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# The role of polymer membrane formation in sustained release drug delivery systems ☆

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**Abstract**

A discussion of the role of polymer membrane-based drug delivery systems is presented. This is followed with a review of recent studies in our laboratories of the membrane formation and drug delivery characteristics of injectable polymer solution platforms. Attention is focused on the role of depot formulation in terms of solvent quality and water miscibility and polymer type (amorphous versus crystallizable), as well as the effects of bath-side additives on the in vitro release behavior. A quantitative model describing the protein release dynamics in fast phase inverting systems (FPI) is also discussed.


*Keywords:* Polymer solutions; Membrane formation; Injectable solutions; Drug delivery; Modeling

## 1. Introduction

The often rate-limiting step in the development of a successful drug delivery system is the determination of a suitable platform for sustained release of the drug. Key issues in the design of drug delivery systems are the avoidance of bursting effects and the attainment of controlled, in vivo release profiles over the lifetime of the depot. The latter considerations usually, though not necessarily, imply attaining zero-order release kinetics. In this regard, polymeric membrane-based delivery systems play a central role in drug delivery technology, finding use in a range of applications from injectable and implantable systems to tablet and coated systems [1–6].

Fig. 1 shows a schematic breakdown of the various classes of membrane-based release devices. The devices are fabricated starting with a suitable biodegradable polymer/solvent system in which the drug is either suspended or dissolved. Additives may be used to vary the water uptake characteristics of the depot, as in the case of protein systems [3,7], or other components may be added to alter the membrane formation characteristics [4,6]. Two major classes are the injectable systems, including microsphere suspensions and solutions, and the ingestible or implantable systems, including tablets and coated implant devices. The membrane may function primarily as a diffusive barrier, or the drug may be intimately encapsulated in the membrane structure.

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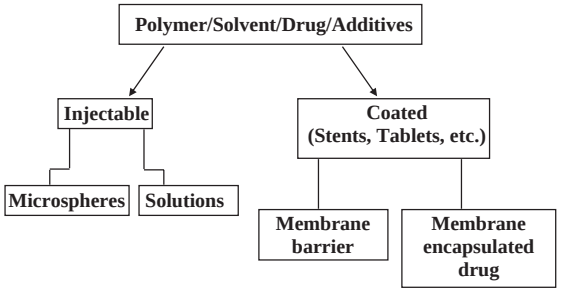


Fig. 1. Categories of polymer membrane-based drug delivery systems.

All of these systems have in common the formation of a membrane carrier by the process known as phase inversion, the primary steps of which are illustrated schematically in Fig. 2. Fabrication involves casting, coating, injecting, or molding the polymer/solvent system. The initially homogeneous, viscous solution of polymer and solvent (or mixture of solvents) with drug (either suspended or dissolved) is induced to phase separate by evaporation of solvent in a quiescent or flowing atmosphere, or by solvent–nonsolvent exchange in a liquid quench environment. Liquid demixing results in a two-phase structure whose morphological details vary depending on the nature of the mass transfer and phase separation processes. The bulk morphology generally consists of interconnected solvent–non-solvent rich liquid droplets, dispersed in a polymer-rich matrix. Most often a skin forms on the topmost layer of the membrane and the substructure may exhibit a honeycomb or finger-like appearance [4,8]. Successful design of delivery systems requires control of the interplay between the dynamics of the phase inversion process, the resultant membrane morphology, and the state of dispersion of the drug in the multiphase matrix.

Injectable, solution-based platforms are unique in that membrane formation and drug release take place in vivo. Such systems offer a paradigm for investigating the interplay of the membrane-formation and drug release characteristics. The following sections present an overview of recent studies in our laboratories that illustrate these issues.

## 2. Injectable systems based on solution platforms

Fig. 3 illustrates the basic features of the injectable solution systems that have been designed for protein-based therapies. The solution, consisting of a biodegradable polymer dissolved in a biocompatible solvent, along with additives and the suspended protein particles, is injected subcutaneously. On contact with the saline–water physiologic fluid, the solution undergoes phase inversion, forming the drug-encapsulating membrane in vivo. Throughout and following phase inversion, the drug dissolves and is transported through the membrane structure to the external environment. Examples of the two morphological classes of the hardened depots are shown on the upper right. So-called fast phase inversion (FPI) structures generally result from solutions based on strong, hydrophilic solvents and are characterized by a highly interconnected network of solvent-water filled pores. Liquid demixing and solidification in these systems generally takes place on the order of seconds

