Cosolvent Effects on the Drug Release and Depot Swelling in Injectable *In Situ* Depot-Forming Systems

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ABSTRACT: Although injectable depot-forming solutions have been commercialized, the factors that influence the overall release kinetics from such systems are still not fully understood. In this work, we address the effect of cosolvent on the issue of excessive burst release of potent bioactives from injectable depot-forming solutions. Specifically, we have evaluated the influence of addition of a relatively hydrophobic cosolvent (triacetin) to more hydrophilic biocompatible solvents such as dimethyl sulfoxide (DMSO) and *N*-methyl-2-pyrrolidone (NMP) on the burst release. Drug release and solvent release results demonstrate that high burst release that occurred when only hydrophilic solvent was used as solvent was significantly reduced by adding triacetin as a cosolvent. The profiles of drug release were in good agreement with the profiles of the hydrophilic solvent DMSO or NMP release, and the suppression of the burst by triacetin addition is due to the suppression of the solvent release. Surprisingly, the swelling of the depot increased with triacetin amount and the depot morphology became more porous compared with the absence of triacetin. Usage of hydrophobic solvent as a cosolvent to reduce the burst release was shown to be more effective on the hydrophobic PdlLA depot and less effective on the relatively hydrophilic RG502 depot. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:1783–1793, 2012

Keywords: Polymeric drug delivery system; controlled release; drug transport; diffusion; biodegradable polymers; depot forming; swelling; cosolvent

INTRODUCTION

The development of injectable *in situ* depot-forming drug delivery systems has received considerable attention over the past few decades as such systems offer a relatively noninvasive means to sustained delivery of proteins and peptides. These injectable systems are classified into four categories according to the mechanism of solidification[1,2]: (1) thermoplastic pastes,[3,4] (2) *in situ* cross-linked polymer systems,[5,6] (3) thermally induced gelling systems,[7,8] and (4) *in situ* polymer precipitation.[9–11] Of these, recent interest has been focused on *in situ* biodegradable injectable systems based on the polymer precipitation mechanism as this system combines the advantages of microparticulate delivery and an implanted device,[12–14] especially following the commercialization of the leuprolide acetate/poly(lactic-*co*-glycolic acid) (PLGA)/*N*-methyl-2-pyrrolidone (NMP) depot system, which can suppress testosterone levels for up to 6 months (Atrigel® system, QLT, Inc, Vancouver, British Canada).[15] In this system, a water-insoluble polymer and a drug were mixed with a biocompatible solvent to form a homogeneous solution or suspension.[12] When this solution or suspension was injected into the aqueous medium, water miscible organic solvent dissipated into the surrounding environment while water migrated into the polymer matrix, leading to the formation of a solid/semisolid depot at the site of injection due to polymer precipitation, followed by sustained release of the incorporated drug over a period of time by the combined effects of diffusion of the drug within the matrix and degradation or erosion of the polymer material.

However, the formation of the solid/semisolid depot from the flowable polymer solution was not instantaneous. Between the time of injection and the completion of the depot formation, initial drug burst release occurred, typically over a period of minutes to several hours, resulting in the release of a large amount of

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drug especially when drug is soluble in the solvent or water, and causing tissue irritation and sometimes systemic toxicity if the drug is particularly toxic.[16]

As the initial burst release is affected significantly by polymer phase inversion dynamics, many approaches related to manipulating the rate of phase inversion of the polymer solution were developed to control the burst release. Increasing the polymer concentration and adjusting the polymer molar mass are commonly used methods but limited because of the low viscosity requirement of the polymer solution during injection. To reduce the burst release while maintaining injectability, several methods were proposed recently, such as compressing the drug with or without hydrophobic agents to form particulates,[17] introducing carriers for the drug to form a mixture,[18] adding a polymeric controlled-release additive,[16] or adjusting the solvent characteristics by mixing a hydrophilic solvent and a hydrophobic solvent at different ratios.[19,20] Compression of the drug into tablets and subsequent grinding yields particulates of drug with lower surface area to mass ratio than that formed by the conventional methods, leading to lower water uptake compared with noncompressed particles. If the drug is liquid, it may be incorporated into a porous solid particle, such as anhydrous calcium phosphate.[17] When a carrier is added into the system, the drug is isolated from the organic solvent and less likely to disperse into the surrounding aqueous medium along with the solvent. Instead, the drug is constrained within the delivery system as it solidifies to form a semisolid implant. Consequently, the initial drug burst release may be suppressed.[18] The polymeric controlled-release additive, preferably water insoluble, such as a poly(lactide-coglycolide)/polyethylene glycol block copolymer (e.g., PLG/PEG-5000), can also be incorporated into the polymer solution to delay phase inversion so as to reduce the burst release.[16]

The burst release can also be controlled by adjusting solvent characteristics to tune the rate of water migration into the polymer matrix.[21] The preferred solvents in an injectable biodegradable drug delivery systems are NMP and dimethyl sulfoxide (DMSO) because of their pharmaceutical precedence[13]; however, NMP or DMSO, being hydrophilic, dissipates into surrounding aqueous medium quickly after injection upon contact with water and thus causes the polymer solution to exhibit rapid phase inversion associated with a high burst release and formation of a porous, solid depot structure. In contrast, triacetin and ethyl benzoate, both more hydrophobic solvents, leave the "depot" very slowly and lead to slower phase inversion and form semifluid structure, resulting in a slow gelation and significant reduction in the burst release.[22,23] We hypothesize that using a mixture of a hydrophilic solvent and a hydrophobic solvent wherein the required solvent miscibility with water can be tuned by varying the mixing ratio will restrict uptake of water into matrix and lead to a lower burst release.

In comparison with the simple administration benefit of the mixed solvent system, both compaction and grinding, or adding a new component (carrier or additive) to the formulation, make the system complicated. In contrast, the hydrophobicity of the mixed solvents can be adjusted readily based on the requirement. Benzyl benzoate (BB) as a hydrophobic solvent and benzyl alcohol (BA) as a hydrophilic solvent have been used as the mixed solvents to understand the effect of the characteristics of the mixed solvents on the drug delivery. However, some of the results were conflicting with respect to drug release.[21,24] Higher burst drug release was found in formulations containing greater proportion of BA as reported by Singh and Singh,[24] whereas the release of the drug was slowed when the hydrophilic component BA was increased as reported by Prabhu et al.[21] These observations were not rationalized or reconciled sufficiently, in our opinion, primarily due to lack of complementary experimentation.

