Phase inversion dynamics of PLGA solutions related to drug delivery
Part II. The role of solution thermodynamics and bath-side mass transfer

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Abstract

The role of solvent properties and bath-side composition on the phase inversion dynamics and in vitro protein release kinetics of polylactic-co-glycolic acid (PLGA) solutions has been examined using dark ground imaging, in vitro release rate, and SEM techniques. Thermodynamic phase diagrams for three model systems (PLGA in 1-methyl-2-pyrrolidinone (NMP), triacetin, and ethyl benzoate) suggest two general classes of precipitation behavior, depending on the relative solvent strength and water miscibility. Drug release from the NMP-based system is primarily governed by the dynamics of phase inversion and exhibits a distinct burst region followed by a much slower release. Alternatively, depots with low solvent/water affinity (PLGA in triacetin or ethyl benzoate) undergo much slower phase inversion, resulting in a less porous, more fluid, two-phase structure that also releases protein more uniformly. Addition of a small chain triglyceride or organic salt to the aqueous receptor bath also evokes a significant increase in the mass transfer rate of protein from the low solvent/non-solvent affinity depots. An interpretation of these results in terms of a qualitative model for the protein release mechanism is also given. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Polymer solution delivery platforms can provide prolonged release of biopharmaceutical agents while offering a greater ease of administration than surgically implanted systems [1,2]. Such systems generally comprise a solution of a biodegradable polymer in a bio-compatible solvent in which the bioactive agent is suspended or dissolved. Delivery is effected by injection directly into the patient. Since the polymer is water-insoluble, contact with the aqueous-based physiologic surroundings causes the solution to undergo liquid de-mixing to produce a two-phase, gelled implant. As a result, formation of the polymer membrane carrier takes place in vivo, simultaneously with the release of the suspended drug. Since the objective is to maintain drug delivery within a specified therapeutic window, this usually implies minimizing the initial burst and achieving
prolonged, zero-order release rate over the lifetime of the polymeric gel. The dynamics of the phase inversion that control the rate of drug release depend on the thermodynamic and mass transfer characteristics of the system (polymer solution + physiologic surroundings). The membrane morphology that forms also plays an important role in the release profile. Thus, the ability to formulate efficient systems for injectable drug delivery requires a quantitative understanding of the dynamics and morphology of the phase inversion process.

In a recent paper [3], we showed that the release rate of protein from a polylactic-co-glycolic acid (PLGA)/solvent depot system was directly related to the rate of phase inversion as well as the morphological characteristics of the formed membrane. The addition of high molecular weight polyvinylpyrrolidone (PVP), triacetin, or water altered the thermodynamics and mass transfer kinetics of a PLGA/NMP polymer solution. Additives that increased the liquid de-mixing rate (i.e. PVP or water) resulted in higher initial protein release rates (<24 h), while the overall morphology, consisting of finger-like voids, as well as the water influx rate remained unchanged. Protein release was postulated to occur primarily by a convective/diffusive process through the open, interconnected void regions of the membrane, rather than through the polymer-rich matrix. Conversely, the addition of a co-solvent with a much lower aqueous miscibility (triacetin) to the PLGA/NMP solution caused a lowering of the phase inversion rate and a significant reduction in the protein burst kinetics. In this case, a morphological transition to a more dense, sponge-like structure also occurred.

While these studies clearly demonstrate that the properties of the polymer solution greatly impact release kinetics, the role of the external environment cannot be ignored. There are a wide variety of external compositions an injectable depot can contact depending on the injection location, age, and physiologic stature of the patient. As an example, in experiments by Yewey et al. [4], the burst of human growth hormone from PLGA microspheres was found to be higher in horse serum than in an aqueous receptor bath. On the other hand, our study [3] showed that the phase inversion dynamics and morphology of the depot were the same, regardless of whether the solutions were quenched in water, a PBS buffer solution, or horse serum. These results strongly suggest that the bath-side mass transfer dynamics have an important influence on the drug release behavior.

In this work, the role of polymer solution thermodynamics and bath-side composition on the phase inversion dynamics and protein release kinetics of a PLGA-based solution delivery system will be further examined. Altering solvent strength and aqueous miscibility of the depot will be shown to have a dramatic effect on the protein release kinetics. Moreover, it will be shown that the composition of the bath-side becomes increasingly important in affecting the drug release rate as the PLGA solution becomes less miscible with water.

