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RESEARCH PAPER

Microspheres Prepared with PLGA Blends for Delivery of Dexamethasone for Implantable Medical Devices

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ABSTRACT

Purpose To develop and characterize microspheres using poly (lactic-co-glycolic acid) (PLGA) blends (PLGA5050 (25 KD) and PLGA6535 (70 KD)) for dexamethasone delivery to prevent foreign body response to implantable biosensors.

Methods A single emulsion based oil/water solvent evaporation/extraction method was used to prepare microspheres.

Results All the microspheres prepared exhibited the typical triphasic release profile, but with different initial burst release, lag phase and zero order release rates. The burst release was reduced when the two PLGA were mixed at a molecular level, whereas increase in burst release was observed when phase separation occurred. Microspheres prepared using PLGA blends had significantly shorter lag phase. The activation energy (Ea) of dexamethasone release from microspheres was similar to the Ea value of PLGA degradation. The release kinetics were significantly enhanced under accelerated conditions (45 and 53°C) without altering the release mechanism of the post-burst phase. A rank order correlation between accelerated and "real-time" release kinetics was observed.

Conclusions Polymer blends of PLGA can produce microspheres with reduced lag time. The accelerated release testing conditions investigated can discriminate the formulations and predict "real-time" release. Such accelerated release testing can be used as a rapid screening method to facilitate formulation development.

KEY WORDS "real-time" and accelerated *in vitro* release · microspheres · PLGA blends

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ABBREVIATIONS

KD	Kilodalton
Mw	Molecular weight
PLGA	Poly(lactic-co-glycolic acid)
PVA	Poly(vinyl-alcohol)
THF	Tetrahydrofuran

INTRODUCTION

In the past several decades, significant progress has been made in the development of biosensors for real time monitoring of glucose to aid in the treatment and management of diabetes (1,2). Continuous glucose monitoring (CGM) provides information on the pattern of change in glucose levels with time, which varies from person-to-person and with individual metabolic events (*e.g.* fed, fasting, exercise, resting). CGM will pave the way towards realization of the "artificial pancreas" concept and ensure tight control of glucose through optimal insulin dosing. However, until now there is no commercially available fully implantable biosensor. A major obstacle to the application of implantable biosensors is their poor *in vivo* stability, which is manifested as a rapid loss in sensitivity following implantation (1). This is mainly due to tissue trauma caused during implantation and the continuous presence of the sensor in the body, which triggers a series of negative tissue responses including acute and chronic inflammation as well as fibrous encapsulation. To overcome the negative tissue response at the implantation site and facilitate the application of implantable biosensors, "smart" biocompatible coatings for implantable sensors that consist of dexamethasone-loaded poly(lactic-co-glycolic acid) (PLGA) microspheres dispersed in a polyvinyl alcohol (PVA) hydrogel have been developed (3–6). The results of previous studies have shown that local

delivery of dexamethasone can eliminate the foreign body response using a rat model (3–5), however, a delayed tissue reaction developed after exhaustion of the drug (6). Accordingly, there is a need to develop microsphere formulations for sustained dexamethasone release over the desired sensor application duration (*e.g.* 1 month, 3 months, or longer).

Microspheres loaded with hydrophobic drugs (*e.g.* dexamethasone) typically exhibit triphasic release profiles with an initial burst release phase (drug diffusion controlled) followed by a lag phase (polymer degradation controlled), and a secondary zero order release phase (a combination of drug diffusion and polymer degradation). Moreover, PLGA microsphere formulations for long-term drug delivery are usually associated with a long lag phase. For example, microspheres prepared using 70 KD PLGA have a lag phase of approximately 45 days, during which a limited amount of drug is released (7). This could be problematic as the drug concentration at the site of action may be too low to provide the required therapeutic effect. Pre-degrading microspheres, mixing different populations of microspheres (with different release profiles), or a combination of these strategies have been investigated to reduce or eliminate the lag phase (3,8). Although pre-degradation can decrease the lag phase of the formulation, the reproducibility between batches is expected to be poor. Mixed populations of microspheres involve preparation of several different batches of formulations, which may also lead to reproducibility issues and unnecessarily complicate product quality control.

Drug release profiles of PLGA microspheres can be tailored by varying the basic characteristics of PLGA polymers, such as polymer molecular weight (Mw) and copolymer ratio (9). Decreasing the polymer Mw and increasing the molar ratio of glycolic acid increases the hydrophilicity of the formulation leading to faster polymer degradation rates. In addition, it is known that PLGA degradation occurs mainly through random hydrolysis of ester bonds and is auto catalyzed under acidic conditions. Therefore, the low Mw PLGA may facilitate the degradation of the high Mw PLGA in the blend *via* increased water absorption and through generation of acidic oligomers that will result in autocatalysis of the polymer matrix. Accordingly, blending low and high Mw PLGA polymers may be a promising strategy to produce microspheres with shortened lag phase in a more reproducible way.

Another challenge associated with the development of long-term drug delivery microsphere formulations is the time required for "real-time" release testing. Accordingly, there is a need for accelerated release testing of such systems for rapid screening purposes during the early stage of formulation development as well as for quality control purposes. Ideally, the mechanism of drug release should remain unchanged under accelerated and "real-time" conditions. However, since accelerated tests require extreme conditions (*e.g.* temperature, pH) to achieve rapid release, it is possible that the release mechanism may alter. Nevertheless, "real-time" and accelerated release profiles should show a rank order correlation (10).

