International Journal of Pharmaceutics 383 (2010) 81–88

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Optimization of PLG microspheres for tailored drug release

N.S. Berchane [a], F.F. Jebrail [b], M.J. Andrews [b,*]

[a] Department of Mechanical Engineering, Texas A&M University, College Station, TX, USA
[b] Los Alamos National Laboratory, Los Alamos, NM, USA

ARTICLE INFO

Article history:
Received 23 June 2009
Received in revised form 3 September 2009
Accepted 4 September 2009
Available online 11 September 2009

Keywords:
Controlled release
Poly(lactide-co-glycolide)
Non-uniform microspheres
Tailored release
Constrained optimization

ABSTRACT

Here we explore the opportunity to design and then produce tailored release of therapeutic drugs from microcapsules. By use of "building blocks," formed from well characterized microcapsule populations, an inverse design algorithm has been developed that provides an optimal (in a least squares sense) combination of building blocks to achieve a desired release history. Previously we have reported experiments and a well validated mathematical model for computing drug release histories from PLG microcapsules, and these form the backbone of the present optimization algorithm. To expand our available basis for finding useful optimal solutions, we also report work to validate the mathematical model for two different molecular weights. Thus, our building blocks comprise populations that differ by microsphere mean diameter, polydispersity, and polymer molecular weight, giving three separate parameters that effect drug release rate, and from which we build a foundation for our tailored release. Here we have taken a basis of six different microcapsule release systems, from which we build a tailored release history using constrained optimization to fit a prescribed release profile. Comparison of predicted release with measurements from the tailored microcapsule populations was found to produce excellent results, with correlation coefficients greater than 0.98. By way of demonstration, a triple pulse design is described that illustrates the power of the method.

Published by Elsevier B.V.

1. Introduction

The research reported herein builds on our previously published modeling and experiments that accurately characterized the release of drugs from PLG microspheres (Berchane et al., 2006, 2007). Tailored drug delivery offers the ability to optimally design a prescribed release profile and has distinct advantages compared with conventional free dosage forms, in particular: improved efficacy, reduced toxicity, and improved patient compliance and convenience. Our 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).

The ideal drug release profile is one that initiates the optimum response in a patient such as zero-order release or pulsatile release (Richards et al., 2003; Narayani and Rao, 1996; Woo et al., 2001; Wise et al., 1987; Schachter and Kohn, 2002; Mathews et al., 1983; Santini et al., 2000). Zero-order release (Narayani and Rao, 1996; Woo et al., 2001; Wise et al., 1987) is desired for a wide range of drugs because it maintains a constant level of drug concentration well within the therapeutic window for extended time periods. Pulsatile release (Richards et al., 2003; Schachter and Kohn, 2002; Mathews et al., 1983; Santini et al., 2000) is attractive for vaccine delivery, as the drug release formulation can be designed to deliver distinct pulses which solves the need for booster shots. Difficulty in achieving the desired drug release rates (simple zero-order profile or a more complex pulsatile release profile), remains to be one of the major challenges in controlled drug delivery. Different parameters have been employed to control the release rate from biodegradable PLG microspheres (Cutright et al., 1974; Berkland et al., 2002; Siepmann et al., 2004; Raman et al., 2005). In addition to microsphere size (Berkland, 2002; Siepmann et al., 2004), and PLG molecular weight (Raman et al., 2005), lactide:glycolide ratio (Cutright et al., 1974) also plays a significant role in controlling drug release kinetics. To gain further control over release rates, some researchers have combined individual microsphere

* Corresponding author at: P.O. Box 1663, Mail Stop D413, Los Alamos National Laboratory, Los Alamos, NM, 87545, USA. Tel.: +1 505 606 1430; fax: +1 505 667 5921.
E-mail address: mandrews@lanl.gov (M.J. Andrews).

0378-5173/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2009.09.010

preparations having different release profiles to achieve desired release kinetics (Berkland et al., 2002). Narayani and Rao (1996) successfully obtained near constant release of anticancer drugs 5-fluorouracil (5-Fu), and methotrexate (MTX) for 6–10 days by mixing drug loaded gelatin microspheres of different size ranges. Similarly, Berkland et al. (2002) mixed known ratios of rhodamine and piroxicam containing PLG microsphere populations having different mean diameters and drug loadings to attain zero-order release. The ratios of the individual populations were determined by trial and error, where multiple linear combinations were examined to identify a combination resulting in linear drug release. It was found that the release profile from a mix of microsphere populations corresponded to mass-weighted linear combination of the individual release profiles, and constant release of rhodamine and piroxicam was achieved for 8 and 13 days, respectively.

This paper continues our work from Berchane et al. (2006, 2007) using PLG microspheres having two different molecular weights, M_w, and three different size fractions prepared using a solvent extraction emulsion technique. The effect of polymer molecular weight on drug release rate from poly(lactide-co-glycolide) (PLG) microspheres is investigated experimentally, and expands the basis of building blocks for our tailored release rates. The mathematical theory developed in our previous paper is used to model the effect of polymer molecular weight on drug release. It is this mathematical model that is then used with a numerical optimization (in a least squares sense) technique, to achieve desired release profiles by combining appropriate proportions of individual microsphere populations (our building blocks). Experiments are reported that use the optimal design, and the experimental data are then compared with desired results. A correlation coefficient is used to characterize the success of the method, with good to excellent agreement between desired and produced results.