2. Experimental

2.1. Materials and methods

Polymer solutions were made up of 1:1 ratios of polylactic-co-glycolic acid (PLGA Resomer 502, MW 12 000, Boehringer-Ingelheim) and solvent. When present, protein was added at a level of 10% by weight. Three solvents with varying polymer solubility and non-solvent affinity were used to elucidate the dependencies on the system thermodynamics and mass transfer characteristics. The solvents: reagent grade 1-methyl-2-pyrrolidinone (NMP), triacetin, and ethyl benzoate (Sigma), all of which are currently used in injectable delivery systems [5], were used as received. Triacetin and deoxycholate, a biosalt found in the human body, derived from oxen bile (Sigma), were also used as bath-side additives. The protein used for release rate and water absorption experiments was chicken egg white lysozyme (Muramidase, mucopptide N-acetyl-hydrolase: EC 3.2.1.17, Sigma L 6876), triple crystallized, dialyzed and lyophilized to a 95% protein level, with the balance primarily the buffer salts, sodium acetate and sodium chloride. The activity of the lysozyme was approximately 50 000 units per milligram protein.

Polymer solutions were prepared by mixing PLGA with solvent in a 10 cm³ glass vial. Solutions readily formed in NMP at room temperature. In order to
effect good solubilization with the other two solvents, it was necessary to seal the mixture and heat it to 37°C for 24 to 48 h, with periodic stirring to break up lumps and remove trapped air bubbles. In a number of cases, depot formulations were allowed to age for at least 72 h at room temperature, prior to use. The aging process leads to an increase in the zero shear viscosity. However, on injection into the receptor bath or optical cells used for in situ phase inversion visualization, the viscosity rapidly and reversibly decreased due to the destruction of whatever network structure had formed. In all cases, no differences were found in the phase inversion or drug release characteristics of the aged and non-aged solutions.

Morphologies of the hardened depots were examined by scanning electron microscopy on an Hitachi-Model S2460N instrument equipped with a Peltier cooled stage, operating at −20°C. Use of the cooling chamber allowed examination of the triacetin- and ethyl benzoate-based gels which otherwise rapidly melt under the focused electron beam. Samples were prepared by injecting 0.5 g of polymer solution into an aqueous bath (with and without additives) held at 37°C. The injected depots formed a disk approximately 1 cm in diameter by 0.1 cm in thickness. Disks were removed from the receptor bath after 4 to 14 days and chilled immediately to −20°C to prevent further morphological changes (triacetin and ethyl benzoate depots revert back to a single-phase solution if water is allowed to evaporate on removal from the bath). Depots were fractured in liquid nitrogen immediately prior to placing on the SEM cold stage for analysis.

Protein release experiments were conducted by placing ~0.5 g of depot formulation on a vertical polypropylene lattice in 10 ml of phosphate-buffered saline (PBS). The pH of the PBS was 7.4. Samples were heated to 37°C and continuously agitated by a shaking mechanism. For bath composition experiments, additives (triacetin or deoxycholate) were blended in the receptor solution at room temperature prior to depot injection and receptor solutions were replaced every 1–4 days. Polypropylene vials were used to minimize protein absorption. Receptor solutions were analyzed using liquid chromatography (HPLC) in a reversed phase POROS® column with UV detection at 210 nm. Lysozyme concentrations were determined using a calibration curve of standards ranging from 0.5 to 100 μg/ml. Five replications were run for each quench experiment and the results reported have a standard deviation within 10% of the mean.

In situ imaging of the phase inversion dynamics was done using the dark ground imaging (DGI) apparatus and techniques described in our previous paper [3]. The phase inversion kinetics were quantified in terms of the propagation rate of the leading edge of the liquid de-mixing zone that developed on exposing the given solution to the non-solvent quench medium. It is important to note that the physical state of the two-phase regions differed considerably, depending on the solvent. The NMP solutions precipitated as a semi-solid mass, and hardened to a solid, ‘rubber-like’ gel that could be readily extracted from the diffusion cell. On the other hand, the triacetin and ethyl benzoate solutions formed a much more fluid, liquid precipitate that remained in a more-or-less semi-fluid state until quenched to lower temperatures. Bulk water absorption in the depot formulations was also measured using Karl Fischer titration (replications=4, standard deviation of results within 12% of mean). Samples were prepared and injected into 37°C PBS receptor solutions in a similar fashion to the protein release experiments. Upon removal from the bath, a 0.05 mg sample was cut from the approximate center of the depot, sealed in a vial, and chilled to −20°C. Samples were thawed at room temperature prior to analysis. Glass transition analyses were also carried out using differential scanning calorimetry (DSC) on a number of samples to corroborate the titration results. Gels were placed in hermetically sealed pans and scanned from −100 to 60°C at 10°C/min on either a Texas Instruments TA-910 or TA-2920 device.