In the current study, the effects of blending low and high Mw PLGA on the *in vitro* drug release kinetics and on the physic-chemical properties of dexamethasone-loaded microspheres were investigated. Accelerated *in vitro* release tests were conducted at different elevated temperatures and compared to the "real-time" release profiles to determine if accelerated release tests can be used as a rapid screening tool for formulation development. The microspheres were characterized using high performance liquid chromatography, differential scanning calorimetry and scanning electron microscopy. A relationship between the formulation composition and drug release kinetics was developed.

MATERIALS AND METHODS

Materials

Dexamethasone, poly(vinyl alcohol) (PVA, Mw 30–70 KD), sodium chloride (ACS grade) and sodium azide were purchased from Sigma–Aldrich (St. Louis, MO). PVA (99% hydrolyzed, Mw 133 KD) was purchased from Polysciences, Inc. (Warrington, PA). PLGA Resomer® RG503H (inherent viscosity 0.32–0.44 dl/g) was a gift from Boehringer-Ingelheim. PLGA Medisorb 65:35 (Mw 70 KD) was a gift from Purdue Pharma. The PLGA Resomer RG503H 50:50 have carboxylic acid end groups and PLGA Medisorb 65:35 is end-capped. Methylene chloride, sodium mono-hydrogen phosphate (ACS grade), acetonitrile (ACN, HPLC grade), and tetrahydrofuran (THF, HPLC grade) were purchased from Fisher Scientific (Pittsburghm, PA). Disodium hydrogen phosphate (ACS grade) was purchased from VWR International. NanopureTM quality water (Barnstead, Dubuque, IA) was used for all studies.

Methods

Preparation of PLGA Microspheres

An oil-in-water (o/w) emulsion solvent extraction/evaporation technique was used to prepare dexamethasone-loaded microsphere formulations. Five different microsphere formulations were prepared in the current study (Table I). The PLGA polymers were dissolved in 8 ml of methylene chloride and 200 mg of dexamethasone was dispersed in this solution using a homogenizer at 10,000 rpm for 1 min. This organic phase was added slowly to 40 ml of a 1% (w/v) aqueous poly (vinyl alcohol) (PVA) (average Mw 30–70 KD) solution and homogenized at 10,000 rpm for 2.5 min. This emulsion was then added to 500 ml of a 0.1% (w/v) aqueous PVA solution and stirred at 600 rpm under reduced pressure to achieve rapid evaporation

of methylene chloride. The hardened microspheres were washed 3 times with de-ionized water and collected *via* filtration (0.45 μm). The prepared microspheres were kept under vacuum overnight and later stored at 4°C until further use.

Characterization of PLGA Microspheres

High Performance Liquid Chromatography (HPLC). The concentration of dexamethasone was determined using a Perkin Elmer HPLC system (series 200) with a UV absorbance detector (Perkin Elmer, Shelton, CT) set at 240 nm. The mobile phase consisted of acetonitrile/water/phosphoric acid (30/69.5/0.5, v/v/v). A Perkin Elmer C18 (4.6 mm × 15 mm) analytical column was used with the flow rate set at 1.2 ml/min. The chromatographs were analyzed by PeakSimple™ Chromatography System (SRI instruments, Torrance, CA).

Particle Size Analysis. The mean particle diameters of the prepared microspheres were determined using an AccuSizer 780A autodiluter particle sizing system (Santa Barbara, CA). Approximately 25 mg of microspheres was dispersed in 1 ml of 0.1% (w/v) PVA solution. 200 μl of the dispersion was used for particle size analysis. All measurements were conducted in triplicate and the results are reported as the mean ± SD.

Drug Loading Tests of the Microspheres. Five milligrams of dexamethasone-loaded PLGA microspheres was dissolved in 10 ml tetrahydrofuran (THF). This solution was filtered (Millex® HV, PVDF 0.45 μm syringe filter) and the dexamethasone concentration was determined *via* HPLC as described before using an injection volume of 5 μl.

Drug loading was determined as: % drug loading = (weight of drug loaded/weight of microspheres) × 100%. All measurements were conducted in triplicate and the results are reported as the mean ± SD.

Thermal Analysis. The glass transition temperature (Tg) of the prepared PLGA microspheres was determined using a TA instrument Q1000 differential scanning calorimeter (DSC) (New Castle, DE). Modulated DSC was used: the samples were heated at a rate of 2°C/min from −20°C to 200°C at a modulating oscillatory frequency of 0.4°C/min. The thermograms were used to determine the glass transition temperature (T_g) using Universal Analysis software (TA Instruments).

Morphology. The morphology of the microspheres was characterized using scanning electron microscopy (SEM). Samples were mounted on carbon taped aluminum stubs and gold coated in a sputter coater for 1 min at 6 mA. The samples were analyzed using a scanning electron microscope (DSM982 Gemini, Carl Zeiss, Inc.) at an accelerating voltage of 2.0 kV.

