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Effect of mean diameter and polydispersity of PLG microspheres on drug release: Experiment and theory

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Abstract

The need to tailor release rate profiles from polymeric microspheres is a significant problem. Microsphere size, which has a significant effect on drug release rate, can potentially be varied to design a controlled drug delivery system with desired release profile. In this work the effects of microspheres mean diameter, polydispersity, and polymer degradation on drug release rate from poly(lactide-co-glycolide) (PLG) microspheres are described. Piroxicam containing PLG microspheres were fabricated at 20% loading, and at three different impeller speeds. A portion of the microspheres was then sieved giving five different size distributions. *In vitro* release kinetics were determined for each preparation. Based on these experimental results, a suitable mathematical theory has been developed that incorporates the effect of microsphere size distribution and polymer degradation on drug release. We show from *in vitro* release experiments that microsphere size has a significant effect on drug release rate. The initial release rate decreased with an increase in microsphere size. In addition, the release profile changed from first order to concave-upward (sigmoidal) as the microsphere size was increased. The mathematical model gave a good fit to the experimental release data. For highly polydisperse populations (polydispersity parameter $b < 3$), incorporating the microsphere size distribution into the mathematical model gave a better fit to the experimental results than using the representative mean diameter. The validated mathematical model can be used to predict small-molecule drug release from PLG microsphere populations.

Keywords: Controlled release; Poly(lactide-co-glycolide); Non-uniform microspheres; Mathematical modeling; Polymer degradation

1. Introduction

Controlled drug delivery offers numerous advantages compared with conventional free dosage forms, in particular: improved efficacy, reduced toxicity, and improved patient compliance and convenience. Consequently there is considerable interest from the pharmaceutical industry in the encapsulation of vaccines and drugs in biodegradable proteinaceous or polymeric micro and nanospheres (Ravi Kumar, 2000). PLG-based microspheres are attractive macromolecular carriers because of their biocompatibility, biodegradability, and non-toxicity. These synthetic polymers degrade at a rate dependent on properties such as polymer molecular weight and lactide:glycolide ratio (Cutright et al., 1974). In addition, PLG microspheres are versatile, and can be prepared using the oil-in-water (o/w) emulsion solvent evaporation technique, which was shown to successfully entrap hydrophobic materials (Beck et al., 1979; Cowsar et al., 1985; Jeffery et al., 1991). Alternatively, PLG microspheres can be prepared through the (water-in-oil)-in-water (w-o-w) solvent evaporation technique that has been shown to be efficient in entrapping water-soluble material (Ogawa et al., 1988; Jeffery et al., 1993; Parikh et al., 2003; Porjazoska et al., 2004).

Difficulty achieving desired release rates is an important limitation in controlled drug delivery. Microsphere size, which has a significant effect on drug release rate, can potentially be varied to design a controlled drug delivery system with desired release profile. Mathematical modeling provides insight into the fundamental processes that govern the release, and once validated with experimental results, it can be used to tailor a controlled drug delivery system with specified drug release profile. Even

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though the majority of the conventional manufacturing techniques used for controlled drug delivery result in polydisperse microspheres (microspheres of non-uniform size distribution), the mean diameter is used to represent the size of the microspheres when modeling drug release. As a consequence, the model does not account for the effect of population polydispersity which is believed to be one of the main causes for the initial drug "burst" release (Berkland et al., 2003).

To minimize the polydispersity effect on release kinetics, some investigators used manufacturing techniques that result in monodisperse populations, while others used sieves to fractionate the microspheres into more uniform size distributions. Berkland et al. (2001) developed a method to produce microspheres of a monodisperse size distribution by spraying a polymer-containing solution through a nozzle. The nozzle was equipped with acoustic excitation and a non-solvent carrier stream to produce uniform droplets. This technology was later used to produce monodisperse PLG microspheres to investigate the effect of microsphere size and polymer molecular weight on drug release (Berkland et al., 2002; Raman et al., 2005). Siepmann et al. (2004) investigated the effect of the size of biodegradable microparticles on release rate of dispersed drug (monolithic dispersions). The manufacturing technique resulted in microspheres with a wide size distribution, and five different size fractions were then obtained by sieving (Siepmann et al., 2004). Alternatively, Bezemer et al. (2000) studied the release of protein from amphiphilic multiblock copolymers, based on hydrophilic poly(ethylene glycol) (PEG) blocks and hydrophobic poly(butylene terephthalate) (PBT) blocks. Despite the wide microsphere size distribution, the effect of microsphere size was only represented in terms of the mean diameter (Bezemer et al., 2000).

In this work the effects of microspheres mean diameter, polydispersity, and polymer degradation on drug release rate from poly(lactide-co-glycolide) (PLG) microspheres are investigated experimentally. Based on the experimental results, a mathematical model is proposed that accounts for the effects of diffusion, polymer degradation, and microsphere size distribution to predict drug release kinetics from polydisperse PLG microsphere populations.

2. Materials and methods

2.1. Materials

The PLG used had a copolymer composition of 50:50, a M_w of ~40 kDa, and is a product of Sigma. The poly(vinyl-alcohol) (PVA) was 87–89% hydrolyzed, with a M_w of 13–23 kDa. In addition to these chemicals, Piroxicam (M_w 331.3), and HPLC grade Dichloromethane (DCM) were purchased from Sigma. Sodium hydroxide was purchased from EM Science. All chemicals were used as provided.