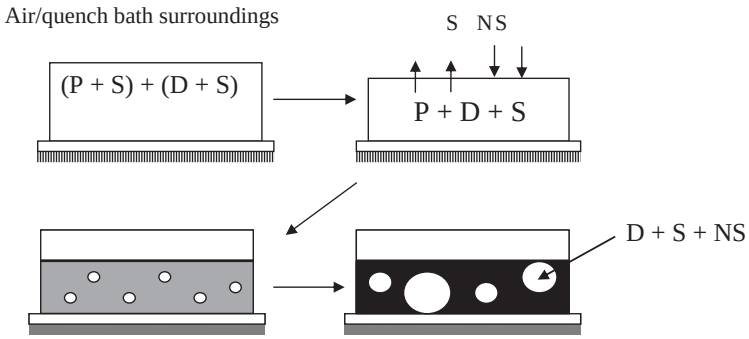


Fig. 2. Schematic of phase inversion process showing transformation of solution consisting of polymer (P) and solvent (S), with dissolved or suspended drug (D), to a two-phase membrane structure.

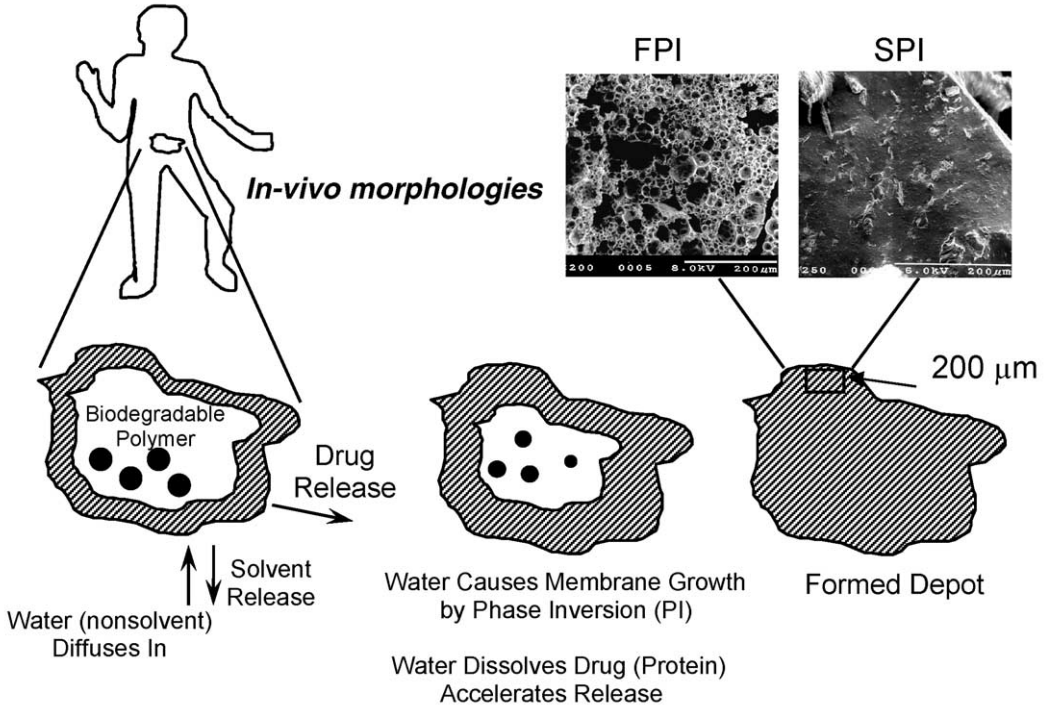


Fig. 3. Schematic illustration of membrane formation/drug release in an injectable system. Morphologies in upper right show fast phase inversion (FPI) and slow phase inversion (SPI) hardened membrane structures.

to minutes. The slow phase inverting systems are generally based on weaker solvents that have low water affinity. Solidification in these systems may take hours to days, and the resultant structures are more or less uniformly dense with few or nor apparent pores. Issues of importance include the interplay between solution formulations, phase inversion, membrane morphology development and the resultant release profiles, as well as considerations of the depot viscosity.