Previously, our group has reported the structure formation in injectable PLGA depots and two kinds of drug release *in vitro* mechanisms.[25–27] To understand the effect of the solvent hydrophobicity on the drug release in this system, the effect of mixed solvent of hydrophilic solvent and hydrophobic solvent at different ratio on the drug release was studied in particular in this paper. NMP was chosen as hydrophilic solvent in this work because of its miscibility with water and reasonable biocompatibility. On the contrary, DMSO has a much higher median lethal dose (LD_{50}) (oral, rat: 14,500 mg/kg, based on the Material Safety Data Sheet or MSDS)) than that of NMP (3914 mg/kg, based on MSDS) and lower cytotoxicity as reported by Kranz et al.[28] Similarly, triacetin as hydrophobic cosolvent is preferred over BB (oral LD_{50}, rat: 1700 mg/kg, based on MSDS) because of its lower systemic toxicity (oral LD_{50}, rat: 3000 mg/kg, based on MSDS). In our previous studies,[29] the effect of polymer hydrophobicity on the phase inversion in pure NMP solvent system has been reported. In this study, details of the influence of triacetin as cosolvent on the reduction of burst were studied in mixed solvent system. Hydrophobic polymer PdlLA and a more hydrophilic polymer, RG502, were chosen as representative polymers to study the effect of the amount of triacetin on the drug release from different type of polymers. The actual release of each solvent over time was also quantified to understand the triacetin influence on the initial burst release. The swelling ratio of the depot and the cross-sectional morphology were also investigated as parameters that could help to understand the details of the drug release profile. In addition, pH and molar mass changes of these depots

were tracked to further evaluate the effect of triacetin on the degradation.

MATERIALS AND METHODS

Materials

Biodegradable polymers PdlLA (Bio Invigor, Taiwan; IV. 0.18) and RG502 (Boehringer Ingelheim, Germany; IV. 0.19) were used in this work. The following chemicals were used as received: DMSO (Fluka, Buchs, Switzerland), NMP (Tedia, Fairfield, Ohio, USA), triacetin (Sigma–Aldrich, Singapore), metoclopramide monohydrochloride (metosalt) (Sigma, St. Louis, MO, USA), chloroform (Tedia, Fairfield, Ohio, USA), acetonitrile (ACN, Tedia), and peanut oil. Phosphate buffer saline (PBS, pH 7.4) was prepared in the laboratory.

Preparation of Formulations

Polymer solutions were prepared by dissolving each polymer and drug with the solvent together until clear solutions were formed. If a mixed solvent was used, triacetin was mixed with DMSO or NMP at various ratios (w/w of triacetin/DMSO or NMP, 5/95, 10/90, 20/80, and 30/70) before the addition of drug and polymer. The concentration of the polymer solution and metosalt drug was kept constant at 40% and 1%, respectively (w/w, based on the total amounts of the polymer and the solvent). *In vitro* release was done by injecting about 0.5 g of polymer solution (with or without drug) into 10 mL of PBS (pH 7.4) in a 15 mL glass bottle, which was kept in a 37°C incubator with shaking at 50 rpm. At predetermined time points, 1 mL of the release medium was removed to characterize the drug and solvent release and replaced with 1 mL of fresh buffer to maintain a constant total medium volume. The drug concentrations in the diluted solutions were determined at 309 nm wavelength by (ultraviolet–visible) UV–Vis spectrophotometry (UV-2501, Shimadzu, Japan). The amount of each solvent (DMSO, NMP, or triacetin) released from the depots without drug loading was quantified at 235 nm wavelength by high-performance liquid chromatography (HPLC) (1200 series; Agilent Technologies, Germany). The chromatographic analysis is performed on an instrument equipped with a VW detector and a ZORBAX 300 SB-C18 column. The operating conditions were as follows: sample volume 10 μL, ACN/water (v/v, 40/60) as mobile phase with 1 mL/min flow rate. Samples were filtered into a 2 mL glass vial through a 0.22 μm disposable syringe filters and placed in an autosampler tray. Quantification was carried out by integration of the peak areas (DMSO: peaks at ~2.6 min, NMP: peaks at ~2.8 min, triacetin: peaks at ~3.7 min). The cumulative release amounts of drug or solvent were calculated based on calibration curves. The experiments for drug and solvent release were repeated at least three times; the mean and standard deviation were calculated.

Triacetin Residual Study

At predetermined time intervals, depots were removed from the buffer solution and wiped lightly with a tissue to remove the surface water and then shifted to a 15 mL centrifuge tube. Four microliters of ACN was added to dissolve the depot to get a clear solution before 6 mL ultrapure water being added to precipitate polymer component to form a suspension. The total solution was centrifuged at 12,890G for 10 min to obtain the supernatant, which was filtered into a 2 mL glass vial through a 0.22 μm disposable syringe filters and placed in an autosampler tray to be measured by HPLC.

Morphology Study

Freeze-dried samples were fixed on an aluminum stub with conductive adhesive tape and then coated with gold for 50 s using an SPI-Modulate™ sputter coater to improve their electrical conductivity. The cross-sectional morphology of the depot was studied using a JEOL (Japan) JSM-5410 LV scanning electron microscope (SEM) at 5 kV.

Swelling Ratio

Freshly collected wet samples were wiped with a tissue to remove the surface water and then weighed. Swelling ratio is calculated using the following formula:

$$\text{Swellingratio } \% = \frac{W}{W_o} \times 100\%$$

where W refers to the weight of the wet depot, W_O is the weight of the original depot.

Degradation

For *in vitro* degradation, samples collected at various time points were washed with deionized water to remove the deposited salts from the buffer and then freeze-dried. The remaining polymer mass was calculated based on the left polymer amount in the dried sample and the initial polymer amount in the depot. The molar mass (MW) of samples were determined by using a GPC system (Shimadzu, Japan) equipped with a LC-20AD solvent delivery module, a SIL-20AC autosampler and a RID-10A differential refractometric detector. Dried samples were dissolved in chloroform at a concentration of 5 mg/mL, filtered into a 2 mL glass vial through a 0.22 μm disposable syringe filters and placed in an autosampler tray. All measurements were carried out with two Polymer Laboratories (PL) gel of 5 μm mixed-C and one PL gel of