2. Materials and methods

2.1. Introduction

The experiments described here were performed in an identical manner as those detailed in Berchane et al. (2007), so next we briefly review the materials, preparation techniques, characterization and *in vitro* release experimental methods.

2.2. Materials

Poly(D,L-lactide-co-glycolide) (PLG) polymer having a copolymer composition of 50:50, and two different M_w (18 kDa: inherent viscosity 0.41 dl/g, and 55 kDa: inherent viscosity 0.87 dl/g; inherent viscosity measured in hexaflouroisopropanol) was purchased from Birmingham Polymers. The poly (vinylalcohol) (PVA) was 87–89% hydrolyzed, with a M_w of 13–23 kDa. In addition to PVA, 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.

2.3. Microsphere preparation

Piroxicam was co-dissolved with PLG (10%, w/v) in dichloromethane (DCM) at 10% of the PLG mass (10% theoretical 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.

PLG microspheres having two different polymer molecular weights (18 and 55 kDa) were prepared at different impeller speeds (Table 1). The correlation developed by Berchane et al. (2006), which relates PLG microsphere population mean diameter to impeller speed, was utilized to determine the impeller speeds that would result in the desired microsphere sizes. Each microsphere preparation was then sieved separately using the appropriate sieve sizes to obtain three different size fractions for each polymer molecular weight: 0.2–20, 20–40, and 63–90 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.

2.4. 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. Piroxicam-free microspheres having 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 drug loading was similar to that reported by Berchane et al. (2007) with a range from 5% to 6% (w/w).

2.5. 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). The suspension was continuously agitated by shaking (Glas-Col, Terre Haute, USA) at 100 strokes per minute in a 37 °C incubator. Once a day the samples were centrifuged, and 1 ml of the supernatant was extracted, and replaced by fresh buffer to ensure sink conditions were always maintained. The microspheres were then vortexed and put back into the incubator. The piroxicam concentration in the supernatant was determined by measuring the absorbance at 276 nm in a spectrophotometer (Gilford Response Spectrophotometer). Piroxicam-free microspheres were treated similarly, and the absorbance from their supernatant was subtracted from all measurements. The microspheres were not observed to change their size or shape over the release period.

Table 1
Characterization of piroxicam-loaded PLG microspheres.

System M_i (i = 1–6)	M_w (kDa)	Impeller speed (rpm)	Sieve fraction (μm)	Mean diameter[a] d_{43} (μm)	Encapsulation efficiency (%)
1	18.0	150	0.2–20	14.9 ± 0.3	28.0
2	18.0	300	20–40	31.2 ± 0.3	23.6
3	18.0	900	63–90	76.2 ± 0.7	33.3
4	55.0	200	0.2–20	12.8 ± 0.2	26.0
5	55.0	400	20–40	32.3 ± 0.3	24.7
6	55.0	1200	63–90	83.2 ± 0.7	24.6

[a] Mean diameter ± standard error.

2.6. Microsphere characterization

Imaging of microspheres was performed with a LEO-VP1530 field emission scanning electron microscope. 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, given in Table 1. In summary, Table 1 describes our six "building block" microcapsule systems, labeled M_1 through M_6.

3. Mathematical model

The theoretical model developed in Berchane et al. (2007) accounts for microsphere size and polymer molecular weight, and is used here to predict drug release profiles from PLG microspheres having different size distribution and polymer molecular weight. A brief description of the model is included for completeness, more details may be found in Berchance (2007).

The PLG microspheres were prepared by co-dissolving the polymer and the drug in DCM which results in a monolithic solution. Desorption of the drug from monolithic systems was first described by Crank (1956). Solving the one-dimensional mass diffusion equation for a sphere, with initial and boundary conditions, gives the cumulative release equation for the total amount of diffusing drug leaving a sphere:

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

and $C(r = R, t > 0) = 0$, $C(r, t = 0) = C_1$, where R is the radius of the microsphere, 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 in the cumulative release equation ($D(t)$) 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 is expressed as (Pitt and Gu, 1987):

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

where $x = \ln(M_w)$. 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.

Hydrolysis, which causes bulk degradation of PLG polymer, starts with water uptake. The degradation process, which results in a decrease in the polymer molecular weight caused by random ester cleavage, is expressed as:

$$M_w(t) = M_w(0)\,\exp(-k_{deg}t) \qquad (3)$$

where $M_w(t)$ is the molecular weight of the polymer at time t, $M_w(0)$ is the molecular weight of the polymer at time $t = 0$, and k_{deg} is the polymer degradation constant. In the present work we investigate drug release from microspheres having different initial polymer molecular weights. This is implemented into the mathematical model by changing the value of polymer molecular weight at time $t = 0$ ($M_w(0)$) in Eq. (3).

The microsphere populations prepared in this work have a non-uniform size distribution. Following the work of Berchane (2007) the size distribution of the microsphere populations is represented by the mass (or equivalent volume) moment mean diameter (d_{43}), also known as De Brouckere mean diameter, which is the center of gravity of the mass fraction size distribution.