Fig. 4 illustrates the approach we have taken to address these issues. The roles of solvent, polymer type (amorphous and crystallizable), quench bath (i.e., release medium) composition, and protein composition have been explored primarily in vitro. In situ visualization of the mass transfer and gelation processes following solution-bath contact using a diffusion cell [6] gives valuable information on small time scales (minutes to hours [6]). Standard dissolution experiments are used to monitor the release kinetics over longer time scales (days to weeks). Modeling of release mechanisms in terms of the system characteristics is used to gain quantitative insights on the interplay of the system variables.

### 2.1. The role of solvent quality on release

The role of solvent quality and water miscibility on the release kinetics is illustrated in Fig. 5 for amorphous PLGA/lysozyme systems releasing in buffered saline solutions (PBS) at 37 °C. The in vitro release data on the right and corresponding hardened depot morphologies on the left show that, as the solvent quality and water miscibility are decreased, a progression occurs from burst-like release followed by shut down, to zero-order release kinetics. The morphologies shown on the left illustrate the progression from a highly porous structure characteristic of the strong, highly water soluble solvent (NMP), to a more uniformly dense structure with the slower releasing ethyl benzoate (EB) solvent. The NMP morphology is characteristic of a fast phase inverting system (FPI) and that of the EB is characteristic of a

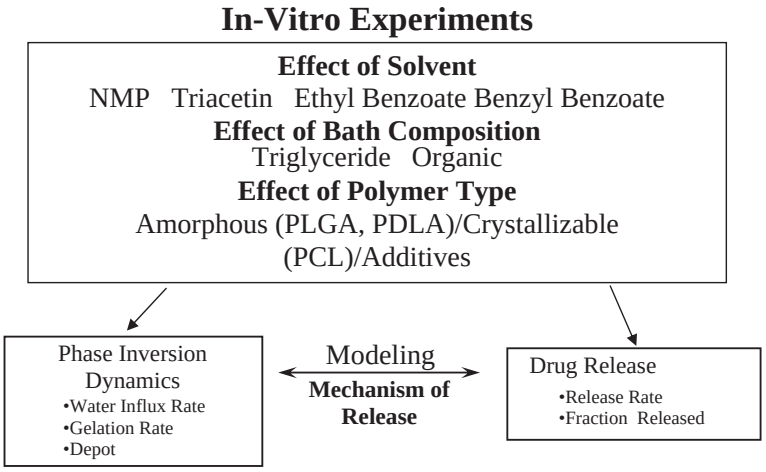


Fig. 4. In vitro injectable delivery studies.

slow phase inverting system (SPI). In situ measurements of the water diffusion and solution gelation rates, as well as water take-up rates, parallel these trends [6,9].

Fig. 6 shows profiles of serum levels of human growth hormone (hGH) (right) in subcutaneously injected rats and the corresponding explanted depot membrane morphologies (left) for various solvents. These data provide in vivo confirmation of the sequence shown in the in vitro experiments [7]. Thus, strong, highly water-soluble solvents lead to rapid phase inversion, highly porous morphologies, and burst-like release followed by shut down. While, relatively weak, low water-soluble solvents lead to

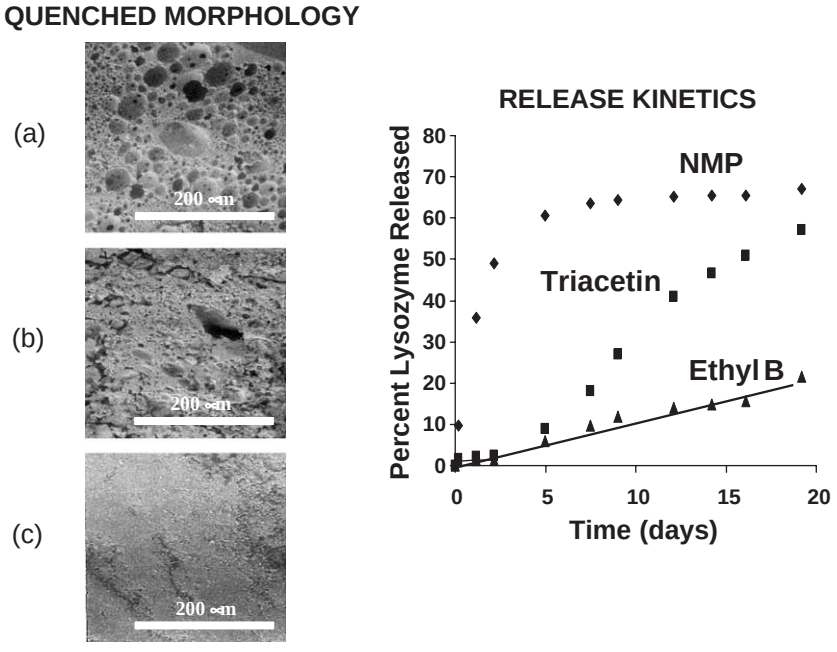


Fig. 5. Effect of solvent quality on in vitro lysozyme release rate and hardened morphology of PLGA solutions. Micrographs a, b, and c correspond respectively to NMP, triacetin and ethyl benzoate solvents.