Accelerated and "Real-Time" *In Vitro* Release Testing

The PLGA microsphere/PVA hydrogel (99% hydrolyzed, Mw 133 KD) composite formulations were prepared as described previously (7,8). Briefly, an appropriate amount of PLGA microspheres were weighed and dispersed into the PVA hydrogel (5% w/v) solution, then this suspension was filled into a pre-made mold (15 × 38 × 2 mm) and subjected to three freeze-thaw cycles consisting of 2 h freezing at −20°C followed by 1 h thawing at 25°C.

In vitro release testing of these formulations was conducted at both elevated temperatures (45 and 53°C) and at body temperature (37°C). The formulations were immersed in 250 ml Pyrex® glass bottles containing 200 ml of 0.1 M phosphate-buffered saline (PBS) (pH 7.4) and incubated at 37, 45, or 53°C under constant agitation (100 rpm). Sink conditions were maintained. At pre-determined time points, 1 ml samples were taken and replaced with fresh PBS. The concentration of dexamethasone in each sample was determined using HPLC as described above. Cumulative percent release at a given time point was calculated as: cumulative percent release = (amount released at sampling time/total amount released) × 100. The values are reported as mean ± standard deviation (n=3).

Statistical Analysis

All the experiments were conducted in triplicate. To determine whether the difference between each formulation is statistically significant or not, a T test was conducted using ANOVA.

Table I Composition of Microsphere Formulations

Formulation	Dexamethasone (mg)	PLGA (70 KD, 6535) (g)	PLGA (25 KD, 5050) (g)
1	200	2	–
2	200	1.5	0.5
3	200	1.33	0.67
4	200	1	1
5	200	–	2

Table II Physical Characteristics of the Microspheres

Formulation	Drug loading (w/w)	Particle size (μm)	T_g (°C)
1	7.10 ± 0.80	6.98 ± 6.53	48.5
2	7.18 ± 0.04	6.51 ± 6.40	47.8
3	7.21 ± 0.03	6.01 ± 5.16	47.2
4	7.28 ± 0.05	5.93 ± 5.71	46.9
5	7.13 ± 0.18	5.64 ± 3.41	42.3

RESULTS

Characterization of PLGA Microsphere Formulations

The drug loading, particle size, and Tg of the prepared microsphere formulations are summarized in Table II. There was no significant difference in the drug loading of the microsphere formulations ($p > 0.05$). The number based mean particle size of formulations F1, F2, F3, F4, and F5 was approximately 6.98, 6.51, 6.01, 5.93, and 5.61 μm, respectively. The difference between the mean particle size of F1 and F2 was not statistically significant ($p > 0.05$), similarly, there was no statistically significant difference between F3, F4, and F5. However, the mean particle sizes of F1 and F2 were significantly larger than those of