2.2. Micropshere preparation

PLG microspheres were prepared by the oil-in-water (o/w) emulsion solvent extraction technique described next. The protocol is detailed in the literature (Beck et al., 1979; Cowsar et al., 1985; Jeffery et al., 1991). Piroxicam was co-dissolved with PLG (10%, w/v) in dichloromethane (DCM) at 20% of the PLG mass (20% theoretical drug loading (w/w)). PVA solution (8%, w/v) was stirred at the desired stirring speed for 5 min in a 400 ml Pyrex beaker with a Caframo ultra high torque stirrer (model BDC1850) having a speed range of 0–1800 rpm. The PLG solution was slowly added to the beaker and stirring was continued for 60 min. Afterwards, the resulting emulsion was added to 1 l of double distilled water, and stirring was continued for an additional 90 min at a speed of 1200 rpm. Microspheres were then collected by filtration, where the filter size used was 0.2 μm to prevent any loss of microspheres.

Three batches of microspheres were prepared at three different impeller speeds (140, 300, and 900 rpm) to produce microspheres having a wide size distribution (0.2–140 μm). The correlation developed by Berchane et al. (2006), which relates PLG micropshere population mean diameter to impeller speed, was utilized to determine the impeller speeds that would result in the desired microsphere sizes. A portion of the microspheres, prepared at different impeller speeds, was stored for drug release investigations from raw batches, while the rest of the microspheres were combined and sieved to obtain five different size fractions: 0.2–20, 20–40, 40–63, 63–90, and >90 μm (average pore sizes of the sieves: 20, 40, 63, and 90 μm; Keison Products, United Kingdom). Once sieved, the microspheres were lyophilized and stored at −20 °C.

2.3. Determination of piroxicam loading

The experimental loading of piroxicam was determined by dissolving 2 mg of microspheres in 1 ml of 0.25 M sodium hydroxide at 37 °C for 48 h. Piroxicam has been shown to be stable in sodium hydroxide solution (d'Arpino et al., 2003), and is thus believed to be stable under extraction. Piroxicam-free microspheres of the same molecular weight were treated similarly. Drug concentration was determined by measuring the absorbance of the piroxicam-containing solution in a quartz cuvette at 276 nm (Gilford Response Spectrophotometer) and subtracting the absorbance of the piroxicam-free solution. The experiments were done in triplicate.

2.4. In vitro release

Drug release was determined by suspending 5 mg of piroxicam-loaded microspheres in 1.3 ml of phosphate buffered saline (PBS, pH 7.4). Piroxicam maintains an unchanged structure in buffer media (Ficarra et al., 1999), and is thus believed to be stable under the *in vitro* release conditions. The suspension was continuously agitated by shaking (Glas-Col, Terre Haute, USA) at 100 strokes/min in a 37 °C incubator. At predetermined intervals, the samples were centrifuged, and 1 ml of the supernatant was extracted, and replaced by fresh buffer. The microspheres were then vortexed and put back into the incubator. Resuspending the microspheres in fresh buffer after centrifugation (by vortexing), and continuous agitation of the suspension throughout the release experiment prohib-

Table 1
Characterization of sieved and raw piroxicam-loaded PLG microspheres

Microsphere population	Mean diameter[a], d_{43} (μm)	a	b	Theoretical drug loading (%, w/w)	Experimental drug loading (%, w/w)	Encapsulation efficiency (%)
>93 μm	–	–	–	20	5.94	29.7
63–90 μm	81.2 ± 0.4	80.5	9.7	20	5.33	26.65
40–63 μm	51.0 ± 0.4	50.9	5.4	20	5.2	26
20–40 μm	29.6 ± 0.3	29.6	6.0	20	4.7	23.5
0.2–20 μm	13.9 ± 0.2	13.8	3.17	20	5.38	26.9
140 rpm	76.0 ± 0.9	75.3	3.78	20	6.05	30.25
300 rpm	33.5 ± 0.4	33.1	3.1	20	5.23	26.15
900 rpm	13.5 ± 0.2	13.3	2.7	20	5.65	28.25

[a] Mean diameter ± standard error.

ited microsphere aggregation and sedimentation. The piroxicam concentration in the supernatant was determined by measuring the absorbance at 276 nm in a spectrophotometer (Gilford Response Spectrophotometer). Drug concentration was less than 10% of the saturation solubility in the release medium at 37 °C, which conforms to sink conditions (Gibaldi and Feldman, 1967). Piroxicam-free microspheres were treated similarly, and the absorbance from their supernatant was subtracted from all measurements. The experiments were done in triplicate.

2.5. Microsphere characterization

Imaging of microspheres was performed with a LEO-VP1530 field emission scanning electron microscope at the Microscopy and Imaging Center (MIC) at Texas A&M University. Samples of the spheres were mounted on aluminum stubs using double adhesive tape. The stubs were then left overnight in a desiccator to dry. The samples were sputter-coated with 4 nm of platinum–palladium in an atmosphere of argon. Scanning was then performed at ambient temperature and vacuum pressure. The mean diameter was quantitatively determined by measuring ∼1000 microspheres from the SEM micrographs using the Scion Image Analysis software. The pixel to distance ratio for each micrograph was entered into the software, and the edges of the spheres were specified by hand. The number of microspheres (∼1000) measured for each population was sufficient to provide an accurate mean diameter (Table 1).