4. Results of experiments and modeling

4.1. In vitro drug release kinetics

Fig. 1 shows experimentally measured *in vitro* release from PLG microspheres having different size distributions and polymer molecular weights. The release profiles shown in the figure are normalized to the total amount of drug release at the end of the study, which was within 10% of the experimental loading given in Table 1. The mean diameters (d_{43}) of the microspheres range from 12.8 to 83.2 μm, and the M_w used were 18 and 55 kDa (Table 1). Inspection of Fig. 1 reveals that microsphere size is a major determinant of the release profile, and drug initial release rate decreased with increase in microsphere size, which confirms the results reported in Berchance (2007). This is also 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, inspection of Fig. 1 reveals that polymer molecular weight is also a major determinant of the release profile, and drug initial release rate decreased with increasing polymer molecular weight. As the polymer molecular weight is increased, the drug has less available space to diffuse through the polymer chains, and the diffusion coefficient decreases, which results in reduced initial drug release rates. The combined effect of varying the microsphere size and polymer molecular weight resulted in release profiles having different durations (10–28 days) and shapes (first-order, near zero-order, and sigmoidal).

4.2. Model results

The Matlab program developed in Berchane et al. (2007) was used to solve the cumulative release equation (Eq. (1)), and predict the release of piroxicam from PLG microspheres having different mean diameters and polymer molecular weights. The measured and modeled release profiles for the populations M_1–M_2 of Table 1 are shown in Fig. 2. Dependence of diffusivity on molecular weight was modeled using Eq. (2). To account for the initial burst release, an initial diffusivity (D_0) is used as a fitting parameter. The value of 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. (3). Fitted values for D_0 and k_{deg} are given in Fig. 2 for each of the microcapsule systems. Size distribution

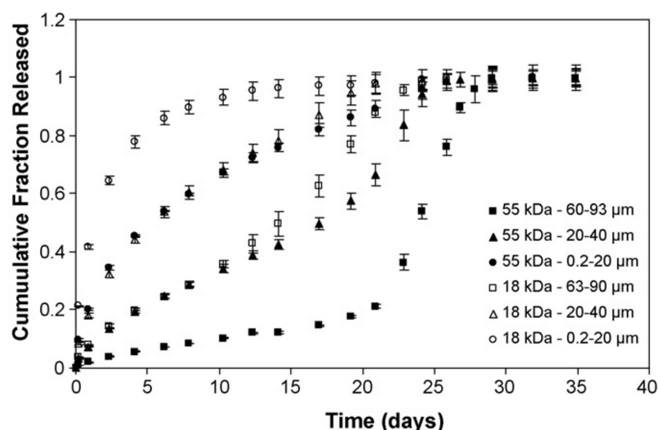

Fig. 1. Effect of microsphere size and polymer molecular weight on piroxicam release from PLG microspheres.

