A Mechanistic Model for Acidic Drug Release Using Microspheres Made of PLGA 50:50

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Abstract

Polyester microspheres are extensively studied for controlled release drug delivery devices, and many models have been developed to describe drug release from the bulk polymer. However, the interaction between drugs and polymers is ignored in most of the existing mathematical models. This paper presents a mechanistic model which captures the interplay between acidic drugs and bioresorbable polyesters. The model considers the autocatalytic effect on polymer degradation arising from carboxylic acid end groups of oligomers and drug molecules. Hence, the enhancing effect of acidic drug on the rate of degradation was fully considered. On the other hand the drug release from polyester microspheres is controlled by drug diffusion from polymer matrix. The drug diffusion coefficient depends strongly on the level of degradation of the polymer. This effect is also included in the model. It is shown that the model can effectively predict experimental data in the literature for both polymer degradation and drug release. Furthermore the model is used to design different systems of microspheres which release drugs with either a zero order profile or burst followed by zero order release profile.

Keywords: Controlled release; Biodegradable polymers; Modelling; Acidic drugs; Microspheres; Zero-order release

1. Introduction

Polylactic acids (PLAs), polyglycolics acid (PGAs) and their copolymers are widely used for drug delivery applications because of their improved biocompatible properties.[1] For polymer based delivery systems there can be one or more important phenomena controlling drug release from the particles including drug diffusion, matrix degradation, swelling, polymer dissolution and erosion.[2] Generally a combination of the mentioned mechanisms is responsible for drug release depending on drug and polymer type. For biodegradable devices made of PLA, PGA or PLGA, drug release is mainly governed by degradation and diffusion simultaneously.

There are a series of published papers on the degradation rate of polyesters with dispersed drug particles.[1, 3-5] Many of them observe that the acidic-basic character of incorporated drugs can considerably alter the degradation rate. For basic drugs incorporation, there can be two opposing effects: a basic drug can enhance degradation, behaving as a catalyst[6] or diminish degradation as a result of drug-polymer interaction.[7] In the case of acidic drugs incorporation, experimental studies agree on the accelerating influence of drugs on degradation rate. This influence has been monitored either by examining the displays of polymer structure for blank or loaded polymers,[8] or comparing the molecular weight changes between blank and loaded polymers.[1] However, to date there has been no mathematical model that considers the catalyst impact of acidic drugs on the rate of degradation. The existing models in the literature are straightforward to capture drug release and changes in polymer properties. However, they do not consider the effect of drug properties on the degradation rate of polyester particles. Therefore, there is a need for a more detailed diffusion reaction models to overcome the limitations of the literature work.

Pan and his coworkers[9, 10] proposed a mathematical framework for modelling the degradation rate by considering the effect of autocatalysis on degradation. In this paper, the mathematical model by Pan *et al.* is extended to the case of acidic drug incorporation to simulate polymer

degradation and drug release. Here, the autocatalytic term is a function of local acidity gained by oligomer and drug dissociation. Microspheres were chosen as dosage forms in this study. Such forms are generally used for controlled drug delivery in either local applications such as injection of drugs into some specific sites or oral drug delivery of easily degraded drugs.[11] Ibuprofen loaded PLGA microspheres can be used in both ways. In the current study we focus on local applications such as intra-articular administration. Nevertheless in the case of oral uptake, most absorption occurs in the small intestine because the gastric emptying time is very short in comparison with the drug release time.[12] The protons absorbed by the particles in this short period is released quickly by diffusion once they enter the intestine system. Consequently the low pH in the stomach has little effect on the particle degradation and drug release. It is shown that the model is able to predict both polymer degradation and drug release profile when compared with experimental in-vitro data in the literature. Finally the model is used to design two systems of microspheres such that their drug release follows a zero order and a burst release profiles respectively. By combining appropriate mixtures of microspheres of different sizes, the desired release profiles can be achieved.

2. Model Development

Figure 1 shows schematically a polyester microsphere loaded with drugs that is considered in the current paper. The degradation behavior of polyester matrix is modelled considering three mechanisms:

1) The hydrolysis reaction between ester bonds and penetrated water molecules
2) The autocatalytic effect arising from the carboxylic acid end groups of the oligomers
3) Further acid catalysis based on drug dissociation.

The hydrolysis reactions take place in the molecular scale whilst the transport process takes place in the device scale. As long polymer chains are broken into short chains, more and more

carboxylic and alcoholic end groups are generated. Meanwhile, water dissolves the drug particles, leading to a further increase in acidity. The solubilized drug diffuses through the polymer matrix accelerating polymer degradation. The previous work by Pan *et al.*[13] demonstrated the autocatalytic effect of short chains on polymer degradation, which proved to be useful for elucidating the degradation mechanism of the blank polymer. For the acidic drug loaded polymers, the autocatalytic effect is determined by the carboxylic acid groups of the oligomers and acidic drug molecules. The model presented here considers this interaction between drugs and polymers. It is assumed that the acid dissociation of oligomers and drugs are both instantaneous compared to the degradation and transport processes.

2.1. A brief summary of the polyester degradation model by Pan and his coworkers[13]

It is convenient to provide a brief summary of the polymer degradation model by Pan *et al.*[13] so that it can be extended for the purpose of this paper. The degradation mechanism of resorbable polymers can be defined as a chain scission of chemical bonds that is accelerated by acidic products. In the autocatalysed hydrolysis reaction, water molecules attack the ester bonds of the polymer chains, resulting in cleavage of the chains. The reaction can be schematically written as

$$\text{Ester bonds} + H_2O \xrightarrow{H^+} \text{COOH} + \text{R'-OH} \qquad (1)$$

where H^+ is the acid catalyst that can come from an external source such as an acidic medium and an internal source such as the carboxylic end groups.