3. Mathematical model

In diffusion-controlled drug release systems, a substance is released from a device by permeation from its interior to the surrounding. There are two main types of diffusion-controlled systems, the reservoir system and the monolithic system (Baker, 1987). In a reservoir system the active agent is enclosed by an inert outer membrane, while in monolithic systems the drug is dispersed uniformly throughout the rate-controlling polymer matrix. If the active agent is dissolved in the polymer matrix, the device is called monolithic solution, while if the drug is dispersed as a solid, the system is called a monolithic dispersion (Baker, 1987). In this work the microspheres were prepared by co-dissolving the polymer and the drug in DCM which results in a monolithic solution.The theoretical framework used to model drug release is based on a diffusion model for dissolved drug release from monolithic microspheres. Desorption of the drug from monolithic systems was first described by Crank (1956). The one-dimensional mass diffusion equation for a sphere of specified diameter d_m and radius R, is expressed by Fick's second law as

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

where C is the concentration of the drug; r the radial location inside the sphere; D is the drug diffusion coefficient in the PLG matrix. Solving the above equation with the following boundary and initial conditions (Crank, 1956):

$$C(r = R, t > 0) = 0; \qquad C(r, t = 0) = C_1$$

gives the following equation for the total amount of diffusing drug leaving a sphere of diameter d_m (Crank, 1956):

$$\frac{M_{t,d_m}}{M_{\infty,d_m}} = \left(1 - \frac{6}{\pi^2}\sum_{j=1}^{\infty}\frac{1}{j^2}\,e^{(-j^2\pi^2 T/R^2)}\right); \quad T = \int_0^t D(t)\,dt \tag{2}$$

where C_1 is the initial drug concentration; M_{t,d_m} and M_{∞,d_m} represent the mass of drug released from a sphere of diameter d_m, at time t and $t = \infty$, respectively.

The drug diffusion coefficient is time-dependent due to bulk degradation of the polymer matrix. As the polymer molecular weight (M_w) decreases, the drug has more available space to diffuse through the polymer chains, and so the diffusion coefficient increases. The dependence of diffusion coefficient of piroxicam on PLG molecular weight was investigated by Raman et al. (2005), and an empirical mathematical equation was obtained to represent this dependence:

$$\ln(D) = -0.347x^3 + 10.394x^2 - 104.95x + 316.95 \tag{3}$$

where $x = \ln(M_w)$. Initial drug burst release is well documented in the literature, and has been attributed to a variety of physical, chemical, and processing parameters, but for the most part, the underlying mechanism is not clearly understood (Huang and Brazel, 2001). To account for this initial burst release, an initial diffusivity (D_0) is used as a fitting parameter. D_0 is used until the time-dependent diffusivity $D(M_w)$ is larger than D_0.

Hydrolysis, which causes bulk degradation of PLG polymer, starts with water uptake. The first stage of the process is confined to a decrease in the molecular weight caused by random hydrolytic ester cleavage, while the second stage is characterized by the onset of weight loss. The first stage of the degradation process is expressed as (Pitt and Gu, 1987):

$$M_w(t) = M_w(0)\,\exp(-k_{deg}t) \tag{4}$$

where $M_w(t)$ is the molecular weight of the polymer at time t; $M_w(0)$ the molecular weight of the polymer at time $t=0$; k_{deg} is the polymer degradation constant. The rate of polymer degradation, represented by the degradation constant (k_{deg}), is dependent on the hydrolysis mechanism taking place. PLG degradation has been widely investigated (Kenley et al., 1987; Lewis, 1990; Chui et al., 1995; Faisant et al., 2002; Siepmann et al., 2004; Raman et al., 2005), and values for k_{deg} reported in the literature range from 0.0638 to 0.104 day^{-1}.

Other degradation studies performed on PLG microspheres have shown dependence of polymer degradation constant (k_{deg}) on microsphere diameter (Berkland et al., 2003). It is believed that large microspheres degrade more quickly than small microspheres because of an increased buildup of the acidic byproducts of polymer hydrolysis in large microspheres (Berkland et al., 2003). In addition, drug release can occur by diffusion through pores formed as a result of polymer erosion which results in higher effective diffusivities than those predicted solely by polymer bulk degradation. In this work the degradation constant, k_{deg}, is used as a fitting parameter, and the obtained values are compared with the reported data in the literature.

3.1. Modeling size distribution

This work considers the release from a microsphere population of non-uniform size distribution. The effect of polydispersity on drug release rate from this population is accounted for in the mathematical model by incorporating the population size distribution into the cumulative release equation (Eq. (2)). When characterizing microspheres for drug release studies, the mass fraction size distribution is used which represents the mass of microspheres in a specific size interval divided by the total mass of the population and the length of the size interval. Since the density of the microspheres is constant, the mass fraction size distribution and the volume fraction size distribution are equivalent, and are thus used interchangeably. In the present work the mean diameter calculated is the mass/volume moment mean diameter (d_{43}), also known as De Brouckere mean diameter, which is the center of gravity of the mass/volume fraction size distribution.