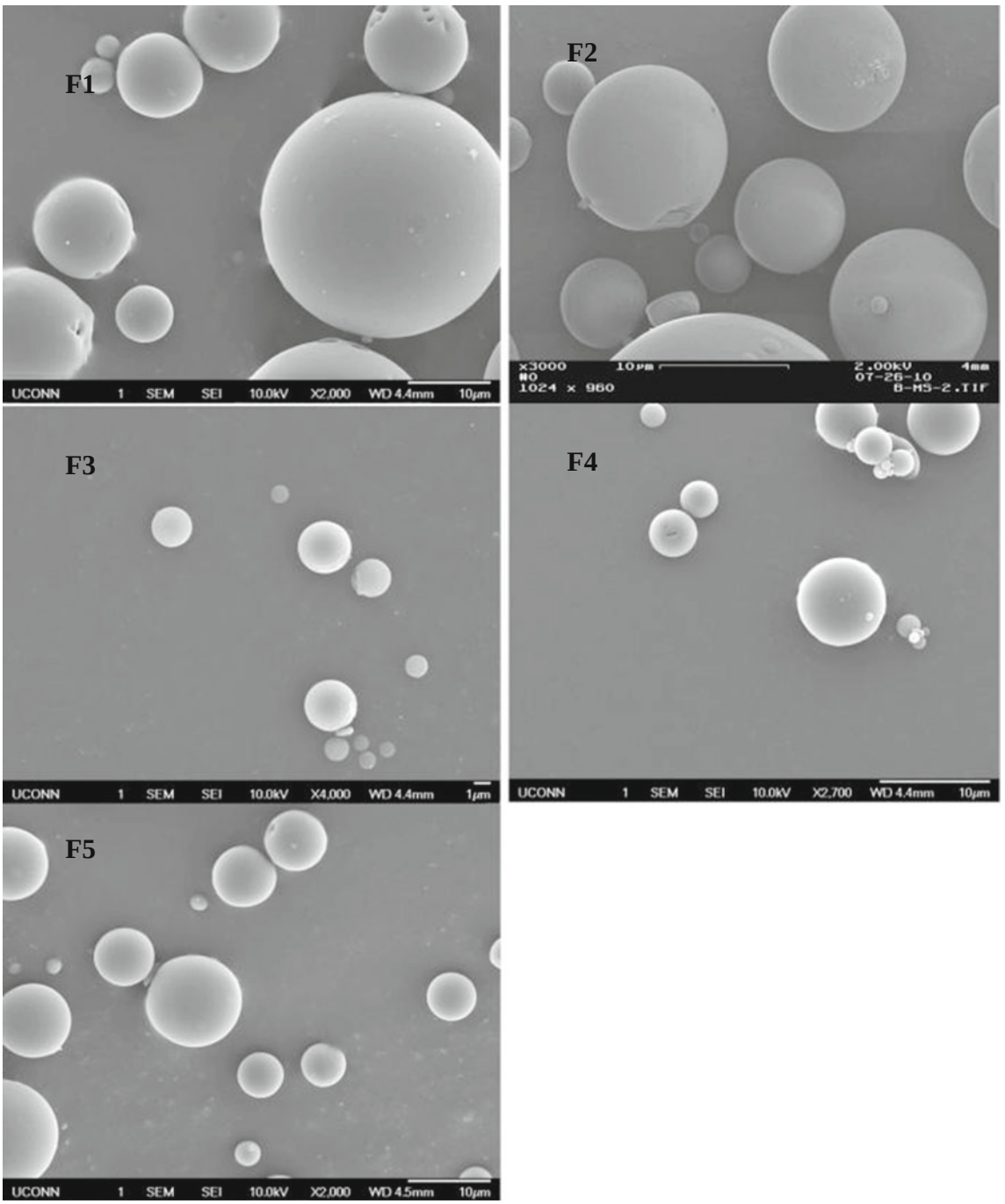

Fig. 1 Scanning electron micrographs of microsphere formulations prepared using blends of PLGA polymers at various mass ratios: F1 (PLGA6535 (70 KD) only); F2 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 3:1, w/w); F3 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 2:1, w/w); F4 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 1:1, w/w); and F5 (PLGA5050 (25 KD) only).

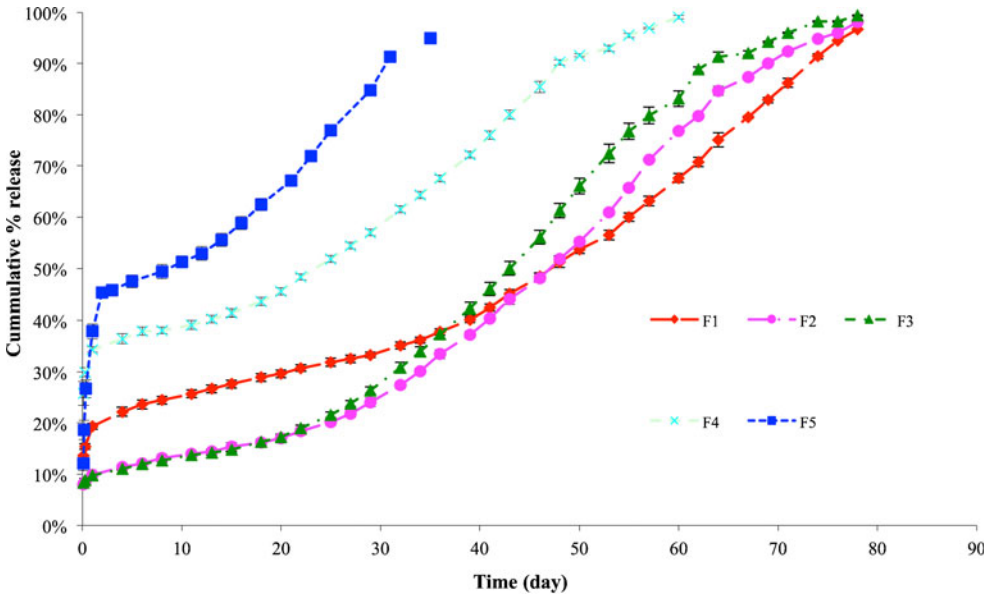

Fig. 2 Dexamethasone release from microsphere formulations (F1 (PLGA6535 (70 KD) only); F2 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 3:1, w/w); F3 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 2:1, w/w); F4 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 1:1, w/w); F5 (PLGA5050 (25 KD) only) in PBS (pH 7.4) at 37°C: (♦) F1; (●) F2; (♦) F3; (▯) F4; and (■) F5 (mean ± SD; $n = 3$).

F3, F4, and F5 ($p < 0.05$). The Tg of the microspheres prepared using PLGA5050 (25 KD) and PLGA 6535 (70 KD) alone were approximately 42.3°C and 48.50°C, respectively (Table II). The Tg of the microspheres prepared using blends of these two polymers was approximately 47°C, which was between the Tg values of the microspheres prepared using the single polymers. SEM micrographs (Fig. 1) showed discrete spherical microspheres with smooth morphology irrespective of formulation compositions.

"Real-Time" *In Vitro* Release Test

Dexamethasone release profiles at 37°C are shown in Fig. 2 for all the microspheres. A typical triphasic release profile was observed with: *1)* an initial burst release phase; *2)* a lag phase; and *3)* a secondary zero order release phase. The time to complete dexamethasone release from the microspheres prepared using PLGA 25 KD (5050) (F5) and PLGA 70 KD (6535) (F1) at 37°C was approximately 35 days and 85 days, respectively. When the microspheres were prepared using blends of these two polymers at a mass ratio of 1 to 1 (F4), drug release was complete in approximately 60 days. The initial burst release of F4 was approximately 35%, which is between F1 (approximately 25%) and F5 (approximately 45%). The lag phase of F4 was reduced to approximately 15 days from 41 days for F1. Interestingly, the microspheres prepared using blends containing larger amounts of the 70 KD PLGA (F2 and F3) showed a reduced initial burst release of approximately 10%. The total release durations of F2 and F3 were around 85 days, which was similar to that of F1. However, the lag phase of both F2 and F3 was much shorter (20 days) compared to F1 (41 days).