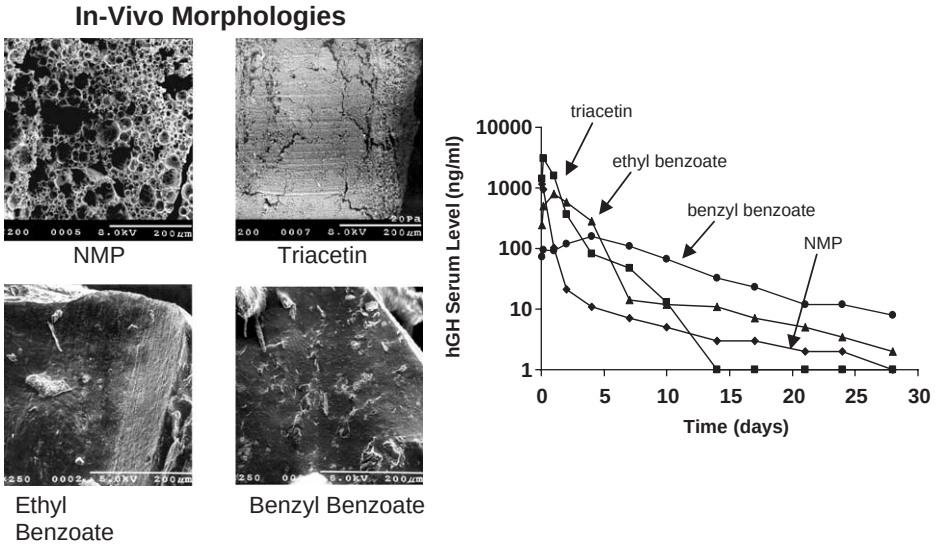


Fig. 6. In vivo release data (right) and hardened morphologies (left) associated with hGH release studies from rats.

slow phase inversion, more dense morphologies, little or no burst, and near linear release kinetics. The relative constancy of the polymer molecular weight over the dissolution time scales demonstrates that the release mechanism is physical diffusion/convection as opposed to erosion [7].

### 2.2. The influence of bath-side additives

While the depot solvent plays an important role, the release kinetics can also be profoundly influenced by the contact bath environment. This is illustrated in Fig. 7. The data on the left illustrate the effect on the lysozyme release profiles for the PLGA system of adding 6wt.% triacetin to the bath-side PBS solution. While the FPI system (NMP) (Fig. 7a) exhibits a decrease in the initial release rate in the presence of the triacetin, both profiles are still characteristic of a rapid phase inversion, high-burst system. Similar reductions in protein release for an NMP depot system quenched in a PBS bath containing additional organic agents have been reported by Yewey et al. [10]. On the other hand, as shown in Fig. 7 (b, c), the slower phase inverting system exhibits a much larger relative increase in release rate on addition of triacetin and a significant elevation in the overall protein release. In situ liquid de-mixing data for the three model systems submerged in a PBS solution containing 6% triacetin [9] show that the phase inversion and drug release dynamics of the 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. However, those for the systems based on relatively weak, hydrophobic solvents can be dramatically increased by the presence of the 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 triacetin-based depot quenched into a triacetin-water bath represents a different situation. For this system, the liquid de-mixing rate actually decreased [9] which 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 [8,11]. Moreover, the increase in protein release rate in the presence of triacetin is due to the increased solubilization of the system by the solvent.