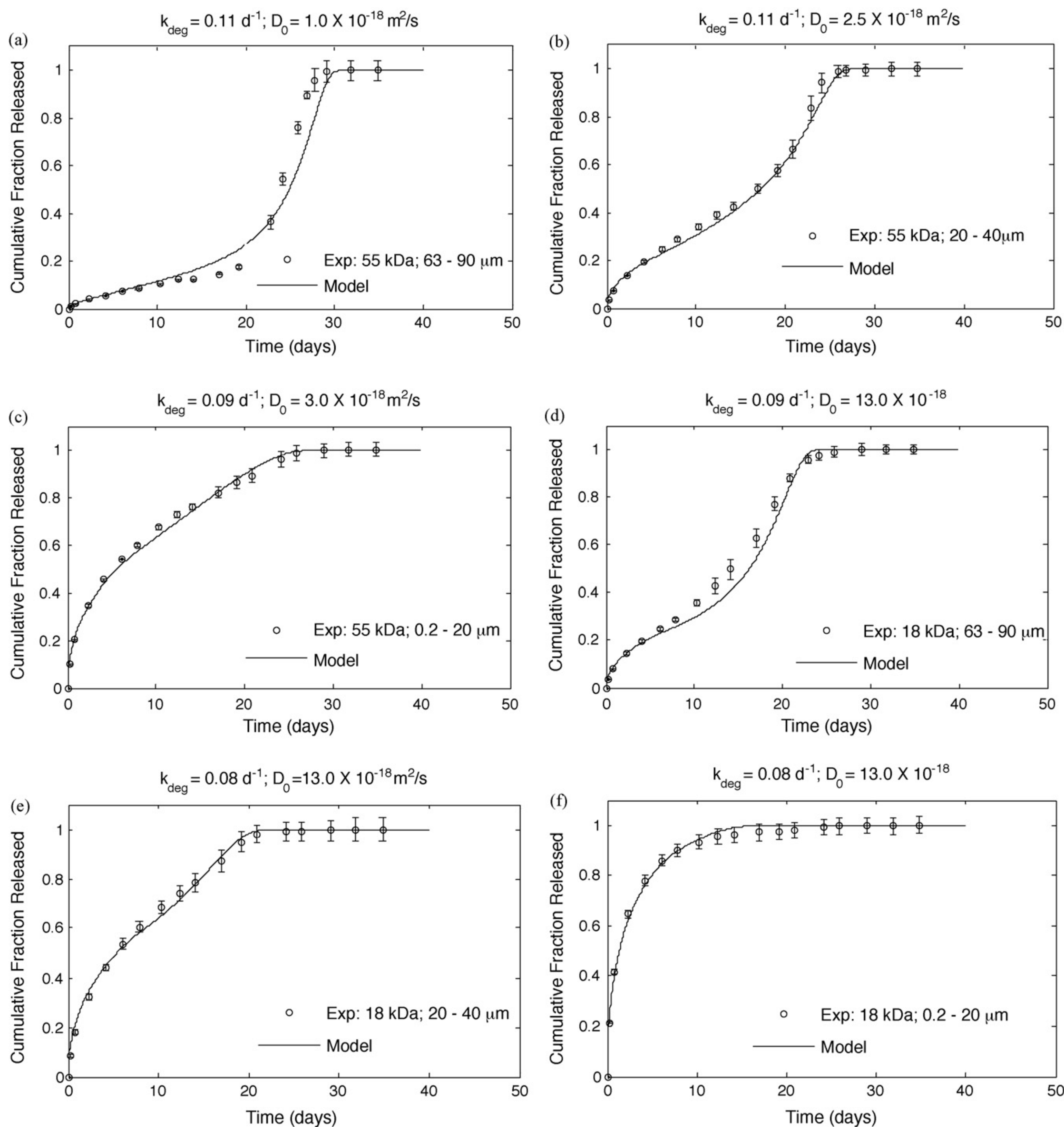

Fig. 2. Comparison of model profiles to experimental results of piroxicam-loaded PLG microspheres: (a) 55 kDa, 63–90 μm; (b) 55 kDa, 20–40 μm; (c) 55 kDa, 0.2–20 μm; (d) 18 kDa, 63–90 μm; (e) 18 kDa, 20–40 μm; and (f) 18 kDa, 0.2–20 μm.

of the microspheres was represented in the mathematical model by the volume moment mean diameter. As mentioned previously, the volume moment mean diameter is the center of gravity of the volume fraction size distribution. It is evident from Fig. 2 that the release profiles generated by the model are in good agreement with the experimental drug release data for the different microsphere populations. It is interesting to note that the degradation constant, k_{deg}, changes slightly for a fixed molecular weight, perhaps due to its use as a fitting constant, or it may be that the "burst release" process, captured by D_0, may also cause slight structural changes across the different size distributions.

5. Tailoring a release history

5.1. Introduction

Based on the different shapes of the individual release profiles depicted in Fig. 1, we hypothesized that it might be possible to achieve desired release rates by mixing appropriate proportions of two or more individual microsphere populations. To this end, a numerical optimization technique was developed, based on the least squares method, that computes the optimum proportions at which individual microsphere populations can be combined

to attain desired release kinetics. The results from the optimization procedure were then tested in the laboratory. The following sections describe the optimization algorithm and report the experimental validation.

5.2. Numerical optimization technique

A numerical optimization technique has been developed based on the least squares method, to compute the optimum proportions at which individual microsphere populations can be combined to attain desired release kinetics. An optimization problem can be formulated mathematically as follows (Luenberger, 1965):

$$\text{Minimize}: E(f); \quad \text{Subject to } f \in S \tag{4}$$

where $E(f)$ is the objective function to be minimized, and f is an $n \times 1$ vector of design parameters whose values are to be determined. For a solution to be feasible, it must belong to the constraint set S, which is a subset of the space $n \times 1$ column vectors R^n. When $S = R^n$, then the problem is an unconstrained optimization. In general, the constraint set is a collection of equality and inequality constraints on f. Few optimization techniques are available for finding the global minimum of a function. Instead, it is typical to search for a local minimum.

Here the objective function is the cumulative error between the target release profile and a linear combination of the available profiles:

$$E(f) = \sum_{i=1}^{m} (f_1 M_{1,i} + f_2 M_{2,i} + \cdots + f_n M_{n,i} - T_i)^2 \tag{5}$$

where m is the total number of points at which the profiles are evaluated, n is the total number of profiles to be combined, $M_1, \ldots, M_n$ are the individual profiles (shown in Fig. 2 as solid lines) to be combined, $f_1, \ldots, f_n$ are the mass fractions of the individual populations to be combined, and T is the target profile. In the present work our available release profiles are characterized in terms of time, microsphere diameter, and molecular weight, so $M = M(t, d_m, M_w)$, and given in Table 1 for the diameter and molecular weight, and shown in Fig. 1 as the release history (measured a fixed times, $i = 1$ to m).

A solution of the optimization problem is feasible only if the values of the mass fractions of the individual profiles $(f_1, \ldots, f_n)$ are constrained to the interval [0,1], and the summation of the mass fractions is equal to one. As a consequence, the problem under consideration is a constrained optimization problem where the goal is to find an f^* that minimizes the objective error function $E(f)$ while satisfying the following set of equality and inequality constraints:

$$\text{Minimize } E(f) = \sum_{i=1}^{m} (f_1 M_{1,i} + f_2 M_{2,i} + \cdots + f_n M_{n,i} - T_i)^2 \tag{6}$$

$$\text{Subject to}: 0 \le f_k \le 1 \quad \text{for } k = 1 \text{ to } n, \text{ and } \sum_{k=1}^{n} f_k = 1 \tag{7}$$

To be clear, the k index refers to one of the six systems of Table 1, and the i index refers to the individual measurements taken over an experiment (i.e. the times at which measurements were taken).