It was shown in previous work by Berchane et al. (2006) that the Rosin–Rammler mathematical distribution function provides an accurate representation of the size distributions of PLG microspheres prepared using our experimental set-up. For constant drug loading throughout the entire population (Table 1), the Rosin–Rammler function also represents the drug mass distribution for the population. The Rosin–Rammler distribution function can be expressed in the following form (Lefebvre, 1989; Berchane et al., 2006):

$$\left(\frac{1}{M_\infty}\frac{dM}{dd_m}\right) = g(d_m) = \frac{b}{a}\left(\frac{d_m}{a}\right)^{b-1}\exp\left(-\left(\frac{d_m}{a}\right)^{b}\right) \tag{5}$$

where M_∞ is the total mass of drug in the microsphere population under consideration; d_m the microsphere diameter; a and b are constants to be obtained from a least squares fit to the experimentally measured size distributions of PLG microspheres. The non-dimensional cumulative mass release equation for the population can then be expressed as

$$\frac{M_t}{M_\infty} = \int_{d_{min}}^{d_{max}} g(d_m)\frac{M_{t,d_m}}{M_{\infty,d_m}}\,dd_m \tag{6}$$

where d_{min} and d_{max} are the diameters of the smallest and largest microspheres in the population respectively, M_t is total mass of drug released from the population at time t. In Eq. (6), $g(d_m)$ is evaluated using Eq. (5), and $M_{t,d_m}/M_{\infty,d_m}$ is evaluated using Eq. (2).

4. Results and discussion

4.1. Microsphere fabrication and characterization

To investigate the effect of microsphere size on drug release rate, three batches of PLG microspheres were prepared at different impeller speeds (140, 300, and 900 rpm). A portion of the micropsheres was removed from each batch, and then the different portions were added together and sieved which resulted in five different size fractions (0.2–20, 20–40, 40–63, 63–90, and >90 μm). SEM micrographs of the sieved microspheres are shown in Fig. 1. The volume fraction size distribution is used when characterizing microspheres for drug release studies. This size distribution represents the mass of microspheres in a specific size interval divided by the total mass of the population and the length of the size interval. Integrating the volume fraction size distribution yields the cumulative volume fraction distribution. Fig. 2 shows the experimental cumulative volume fraction distributions for raw and sieved microspheres, plotted against the diameter of PLG microspheres. From inspection of the micrographs, it is apparent that the microspheres appear rigid and nicely spherical with a smooth surface. It is also evident from the micrographs and the size distributions that the majority of the fractionated microspheres lie within the mean pore diameter of the sieves used (Figs. 1 and 2(a)).

The cumulative Rosin–Rammler distribution function was shown by Berchane et al. (2006) to give the best representation of the cumulative volume fraction experimental data. This function is expressed in the following form (Lefebvre, 1989):

$$\frac{V}{V_{tot}} = G_V(d_m) = 1 - \exp\left(-\left(\frac{d_m}{a}\right)^{b}\right) \tag{7}$$

where V is total volume contained in microspheres of diameter less than d_m; V_{tot} the total volume of the microsphere population; d_m is the microsphere diameter. The Rosin–Rammler relationship describes microsphere size distribution in terms of

