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

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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