Such a constrained optimization problem is considerably more difficult to solve than the unconstrained problem. Although there are several approaches to solve the problem of Eqs. (6) and (7), the method of penalty functions is used in this work. Using penalty functions, the constrained optimization problem can be converted to unconstrained problem. The basic idea is to make the constraints implicit by adding terms to the objective function. These terms are zero when the constraints are satisfied but become large when the constraints are violated. As a consequence, solutions that violate the constraints are penalized because they incur large costs in the objective error function (Luenberger, 1965). To satisfy the constrained optimization problem, the following penalty functions were added to the objective error function:

$$(\min(0, f_k))^2, \ (\min(0, 1 - f_k))^2 \ \text{ for } 1 \le k \le n, \text{ and } \left(1 - \sum_{k=1}^{k=n} f_k\right)^2 \tag{8}$$

where the first two penalties ensure that the values of the mass fractions are constrained to the interval [0,1], and the third penalty ensures that the summation of the mass fractions is equal to one. The resulting objective error function was:

$$E(f) = \sum_{i=1}^{m} (f_1 M_{1,i} + f_2 M_{2,i} + \cdots + f_n M_{n,i} - T_i)^2 + \sum_{k=1}^{n} \left(\mu(\min(0, f_k)^2 + \min(0, 1 - f_k)^2) + \lambda \left(1 - \sum_{k=1}^{n} f_k\right)^2 \right) \tag{9}$$

where the multipliers μ and λ take values of 10^6 and 500, respectively. The majority of optimization algorithms make use of the following basic idea. Given an initial guess f^0, find an $n \times 1$ direction vector d^0 along which the value of the objective error function $E(f)$ decreases. Then, search for the minimum value of f along this direction starting at f^0 (Luenberger, 1965). Commonly used optimization techniques include the steepest descent method, the conjugate-gradient method, the Quasi-Newton optimization technique, and the simulated annealing method (Press et al., 1992). These techniques differ mainly in the way they construct the direction vector d^j. In this work the steepest descent optimization technique (Luenberger, 1965) was used to solve the inverse problem. The appeal of the steepest descent method is that it is conceptually simple and easy to program, and since we only have six parameter values to determine (f_1 to f_6) we need not be concerned about computational cost. However, for many other problems the steepest descent method can take an unacceptably large number of iterations to converge. The slow convergence rate of the steepest descent method can be increased by choosing the search direction in a more sophisticated way. For example, the conjugate-gradient method uses an effective approach that takes a linear combination of previous search directions to determine the new search direction (Press et al., 1992). Alternatively, the Quasi-Newton optimization technique utilizes both the first and second partial derivatives of the error function with respect to the components of f to determine the search direction (Press et al., 1992). Unfortunately, the minimum found by the previous methods is not necessarily a global minimum. One strategy for attempting to find a global minimum is to solve the optimization problem repeatedly, starting from different initial guesses. The best local minimum found can then be taken as an approximation to the global minimum. However, determining a suitable sequence of initial guesses can be a daunting task, and an exhaustive search is computationally prohibitive. An alternative approach is the simulated annealing method which consists of a random global search based on simulating annealing followed by an efficient local search (Press et al., 1992).

5.3. Steepest descent method

The steepest descent method (Luenberger, 1965) is used in this work to solve the optimization problem. Starting with an initial guess, f^0, we determine a search direction, d^0, and perform a line search along that direction. The result of the line search is taken as an updated estimate, and the process is repeated. The search