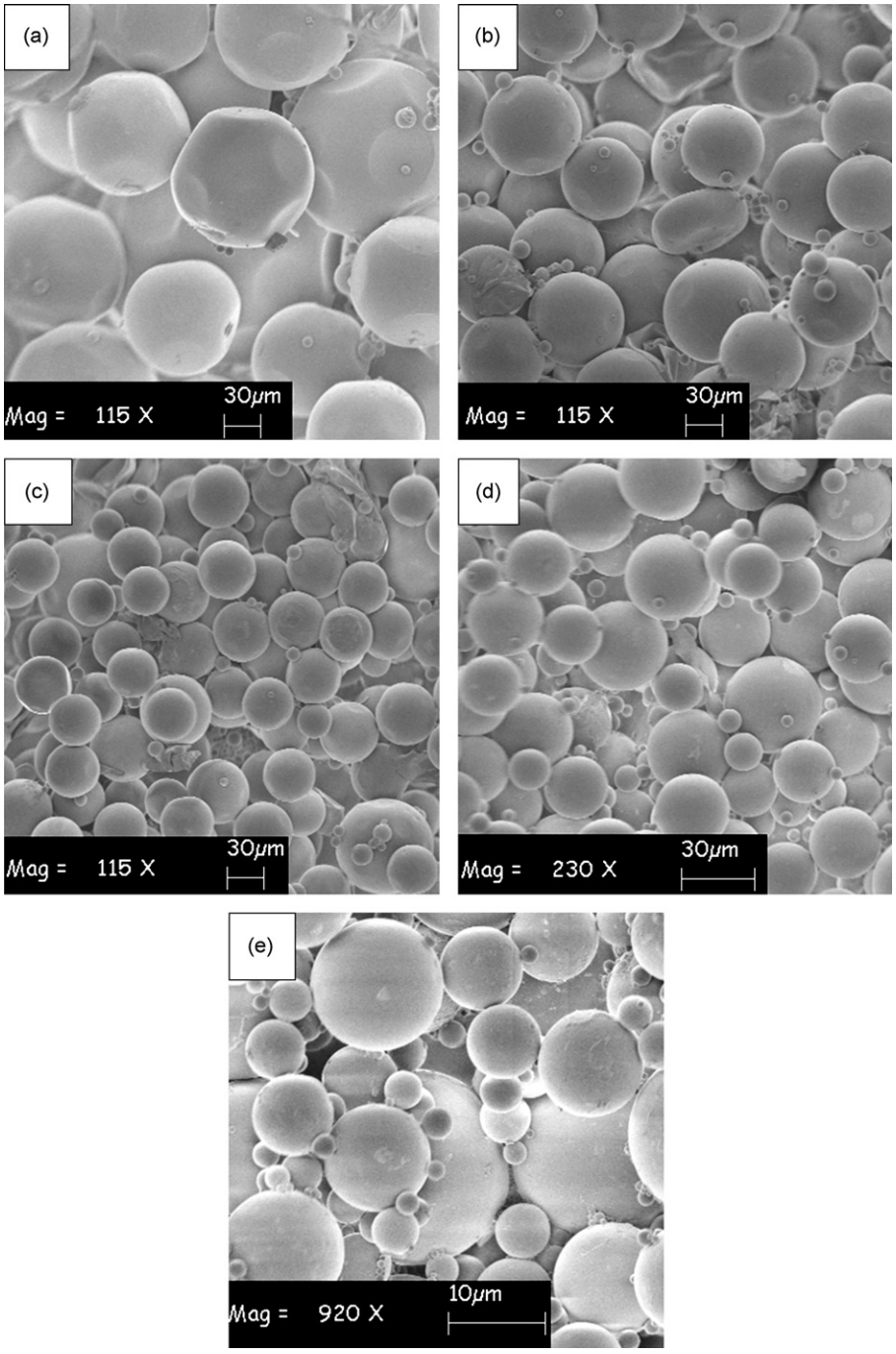

Fig. 1. SEM micrographs of sieved piroxicam-loaded PLG microspheres: (a) >90 μm; (b) 63–90 μm; (c) 40–63 μm; (d) 20–40 μm; (e) 0.2–20 μm.

the parameters *a* and *b*, where *a* provides a measure of the distribution mean diameter, while *b* provides a measure of the spread of the microsphere sizes. If *b* is infinite, the microspheres are all of the same size, and as the value of *b* decreases, the spread of the microspheres increases (Lefebvre, 1989). The parameters *a* and *b* are obtained from a least squares fit of the Rosin–Rammler cumulative volume fraction distribution function (Eq. (7)) to the experimental cumulative volume fraction distributions (Fig. 2). The values for *a* and *b* are given in Table 1. The parameter *b*, which provides a measure of polydispersity, ranges from 2.7 to 3.78 for raw populations and from 3.17 to 9.7 for sieved populations (Table 1). This shows that sieving was effective in reducing the polydispersity of the microsphere populations, and is important because one of the objectives of this work was to fabricate microsphere populations of varying polydispersity to investigate the effect of polydispersity on drug release rate.

4.2. *In vitro* drug release kinetics

Fig. 3 shows experimentally measured *in vitro* release of sieved piroxicam-loaded PLG microspheres having different size fractions. The release profiles shown in the figures are nor-

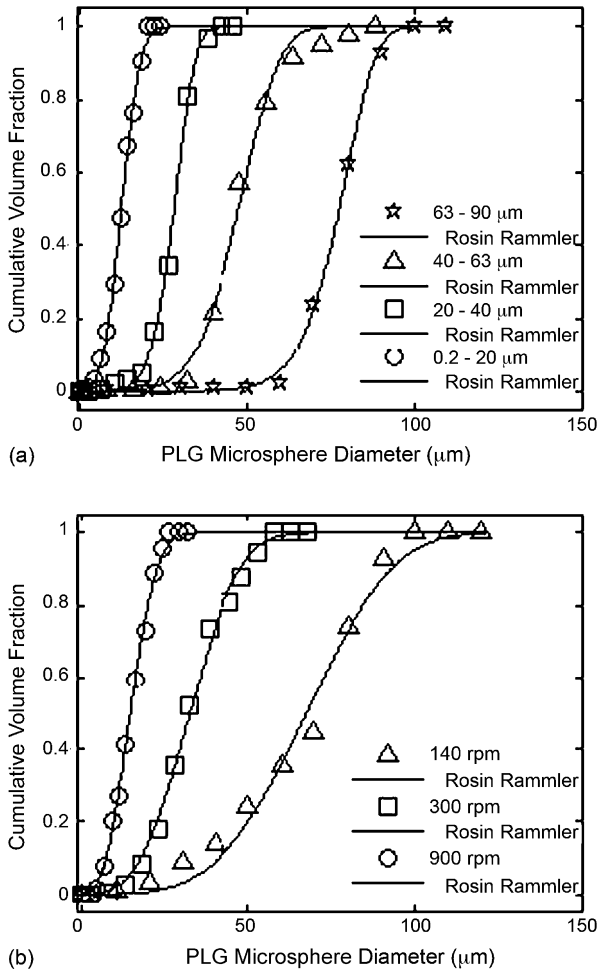

Fig. 2. Cumulative volume fraction distribution of (a) sieved and (b) raw, piroxicam-loaded PLG microspheres.

malized to the total amount of drug released at the end of the study, which was within 10% of the experimental loading shown in Table 1. The mean diameters (d_{43}) of the microspheres range from 13.9 to 81.2 μm (Table 1). Inspection of Fig. 3 reveals that size is a major determinant of the release profile, and drug initial release rate decreased with increasing system size. This is consistent with Fick's law of diffusion which attributes this decrease in drug release rate to an increase of diffusion pathways (reduced surface area to volume ratio for large spheres). In addition, microsphere populations having a mean diameter of 29.6 μm and above exhibit concave-upward (i.e. sigmoidal) profile, with a high initial rate of drug release ("burst release") which then slows down before it progresses again into a more rapid release phase before leveling off. This sigmoidal profile is most obvious for populations with large mean diameters ($d_{43} > 51.0$, Fig. 3(a)–(c)), and to a lesser extent in the 29.6 μm mean diameter population (Fig. 3(d)), which exhibits a near constant release (zero order profile). Although the initial burst release has been reported in numerous publications in our field, knowledge about the underlying mechanism is limited. One potential explanation for this burst release is that some drug becomes trapped on the surface of the polymer matrix during the manufacturing process (Huang and Brazel, 2001). The sigmoidal shape is believed to be a result of polymer degradation. As the polymer degrades, its molecular weight decreases, which causes an increase of the diffusion coefficient of the drug through the polymer matrix. This is translated into an increase in the drug release rate which gives rise to the sigmoidal profile. The 13.9 μm population (our smallest), and contrary to the other populations, exhibits first order release (Fig. 3(e)). It is believed that this is a result of the rapid initial rate of release with ~50% of encapsulated drug released within the first 3 days, during which polymer degradation effects are still negligible. In addition, polymer degradation proceeds at a slower rate for smaller microspheres (Berkland et al., 2003).