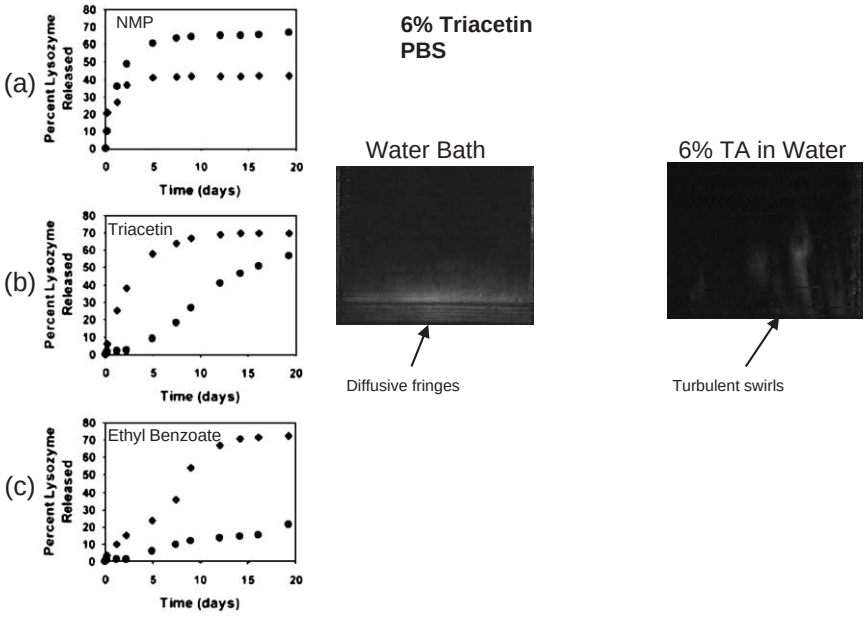


Fig. 7. Influence of 6 wt.% triacetin in bath-side PBS on lysozyme release rates (left) from three different solvent-based systems. Photos on right are in situ dark ground images of the bath-side showing diffusive release (left picture) into pure PBS solution and convective release (right panel) into solution with added triacetin.

The photos on the right show in situ dark ground images of the bath-side interfacial region for the ethyl benzoate solvent system corresponding to the presence or absence of triacetin in the bath. The fringes in the image on the left illustrate the release of the lysozyme after two minutes of contact time with the pure PBS bath is diffusive. The image on the right shows the effect on the bath-side release 30 s after removal of the pure PBS solution followed by immediate replacement with the PBS/triacetin mixture. The presence of the swirls indicates a turbulent-like convective release that reflects a combination of effects due to the increased depot-side phase inversion rate and the mass transfer characteristics of the bath. The latter reflect the influence of the triacetin on the bath-side viscosity and surface tension. From these results, it is clear that optimization of the release characteristics of a given depot requires attention to compounds that may be present in the external environment to alter 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.

### 2.3. The influence of depot additives in FPI systems

Although the SPI systems have the advantage of much-reduced bursting behavior and more or less uniform release kinetics, they suffer from the disadvantage of relatively high viscosities, which limits their injectability. Moreover, their relative hydrophobicity makes them susceptible to inhibition of the release due to foreign protein absorption. Preferential segregation of hydrophobic/hydrophilic copolymer additives is a valuable tool that can be used to improve not only the biocompatibility of NMP-based depots, but their release properties as well. The basic premise is that hydrophilic materials preferentially segregate to hydrophilic regions (depot surface + polymer lean phase) during the phase inversion process [12,13]. Thus, the more hydrophilic depot surface will reduce hydrophobic interactions and repel proteins, while the increased diffusion barrier within the interconnected polymer lean phase can have a potentially favorable effect on both the release rate and overall release time. One such modification is through the addition of the triblock copolymer Pluronic [13]. Although addition of the Pluronic