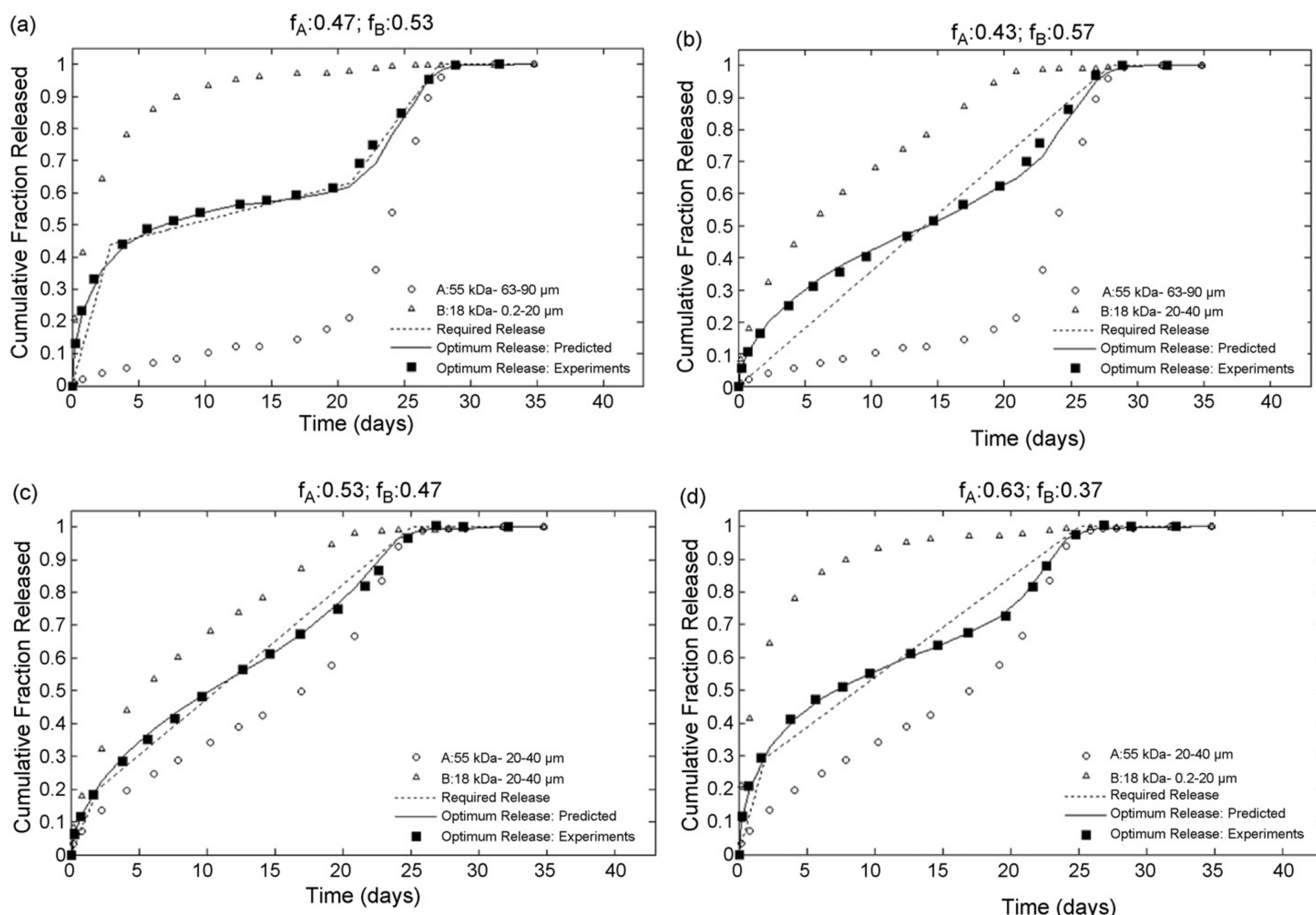

Fig. 3. Combining appropriate proportions of two individual PLG microsphere populations to achieve desired drug release profiles: (a) pulsatile, (b) zero-order, (c) near zero-order, and (d) near zero-order.

direction is determined by evaluating the gradient vector of partial derivatives of E with respect to the components of f:

$$\nabla E_k(f) = \frac{\partial E(f)}{\partial f_k} \quad 1 \le k \le n \tag{10}$$

where $\nabla E(f)$ is the direction of steepest ascent, and $d^0 = -\nabla E(f)$ is the direction of steepest descent. If α^j denotes the optimal step length resulting from searching along the direction d^j, starting from the point f^j, then the values of f are updated as follows:

$$f_k^{j+1} = f_k^{j} - \alpha^j \nabla E_k^{j}(f) \quad 1 \le k \le n \tag{11}$$

where j denotes the iteration number, and in this work α^j takes a value of 0.0002. The iterative process is repeated until the components of the direction vector d^j fall below a user-specified error tolerance, ε, set as 0.015.

5.4. *Release from mixtures of individual microsphere populations*

To test the optimization algorithm we constructed several desired release profiles, shown as dashed lines in Fig. 3. In particular, pulsatile, zero-order, and near zero-order release profiles in Fig. 3(a)–(d). After the desired release profiles were constructed, the numerical optimization technique was utilized to identify the best candidates to be combined and their optimum proportions. The initial goal was to achieve the desired profiles by combining two individual populations. In Fig. 3 the dashed line is the target profile, while the solid line is the predicted optimum release. To validate the predicted release, *in vitro* release experiments of a mixture of the individual populations at the determined proportions were performed.

In Fig. 3(a) the desired release has a pulsatile profile that delivers its first pulse (~45% of the total drug load) in the first 3 days, and then delivers its second pulse (~40% of the total drug load) from day 22 to day 28. Using the numerical optimization technique, it was determined that the optimum release can be achieved by mixing the 63–90 μm/55 kDa microsphere population and the 0.2–20 μm/18 kDa microsphere population at mass fractions of 0.47 and 0.53, respectively. From inspection of Fig. 3(a), it is evident that the predicted optimum release profile is in good agreement with the desired release, with a correlation coefficient of $R^2 = 0.988$, and that the pulsatile release was successfully achieved by combining microsphere populations.

The desired release in Fig. 3(b) has a zero-order profile that delivers its drug load at constant rate for 28 days (3.57% of total drug load delivered per day). Using the numerical optimization technique, it was determined that the optimum release can be achieved by mixing the 63–90 μm/55 kDa microsphere and the 20–40 μm/18 kDa microsphere populations at mass fractions of 0.43 and 0.57, respectively. Inspection of Fig. 3(b) shows that designing a truly zero-order release by mixing two individual populations had a limited success ($R^2 = 0.965$).