In Vitro Release Test at Elevated Temperatures

The release profiles at 43°C and 53°C are shown in Fig. 3a and b, respectively. The overall drug release was accelerated at both elevated temperatures, especially when the temperature was higher than the microsphere Tg. The time to complete drug release was reduced from 35 days (F5), 60 days (F4), and 85 days (F1, F2, and F3) at 37°C to 10, 20, and 27 days at 45°C, respectively. No lag phase was observed in the release profiles of F4 and F5 at 45°C. The initial burst release of F5 increased from approximately 45% to approximately 73%, whereas the initial cumulative % release of F4 remained almost unchanged (approximately 35%). Unlike F4 and F5, the overall release patterns of F1, F2, and F3 at 45°C were similar to those obtained at 37°C (typical triphasic release profiles). Interestingly, it was observed that the cumulative % release from F1, F2, and F3 during the first 2 h was smaller compared to the amount released at 37°C. For example, as shown in Fig. 3c, the cumulative % release during the first 2 h decreased from approximately 13% to approximately 9% for F1. However, the overall dexamethasone release rates were faster at 45°C than those at 37°C. As shown in Fig. 3b, no lag release phase was observed in the release profiles of all the formulations at 53°C. Drug release characteristics changed from the typical triphasic profile at 37°C to a biphasic profile with the initial burst release, followed by a zero-order release phase. The release durations were shortened to 3 days (F5), 5 days (F4) and 8 days (F1, F2, and F3) and the initial burst release of all the formulations were greatly enhanced at 53°C.

The activation energy of dexamethasone release from each formulation was calculated according to the Arrhenius equation: $k = A \times e^{-Ea/RT}$, where k is the zero-order release rate, A is a constant (pre-exponential factor), Ea is the activation