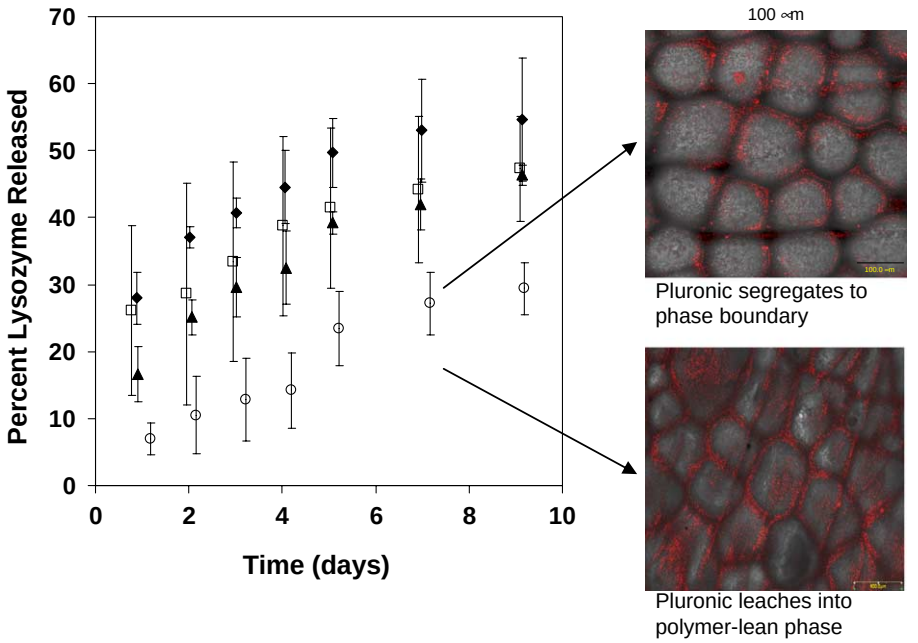


Fig. 8. The effect of Pluronic on lysozyme release rates (left) from formulations with NMP/PDLA/Pluronic/ lysozyme weight ratios of: 72/18/0/10 (♦); 72/14.4/3.6/10 (□); 72/12.6/5.4/10 (▲); 72/10.8/7.2/10 (○). Micrographs on right shows Pluronic segregation to solvent-rich phase (top) and accumulation within solvent rich regions (bottom) for highest Pluronic concentration.

actually increases the phase inversion rate FPI and appearance of the FPI morphology due to the increased water uptake associated with the hydrophilic PEO blocks [13], this can be more than compensated for through reduced protein diffusion rates due to the presence of the Pluronic in the liquid pores. The data in Fig. 8 illustrate the reduction in lysozyme release rate that occurs with increased Pluronic (graph on left); while the confocal images of stained Pluronic on the right show a build up in the solvent-rich cavities (white regions) that apparently causes the reduced diffusion in the pore phase leading to essentially zero order kinetics [13]. Measurements of the Newtonian viscosities at 25 and 37 °C for the PDLA/L101 systems and the 50 wt.% PLGA/ethyl benzoate system show a 7 times reduction in viscosity at room temperature, significantly improving the injectability characteristics.

## 3. Modeling of FPI release mechanisms

Fig. 9 illustrates a model we recently developed to quantify the release behavior of the FPI systems [14]. In this case the interconnected nature of the porous phase is modeled through the use of a parallel system of solvent-rich and polymer-rich cylinders, representing the two phases, respectively, with the overall membrane structure porosity as a parameter. Diffusion equations for the system and parameters used along with the model integration algorithm are given elsewhere [14]. In addition to the system porosity, key parameters that affect the calculated release profiles are the protein diffusivity in the solvent rich regions, and the bath-side mass transfer characteristics. The latter effect is characterized in terms of the Nusselt number, Nu, for mass transfer [14]. Fig. 10 shows predictions of the lysozyme release rate profiles to illustrate both effects. The graph on the left illustrates that burst-like rapid release profiles, characteristic of FPI systems (high Nu curves) can be altered to exhibit essentially zero-order release depending on the bath-side mass transfer characteristics (low Nu). Likewise, depending on the diffusivity in the solvent-rich phase (graph on right), release profiles can be altered from typical FPI bursting/shutdown behavior to a more nearly uniform release rate characteristic of zero-