Phase boundaries for the PLGA/solvent/water systems were determined by quenching various composition solutions to the desired temperature (37°C) and noting the onset of turbidity. Tie lines within the binodal region were then determined by separating compositions within the miscibility gap, and analyzing for solvent, water, and polymer content using HPLC and Karl Fischer techniques. A mass balance was used to confirm the accuracy of the analysis. The locus of glass transition com-
positions at 37°C on the phase diagrams was calculated using the Kelley–Bueche equation [9] and confirmed by DSC analysis of a few compositions.

Finally, qualitative determinations of the lysozyme solubility in the three solvents, and in mixtures of these with water, were made using visual observations of the end point of the macroscopic solubilization. Lysozyme was found to be effectively insoluble in the pure solvents. In the case of the NMP, solubility began to increase at water levels above 50%. In the case of the triacetin and ethyl benzoate, since water solubility is low (<7 and <2.4%, respectively) lysozyme solubility in these systems was negligible.

3. Results and discussion

The thermodynamic properties of a polymer–solvent–non-solvent system will be strongly affected by the solvent quality and the solvent–non-solvent interactions [6]. Studies of phase inversion in quenched polymer/solvent systems have shown that the interplay between the thermodynamic and mass transfer characteristics leading to a given membrane structure are quite complex (see for example Refs. [7,8] and references therein). Nonetheless, useful qualitative predictions of the quench dynamics can be made from considerations of the ternary non-solvent–solvent–polymer phase diagram alone.

3.1. Nature of solvent

Solutions comprised of 50 wt.% PLGA in either NMP, triacetin, or ethyl benzoate were used since they span the range from a relatively strong solvent with high water miscibility (NMP) to solvents of lesser power, having progressively lower water miscibility (triacetin and ethyl benzoate). Fig. 1 shows the ternary phase diagrams for each of these systems. In the discussion to follow we assume that quench compositions are above the plait point, since this is the usual case. Consequently, the two-phase structure that forms will consist of a polymer-rich, continuous phase with droplets of the polymer-lean phase suspended in it.

The NMP/PLGA/water phase diagram shown in Fig. 1(a) is typical of a system in which the solvent and non-solvent are completely miscible [6]. In addition to a well-defined binodal region, there is also a glass transition region, denoted by the line shown in the upper left corner, representing the locus of compositions within which the ternary solution is in the glassy state [9]. The steep slopes of the binodal tie lines (dotted lines) indicate that relatively large increases in polymer composition will occur upon phase separation. In addition, the complete miscibility of NMP in water means the NMP can...
readily transfer to the bath-side. Taken together, these factors will accelerate hardening of the polymer-rich matrix by further driving the composition to the glass transition region. From the lever arm rule, one would also expect a measurable fraction of the dispersed droplet phase to form under most conditions, thereby enhancing the formation of an open, porous network in the solid gel [3].

These features are to be contrasted with the triacetin and ethyl benzoate ternary systems. As a result of the limited water miscibility (\(\sim 7\%\) triacetin and \(\sim 0.4\%\) ethyl benzoate), the binodal tie lines intersect the horizontal axis of the phase diagram at finite solvent compositions in both systems and exhibit significantly lower slopes than those of the NMP system. Thus, phase separation results in a less concentrated, more fluid polymer-rich matrix, with a relatively low fraction of dispersed phase.

3.2. Water absorption and gelation rate

Our earlier study indicated that addition of triacetin to an NMP/PLGA solution decreased the water uptake and liquid de-mixing rates of the system [3]. Figs. 2 and 3 illustrate that similar trends hold for the three model depots. These data show that decreasing the solvent/non-solvent affinity leads to lower water absorption and phase separation rates.