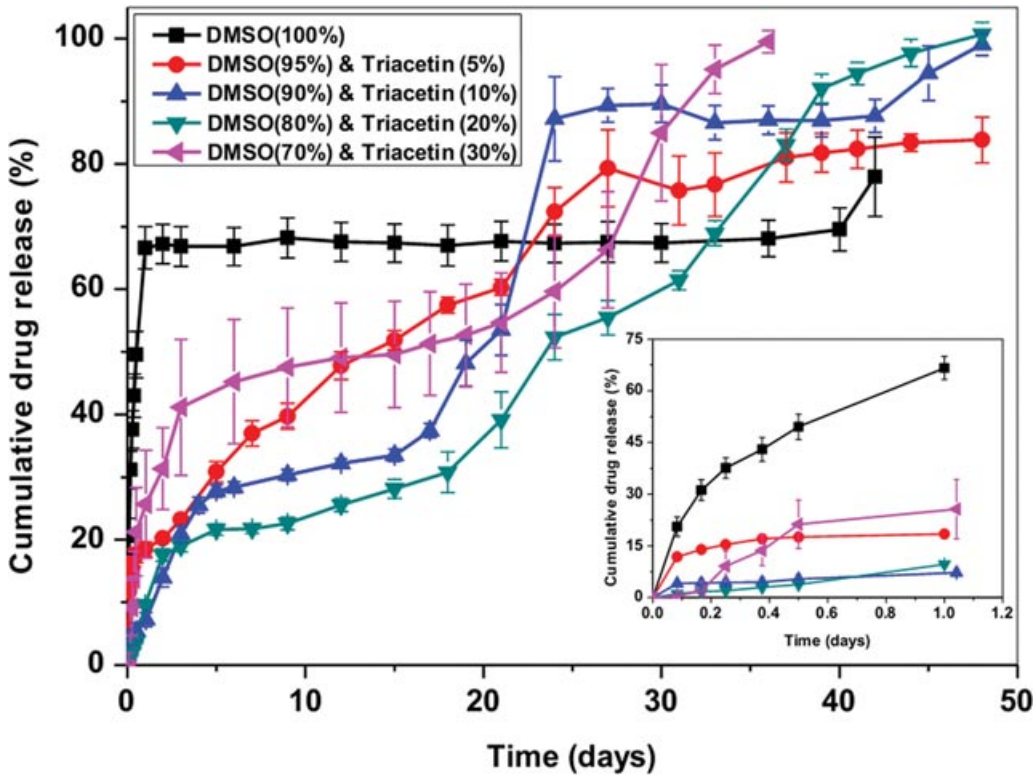

Figure 1. Effect of the amount of triacetin on metosalt release from injectable PdlLA depots with DMSO solvent in PBS (pH 7.4). The inset shows the initial burst release profiles.

5 μm mixed-E columns connected in series, with chloroform as the mobile phase at a flow rate of 1 mL/min. Twelve polystyrene standards with narrow Mw distribution in the range of 162–30,000 Da were used for calibration.

pH Measurement

pH measurements were conducted at room temperature using a Seven Easy bench top pH meter (Mettler–Toledo, Singapore) equipped with an Inlab Expert Pro electrode. The pH of the sample polymer solutions in PBS buffer was measured at predetermined time intervals to determine any changes in the pH.

RESULTS AND DISCUSSION

Triacetin Effect on the Drug Release

Hydrophobic polymer PdlLA was chosen as matrix material and kept at 40% concentration, whereas the hydrophilic solvent DMSO or mixture with triacetin was used as solvent. When the polymer solution was injected into the buffer solution (pH 7.4), a polymer skin was formed immediately. Nonsolvent/solvent exchange then occurred through this skin concurrent with drug efflux. The release of metosalt was studied by UV–Vis spectrophotometry as described in the *Methods* section. Figure 1 demonstrates that the rate of burst release of the drug from PdlLA depots with pure DMSO solvent is the highest among all the formulations. After burst release, there is very little drug release for a long period until the depot collapses. By using triacetin as cosolvent, the high burst release is reduced significantly and the level of the reduction is proportional to the amount of triacetin, up to ~20% by weight of triacetin. The addition of 5% triacetin reduces the burst release from ~67% to ~15%, whereas 10% and 20% triacetin reduce burst release to ~8%, and the trend is maintained with 30% triacetin (although subsequent release from the 30% triacetin is faster). After the burst release, sustained drug release is obtained from the depots with triacetin.

The initial burst release is related to the phase inversion dynamics of the polymer solution; the subsequent release is mainly controlled by the swelling of the depot and the degradation of the polymer material, which will be described later.

In comparison to the higher burst release from PdlLA depots in pure DMSO solvent system, the burst release from PdlLA depots in pure NMP solvent is relatively lower, which can also be reduced by triacetin addition but not so significantly, as shown in Figure 2.

Triacetin can also be used as the cosolvent to reduce the initial burst release from the hydrophilic polymer RG502 depots, regardless of which solvent, DMSO or NMP, it is mixed with. As shown in Figure 3, the initial burst release is reduced when triacetin is added;

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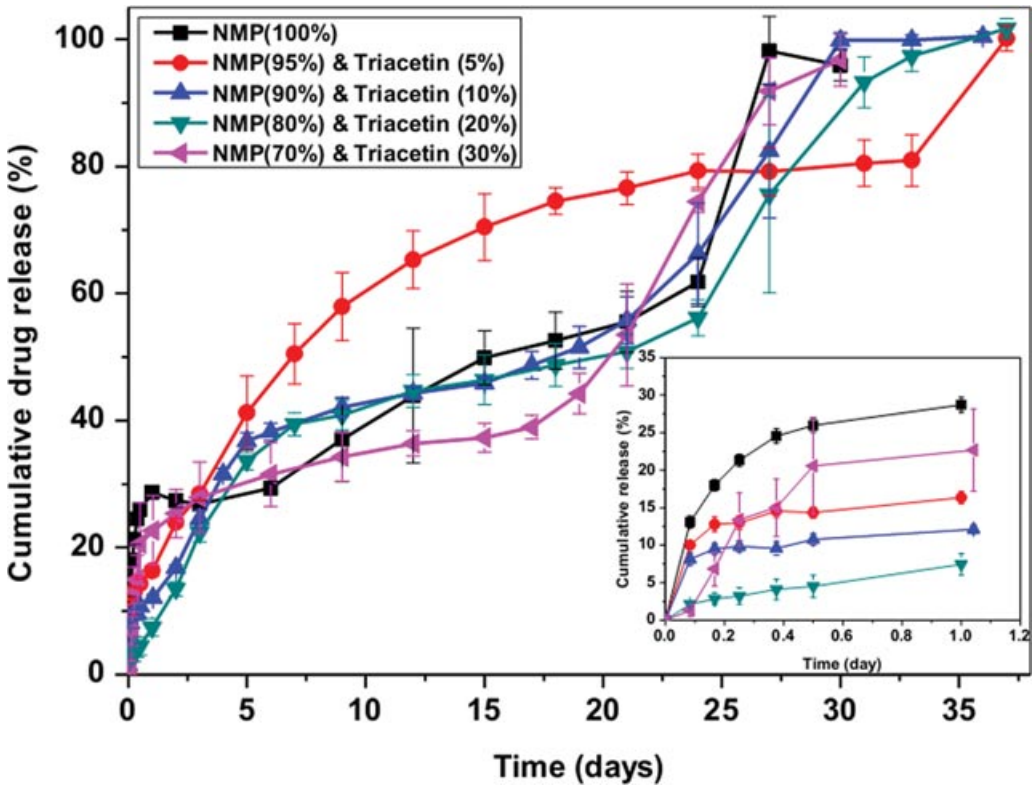

Figure 2. Effect of the amount of triacetin on metosalt release from injectable PdlLA depots with NMP solvent in PBS (pH 7.4). The inset shows the initial burst release profiles.

the subsequent release kinetics is similar, with an acceleration of release noted for 10% triacetin addition. We attribute this to greater solvent retention caused by addition of the cosolvent triacetin (see discussion below), that in turn leads to a more "plasticized" core polymer allowing for faster diffusion rates.