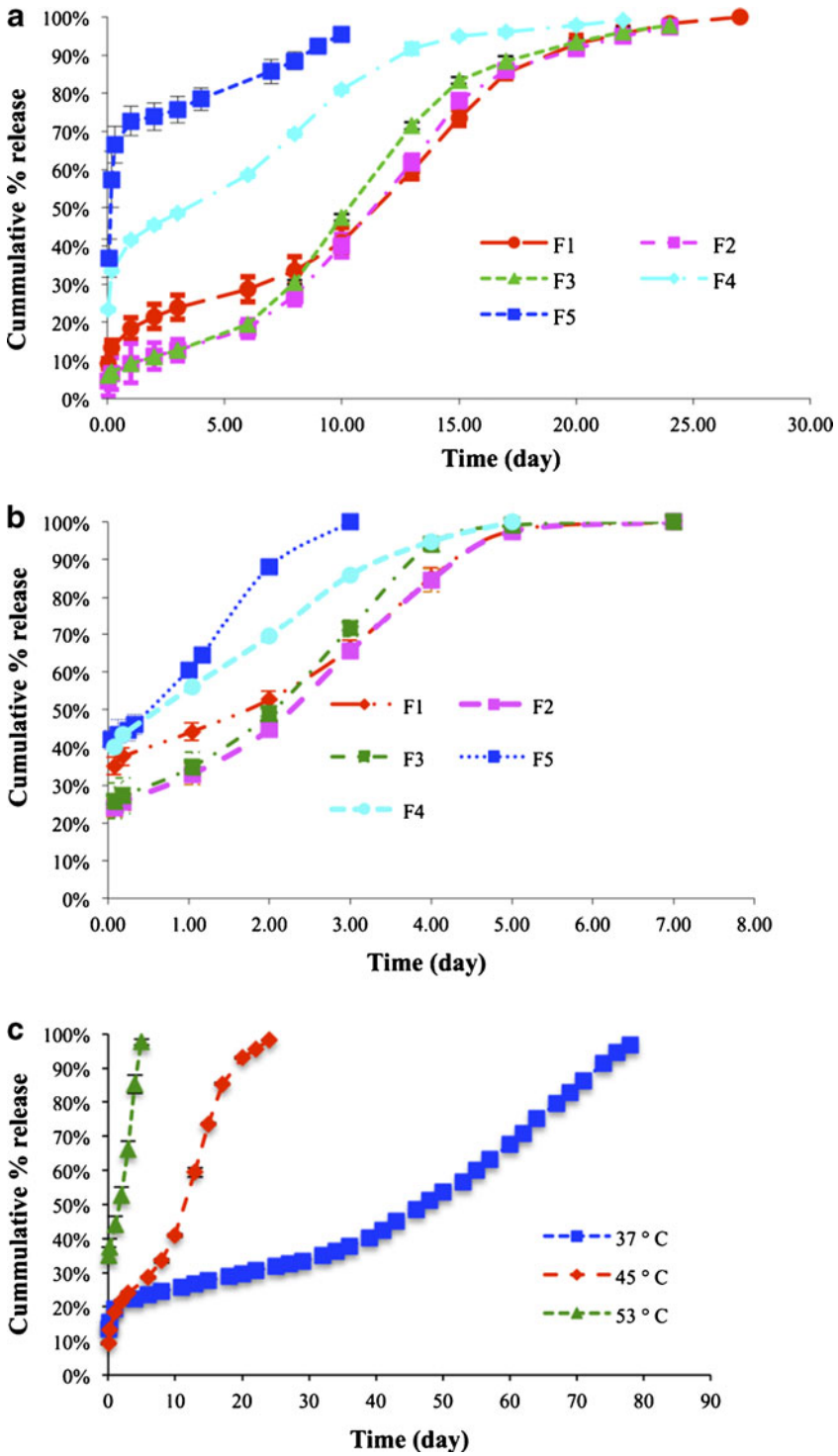

Fig. 3 (**a**) Dexamethasone release from microsphere formulations (F1 (PLGA6535 (70 KD) only); F2 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 3:1, w/w); F3 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 2:1, w/w); F4 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 1:1, w/w); F5 (PLGA5050 (25 KD) only) in PBS (pH 7.4) at 45°C: (●) F1; (■) F2; (♦) F3; (◆) F4; and (■) F5 (mean ± SD; $n = 3$). (**b**) Dexamethasone release profiles at 53°C: (◆) F1; (■) F2; (■) F3; (◆) F4; and (■) F5 (mean ± SD; $n = 3$). (**c**) Dexamethasone release profiles of F1 at (♦) 53°C; (◆) 45°C; and (■) 37°C (mean ± SD; $n = 3$).

energy, R is the universal gas constant (J K^{-1} mol^{-1}) and T is the absolute temperature.

The Ea was calculated through plotting ln k *versus* 1/T, where the slope was −Ea/R. Based on the experimental values of k at 45 and 53°C, the calculated activation energy of dexamethasone release from formulations F1, F2, and F3 was 123.82, 116.08, and 114.43 KJ/mol, respectively (shown as solid squares in Fig. 4). The Ea of dexamethasone release from the microspheres decreased with increasing amount of low Mw PLGA present in the polymer blends and it appeared that the Ea of these formulations was linearly related to the formulation composition. To validate this linear relationship, the Ea values

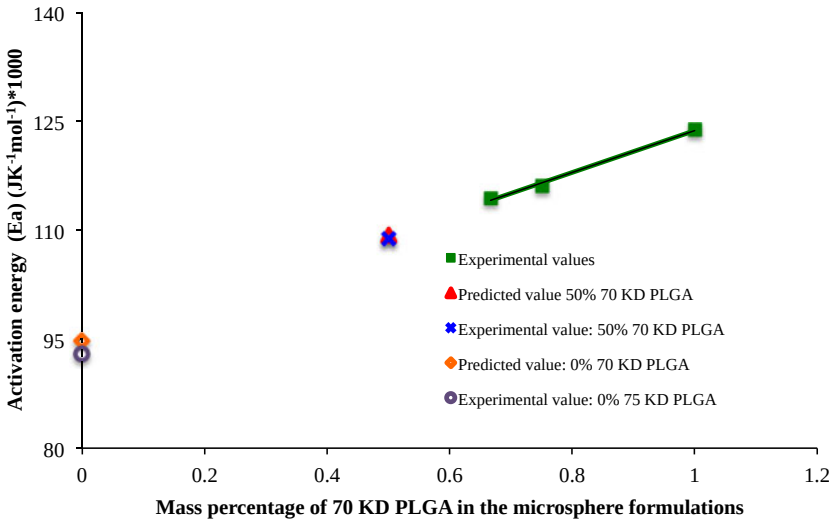

Fig. 4 The activation energy of dexamethasone release from different microsphere formulations as a function of formulation composition.

of F4 and F5 were calculated. The Ea values of F4 and F5 were 109.31 kJ/mol (shown as open triangle in Fig. 4) and 93. 12 kJ/mol (shown as open diamond in Fig. 4), respectively. Both calculated values were in agreement with the experimental values, where 108.88 kJ/mol was the experimental Ea value of F4 (shown as a cross in Fig. 4) and 93.11 kJ/mol was the experimental Ea value of F5 (shown as an open circle in Fig. 4).

In addition, Ea value of F3 was used to predict the release rate constant at 37°C (2.41 day^{-1}) (open diamond), which was in agreement with the experimental value (2.03 day^{-1}) (open square) as shown in Fig. 5. Based on this, both elevated temperature conditions investigated appeared to be appropriate accelerated conditions. However, 53°C is considered the preferred temperature since the release rate is fastest and the release duration is shortened from approximately 85 days down to 7 days.

Phase Behavior

As shown in Figs. 2 and 3, the release profile of F4 (prepared using low and high Mw PLGA at a 1 to 1 mass ratio) is in the middle of the release profiles of the formulations prepared using either one of these two polymers alone (F1 and F5). It was speculated that phase separation occurred in F4 during release. On the other hand, formulations prepared using blends with larger amounts of high Mw PLGA (F2 and F3) showed lower initial burst release compared to F1 and F5. This indicated that a denser polymeric matrix was achieved and these two polymers might be mixed at the molecular level inside the microspheres. In order to further investigate this, formulations F2, F3, and F4 were incubated at 40°C for 24 h prior to DSC analysis. 40°C was chosen as the incubation temperature since this is below the Tg of these formulations, but still high enough to provide sufficient molecular mobility to allow structural relaxation in a short period of time. As shown in Fig. 6, the F4 formulation phase separated following incubation as manifested by two individual Tgs. However, only a single Tg was observed in the F2 and F3 formulations indicating that the two polymers present in the microspheres were molecularly mixed.