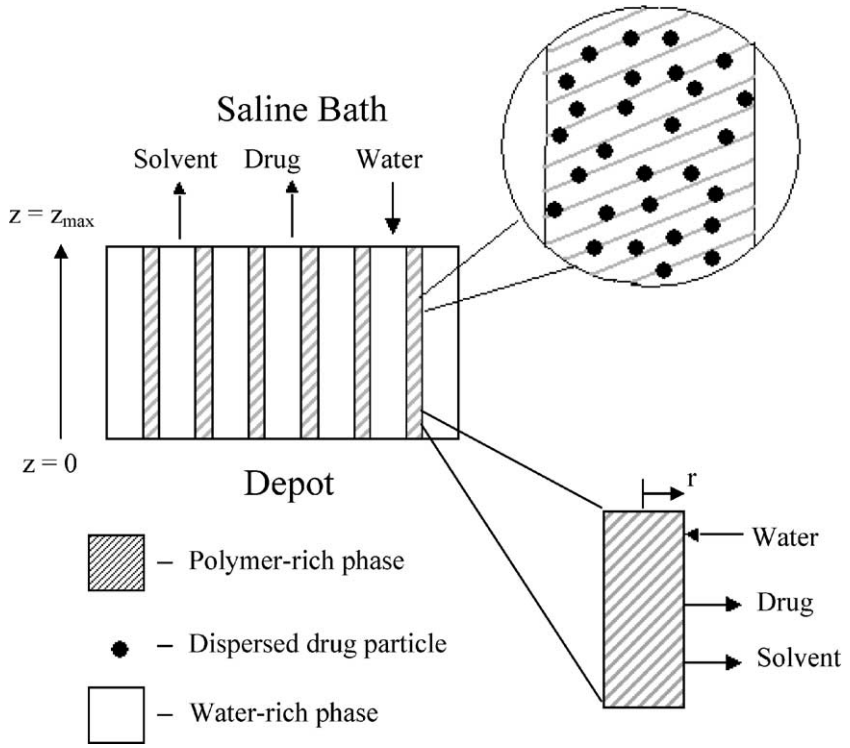


Fig. 9. Model of depot morphology for FPI systems.

order kinetics. The latter effect is seen in the Pluronic data described in Fig. 8. Good fits of FPI release profile data and Pluronic- modified release profiles with the model have been shown [14]. Modeling approaches such as these, point to the value of quantitative understanding of mechanisms to control and predict the release behavior.

## 4. The role of polymer crystallizability

The role of polymer crystallizability in the release kinetics of an injectable system can be profound. Studies suggest that in polymer matrix systems, the onset of crystallization often coincides with a period of accelerated drug release wherein the semi-crystalline

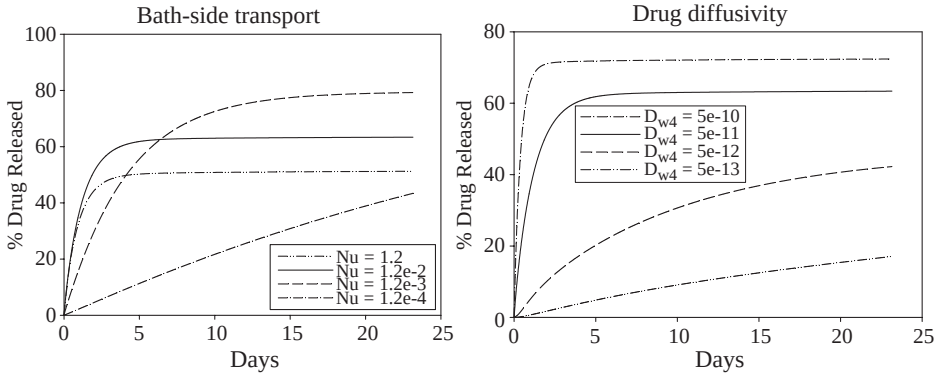


Fig. 10. Model predictions of effects of bath-side mass transfer Nusselt number, Nu, (left) and dispersed droplet phase diffusivity, $D_{W4}$, (right) on lysozyme release from FPI systems.

material develops a microporous structure in which the accelerated drug release occurs through the water-filled pores [15–17]. Another example is the release characteristics of blends of an amorphous polymer, Poly (D,L-Lactide) (PDLA) and a crystallizable polymer, Poly(ϵ,-caprolactone) (PCL) dissolved in ethyl benzoate (EtB) with 10wt.% lysozyme [15]. The PCL pure component melting point is such that the blend solution is initially amorphous so that it can be readily injected; however, on addition of water (by diffusion of water into the depot) the melting point is raised and crystallization can begin. Crystallization may result from an increase in the melting point of the PCL solution due to a decrease in the solvent quality of the water–ethyl benzoate mixture resulting from the solvent–nonsolvent exchange, or it may result from liquid de-mixing, leading to the formation of a polymer-rich phase with a higher melting temperature than the initial bulk polymer concentration. Morphologies of the microporous precipitated structures suggest a combination of both effects may be occurring [15]. In either case the release kinetics show a strong influence of the crystallization. Fig. 11 shows a comparison of the crystallization transformation data (determined calorimetrically) with the PCL/ethyl benzoate protein release data. Interestingly, the transformation of the depot corresponds with the protein release profile well, suggesting that the crystallization process is integrally tied to the protein release kinetics. An additional novel feature of the PCL/ethyl benzoate protein release curve is that this depot releases almost 100% of the incorporated protein. While all of the systems exhibit some evidence of crystallization (Fig. 11), the depots that have lower degrees of crystallinity do not exhibit the novel features associated with the onset of crystallinity seen in the most crystalline systems. Rather, these systems show a prolonged period of slow protein release. Systems with low degrees of crystallinity are characterized by a non-porous morphology (see Fig. 5 here and Fig. 4d in [15]) and a more uniform and slower protein release rate. On the other hand, highly crystalline systems are characterized by a porous morphology that is indicative of solid–liquid (s–l) de-mixing and a protein release curve that shows a delayed burst profile.