The burst release of the drug from PdlLA depots is much higher than that from RG502 depots in the same solvent system. We have explained this observation in the previous article.[29] Briefly, the higher initial burst release from hydrophobic polymer PdlLA depot was due to its relatively faster phase inversion (solvent exchange) and subsequent formation of a highly porous structure, whereas the more hydrophilic polymer RG502 depots underwent a slower phase inversion resulting in lower initial solvent and drug efflux and a less porous and more fluid polymer matrix formation.

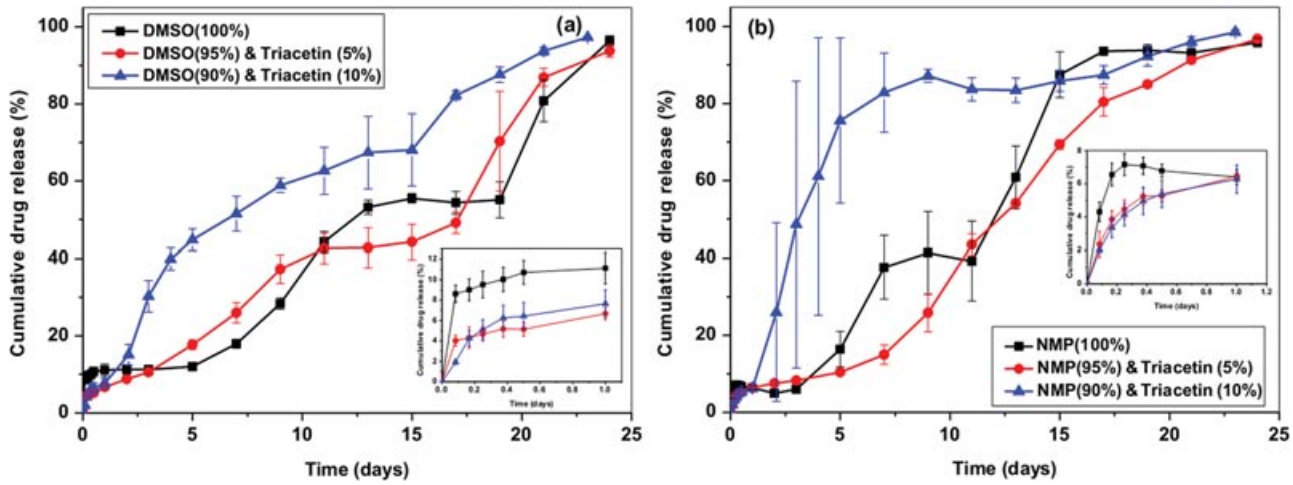

Figure 3. Effect of the amount of triacetin on metosalt release from injectable RG502 depots with (a) DMSO or (b) NMP in PBS (pH 7.4). The inset shows the initial burst release profiles.

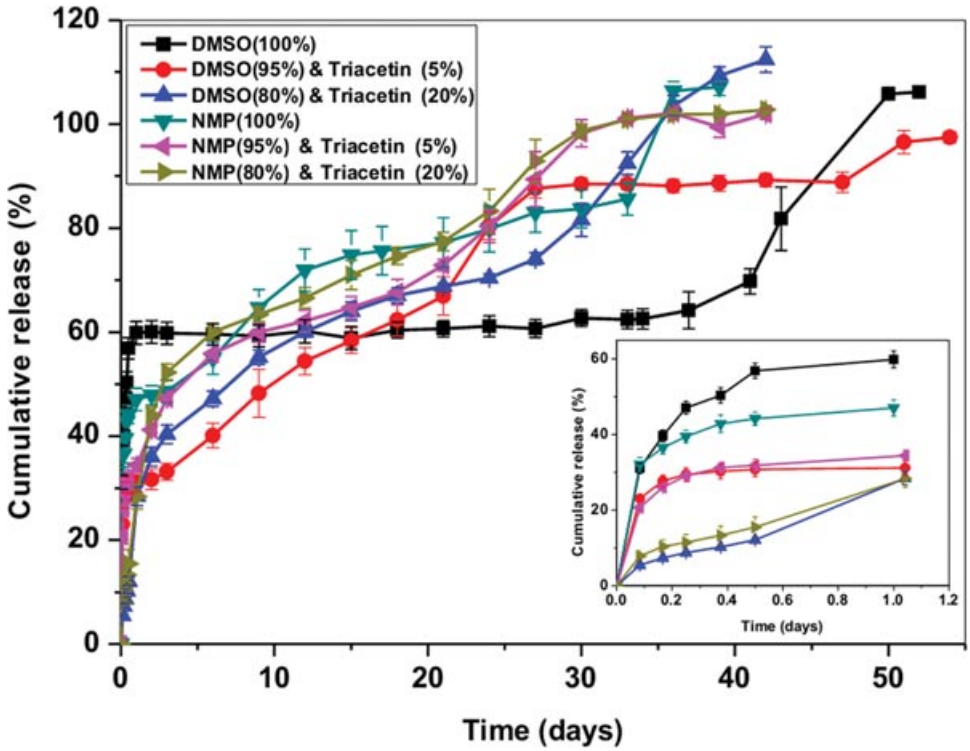

Figure 4. Effect of the amount of triacetin on DMSO or NMP release from injectable PdlLA depots without drug loading in PBS (pH 7.4). The inset shows the initial burst release profiles.