Fig. 4 shows the release from raw microsphere populations prepared at three different speeds (140, 300, and 900 rpm). The mean diameters of the microspheres range from 13.5 to 76 μm (Table 1). The drug release profiles from raw populations exhibit the same behavior as those from sieved populations having comparable mean diameters. Microspheres prepared at 140 and 300 rpm (having mean diameters of 76.0 and 33.5 μm, respectively) have concave-upward (i.e. sigmoidal) profile, while microspheres prepared at 900 rpm (13.5 μm mean diameter) exhibit first order release.

4.3. Model results

A Matlab program was written to solve the derived cumulative release equations (Eqs. (2) and (6)), with a time-dependent diffusivity and two fitting parameters (D_0 and k_{deg}), to predict the release of piroxicam from PLG microspheres having different mean diameters and size distributions. Dependence of diffusivity on molecular weight was modeled using Eq. (3). To account for the initial burst release, an initial diffusivity (D_0) is used as a fitting parameter. D_0 is used until the time-dependent diffusivity $D(M_w)$ is larger than D_0.

Since the molecular weight of PLG polymer varies with time, it was modeled using Eq. (4). The rate of polymer degradation, represented by the degradation constant (k_{deg}), is dependent on the hydrolysis mechanism taking place. PLG degradation has been widely investigated (Kenley et al., 1987; Lewis, 1990; Chui et al., 1995; Faisant et al., 2002; Siepmann et al., 2004; Raman et al., 2005), and reported values for k_{deg} range from 0.0638 to 0.104 day^{-1}. Here k_{deg} is used as a fitting parameter, and the obtained values are compared with the reported data in the literature.

Size distribution of the microspheres was represented in the mathematical model in two different approaches to investigate the use of the population size distribution model, and the alternative mean diameter model. For accurate modeling of the drug release profile, the size distribution of the populations was incorporated into the model, and Eq. (6) was solved. Alternatively, Eq. (2) was solved which utilizes the volume moment mean diameter to represent the size distribution of the population. As mentioned in Section 3.1, the volume moment mean diameter is the center of gravity of the volume fraction size distribution. The aim was to investigate the effect of polydispersity on drug release rate. Fig. 5 shows the release profiles generated by the model compared with the experimental drug release data for sieved