DISCUSSION

The microspheres prepared with 25 KD and 70 KD PLGA, either alone or in combination, had similar drug loading and surface morphology, but different mean particle size. It is speculated that the reduced particle size with decrease in polymer Mw is a result of reduced inherent polymer viscosity as the polymer concentration was constant in each formulation. Since the theoretical drug loading of all the formulations prepared was the same (approximately 9%, w/w) and the actual drug loading of all formulations was comparable, this indicates that varying the formulation composition does not affect the encapsulation efficiency.

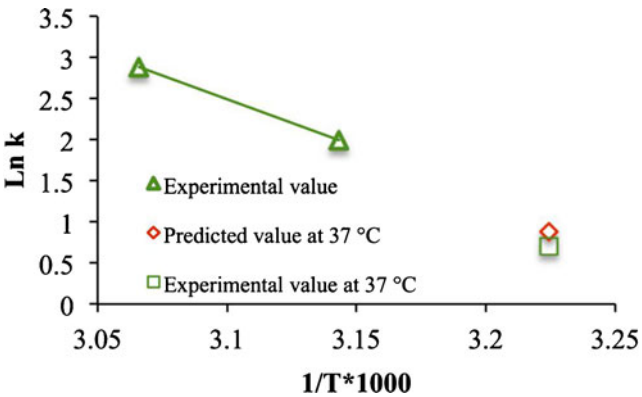

Fig. 5 Arrhenius plot of the rate of dexamethasone release from formulation F3 microspheres (PLGA6535 (70 KD):PLGA5050 (25 KD) = 2:1, w/w) (pH 7.4 PBS buffer) as a function of temperature at 45°C, and 53°C (shown in as *open triangle*). Rate constants at 37°C for predicted and experimental values are shown as an *open diamond* and an *open square*, respectively.

Formulations F1, F2, F3, F4, and F5 at 37°C all showed a triphasic release profile which is typical of dexamethasone (a hydrophobic drug) loaded in PLGA microspheres. However, the burst release, lag phase, and zero order release rate of each formulation was different (Fig. 2). The reduced burst release with increase in polymer Mw (comparison of F1 (70 KD) to F5 (25 KD)) is speculated to be a result of increased polymer hydrophobicity and consequent decreased drug diffusion. Likewise, the prolonged lag phase (41 days for F1 compared to 7 days for F5) is considered to be a consequence of the increased time required for polymer degradation at the higher Mw. In the case of microspheres prepared using polymers blends, the observed decrease in the lag phase and increase in the zero order release rate with increasing amount of the low Mw PLGA can be explained as: *1)* larger amount of low Mw PLGA leads to higher relative hydrophilicity of the prepared microspheres, thus easier water penetration and faster polymer degradation; and *2)* increase in local acidity as a result of accumulation of acidic oligomers and monomers as a result of degradation of the low Mw PLGA further accelerates microspheres erosion.

Formulations F2 and F3 prepared using blends with smaller amounts of the low Mw PLGA showed the lowest cumulative % release in the burst release phase at all *in vitro* release temperatures investigated (Figs. 2 and 3). It is speculated that the presence of the low Mw PLGA reduces polymer precipitation rate during microsphere solidification and prolongs the duration of a semi-solid state prior to the glassy state. Therefore, there is more time for the polymer chains to rearrange into a lower energy state resulting in microspheres with higher density and reduced drug diffusion. However, instead of further decrease in the burst release with increase in the amount of low Mw PLGA in the blends, an increased burst release was observed when equal amounts of low and high Mw PLGA were used to prepare the microspheres. The % cumulative release in the burst release phase of F4 was in the middle of F1 and F5. It is speculated that unlike the PLGA polymers in formulations F2 and F3, which are mixed at a molecular level, polymers in F4 are phase separated leading to the observed increase in the burst release. This was supported by the results of the phase behavior study (Fig. 6). The phase separation in F4 was evident by two individual Tgs. This suggests that polymer miscibility plays an important role in the performance of microspheres prepared with polymer blends and it is affected by the concentration of each polymer present in the mixture. The similarity in the cumulative % release of formulations F2 and F3 indicates that when the polymers are mixed at a molecular level, the composition of the mixture does not affect the initial burst release phase.