Triacetin Effect on the Solvent Release

As the hydrophilic drug is dissolved completely in the organic solvent used, solvent efflux from the depot will also carry the dissolved drug with it. We therefore quantified the solvent release by HPLC to determine the effect of triacetin on the rate of nonsolvent/solvent exchange. For the purpose of simplifying the system, solvent release from both the pure solvent system and mixed solvent system were measured without any drug loaded to compare the variation of the solvent release. The mixture of triacetin with DMSO or NMP was used as a mixed solvent, and PdlLA was used as the polymer material. As shown in Figure 4, the burst release of DMSO is faster than that of NMP in pure solvent system. After the burst release, there is almost no DMSO release for a long period until the depot collapses, which mirrors the drug release behavior during the same period (Fig. 1). After incorporation of triacetin in the polymer solution, not only is the burst release of either DMSO or NMP reduced significantly but also the subsequent release is modulated, especially for DMSO solvent system.

A higher solubility parameter of DMSO [26.7 $(J/cm^3)^{1/2}$] compared with that of NMP [23.2 $(J/cm^3)^{1/2}$] illustrates its relatively higher affinity to water, which leads to faster phase inversion of polymer solution along with the denser depot structure formed in pure DMSO solvent system. The faster phase inversion makes the burst release higher but the denser depot structure formed subsequently makes it difficult for water to influx and swell the depot, resulting in almost no nonsolvent/solvent exchange and consequently very little drug release until degradation starts to occur.

Triacetin is a relatively hydrophobic solvent as it has only 7% miscibility with water by weight consistent with its lower solubility parameter [21.0 $(J/cm^3)^{1/2}$]. The increased hydrophobicity of the mixed solvent slows down the nonsolvent/solvent exchange rate and thus reduces the initial solvent release rate along with initial drug release rate. A larger amount of triacetin (30%) may exceed the critical point at which depot formation transforms from a solid state to a rubbery state (as more solvent is retained and a "plasticized" polymer phase is obtained), which is easily deformed and results in a high initial release.

When the polymer solution with mixed solvent is injected into the buffer solution, the hydrophilic solvent DMSO or NMP near the surface leaves the polymer solution quickly to shape the depot almost immediately. The hydrophobic solvent triacetin restricts fast water ingress into the matrix, delays phase inversion, and ultimately suppresses the burst release (by slowing down the release of solvent). Thus, the rate of the solvent and drug release can be tailored by regulating the solvent miscibility with water through mixing the hydrophilic solvent and hydrophobic solvent at various ratios. A combination of a hydrophilic

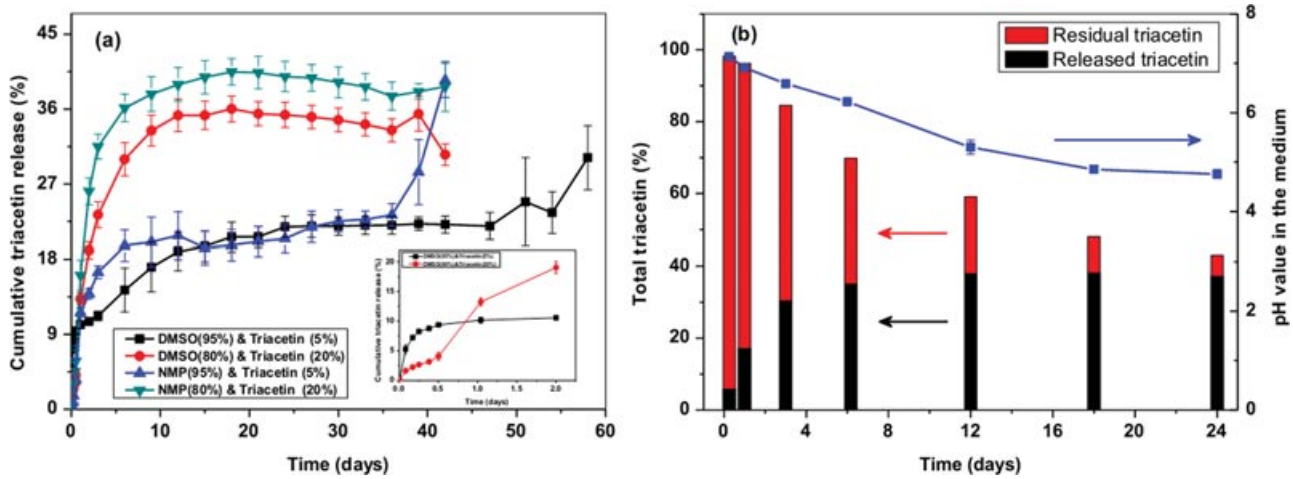

Figure 5. (a) Release profiles of triacetin from injectable PdlLA depots without drug loading in PBS (pH 7.4). (b) Total triacetin amount left at different period (including released triacetin in the medium and residual triacetin in the depot) and pH value change in the buffer medium for formulation with DMSO/triacetin (80/20, w/w) mixed solvent. The inset shows the initial burst release profiles.

solvent and a hydrophobic solvent can overcome the shortcoming of the fast phase inversion caused by pure hydrophilic solvent, and enhance the subsequent release by allowing the formation of a more "rubbery" (plasticized) structure because of solvent retention inside the depot.

Triacetin Release

As the addition of triacetin influences the release of the drug and solvent significantly, its release characteristics are also of some interest. The triacetin release was quantified by HPLC along with DMSO or NMP release. As triacetin is miscible with DMSO or NMP, the release profiles of triacetin were predicted to be similar to the profiles of hydrophilic part (DMSO or NMP) of mixed solvent. At the initial stage, as shown in Figure 5a, the rate of the triacetin release is similar to the rate of DMSO release, which means that the triacetin diffuses out of the depot together with DMSO. At 12th day, ~40% and ~20% of triacetin are released from formulation composed of 20% and 5% triacetin, respectively. However, beyond 12 days, there is hardly any triacetin release in the case of 20% triacetin loading, and another burst release in the case of 5% triacetin loading. Cumulative triacetin release is only ~40% even after the depot collapses and almost disappears due to the erosion. It is different from DMSO or NMP release, which has complete release after depot collapse. Triacetin release from depots with 20% triacetin is faster than that with 5% triacetin. It is related to the different swelling ratio brought by different amount of triacetin, which is discussed later.

The residual triacetin amount left in the depot was measured by HPLC. Figure 5b shows that for depots with DMSO/triacetin (80/20, w/w), almost no triacetin is lost during the first day, whereas ~15%, ~30%, ~40%, and ~50% of the triacetin is lost at 3rd, 6th, 12th, and 18th days, respectively. The pH of the buffer medium decreases with time. As is known, triacetin hydrolyzes to glycerol and acetic acid when it dissolves in the water. Apart from this, the heterogeneous degradation of the depot (shown in our previous study)[30] may also lead to a lowered pH inside the depot over time, which can then catalyze triacetin decomposition.[30] Triacetin plays an important role in delaying polymer phase inversion at the early stage and plays a less important role in the later stages.