Upon injection into an aqueous bath, the NMP-based depot rapidly absorbs water, leading to rapid phase separation. Though solidification of the entire sample occurs fairly quickly, further weight gain due to water absorption is observed for several days. The hardening PLGA-rich phase, still containing NMP, also swells to nearly twice its original volume. The triacetin and ethyl benzoate-based depots, on the other hand, absorb water and phase separate at substantially lower rates (Figs. 2 and 3). Moreover, as noted in Section 2, the two-phase system that forms tends to remain in a more or less viscous emulsion state rather than forming a solid gel as the NMP system does. In addition, where the water absorption profile in the NMP system was rapid and then tapered off, the triacetin and ethyl benzoate systems are seen to take on water at a constant rate for up to 2 weeks (Fig. 3). Direct visual observations of the PLGA depots suggest that phase inversion progresses from the outside of the solution inward at a rate equal to the bulk absorption rate. This effect can be extremely beneficial with respect to consistency of the protein release rate from the quenched solution.

The drug component or other formulation ingredients can also impact the water absorption to the depot [10,11]. Fig. 4 shows the effect of the lysozyme on the water influx in the ethyl benzoate system. The relative increase in water uptake due to
6. The release curve for the NMP system displays the typical profile of a rapidly precipitating system, i.e. a large burst followed by a prolonged period of little protein release. The large volume of interconnecting network pores shown in the morphology of this system (Fig. 6(a)) is consistent with our model of the initial release mechanism [3]. The overall release rate is likely a reflection of both the lysozyme solubilization and diffusion through the pores. Moreover, the shutdown in release can be understood on the basis of our discussion of the phase diagram. Once the interconnected pores are emptied of protein, further release of solute trapped in the hardened polymer matrix will be inhibited due to the very low diffusivity. In consequence, release of the remaining protein would be expected to occur only after bioerosion of the PLGA begins, which, for these systems, happens on a longer time scale [12].

The release of protein from the triacetin and ethyl benzoate depots is seen to be considerably lower than that of the NMP depot. Shah and coworkers [13] also noted a similar pattern of decrease in drug release on addition of a medium chain triglyceride to their formulation. Following the general trend of lower solvent/non-solvent affinity, the rate of release of the ethyl benzoate system is lower than that of the triacetin system. It should also be noted that since the triacetin has a finite water solubility, it will tend to diffuse out of the polymer-rich phase into the bath, whereas, the ethyl benzoate, with its near zero solubility, does not.

The morphologies of the lower aqueous affinity systems are also considerably different. While pores are visible in the triacetin system (Fig. 6(b)), they are much less pronounced and show little interconnection compared to the NMP structure (Fig. 6(a)). (Occasional large cavities, such as the one near the center of the triacetin structure, are likely due to dissolved protein). This morphology is consistent with expectations based on the reduced slopes of the binodal tie lines (Fig. 1(b)). Since the composition of the polymer-rich phase that forms on liquid demixing does not undergo as sharp an increase, the matrix remains in a more or less fluid, emulsified state for longer periods of time. In consequence of these two features (lower amounts of droplet phase and greater fluidity of the polymer-rich matrix), release of protein by diffusion through the polymer-

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3.3. Release rate and morphology

Fig. 5 shows the in vitro release rate of lysozyme into an aqueous receptor solution. The corresponding morphologies of the gelled systems are shown in Fig.

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Fig. 4. Water absorption for PBS-quenched 50 wt.% PLGA/ethyl benzoate solutions with; 0 wt.% lysozyme (■); 10 wt.% lysozyme ( ● ) added to the formulation.

Fig. 5. Lysozyme release rate from 50 wt.% PLGA/solvent solutions; NMP (●); triacetin (■); ethyl benzoate (▲) quenched into a PBS solution.
rich matrix may be the rate-preferred mechanism for this system, rather than through the droplet phase, as was characteristic of the NMP system. As noted earlier, since triacetin has a finite solubility in water, the matrix may undergo a slow increase in polymer concentration due to loss of the triacetin by transfer to the bath, leading to a relative decrease in the release rate, similar to the NMP system (Fig. 5).

A regular morphological structure is nearly completely absent from the gelled ethyl benzoate depot (Fig. 6(c)). The relative lack of morphological features and reduced protein release rate are consistent with expectations based on the thermodynamic phase diagram for this system. It is apparent that an appreciable polymer-lean phase is not created on de-mixing. Moreover, the relative lack of water solubility of the ethyl benzoate should insure that the polymer matrix remains in a more-or-less fluid state throughout most of the release period. As noted earlier, the lysozyme solubility is severely limited in
the polymer matrix. In consequence, one would expect the release mechanism to be dominated by protein solubilization and uniform diffusion through the slowly enriching polymer phase.