Pan *et al.*[13] used the following rate equation for the polymer chain scission:

$$\frac{dR_s}{dt} = k_1 C_e + k_2 C_e C_{H^+} \qquad (2)$$

in which R_s, C_e and C_{H^+} represents the mole concentrations of chain scission, ester bonds and H^+ respectively. The first term on the right hand side reflects the non-catalytic part while the

second term reflects the autocatalytic part of the hydrolysis reaction; k_1 and k_2, the kinetic rate constants for non-catalytic and autocatalytic hydrolysis reactions respectively. Water concentration is assumed to be abundant inside the polymer, so it does not appear in the rate equation. As polymer chains are cleaved by the hydrolysis reaction, more and more short chains are produced. Pan *et al.*[13] separated the short chains from long chains in the sense that the short chains are water soluble and can diffuse out of the polymer while the long chains cannot. Following *Pan et al.*[13] the short chain production due to chain scission can be calculated as

$$R_{ol} = \alpha C_{e0}\left(\frac{Rs}{C_{e0}}\right)^{\beta} \tag{3}$$

in which R_{ol} represents the mole concentration of ester bonds of short chains produced by hydrolysis. The ester bond concentration of the long chains, C_e, are consumed by the production of short chains and can be expressed as[13]

$$C_e = C_{e0} - R_{ol} = C_{e0} - \alpha C_{e0}\left(\frac{Rs}{C_{e0}}\right)^{\beta} \tag{4}$$

Here, C_{e0} represents the initial concentration of ester bonds and α and β are empirical constants reflecting probability of short chain production due to chain scissions.

Substituting Eq. (4) into Eq. (2) gives a final expression for chain scission rate equation

$$\frac{dR_s}{dt} = C_{e0}\left[1-\alpha\left(\frac{Rs}{C_{e0}}\right)^{\beta}\right](k_1 + k_2 C_{H^+}) . \tag{5}$$

Once an ester bond is broken, carboxylic and alcoholic end groups are formed. The carboxylic groups have a high degree of acid dissociation; their equilibrium reaction can be expressed as

$$R_1\text{-COOH} \rightleftharpoons R_1\text{-COO}^- + H^+ \tag{6}$$

in which R_1-COOH represents short chains with carboxylic ends. The acid dissociation constant for short chains, K_a, can be expressed by

$$K_a = \frac{C_{H^+} C_{R_1\text{-}COO^-}}{C_{R_1\text{-}COOH}}. \quad (7)$$

Here, C_{R_1-COOH} and $C_{R_1-COO^-}$ represent the concentrations of R_1-COOH and R_1-COO^- respectively. Using C_{ol} to represent the current concentration of the short chains and m the average degree of polymerization of the short chains, we then have

$$C_{R_1-COOH} = \frac{C_{ol}}{m}. \quad (8)$$

For aliphatic polyesters, without any further internal or external proton source, the charge balance requires that $C_{H^+} = C_{R_1-COO^-}$ and the equilibrium expression leads to $C_{H^+} = (K_a C_{R_1-COOH})^{0.5}$.[9, 10] However, this is invalid when other proton sources, such as acidic drugs, are introduced into the polymer.

2.2. Extension of the autocatalytic term in the model to account for acidic drugs

In a drug-loaded polyester, there are three possible sources of protons that can act as catalyst for the hydrolysis reaction:

1) carboxylic acid end groups of the polymer chains
2) dissociation of acidic drug that gives rise to proton generation
3) pH of the buffer medium

The equilibrium expression for the dissociation of short chains is given in Eq. (6). While carboxylic groups of short chains dissociate, the solid drug particles dissociate in the water concurrently which generates protons and anionic drug. The most common functional group conferring acidity to drugs is the carboxylic group.[14] The dissociation reaction for carboxylic drugs can be schematically written as

$$R_2\text{-}COOH \rightleftharpoons R_2\text{-}COO^- + H^+ \quad (9)$$

Here R_2-COOH is a general representation for carboxylic acid drugs. R_2 can be any functional group including a benzene ring likewise in Ibuprofen or an ester functional group such as in Acetyl Salicylic Acid (ASA, Aspirin). Some other functional groups can also provide an acidic character to the drugs such as phenol groups[14] and Eq. (10) can be modified to account for these different drugs. The H^+ produced by drug dissociation is available as further catalyst of the hydrolysis reaction. The acid dissociation constant for drug, $K_{a,drug}$, can be expressed as

$$K_{a,drug} = \frac{C_{H^+} C_{R_2-COO^-}}{C_{R_2-COOH}}. \tag{10}$$

Here, C_{R_2-COOH} and $C_{R_2-COO^-}$ represent the concentrations of R_2-COOH and R_2-COO^- respectively. The proton concentration donated by the surrounding medium is referred to as $C_{H_0^+}$ and the charge conservation requires that

$$C_{H^+} = C_{R_1-COO^-} + C_{R_2-COO^-} + C_{H_0^+}. \tag{11}$$

In our calculations, $C_{H_0^+}$ is calculated assuming that the pH of the medium is 7.4.