Triacetin Effect on the Swelling Ratio

As the drug release following the burst release is largely influenced by swelling and degradation, the swelling ratio was investigated first. Surprisingly, the swelling ratio results show that water uptake ability increases by increasing the amount of triacetin up to about 20% by weight, as shown in Figure 6. After all, the cosolvent triacetin added is hydrophobic, which should be repulsive to the water closing. The swelling ratio of PdlLA depots in pure DMSO solvent system can reach only ~150% at 15th day. When triacetin is added as cosolvent, PdlLA depots with DMSO/triacetin (80/20, w/w) mixed solvent can swell as high as ~470% but the maximum swelling ratio of PdlLA depots with NMP/triacetin (80/20, w/w) mixed solvent is only ~250%. When triacetin amount is increased as high as 30%, the maximum swelling ratio of depots with DMSO/triacetin and NMP/triacetin mixed solvent is ~230% and ~220%, respectively.

Without triacetin addition, PdlLA polymer solution forms depot almost immediately upon contact with water and generates a dense structure, which resists

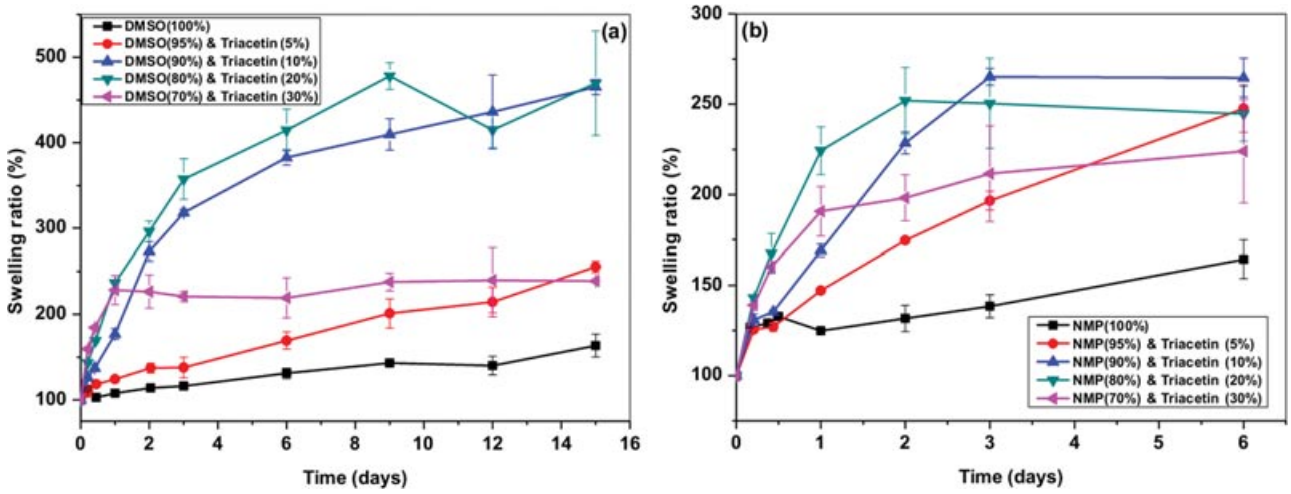

Figure 6. Swelling ratio of injectable PdlLA depots with (a) DMSO or (b) NMP and 1% drug loading in PBS (pH 7.4).

further water ingress/swelling. In contrast, the presence of triacetin restricts the water/solvent exchange and delays the phase inversion development. On the contrary, less water uptake (less polymer precipitation) in the depot in the early stages indicates a more "rubbery" and permeable gel structure, which combined with the subsequent solvent exchange results in greater swelling for these samples and consequent pore formation. Depots with DMSO/triacetin mixed solvent swell more and longer compared to depots with NMP/triacetin mixed solvent. This could again be related to the relative rapidity of DMSO/water exchange versus NMP/water exchange.

Triacetin Effect on the Morphology

Figures 7 and 8 show the cross-sectional images of PdlLA depots in DMSO/triacetin mixed solvent and their SEM cross-sectional morphologies as a function of time. The cross-section of depots with pure DMSO solvent exhibits much denser structures even after 30 days, as shown macroscopically in Figures 7 and 8. In contrast, when triacetin is added as a cosolvent, a porous structure is developed and more pronounced for depots with a higher triacetin amount, which is in agreement with the results of the swelling ratio. Even 5% triacetin can make the depot swell very well and have a much more porous structure.

The porous structure facilitates the diffusion of the solvent and the degraded products outward and thus brings down the aggregation of the acidic products in the interior of the depot and thereby the drug release. We postulate that addition of 30% triacetin delays phase inversion to such an extent that a certain amount of solvent associated with cosolvent triacetin is trapped within the depot, and this solvent/cosolvent is not lost during the process of freeze-drying, leading to a semifluid depot forming in the bottle.

Triacetin Effect on the pH of the Release Medium

On the basis of many previous studies, the change of pH value in the medium can influence the degradation of the depot. The measured pH values show a decrease over time, with the extent of the decrease being dependent on the amount of triacetin added to the formulation, as shown in Figure 9. The pH value of the medium for the formulation without triacetin remains almost unchanged for 48 days. But for the formulation with triacetin, pH value begins to decrease soon after a few days; the higher the amount of triacetin added, the lower the pH value decreased. This implies that triacetin addition can accelerate polymer degradation and also enable the faster escape of low-molar mass oligomers. On the basis of the swelling ratio results, it is clear that greater swelling caused by triacetin is facilitating faster escape of degradation products leading to a decrease in pH value.

Triacetin Effect on the Degradation and Mass Loss

The measured Mw change in general also shows a faster decrease with added triacetin, except for the 5% triacetin, which does not fit the trend (Mw decrease is higher for 5% triacetin than for both 10% triacetin and 20% triacetin) (Fig. 10a). Mass loss is not very different for the different triacetin amounts in the first 36 days (Fig. 10b). This implies that the small mass that leaches out for the higher triacetin loadings before 36 days consists of relatively shorter oligomers, leading to a disproportionate decrease in pH.