In examining the liquid de-mixing rates, phase diagrams, morphologies, and release kinetics associated with these model systems, it is evident that solution-based systems can be divided into two classes. Systems based on strong solvents with relatively high water affinities are characterized by rapid water absorption and liquid de-mixing rates, the formation of relatively hard polymer matrices with interconnected highly porous dispersed phases, and protein release rate profiles characterized by appreciable bursting followed by a shallower, low level release profile. On the other hand, solutions based on weaker solvents with low water miscibility, are characterized by slower, more uniform liquid de-mixing, formation of a relatively non-porous morphology with a more fluid polymer matrix, and a more uniform and lower protein release rate. Fig. 7 depicts the different release rate mechanisms resulting from the different morphologies. Protein release from the PLGA/NMP system is predominantly controlled by the phase inversion dynamics governing the formation of the interconnected pore phase through which transfer occurs, with little or no transfer occurring through the hardened matrix phase. Release from the slowly gelling systems is determined more by the mass transfer kinetics within the continuous, polymer-rich phase, since an appreciable, interconnected porous phase is not available. As will be shown in the next section, however, the bath-side mass transfer characteristics can have a dominant effect on the release profile, particularly for the weaker solvent systems.

3.4. Effect of bath composition

The impact of altering the bath side composition on the phase inversion dynamics of membrane-forming systems is well documented [14]. In that the dynamics of phase inversion play a significant role in protein delivery from polymer solutions, it is expected that protein release would be influenced by the chemistry of the injection site. There are many potential reactions between a PLGA solution depot and the physiological surrounding into which it is injected. For example, acids and bases are known to have pronounced effects on PLGA erosion rates [15]. The impacts of two bath-side additives on protein release from the model depot systems are studied in particular in this work. These additives are triacetin, a short chain triglyceride, and deoxycholate, a small organic biosalt. Both triglycerides and organic salts are found in the subcutaneous space, the primary target for systemic drug delivery from polymer solution depots.

3.5. Triglyceride in the bath

Figs. 8 and 9 and Table 1 summarize the phenomena observed when a 6% solution of triacetin is added to the bath, or, directly mixed with the ethyl benzoate depot. Fig. 8 shows the effect on the lysozyme release from the three model PLGA solutions with triacetin on the bath side. The NMP system (Fig. 8(a)) exhibits a decrease in the initial release rate (burst) in the presence of the triacetin, however, comparison to Fig. 5 shows that both rate profiles would be characteristic of a rapid phase inversion, high-burst system. Yevey et al. [10] reported a similar reduction in protein release for an NMP depot quenched in a PBS bath containing additional organic agents. On the other hand, as shown in Fig. 8(b) and (c), the slower phase inverting systems exhibit a much larger relative increase in release rate on addition of triacetin. The release curves for all three systems show the trend of decreasing initial release rate with decreasing S/NS affinity, however, there is a significant elevation in the overall protein release rate for the ethyl benzoate and triacetin systems when triacetin is present in the bath.

Fig. 9 shows data for the liquid de-mixing fronts for the three model systems submerged in a PBS solution containing 6% triacetin. Comparison of the behavior of the NMP-based depot exhibited in Figs. 9, 2 and 8(a) clearly shows that the phase inversion and drug release dynamics of the depot system based on a strong, hydrophilic solvent (NMP) are relatively insensitive to the presence of a weak, less hydrophilic solvent (triacetin) on the bath side. On the other hand, the behavior of the ethyl benzoate-based depot (Figs. 9, 2 and 8(c)) shows that both the phase inversion dynamics and the drug release characteris-
Fig. 7. Schematic comparison of the protein diffusional path for depots made from the three model PLGA/solvent systems; (a) NMP; (b) triacetin; (c) ethyl benzoate. Shaded regions indicate polymer-rich matrix, pores represent solvent-rich droplet phase.

tics of a system based on a relatively weak, hydrophobic solvent can be dramatically increased by the presence of a relatively more hydrophilic solvent on the bath side. Similar increases in the liquid de-mixing and drug release rates were also observed for depots based on a 44/6 mixture of ethyl benzoate and triacetin quenched into a pure water bath. As the triacetin content of the ethyl benzoate depot increases (either through diffusion from the bath side or pre-mixing with the depot), the overall depot viscosity decreases and the capacity for water uptake increases. These events, in turn, accelerate the liquid de-mixing process which promotes an accelerated release of protein. The drop in viscosity of the
system was readily observed visually, as the depot transformed from the original thick polymer solution to one with water-like consistency.