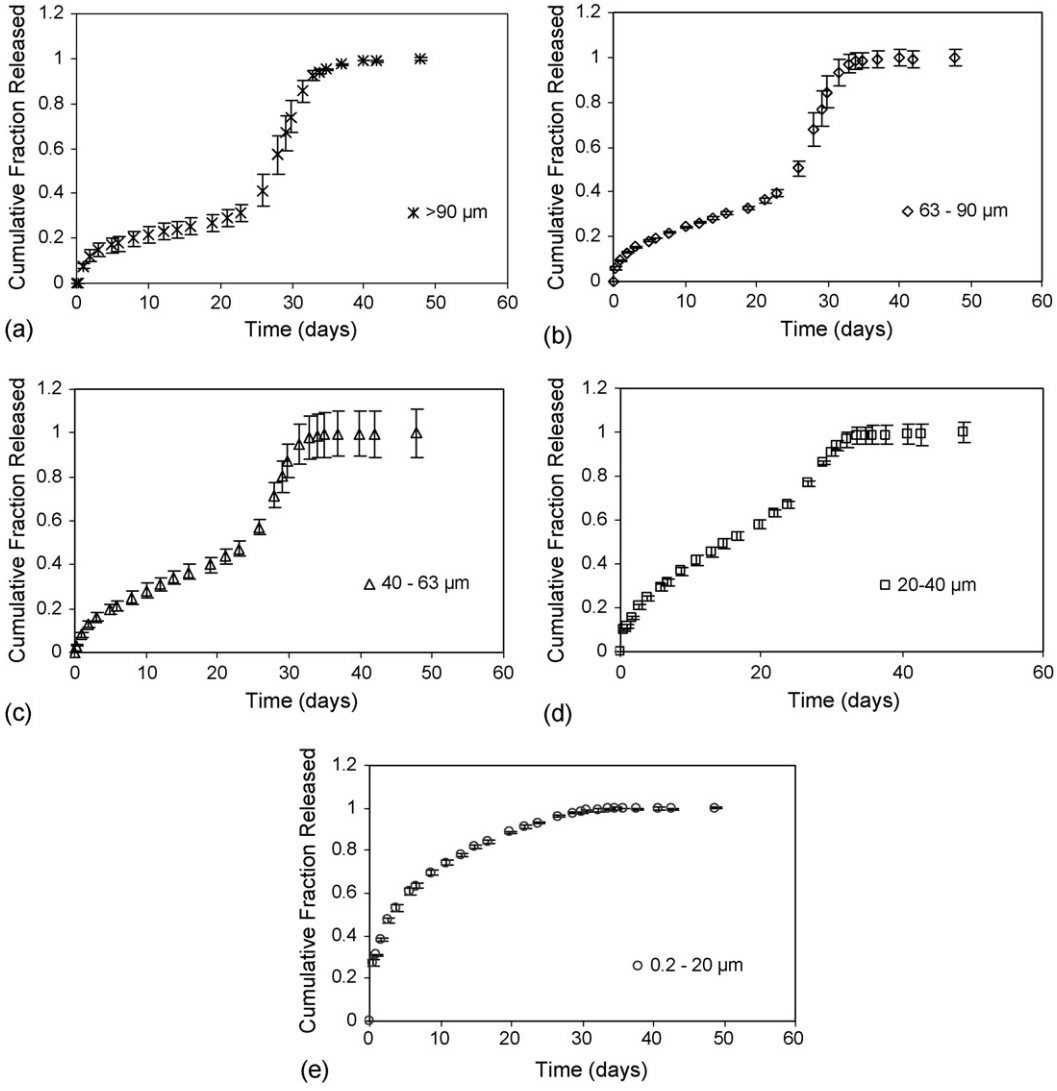

Fig. 3. Experimental piroxicam release from sieved PLG microspheres: (a) >90 μm; (b) 63–90 μm; (c) 40–63 μm; (d) 20–40 μm; (e) 0.2–20 μm.

microsphere populations. The solid lines represent modeling results based on size distribution, while dashed lines represent modeling results based on mean diameter. It is evident from Fig. 5 that the model based on size distribution is in good agreement with all the experimental results, and that the deviation of the mean diameter-based model from experimental results increases as the polydispersity of the population increases. Here we use the value of the parameter b (Table 1), obtained by curve fitting the cumulative Rosin–Rammler function to the experimental cumulative volume fraction distributions, to represent the degree of polydispersity of the populations. For the 0.2–20 μm population (value of b equal to 3.17, Table 1), the deviation is considerable (Fig. 5(d), $R^2 = 0.952$). Alternatively, populations that have a value of b greater than 3.0 (20–40, 40–63, and 63–90 μm, in Table 1), the deviation is negligible (Fig. 5(a)–(c), $R^2 > 0.994$). Thus, for populations having a value of $b \sim 3$, the effect of polydispersity on drug release is significant, and as a result incorporating the size distribution of the population into the model is necessary to provide an adequate fit for practical use. Consequently, it is recommended that the size distribution be incorporated into the model, when working with highly polydisperse populations (value of b equal to or less than 3).

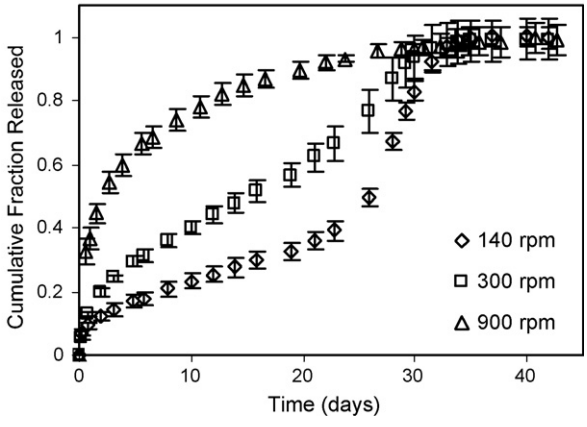

Fig. 4. Effect of microsphere size on piroxicam release from raw PLG microspheres.

From Fig. 5, it can be observed that the degradation constant (k_{deg}), obtained by curve fitting, increased from 0.07 day^{-1}