The anomalous faster degradation of depots with 5% triacetin is likely due to the heterogeneous degradation occurring in the interior of the depot. In this case, the oligomers have not leached out quickly enough, and the resultant lowered pH inside the core

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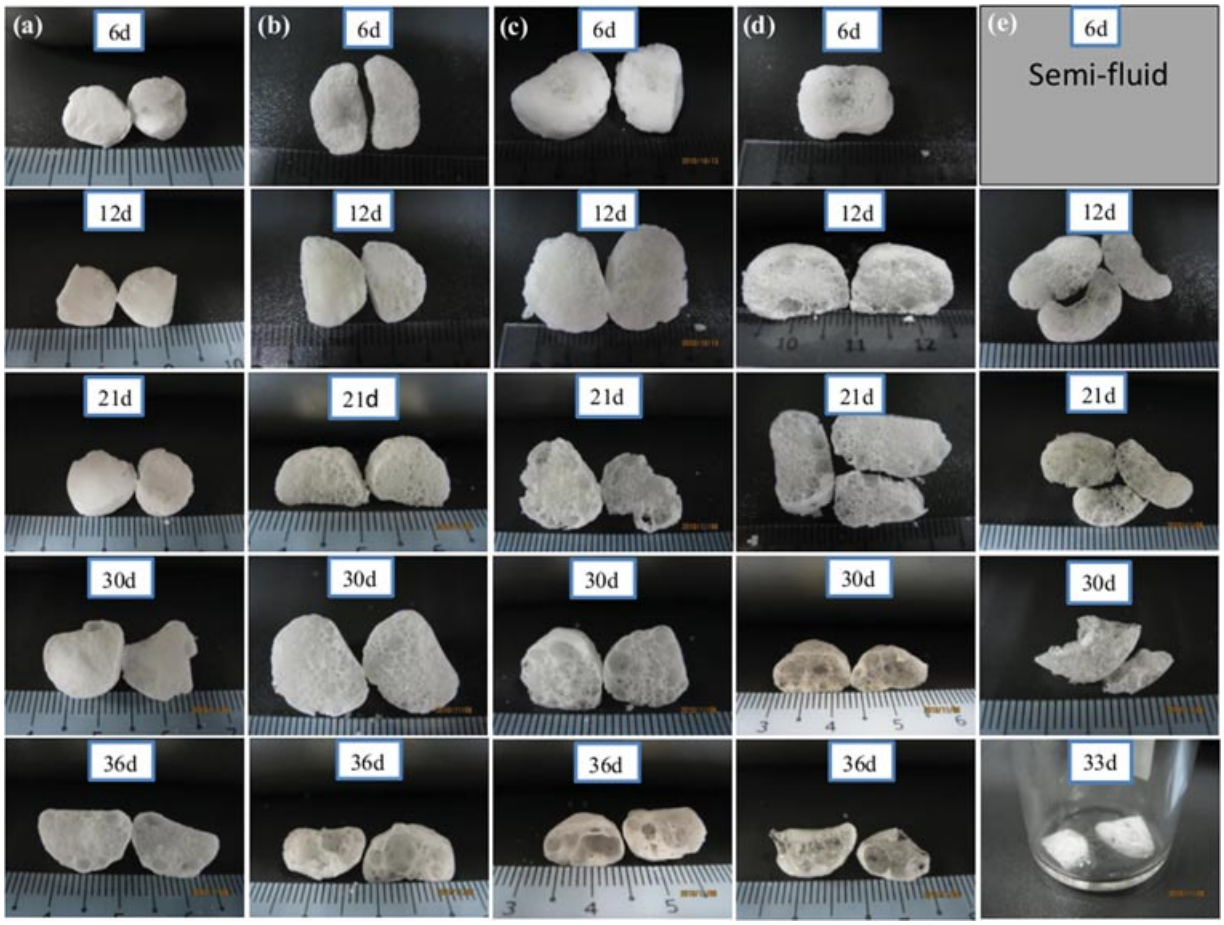

Figure 7. Cross-sectional images of the PdlLA depots with DMSO/triacetin mixed solvents at various ratios: (a) 100/0 (w/w); (b) 95/5 (w/w); (c) 90/10 (w/w); (d) 80/20 (w/w); and (e) 70/30 (w/w).

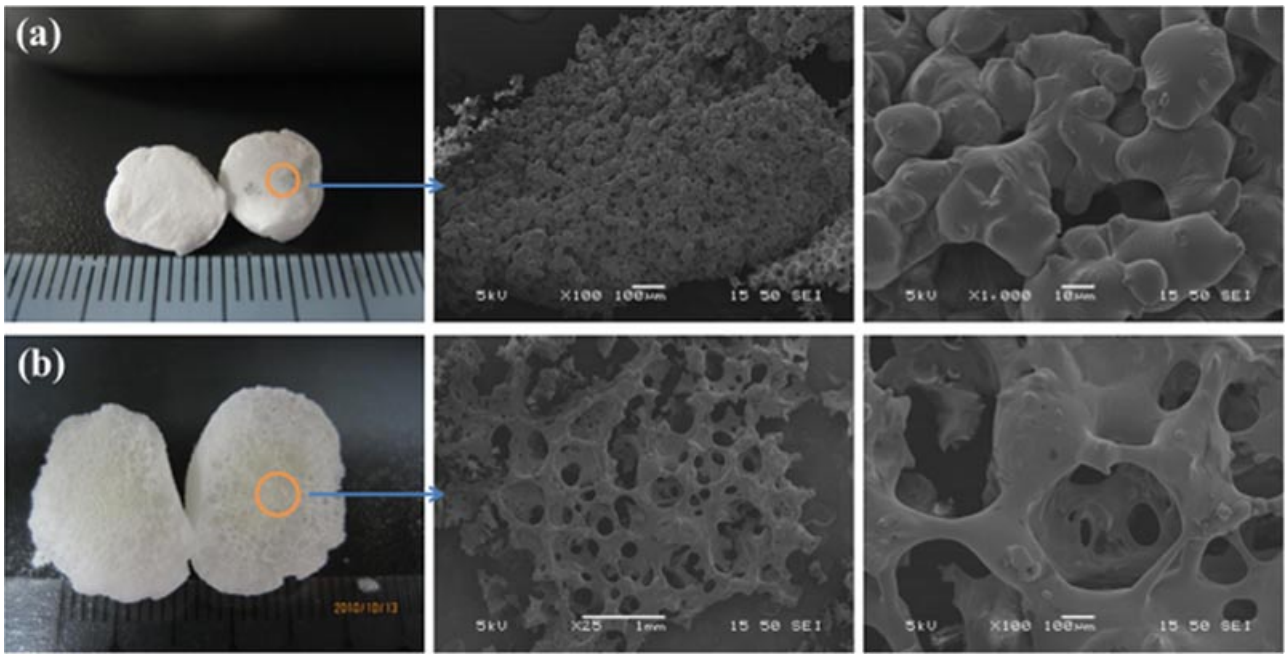

Figure 8. Cross-sectional morphology of the PdlLA depots with DMSO/triacetin mixed solvent at various ratios at 12 days: (a) 100/0 (w/w) and (b) 90/10 (w/w).