The desired release in both Fig. 3(c) and (d) has a near zero-order profile that starts with a high initial drug release rate for two (2) days and then shifts to a lower release rate for the additional 23 days. In Fig. 3(c) the desired release delivers 20% of the total drug load in the first two (2) days, while the desired

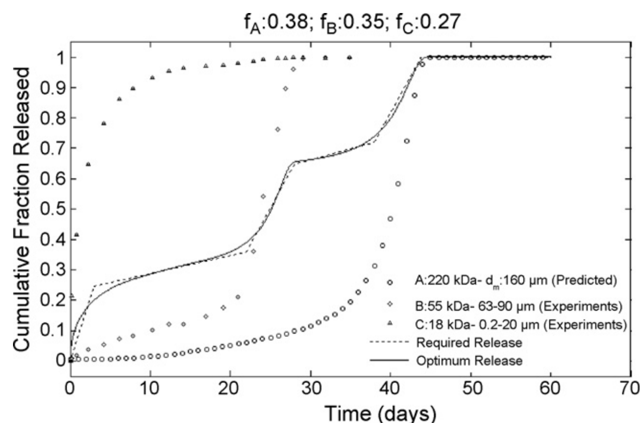

Fig. 4. Designing a drug release profile having three distinct pulses.

release in Fig. 3(d) delivers 30% of the total drug load in that same time period. The optimum release in Fig. 3(c) was achieved by mixing the 20–40 μm/55 kDa microsphere population and the 20–40 μm/18 kDa microsphere population at mass fractions of 0.53 and 0.47, respectively. It is evident from Fig. 3(c) that the predicted optimum release profile is in good agreement with the desired release (R^2 = 0.994). Alternatively, the optimum release in Fig. 3(d) was achieved by mixing the 20–40 μm/55 kDa microsphere population and the 0.2–20 μm/18 kDa microsphere population at mass fractions of 0.63 and 0.37, respectively. From inspection of Fig. 3(d), it is evident that the predicted optimum release profile is in fair agreement with the desired release (R^2 = 0.981).

In addition, Fig. 3(a)–(d) shows that the experimental optimum release profiles are all in good agreement with the predicted optimum release profiles. This validates the predicted release profiles, and shows that the measured release from a combination of microsphere populations corresponds to a mass-weighted linear combination of the individual profiles.

More complex drug release profiles can be achieved by mixing individual PLG microsphere populations having a wider range of sizes and polymer molecular weights. In addition, other key parameters such as polymer composition in general and lactide:glycolide ratio in particular, can be utilized to prepare PLG microspheres having a wide variation of drug release profiles. As an illustration of the power of the optimization method, a predicted drug release profile is shown in Fig. 4 that has three distinct pulses. The dashed line is the target profile, while the solid line is the predicted optimum release. The target release has a pulsatile profile that delivers its first pulse (~25% of the total drug load) in the first 3 days, and then delivers its second pulse (~29% of total drug load) from day 22 to day 28, and finally delivers its third pulse (~ 28 % of total drug load) from day 38 to day 44. The mathematical model was used to predict drug release from PLG microspheres having a mean diameter of 160 μm and a molecular weight of 220 kDa (population A in Fig. 4). Then using the numerical optimization technique, it was determined that the optimum release can be achieved by mixing the 160 μm/220 kDa microsphere population, the 63–90 μm/55 kDa microsphere population, and the 0.2–20 μm/18 kDa microsphere population at mass fractions of 0.38, 0.35, and 0.27, respectively. From inspection of Fig. 4, it is evident that the predicted optimum release is in excellent agreement with the desired release (R^2 = 0.998).

6. Conclusions

Piroxicam-loaded PLG microspheres have been prepared using the oil-in-water (o/w) emulsion technique. The effect of microsphere mean diameter, and polymer molecular weight on drug release rate from the microspheres was investigated. The mathematical model developed by Berchane (2007) was used to predict drug release from PLG microspheres having different size and polymer molecular weight. It was shown that the initial drug release rate decreased with an increase in polymer molecular weight. The combined effect of varying the microsphere size and polymer molecular weight resulted in release profiles having different durations (10–28 days), and shapes (first-order, zero-order, sigmoidal). The model results were in good agreement with the experimental results. It was also shown that the mixture release profiles corresponded to a mass-weighted linear combination of the individual profiles. A numerical optimization technique was developed to tailor desired drug release profiles by combining individual microsphere populations in appropriate proportions. Using the numerical optimization technique, appropriate proportions of individual microspheres were determined that generated target release profiles, in particular, zero-order, and pulsatile. The conventional microsphere preparation impeller set-up used in this work produced microsphere populations of non-uniform size distribution, and as a result precise matching to desired profiles was limited by the polydispersity of the microcapsule populations that formed our building blocks. In the near future new manufacturing techniques will produce monodisperse microsphere populations that will eliminate the need for sieving, and provide precise building blocks for further optimization of designed release histories.

References

Beck, L.R., Cowsar, D.R., Lewis, D.H., Cosgrove, R.J., Riddle, C.T., Lowry, S.L., Epperly, T., 1979. A new long-acting injectable microcapsule system for the administration of progesterone. Fertil. Steril. 31, 545–551.

