of induction times for pore formation

Abbreviations

PLGA = poly(lactic-co-glycolic acid)
PLA = poly(lactic acid)
SA = sebacic ahydride
CPH = 1,6-bis-*p*-carboxyphenoxy hexane
PSA = poly sebacic anhydride
BSA = bovine serum albumin

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References

1 R. Langer and J. Folkman, *Nature*, 1976, **263**, 797–800.
2 S. Freiberg and X. X. Zhu, *International Journal of Pharmaceutics*, 2004, **282**, 1–18.
3 R. A. Jain, *Biomaterials*, 2000, **21**, 2475–2490.
4 W. Jiang, R. K. Gupta, M. C. Deshpande and S. P. Schwendeman, *Advanced Drug Delivery Reviews*, 2005, **57**, 391–410.
5 L. Brannon-Peppas, *International Journal of Pharmaceutics*, 1995, **116**, 1–9.
6 S. S. D'Souza, J. A. Faraj and P. P. DeLuca, *AAPS PharmSciTech*, 2005, 6.
7 F. Alexis, *Polymer International*, 2005, **54**, 36–46.
8 E. K. Shen, m. Dziadul, B. Mee-Kyung Lim and B. Narasimhan, *Journal of Controlled Release*, 2002, **82**, 115–125.
9 G. Wei, G. J. Pettway, L. K. McCauley and P. X. Ma, *Biomaterials*, 2004, **25**, 345–352.
10 M. Takenaga, Y. Yamaguchi, A. Kitagawa, Y. Ogawa, Y. Mizushima and R. Igarashi, *Journal of Controlled Release*, 2002, **79**, 81–91.
11 C. Sturesson, P. Artursson, R. Ghaderi, K. Johansen, A. Mirazimi, I. Uhnoo, L. Svensson, A. C. Albertsson and J. Carlfors, *Journal of Controlled Release*, 1999, **59**, 377–389.
12 M. Sandor, D. Enscore, P. Weston and E. Mathiowitz, *Journal of Controlled Release*, 2001, **76**, 297–311.
13 J. E. Rosas, R. M. Hernandez, A. R. Gascon, M. Igartua, F. Guzman, M. E. Patarroyo and J. L. Pedraz, *Vaccine*, 2001, **19**, 4445–4451.
14 X. Luan and R. Bodmeier, *Journal of Controlled Release*, 2006, **110**, 266–272.
15 K. Fu, R. Harrell, K. Zinski, C. Um, A. Jaklenec, J. Frazier, N. Lotan, P. Burke, A. M. Klibanov and R. Langer, *Journal of Pharmaceutical Sciences*, 2003, **92**, 1582–1591.
16 W. Friess and M. Schlapp, *Journal of Pharmaceutical Sciences*, 2002, **91**, 845–855.
17 F. Cui, D. Cun, A. Tao, M. Yang, K. Shi, M. Zhao and Y. Guan, *Journal of Controlled Release*, 2005, **107**, 310–319.
18 A. S. Determan, Brian G. Trewyn, Victor S.-Y. Lin, Marit Nilsen-Hamilton and Balaji Narasimhan, *Journal of Controlled Release*, 2004, **100**, 97–109.
19 C. S. Chaw, Y. Y. Yang, I. J. Lim and T. T. Phan, *Journal of Microencapsulation*, 2003, **20**, 349–359.
20 S. A. Elkheshen and M. A. Radwan, *Journal of Microencapsulation*, 2000, **17**, 425–435.
21 Y. Wang, P. Challa, D. L. Epstein and F. Yuan, *Biomaterials*, 2004, **25**, 4279–4285.
22 J. Siepmann and A. Gopferich, *Advanced Drug Delivery Reviews*, 2001, **48**, 229–247.
23 D. Y. Arifin, L. Y. Lee and C. H. Wang, *Advanced Drug Delivery Reviews*, 2006, **58**, 1274–1325.
24 A. G. Thombre and K. J. Himmelstein, *AIChE Journal*, 1985, **31**, 759–766.
25 W. M. Saltzman and R. Langer, *Biophysical Journal*, 1989, **55**, 163–171.
26 A. Göpferich and R. Langer, *AIChE Journal*, 1995, **41**, 2292–2299.
27 J. Siepmann, N. Faisant and J. P. Benoit, *Pharmaceutical Research*, 2002, **19**, 1885–1893.
28 R. P. Batycky, J. Hanes, R. Langer and D. A. Edwards, *Journal of Pharmaceutical Sciences*, 1997, **86**, 1464–1477.
29 C. Raman, C. Berkland, K. Kim and D. W. Pack, *Journal of Controlled Release*, 2005, **103**, 149–158.
30 G. Jiang, B. C. Thanoo and P. P. DeLuca, *Pharmaceutical Development and Technology*, 2002, **7**, 391–399.
31 F. Burkersroda, L. Schedl and A. Gopferich, *Biomaterials*, 2002, **23**, 4221–4231.
32 J. Siepmann, K. Elkharraz, F. Siepmann and D. Klose, *Biomacromolecules*, 2005, **6**, 2312–2319.
33 G. Schliecker, C. Schmidt, S. Fuchs, R. Wombacher and T. Kissel, *International Journal of Pharmaceutics*, 2003, **266**, 39–49.
34 X. H. Zong, Z. G. Wang, B. S. Hsiao, B. Chu, J. J. Zhou, D. D. Jamiolkowski, E. Muse and E. Dormier, *Macromolecules*, 1999, **32**, 8107–8114.
35 M. Hakkarainen, A. C. Albertsson and S. Karlsson, *Polymer Degradation and Stability*, 1996, **52**, 283–291.
36 S. Fredenberg, M. Reslow and A. Axelsson, *Pharmaceutical Development and Technology*, 2005, **10**, 299–307.
37 E. Mathiowitz, E. Ron, G. Mathiowitz, C. Amato and R. Langer, *Macromolecules*, 1990, **23**, 3212–3218.
38 M. J. Kipper, S. Seifert, P. Thiyagarajan and B. Narasimhan, *Journal of Polymer Science, Part B: Polymer Physics*, 2005, **43**, 463–477.
39 A. C. R. Grayson, G. Voskerician, A. Lynn, J. M. Anderson, M. J. Cima and R. Langer, *Journal of Biomaterials Science, Polymer Edition*, 2004, **15**, 1281–1304.
40 J. Panyam, M. M. Dali, S. K. Sahoo, W. Ma, S. S. Chakravarthi, G. L. Amidon, R. J. Levy and V. Labhasetwar, *Journal of Controlled Release*, 2003, **92**, 173–187.
41 A. Gopferich and J. Tessmar, *Advanced Drug Delivery Reviews*, 2002, **54**, 911–931.
42 T. G. Park, *Biomaterials*, 1995, **16**, 1123–1130.
43 D. Klose, F. Siepmann, K. Elkharraz, S. Krenzlin and J. Siepmann, *International Journal of Pharmaceutics*, 2006, **314**, 198–206.
44 S. K. Saha and H. Tsuji, *Macromolecular Materials and Engineering*, 2006, **291**, 357–368.
45 A. Gopferich and R. Langer, *Journal of Controlled Release*, 1995, **33**, 55–69.
46 J. He, C. Zhong and J. Mi, *Drug Delivery: Journal of Delivery and Targeting of Therapeutic Agents*, 2005, **12**, 251–259.
47 M. Dunne, O. I. Corrigan and Z. Ramtoola, *Biomaterials*, 2000, **21**, 1659–1668.
48 A. Göpferich, *Macromolecules*, 1997, **30**, 2598–2604.