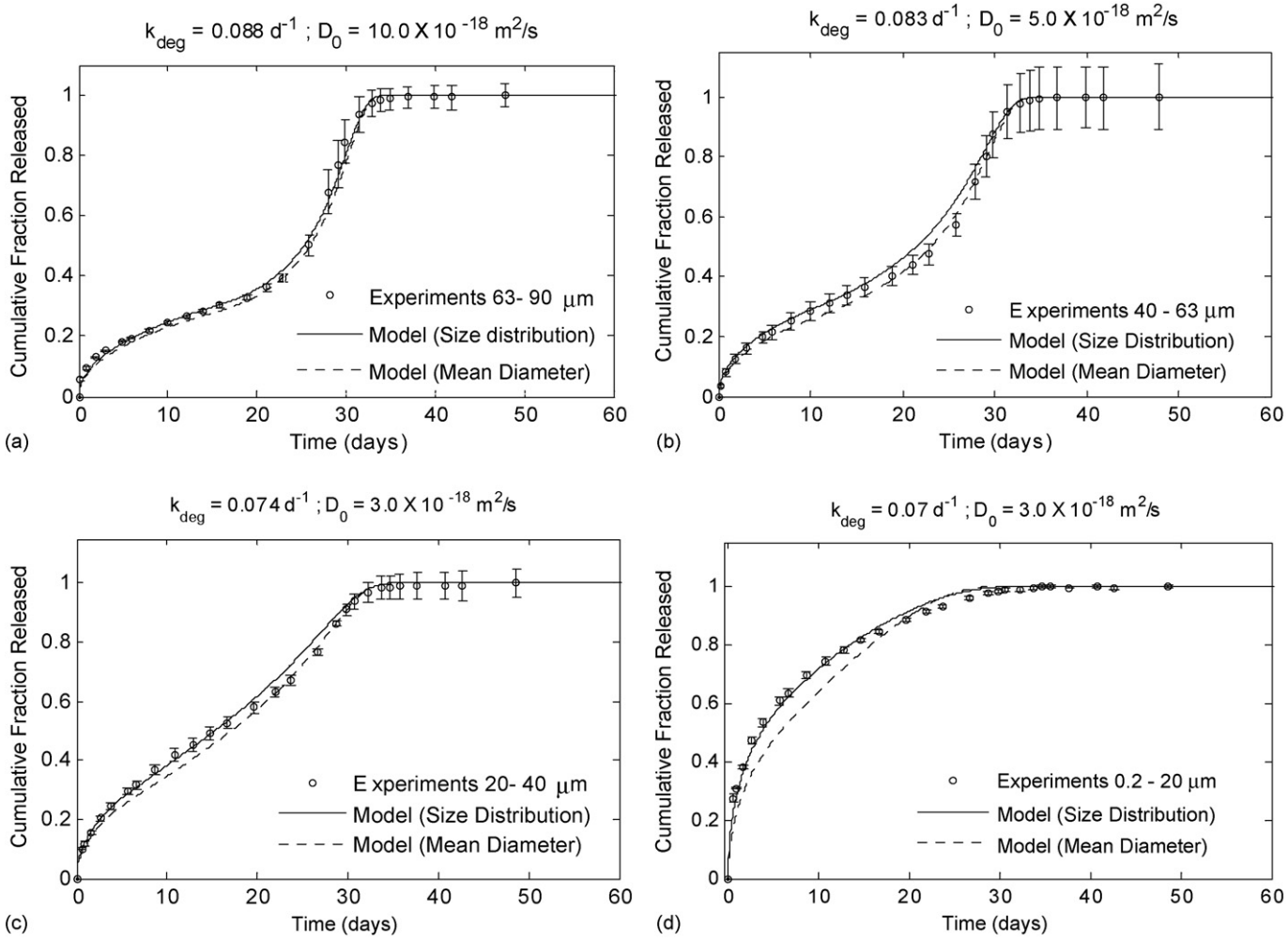

Fig. 5. Comparison of model profiles to experimental piroxicam release from sieved PLG microspheres: (a) 63–90 μm; (b) 40–63 μm; (c) 20–40 μm; (d) 0.2–20 μm.

for the microsphere population having a mean diameter of 13.9 μm (0.2–20 μm population, Fig. 5(d)) to 0.088 day^{-1} for the microsphere population having a mean diameter of 81.2 μm (63–93 μm population, Fig. 5(a)). This is consistent with published work which report that large microspheres degrade faster than small microspheres because of an increased buildup of acidic byproducts (Berkland et al., 2003). In addition, the values for k_{deg} obtained in this work are in good agreement with data reported in the literature which range between 0.0638 and 0.104 day^{-1} (Kenley et al., 1987; Lewis, 1990; Chui et al., 1995; Faisant et al., 2002; Siepmann et al., 2004; Raman et al., 2005).

It has been previously mentioned that an initial diffusivity (D_0) is used in this work to account for the initial drug burst release. Although this burst release is well documented in the literature, the underlying mechanism is not clearly understood (Huang and Brazel, 2001). It has been hypothesized that polydispersity is one of the main causes for the initial drug burst release, due to the presence of small microspheres which encapsulate sufficient amount of drug that is released more rapidly (Berkland et al., 2003). Here we investigate this hypothesis by considering the release from the 63–90 μm sieved population (Fig. 5(a)). This population has a value of b equal to 9.7 (Table 1), which indicates negligible polydispersity effect on drug release. However, by inspecting Fig. 5(a), it is observed that this population has high initial rate of drug release with an initial diffusivity (D_0, obtained by curve fitting the size distribution-based mathematical model to the experimental results) equal to 10.0×10^{-18} m^2/s. This value is significantly higher than the time-dependent diffusivity, $D(M_w)$, at time $t = 0$ ($D(M_w(0)) = 1.7 \times 10^{-18}$ m^2/s), which indicates that the simple diffusion model does not account for this initial burst release. Thus although this population has negligible polydispersity effect, it exhibits an initial drug burst release that cannot be merely explained by the simple diffusion model. This leads us to the conclusion that polydispersity is not the main cause for this initial burst release. The same conclusion can be made from recent work published by Raman et al. (2005), which investigated drug release rates from monodisperse PLG microspheres. Despite the uniformity of the microsphere populations, a high initial rate of drug release was observed which also cannot be explained by the diffusion model (Raman et al., 2005). One potential explanation for the burst effect is that some drug becomes trapped on the surface of the polymer matrix during the manufacturing process (Huang and Brazel, 2001).

5. Conclusions

Piroxicam-loaded PLG microspheres have been prepared using an emulsion technique. The effect of microsphere mean diameter, polydispersity, and polymer degradation on drug release rate from the microspheres was investigated. A mathematical model is reported that predicts drug release from polydisperse PLG microspheres. The model accounts for the effects of diffusion, polymer degradation and microsphere size distribution. It was shown that drug initial release rate decreased with an increase in microsphere size. Also, the release profile changed from first order to concave-upward as the microsphere size was increased. Polydispersity did not have a significant effect on drug release rate for populations having a polydispersity parameter (b) larger than 3. Alternatively, for distributions having a value of b close to or below 3, incorporating the size distribution of the population into the model provided a better fit to the experimental results. In addition it was shown that polydispersity was not the main cause for the initial "burst" release. The model results were in good agreement with experimental results, and thus can be used to predict drug release from polydisperse populations of microspheres.

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