As indicated in Fig. 11, the protein release data for the pure PCL system exhibit a one-to-one relation to the amorphous-to-crystalline transformation in the depot. These data suggest that protein is excluded from the crystalline phase during s–l de-mixing and, thereby, pushed into the more mobile polymer–lean phase, thus expediting its release. Additionally, the near 100% release of the protein further suggests that a negligible amount remains trapped in the amorphous regions of the semi-crystalline structure. Such an interpretation is consistent with the mechanism of texture development in semi-crystalline systems in the presence of non-crystallizable diluents [18], solvents [19], or mixtures of solvent and nonsolvent [20] in which exclusion of the non-crystallizable material from the growing

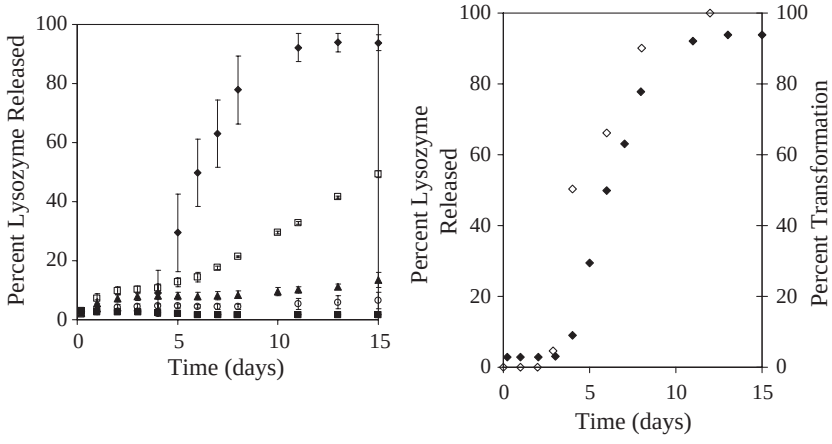


Fig. 11. Lysozyme release rate (left) from formulations with PCL/PDLA/ethyl benzoate/lysozyme weight ratios of: 45/0/45/10 (♦); 31.5/13.5/45/10 (□); 22.5/22.5/45/10 (π); 13.5/31.5/45/10 (○); 0/45/45/10 (■). Comparison of the lysozyme release rate (♦); and the transformation rate (◇) (right) for the pure PCL solution.

crystal front leads to the formation of open inter- and intra-crystalline regions rich in the non-crystallizable diluent. A qualitative model of this release mechanism is given elsewhere [15].

Finally, it should be noted that an issue of importance with injectable systems is that of drug stability, which is generally related to the water content within the device. For example, moisture-induced degradation/aggregation can be a major contributor to the loss of protein activity [21]. An added advantage in the use of relatively water insoluble solvents such as ethyl benzoate is that the combination of solvent and reduced water uptake provides a more stable environment for the protein. Release experiments for such systems in which the activity of the lysozyme has also been monitored demonstrate shown that a large fraction (>3/4) of the total lysozyme released is in the biologically active form even with the addition of water-soluble excipients [22]. On the other hand, since lysozyme is a rather stable molecule, issues concerning compatibility of the solvent and the use of stabilizing excipients should always be considered in the development of other therapeutically relevant (and often more labile) proteins.

## 5. Summary and conclusions

Injectable polymer solutions represent an important class of membrane-based drug delivery platforms. Control of the release kinetics depends on the interplay of the polymer, solution formulation, and in vivo quench conditions and release profiles can be varied over wide ranges depending on the associated phase inversion dynamics. Drug delivery from polymeric platforms can be optimized through quantitative understanding of the interplay between phase inversion and the release mechanisms.

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