2.3. Diffusion equations of short chains and drug molecules

Both the short polymer chains and the dissolved drug molecules are capable of diffusion through the polymeric matrix. For the microspheres these diffusions are spherically symmetric and transportation occurs only in the radial direction *r*. It is assumed that the diffusions follow the Fick's law such that

$$\frac{dC_{ol}}{dt} = \frac{dR_{ol}}{dt} + \frac{d}{dr}\left(D_{ol} \frac{dC_{ol}}{dr} \right) \tag{12}$$

and

$$\frac{dC_{drug}}{dt} = \frac{dR_{drug}}{dt} + \frac{d}{dr}\left(D_{drug} \frac{dC_{drug}}{dr} \right). \tag{13}$$

Here, C_{drug} (= C_{R_2-COOH} in Eq. 10) represents the current drug concentration, t the time, r the radius of the microspheres, and D_{ol} and D_{drug} the diffusion coefficients for the short chains and drug molecules. The first term on the right-hand side of Eq. (12) represents the production rate of short polymer chains due to chain scission, and that of Eq. (13), the rate of drug dissolution. It will be seen in later part of this paper that the drug release profile can be satisfactory predicted using Fickian diffusion law. The loss of short chains and drug molecules generates porosity inside the matrix, which leads to a significant increase in the diffusion coefficients. Therefore variable effective diffusivities, D_{ol} and D_{drug}, are used in the equations following Pan *et al.*[15]

$$D_{ol} = D_{ol,0} + \left(1.3V_{pore}{}^{2} - 0.3V_{pore}{}^{3}\right)\left(D_{ol,pore} - D_{ol,0}\right) \tag{14}$$

and

$$D_{drug} = D_{drug,0} + \left(1.3V_{pore}{}^{2} - 0.3V_{pore}{}^{3}\right)\left(D_{drug,pore} - D_{drug,0}\right) \tag{15}$$

in which $D_{ol,0}$ and $D_{drug,0}$ denote the diffusivities of oligomers and drug molecules in the fresh bulk polymer, V_{pore}, the porosity due to the loss of oligomers and drug molecules, and $D_{ol,pore}$ and $D_{drug,pore}$, the diffusion coefficients of oligomers and drugs in liquid-filled pores respectively. In this study $D_{ol,pore}$ and $D_{drug,pore}$ are simply taken as 1000 times of their counter parts in the fresh bulk polymer.[15] The volume fractions of pores due to loss of oligomers and drugs are given by

$$V_{pore,ol} = \frac{R_{ol}}{C_{e,0}} - \frac{C_{ol}}{C_{e,0}} \tag{16}$$

and

$$V_{pore,drug} = 1 - \frac{C_{drug}}{C_{drug,0}}. \tag{17}$$

The total porosity, V_{pore}, can be calculated using

$$V_{pore} = V_{pore,ol}\,(1 - f_{drug}) + V_{pore,drug}\,f_{drug} \tag{18}$$

where f_{drug} is volume ratio of drug to the polymer phase.

The initial conditions are given by

$R_s(r,0)=0$

$C_{ol}(r,0)=C_{ol,0}=0$

$C_{drug}(r,0)=C_{drug,0}$ (19)

and the boundary conditions (concentrations at particle surface) are assumed as:

$C_{ol}=0$

$C_{drug}=0.$ (20)

For initial drug concentration, two special cases are considered. In the first case, the drug loading is below the solubility limit. An infinite dissolution rate for the drug molecules is assumed and the initial drug concentration is simply taken as the drug loading. This can be schematically represented as

$$\text{If } \frac{V_{drug}}{V_{unit}} < C_s \quad \text{then} \quad C_{drug,0} = \frac{V_{drug}}{V_{unit}}. \tag{21}$$

In the second case, the drug loading is above the solubility limit, the drug dissociation rate becomes a limiting factor.[16, 17] In this case the initial drug concentration is taken as the solubility of the drug which can be represented as

$$\text{If } \frac{V_{drug}}{V_{unit}} > C_s \quad \text{then} \quad C_{drug,0} = C_s. \tag{22}$$

It is assumed that drug dissolution is instantaneous and the drug concentration at any r remains at C_s until all loaded drug at that location has dissolved.

Equations (5), (7), (8) and (10-22) form the complete mathematical model for polymer degradation and drug release. Finally, the number averaged molecular weight of the polyester at any particular location can be calculated as[13]

$$M_n = M_{n0} \frac{1 - \alpha(\frac{R_s}{C_{e0}})^{\beta}}{1 + N_{dp0}(\frac{R_s}{C_{e0}} - \frac{a}{m}(\frac{R_s}{C_{e0}})^{\beta})} \quad (23)$$

where M_{n0} is the initial molecular weight of the polymer; N_{dp0} is the average degree of polymerization.

Applying the initial and boundary conditions, these equations are solved numerically using the central finite difference method for spatial discretization.[18] The direct Euler scheme was used for the time integration. A particle radius was discretized into 100 finite difference nodes and a very small time step was used. Numerical convergence was ensured by increasing the number of finite difference nodes and reducing the time step length such that no change in the numerical solution can be found.

3. Results

3.1. Comparison between model prediction and experimental data obtained in the literature

Siepmann *et al*.[19] and Klose *et al.*[1] carried out a set of experiments using microspheres made of PLGA 50:50 in phosphate buffer (pH 7.4) at 37 ºC. Here their experimental data are used to test the model presented in the previous section. A common set of parameters in the model of polymer degradation are used for both blank and drug-loaded samples. The following experimental data are taken from their papers:

- average molecular weight as a function of time for blank microspheres undergoing autocatalytic degradation[19]
- average molecular weight as a function of time for acidic drug (ibuprofen) loaded microspheres undergoing autocatalytic degradation
- ibuprofen release from microspheres[1]

Figure 2 presents comparison between the model prediction and experimental data for average molecular weight changes of blank microspheres. Two different sizes are used in the comparison. The kinetic parameters of the model used in the model prediction are summarized in Table 1.