Accelerated release testing did not give an accurate prediction of the burst release phase. The cumulative % burst release of all the formulations at 53°C was significantly enhanced compared to at 37°C due to enhanced drug diffusion. At 45°C which is close to but lower than the Tg of F1, F2, and F3, the chain mobility of these microspheres is sufficiently high

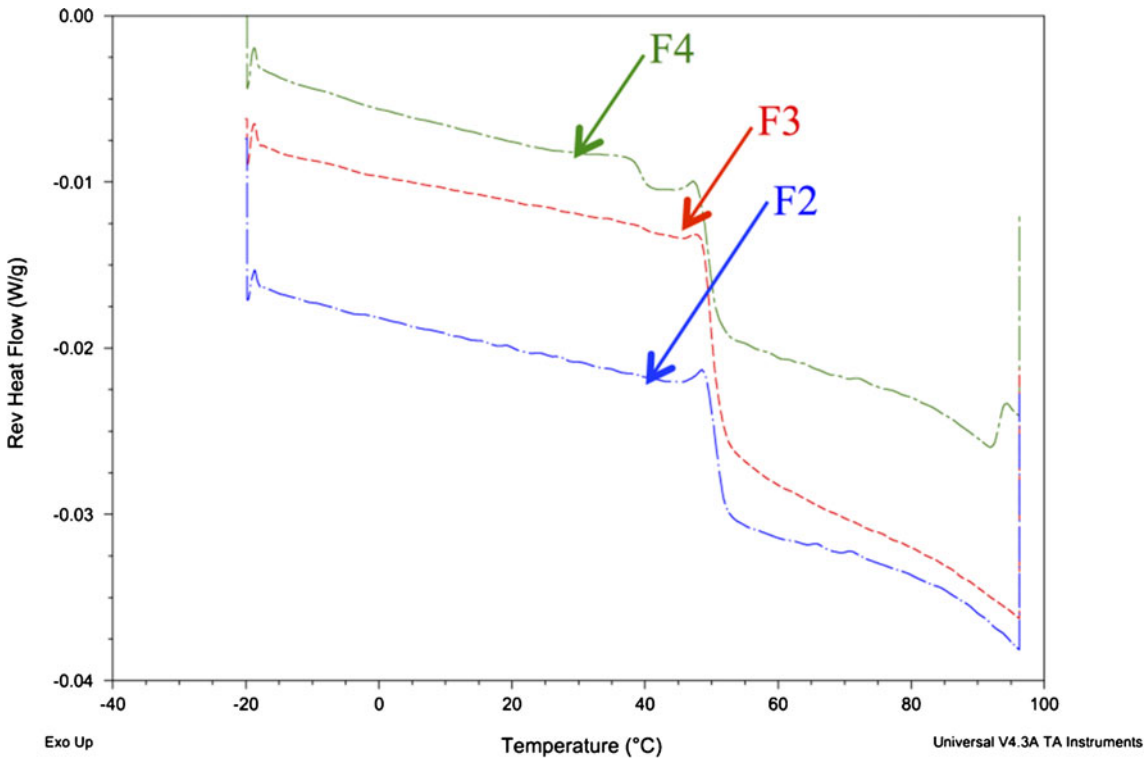

Fig. 6 DSC thermograms of F2 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 3:1, w/w); F3 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 2:1, w/w); F4 (PLGA6535 (70 KD):PLGA5050 (25 KD) = 1:1, w/w) following incubation at 40°C for 24 h.

to allow structural relaxation resulting in reduced dexamethasone diffusion. This explains the observed decrease in the initial cumulative % release from F1, F2, and F3 in the first 2 h at 45°C. However, the absorbed water plasticizes the PLGA matrix, which in turn deceases the Tg of the microspheres over time. This leads to faster release rates once the Tg is lower than the release media temperature, since the rubbery state makes the polymer more susceptible to hydrolysis.

Although the initial burst release phase changed significantly at elevated temperatures, the accelerated tests were able to predict the secondary zero order release phase at 37°C (Fig. 5). This indicates that the mechanism of release during the post-burst release phase is not altered under these accelerated conditions. In addition, the Ea for dexamethasone release (94.91 kJ/mol) from F5 for the post-burst release (degradation-controlled phase) is in agreement with the reported Ea value for the degradation of PLGA (25 KD) polymer (99.10 kJ/mol) (11). This further indicates that the dexamethasone release follows polymer erosion for the secondary zero order release phase. The observed linear decrease in the Ea for dexamethasone release with increase in the amount of low Mw PLGA in the blends provides additional proof that the low Mw PLGA accelerates the degradation of the high Mw PLGA (Fig. 4).

It is of importance that accelerated release tests are able to discriminate between formulations. The accelerated tests at both 45 and 53°C showed similar rank order correlations between the five formulations investigated (Fig. 3). As discussed above, the release mechanism for the post-burst release phase remained unchanged at elevated temperatures, the five formulations that showed predominantly polymer degradation-controlled release exhibited a linear correlation between "real-time" and accelerated post-burst release.

CONCLUSIONS

The current study demonstrated the feasibility of using mixtures of PLGA polymers with different Mw to tailor the release profiles of microsphere formulations. The miscibility of the polymers in the blends plays an important role in the burst release phase and is affected by polymer concentration. The lag phase of microspheres prepared using blends of low and high Mw PLGA was significantly shortened compared to microspheres prepared using only the high Mw PLGA. The Ea value of dexamethasone release from the microspheres prepared using polymer blends is a function of the formulation composition. The similarity between the Ea values of dexamethasone release and PLGA degradation indicates that post-burst release is polymer erosion controlled. Elevated temperature accelerated the drug release kinetics without altering the release mechanism of the post-burst release phase. The observed rank order correlation between the accelerated and "real-time" release profiles indicates that accelerated release tests at the elevated temperatures investigated can discriminate formulations and predict "real-time" performance. Accordingly, elevated temperature accelerated *in vitro* release testing may be employed as a rapid screening test to facilitate the development of PLGA based long-term drug delivery microspheres.

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