Berchane, N.S., Jebrail, F.J., Karson, K.H., Rice-Ficht, A.C., Andrews, M.J., 2006. About mean diameter and size distributions of poly(lactide-co-glycolide) (PLG) microspheres. J. Microencapsul. 23, 539–552.

Berchane, N.S., Carson, K.H., Rice-Ficht, A.C., Andrews, M.J., 2007. Effect of mean diameter and polydispersity on drug release: experiment and theory. Int. J. Pharm. 337, 118–126.

Berkland, C., King, M., Cox, A., Kyekyoon, K.K., Pack, D.W., 2002. Precise control of PLG microspheres size provides enhanced control of drug release rate. J. Control. Release 82, 137–147.

Cowsar, D.R., Tice, T.R., Gilley, R.M., English, J.P., 1985. Poly(lactide-co-glycolide) microcapsules for controlled release of steroids. Methods Enzymol. 112, 101–116.

Crank, J., 1956. The Mathematics of Diffusion. Oxford University Press, London.

Cutright, D.E., Perez, E., Beasley, J.D., Larson, W.J., Posey, W.R., 1974. Degradation rates of polymers and co-polymers of polylactic and polyglycolic acids. Oral Surg. Oral Med. Oral Pathol. 37, 142–152.

Jeffery, H., Davis, S.S., O'Hagan, D.T., 1991. The preparation and characterisation of poly(lactide-co-glycolide) microparticles. I. Oil-in-water emulsion solvent evaporation. Int. J. Pharm. 77, 169–175.

Jeffery, H., Davis, S.S., O'Hagan, D.T., 1993. The preparation and characterization of poly(lactide-co-glycolide) microparticles. II. The entrapment of a model protein using a (water-in-oil)-in-water emulsion solvent evaporation technique. Pharm. Res. 10, 362–368.

Luenberger, D.G., 1965. Introduction to Linear and Nonlinear Programming. Addison-Wesley, MA.

Mathews, D.R., Lang, D.A., Burnett, M.A., Turner, R.C., 1983. Control of pulsatile insulin secretion in man. Diabetologia 24, 231–237.

Narayani, R., Rao, K.P., 1996. Gelatin microsphere cocktails of different sizes for the controlled release of anticancer drugs. Int. J. Pharm. 143, 255–258.

Ogawa, Y., Yamamoto, M., Okada, H., Yashiki, T., Shimamoto, T., 1988. A new technique to efficiently entrap leuprolide acetate into microcapsules of polylactic acid or copoly(lactic/glycolic acid). Chem. Pharm. Bull. 36, 1095–1103.

Parikh, R.H., Parikh, J.R., Dubey, R.R., Soni, H.N., Kapadia, K.N., 2003. Poly(D,L-lactide-co-glycolide) microspheres containing 5-fluorouracil: optimization of process parameters. AAPS Pharm. Sci. Technol. 4 (Article 13).

Pitt, C.G., Gu, Z., 1987. Modification of the rates of chain cleavage of poly(ε-caprolactone) and related polyesters in the solid state. J. Control. Release 4, 283–292.

Porjazoska, A., Goracinova, K., Mladenovska, K., Glavas, M., Simonovska, M., Janjevic, E.I., Cvetkovska, M., 2004. Poly(lactide-co-glycolide) microparticles as systems for controlled release of proteins—preparation and characterization. Acta Pharm. 54, 215–229.

Press, W.H., Flannery, B.P., Teukolsky, S.A., Vetterling, W.T., 1992. Numerical Recipes in Fortran: The Art of Scientific Computing. Cambridge University Press, Cambridge.

Raman, C., Berkland, C., Kyekyoon, K.K., Pack, D.W., 2005. Modeling small-molecule release from PLG microspheres: effects of polymer degradation and nonuniform drug distribution. J. Control. Release 103, 149–158.
Richards, A.C., Choi, I.S., Tyler, B.M., Wang, P.P., Brem, H., Cima, M.J., Langer, R., 2003. Multi-pulse drug delivery from a resorbable polymeric microchip device. Nat. Mater. 2, 767–772.
Santini, J.T., Richards, A.C., Scheidt, R., Cima, M.J., Langer, R., 2000. Microchips as controlled drug-delivery devices. Angew. Chem. Int. Ed. 39, 2396–2407.
Schachter, D.M., Kohn, J., 2002. A synthetic polymer matrix for the delayed release or pulsatile release of water-soluble peptides. J. Control. Release 78, 143–153.
Siepmann, J., Faisant, N., Akiki, J., Richard, J., Benoit, J.P., 2004. Effect of the size of biodegradable microparticles on drug release: experiment and theory. J. Control. Release 96, 123–134.
Wise, D.L., Trantolo, D.J., Marino, R.T., Kitchell, J.P., 1987. Opportunities and challenges in the design of implantable biodegradable polymeric systems for the delivery of anti-microbial agents and vaccines. Adv. Drug Deliv. Rev. 1, 19–39.
Woo, B.H., Kostanski, J.W., Gebrekidan, S., Dani, B.A., Tahanoo, B.C., Deluca, P.P., 2001. Preparation, characterization and in vivo evaluation of 120-day poly(DL-lactide) leuprolide microspheres. J. Control. Release 75, 307–315.