Table 1. Model parameters used for the predictions in Figures 2-6

C_{e0} (mol/m^3)	20615
$C_{ol,0}$ (mol/m^3)	0
M_0 (g/mol)	65 g/mol*
M_{w0} (g/mol)	29000-35000
m	4
α	0.4
β	1.0
K_{a_ol}	1.35×10^{-4}
$D_{ol,0}$ (m^2/week)	1×10^{-12}
$D_{ol,pore}$(m^2/week)	$1000 \times D_{ol,0}$
k_1 (1/week)	8×10^{-4}
k_2 ($\sqrt{m^3 / mol / week}$)	1×10^{-1}

* M_0 is the molar mass of PLGA taken as the average of PLA and PGA

Figure 3 shows the comparison between model prediction and experimental data for average molecular weight changes over time. Drug free and drug loaded PLGA microspheres are used in the comparison. The following drug related parameters were used in the predictions: $K_{a\_drug}=6.3 \times 10^{-6}$, $D_{drug,0}=1.5 \times 10^{-10}$ m^2/week, drug loading=4% w/w and $D_{drug,pore} = 1000 \times D_{drug,0}$. All the other parameters are common for the blank and loaded microspheres (see Table 1). Compared to the drug free microspheres, ibuprofen loaded PLGA microspheres exhibit significantly faster degradation pattern. In a drug-loaded microsphere, 50% of the initial molecular weight has been reached at 4 days, while it is 7.5 days for drug free microspheres. The enhanced rate of degradation is attributed to the decreased micro pH based on the acidic drug dissociation. The individual contributions of drug and oligomers on the proton concentration are compared in Figure 4 through the degradation process. It can be seen that at the early stage of degradation, most of the proton is dominated by the acidic drugs while the contribution of the short chains are insignificant. As more and more drugs are released and short chains are produced, the order is switched and short chains start to dominate on the proton

concentration. It is worth noting that the calculations used the disassociation constants, $K_{a,\,drug}$ and K_a, which are taken from independent literature.[20, 21]

Figure 5 shows the comparison between the model prediction and experimental data for drug release profile. The drug release from PLGA microspheres is mainly governed by diffusion in the bulk polymer through the generated porous channels which are a product of degradation. It can be observed from the figure that Fickian diffusion is able to predict the drug release profile well. However the effective diffusivity increased significantly with polymer degradation, as shown in Figure 6, which has to be considered in the model. To demonstrate this key issue, drug release calculated using a constant diffusion coefficient is also presented in Figure 5 for comparison. As seen from Figure 5, using a constant diffusion coefficient would predict 28 days for the complete drug release as opposed to about 10 days when the variable diffusion coefficient is used.

By observing Figures 2, 3 and 5, it can be concluded that the mathematical model presented in section 2 is able to predict the experimental data both for polymer degradation and drug release. In our calculations, the model parameters were determined by varying them over a range to obtain the best prediction. The hydrolysis rate constants, k_1 and k_2, in Table 1 are determined using the blank polymer data as shown in Figure 2. It is worth highlighting that the model is able to predict the degradation behavior of drug loaded polymers using the rate constants obtained by using the blank polymers.

3.2. Design of microspheres to achieve desired profile of drug release

It is desirable to have a zero order release profile in order to maintain a constant drug concentration. The burst effect in ordinary drug delivery systems is may result in toxicity or other side effects.[22] Even if no harm is done during the burst, an excess amount of drug is wasted and this can result in some economic concerns.[23] Drug release from polyester

microspheres depends on parameters such as the microsphere diameter and drug loading. Guided by a simple analysis, Berkland *et al.*[22] showed that a zero order release profile can be achieved by mixing two different microspheres which have concave and convex release profiles respectively. Taking inspiration from the study by Berkland *et al.*[22] and Narayani and Panduranga Roa,[24] we demonstrate that the mathematical model presented in this paper can be used to design such systems.

Figure 7 shows a convex, concave and nearly zero order release profiles, all calculated using the mathematical model and the parameters that were used in section 3. The convex release profile was obtained by using microspheres of 75μm in radius with a drug loading of 400 mol/m^3. The outer layer of the sphere with a thickness of 0.2r was not loaded with any drug. This outer layer can be considered as a drug free coating that retards the initial drug release. The concave release profile was obtained by using microspheres of 150μm in radius with the same drug loading. The outer layer of the sphere with a thickness of 0.6r was not loaded with any drug. Such a thick coating prevents drug release in the initial stage and hence produced the convex release profile. The nearly zero release profile was obtained by mixing the two types of spheres with 1:2 (w/w) ratios of the thinly coated microspheres (concave profile) over the thickly coated microspheres (convex profile).

The long term linear release of drug from particles was crucial in most of the applications. In some certain cases, an initial burst release followed by a linear release may be required, likewise in wound treatment. One of the biggest problems with burst release is that it cannot be well controlled.[23] Figure 8 shows a convex, concave and burst followed by zero order release profile all calculated using the mathematical model. The convex release profile was obtained by using microspheres of 75μm in radius with a uniform drug loading of 400 mol/m^3. The concave release profile was obtained by using microspheres of 150μm in radius with the same drug loading. The outer layer of the sphere with a thickness of 0.6r was not loaded with any

drug. This is exactly the same as case (b) in Figure 7. The burst followed by nearly zero release profile was obtained by mixing the two types of spheres with 1:2 (w/w) ratios of the uniformly loaded microspheres (concave profile) over the thickly coated microspheres (convex profile).

4. Discussions

A mechanistic based mathematical model is presented which can be used to calculate polyester degradation and drug release. The model is generally valid although microspheres are used here as a demonstrating example. The underlying assumptions in the mathematical model were motivated by experimental studies in the literature which demonstrated the influence of acidic drug on autocatalysis of polyester devices. It is shown that the model can predict polymer degradation and drug release fairly well. A key element of the model is that the drug diffusion coefficient strongly depends on the polymer degradation. This study shows that without considering this interaction it is unlikely to capture the observed profile of drug release. It is worth noting that the model is able to predict the degradation behavior of drug loaded polymers using the kinetic constants for polymer degradation obtained using blank polymers. To demonstrate potential applications of the mathematical model, it is shown that the model can be used to design systems of microspheres of different sizes and patterns of drug loading to achieve zero order release or burst followed by zero order release. These systems will have significant practical implications for various applications.