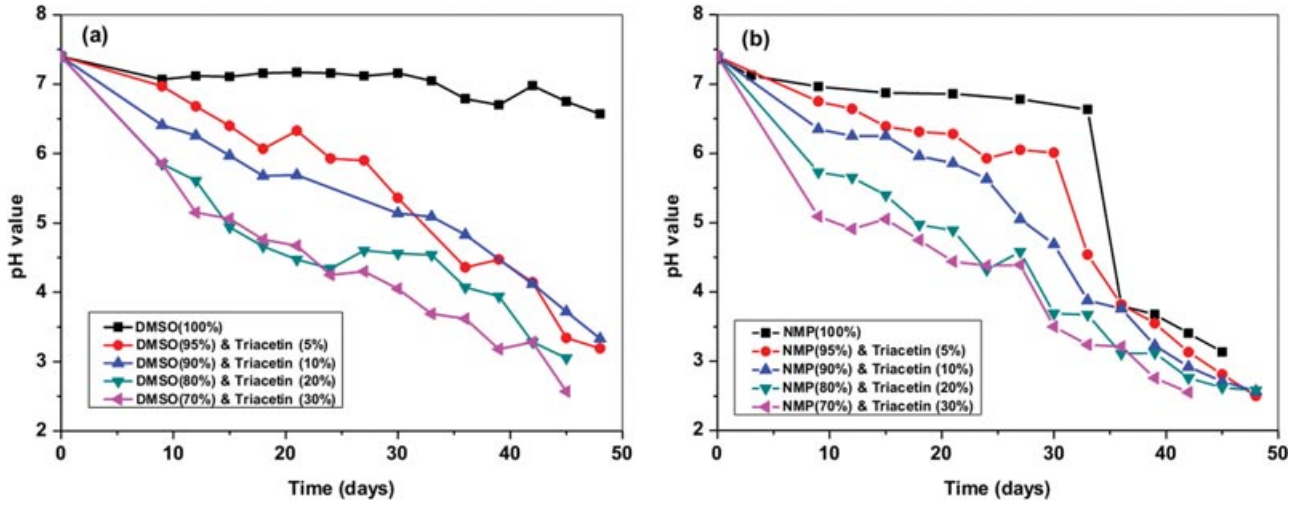

Figure 9. Change in medium pH value as a function of immersion time for PdlLA depots with (a) DMSO or (b) NMP solvent and 1% drug loading.

leads to acceleration of degradation. The depots with pure DMSO have a denser structure because of a faster phase inversion. Degradation is still heterogeneous in nature but depends on triacetin levels. For depots with 10% and 20% triacetin, the higher swelling and more porous structure facilitate leaching out of the degraded products, which does not allow for the autocatalytic effect typically observed in these systems. At 5% triacetin, the depot structure is not porous enough for this to happen, and this combined with higher water uptake (relative to pure DMSO depots) leads to the observed results.

Thus, our explanation for the degradation behavior may be summed up as follows:

- Addition of triacetin generally increases swelling (or cosolvent retention), thus facilitating escape of oligomers.
- The level of the swelling decides the extent of the heterogeneous degradation and thus the rate of the Mw decrease.
- The leached-out oligomers decrease pH and facilitate further degradation, whereas the nonreleased polymer with high carboxylic acid content is expected to accelerate the polymer degradation.
- In general, the mass that is leached out of high-triacetin-loaded depots is quite small, thus leaving behind a greater concentration of acidic products in the depot catalyzing the chain hydrolysis, leading to the observed greater decrease of pH and thus Mw change.

CONCLUSIONS

In summary, the burst release that is a disadvantage of injectable *in situ* depot-forming systems can

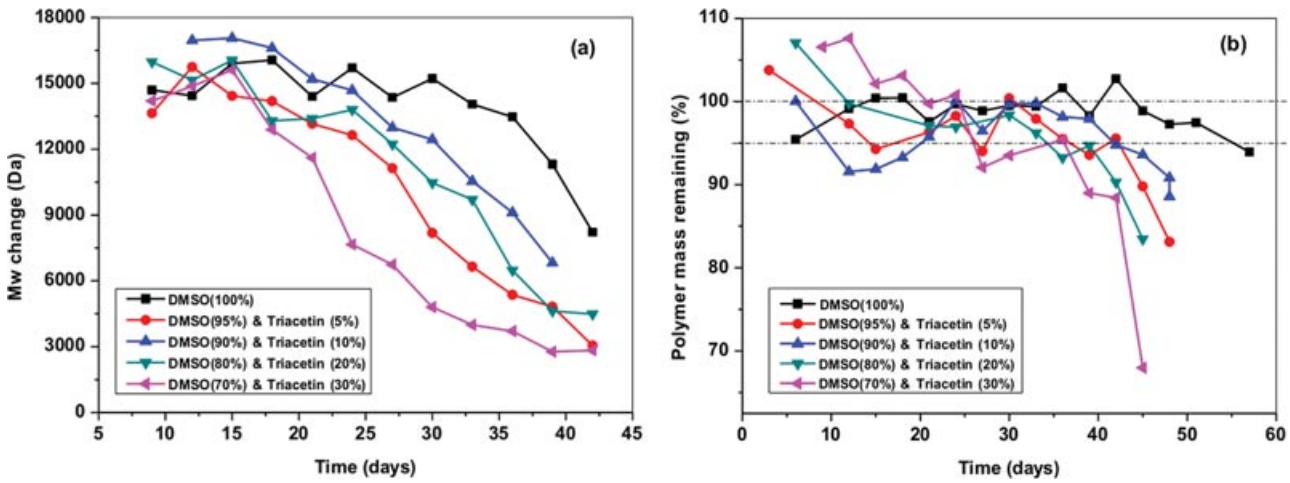

Figure 10. Mw change (a) and polymer mass remaining (b) of injectable PdlLA depots with 1% drug loading as a function of time in PBS (pH 7.4).

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be reduced by using a mixture of hydrophilic and hydrophobic solvents. In mixed solvent systems, hydrophilic solvent (DMSO or NMP) leaves the depot quickly (and helps to shape the depot), whereas the hydrophobic solvent triacetin delays the phase inversion to reduce the subsequent solvent and drug release. The higher the amount of triacetin added, the more the reduction of the burst release (up to ~20% of triacetin loading by weight). Triacetin as cosolvent affects the solvent release at the early stage only. The more "rubbery" (or permeable) structure of the depot caused by triacetin addition allows greater swelling to form a more porous structure, which significantly controls and affects the subsequent solvent and drug release as well as the degradation. The effect of triacetin on the reduction of the burst release and on the subsequent release depends also on the polymer hydrophobicity; the effect is greater on the hydrophobic PdlLA polymer and less on hydrophilic RG502 polymer.

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