As shown in Table 1, four of the depot/quench systems: ethyl benzoate/triacetin–water, ethyl benzoate and triacetin/water, NMP/water, and NMP/triacetin–water exhibit similar rapid de-mixing and drug release rates. It should be noted, however, that, for the reasons discussed earlier with regard to Fig.

7, the dominant diffusive release path for the first two systems would still be through the bulk liquid, while that of the NMP-based systems would be through the interconnected pores. The triacetin-based depot quenched into a triacetin–water bath represents a different situation. For this system, the reduced liquid de-mixing rate shown in Fig. 9 reflects the expected trend associated with a given polymer–solvent–non-solvent system, namely a reduction in the de-mixing kinetics on addition of solvent to the bath side [8,14]. Moreover, the increase in protein release rate in the presence of triacetin is due to the increased solubilization of the system by the solvent.

From these results, it is clear that formulators must pay particular attention to compounds that may enter the drug release profile of the system. This is especially true for depots with low solvent/non-solvent affinity where protein release is highly dependent on the properties of the polymer solution.

3.6. **Organic salt in the bath**

Fig. 10 compares the lysozyme release from an ethyl benzoate/PLGA depot submerged in a deoxycholate bath of varying compositions. Adding deoxycholate to the bath clearly produces an increase in the steady-state protein release rate. The pH of the bath solution containing deoxycholate was buffered.
Table 1
Summary of trends in PLGA phase inversion dynamics and protein release rates for various solvent/bath conditions

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<th>Water Absorption Rate</th>
<th>Liquid-liquid Front Propagation Rate</th>
<th>Protein Release Rate</th>
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at 7.4 to avoid accelerating PLGA degradation via acid- or base-catalyzed hydrolysis. Comparison to the triacetin results shows that a 2–3% deoxycholate level produces a similar release rate profile as that produced by addition of 6% triacetin to the bath. Although the accelerated release is observed with both triacetin and deoxycholate, they are governed by different phenomena. Visual observations of depots in the deoxycholate bath showed surface erosion rather than alteration of the bulk gel. Upon injection into the bath, the depots form a flaky skin across the surface, indicative of a system undergoing bioerosion. Size exclusion chromatography of an ethyl benzoate system submerged for 1 week revealed a significant degradation in polymer molecular weight at the surface relative to the bulk depot. When the bath is sufficiently agitated, the surface skin is carried into the bulk bath reservoir, exposing a new surface. In this way, the system erodes until all the protein is released.

Dark ground imaging of all three model depot systems injected into a bath containing deoxycholate showed no changes occurred in the liquid de-mixing rates relative to those observed in the standard PBS bath. This means that bulk water absorption and the phase inversion dynamics are not impacted by the addition of the organic salt. Instead, the increased protein release is a result of increased PLGA erosion at the surface of the injected depot.

4. Conclusions

In this study the effect of lowering the solvent/
non-solvent affinity on phase inversion dynamics and subsequent in vitro protein release from two classes of polymer solution depots has been examined. We find that drug release from an NMP-based system, defined by steep tie lines and a nose-like binodal on the ternary phase diagram, is primarily governed by the dynamics of phase inversion leading to the formation of a porous, rubbery gel structure. This system exhibits two distinctive regions in the cumulative release profile: an initial burst, followed by a much slower long term release rate. Alternatively, depots based on relatively weak solvents (triacetin and ethyl benzoate) with low solvent/non-solvent affinity undergo phase inversion more slowly, resulting in a system in which protein release is more uniform and governed by the mass transfer characteristics of the two-phase liquid structure that forms. Specifically, slowing the gelation of a polymer solution depot through formulation causes morphological changes in the polymer solution that are favorable to sustained protein release. Furthermore, the addition of a small chain triglyceride or organic salt to the aqueous receptor bath evokes a significant increase in the mass transfer rate of protein from the low solvent/non-solvent affinity depots. It is evident that formulators must pay equal attention to the chemical composition of both the depot and the injection site when developing sustained release PLGA solution platforms.

From these results, it is concluded that release kinetics of a protein from a polymer solution placed in an aqueous environment are a function of the dynamics of phase inversion, which in turn can be related to the thermodynamics and mass transfer characteristics of the depot/bath system.

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