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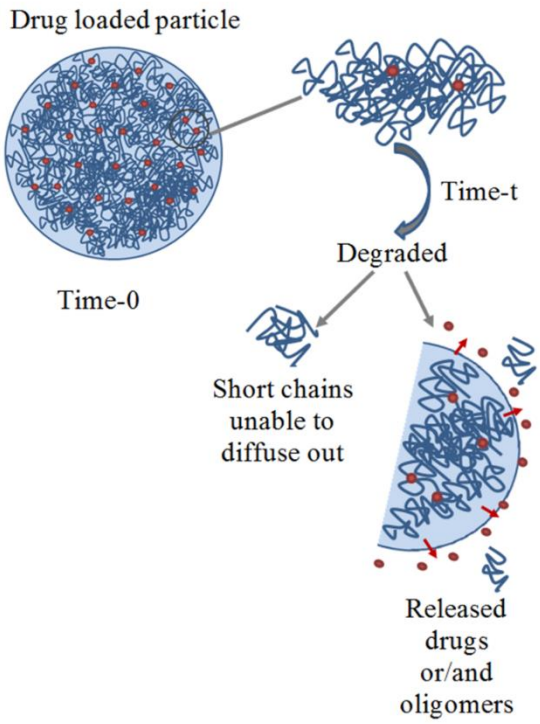

Figure 1. Schematic illustration of drug and oligomer release from a drug-loaded microsphere.

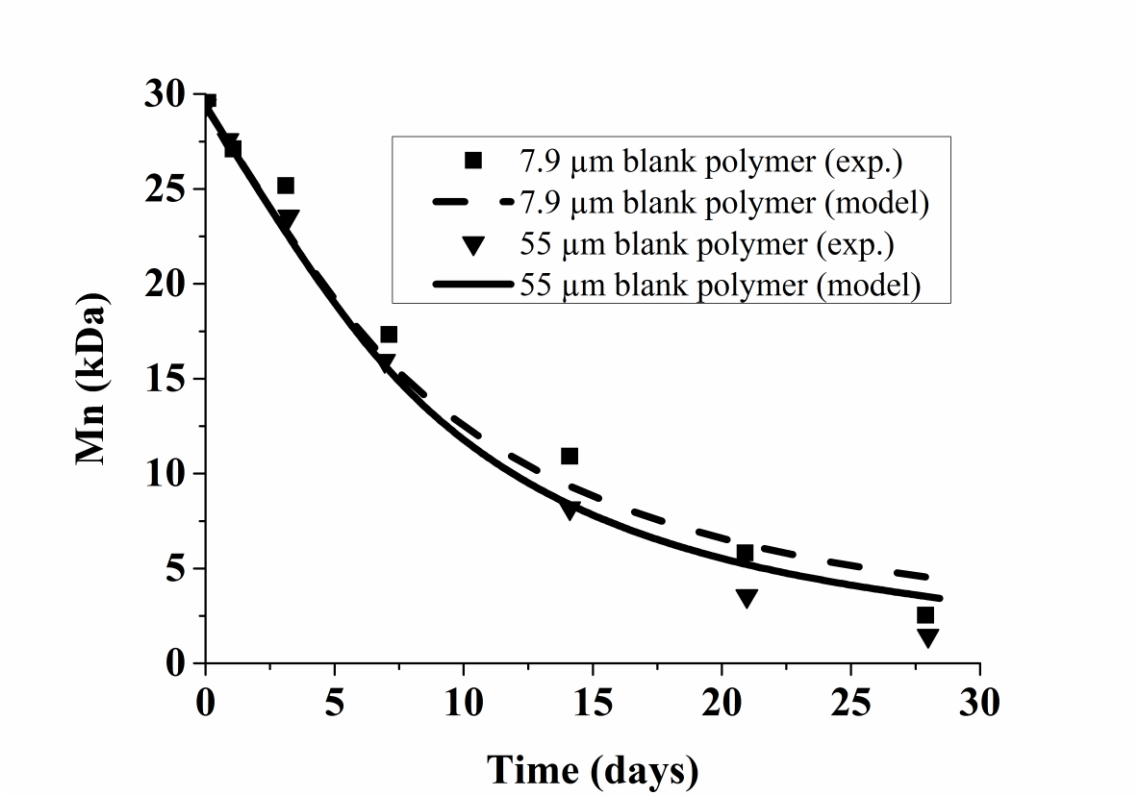

Figure 2. Comparison between model prediction and experimental data for blank particles with different sizes. The dashed and solid lines represent the model predictions for microspheres of average size of r = 7.9µm and 55µm respectively. The discrete symbols represent the experimental data.[19]

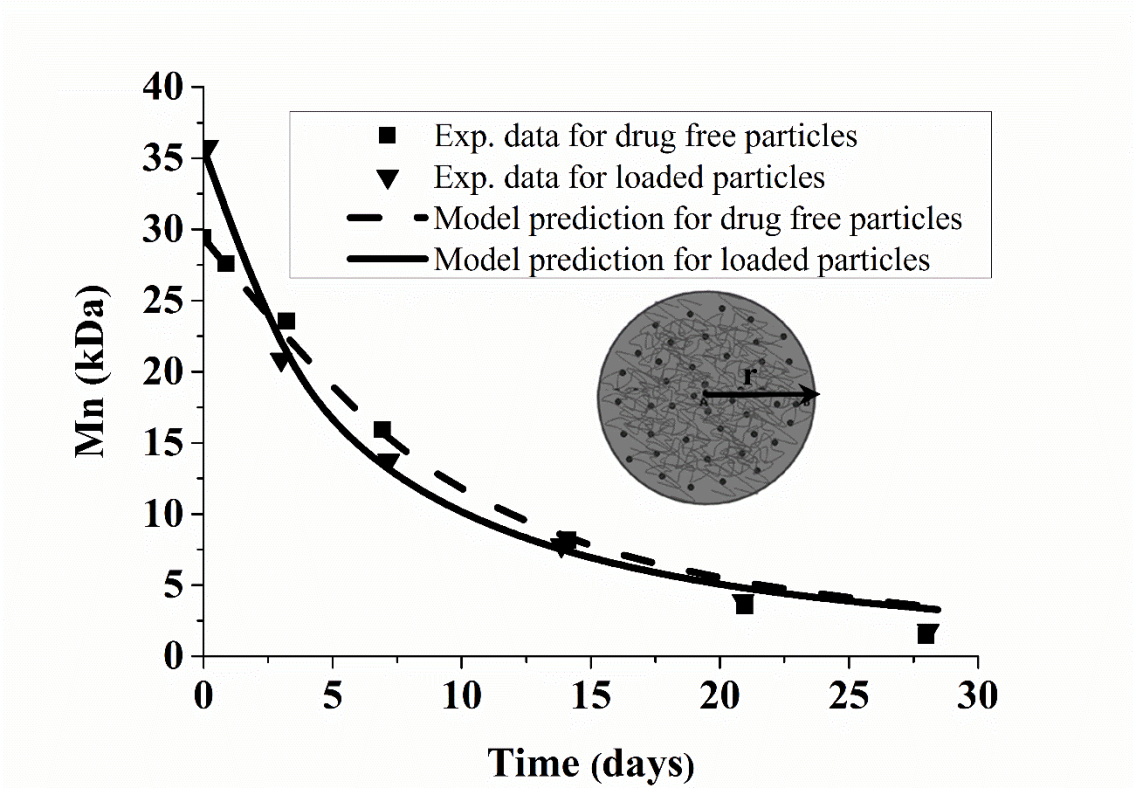

Figure 3. Comparison between model prediction and experimental data for degradation of blank and ibuprofen loaded PLGA microspheres. The dashed and solid lines represent model predictions for drug free and drug loaded particles respectively. The discrete symbols represent the experimental data.[1, 19]

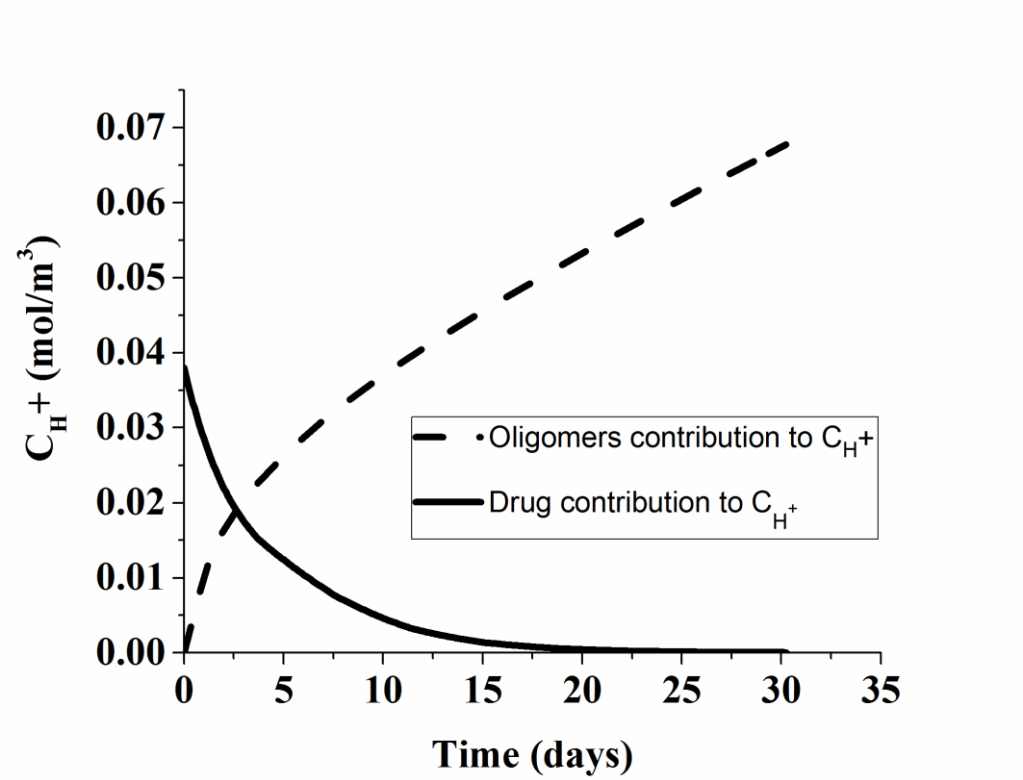

Figure 4. Independent contributions of drug and oligomers to the proton concentration throughout the degradation process.

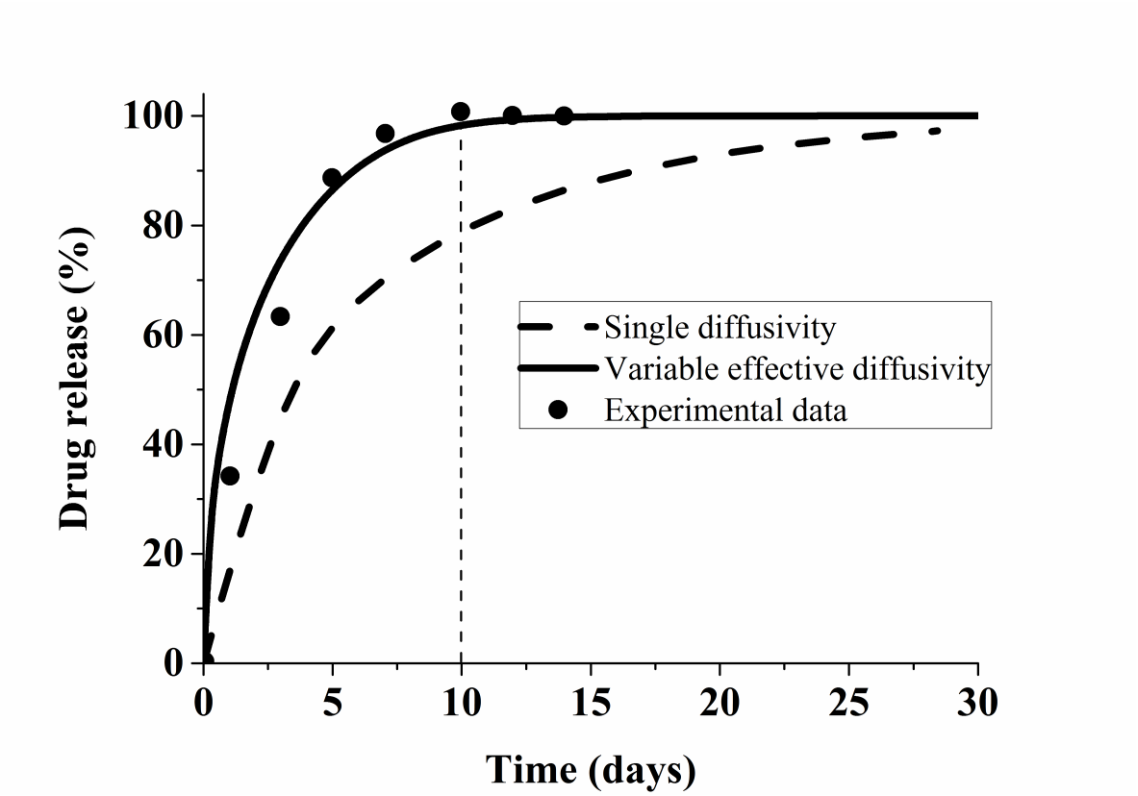

Figure 5. Comparison between the model prediction (solid line) and experimental data[1] (discrete symbols) for drug release. The dashed line is model prediction using a constant drug diffusion coefficient. The size of the microsphere is 52μm.

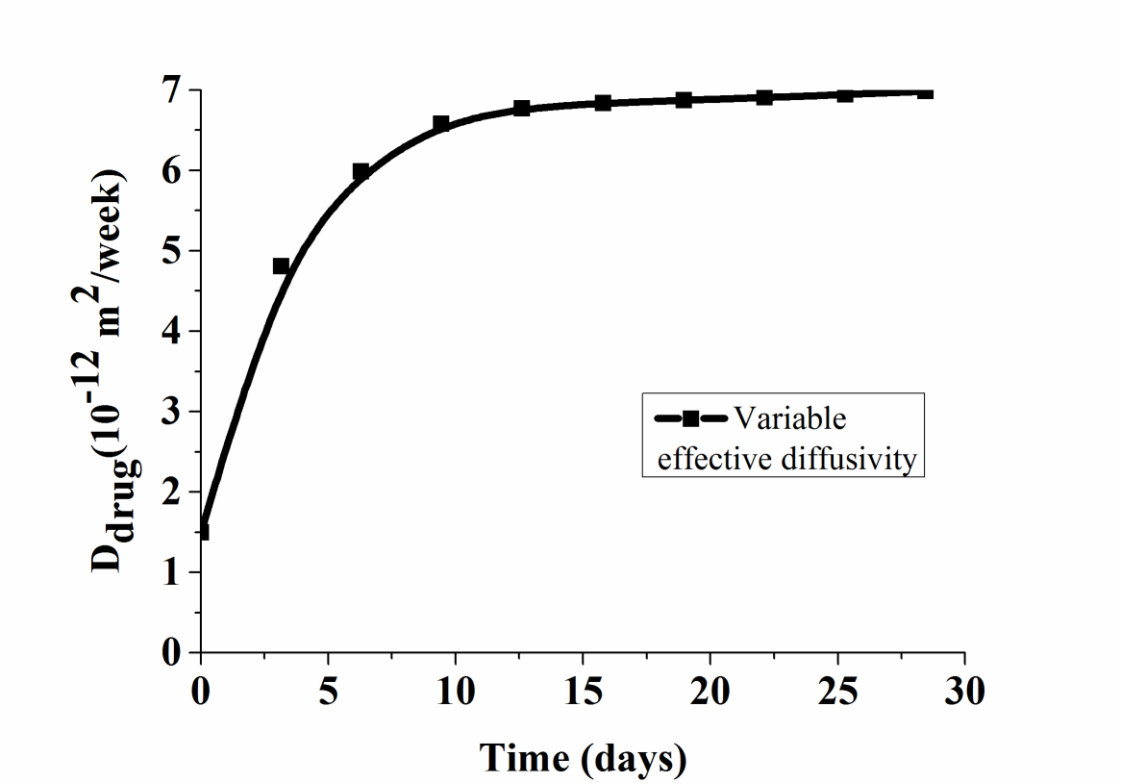

Figure 6. Variable diffusivity of ibuprofen calculated using Eq. 18 for micro-particle of r = 52µm.

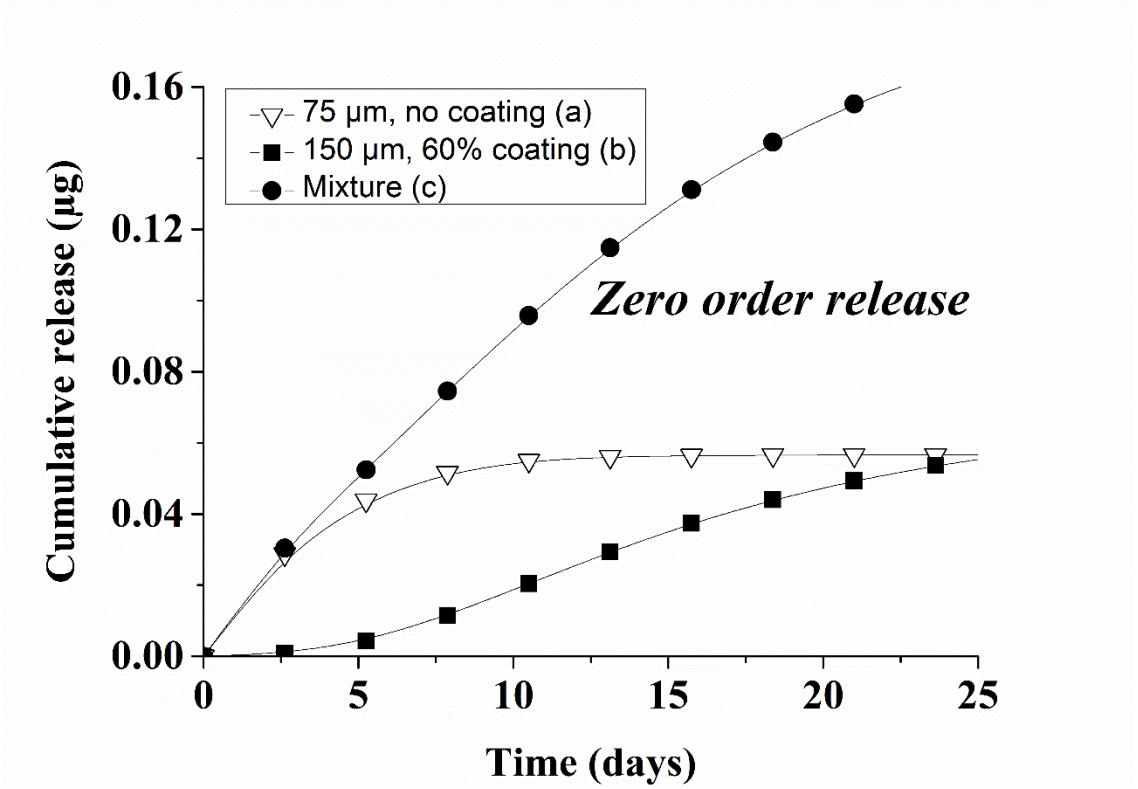

Figure 7. Calculated profiles of drug release using microspheres of (a) 75µm in radius with drug loading of 400 mol/$m^3$and a drug free outside layer of 0.2r, (b) 150µm in radius with a drug loading of 400 mol/$m^3$and a drug free outside layer of 0.6r and (c) mixture of (a) and (b) with 1:2 (w/w) ratio of (a) over (b).

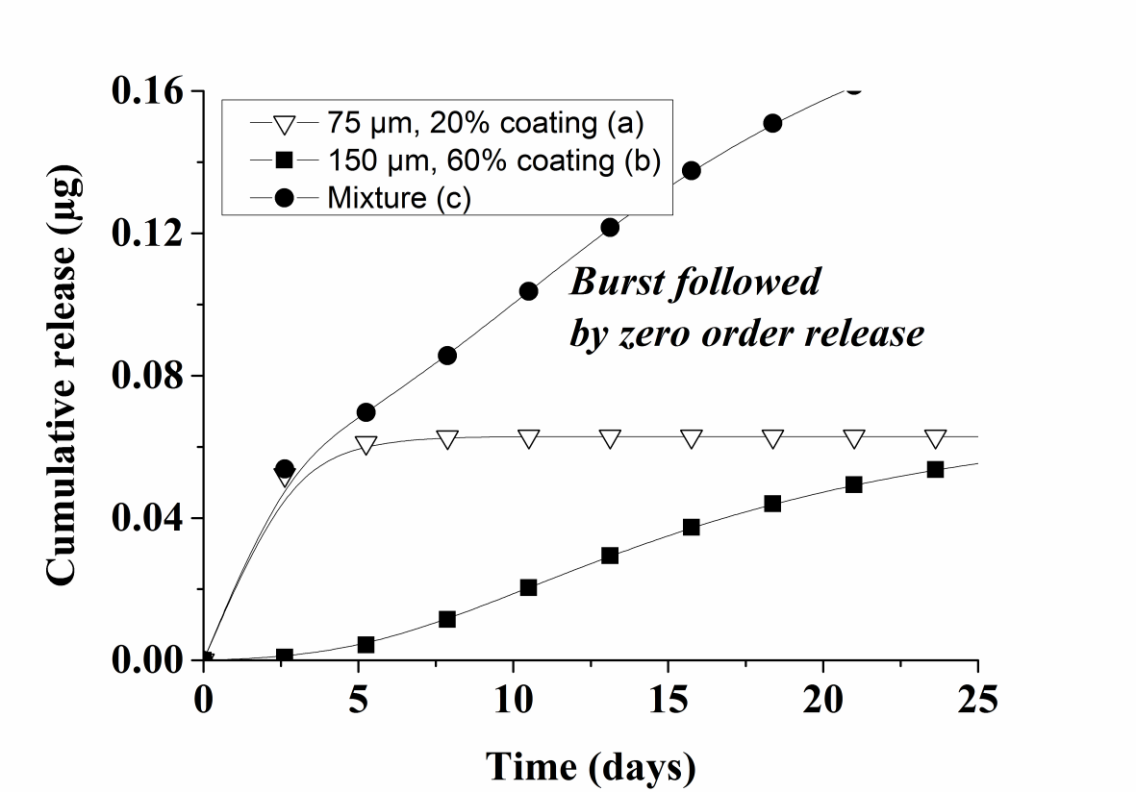

Figure 8. Calculated profiles of drug release using microspheres of (a) 75μm in radius with a uniform drug loading of 400 mol/m^3, (b) 150μm in radius with a drug loading of 400 mol/$m^3$and a drug free outside layer of 0.6r and (c) mixture of (a) and (b) with 1:2 (w/w) ratio of (a) over (b).