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Diffuse-interface theory for structure formation and release behavior in controlled drug release systems

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Abstract

A common method of controlling drug release has been to incorporate the drug into a polymer matrix, thereby creating a diffusion barrier that slows the rate of drug release. It has been demonstrated that the internal microstructure of these drug–polymer composites can significantly impact the drug release rate. However, the effect of processing conditions during manufacture on the composite structure and the subsequent effects on release behavior are not well understood. We have developed a diffuse-interface theory for microstructure evolution that is based on interactions between drug, polymer and solvent species, all of which may be present in either crystalline or amorphous states. Because the theory can be applied to almost any specific combination of material species and over a wide range of environmental conditions, it can be used to elucidate and quantify the relationships between processing, microstructure and release response in controlled drug release systems. Calculations based on the theory have now demonstrated that, for a characteristic delivery system, variations in microstructure arising due to changes in either drug loading or processing time, i.e. evaporation rate, could have a significant impact on both the bulk release kinetics and the uniformity of release across the system. In fact, we observed that changes in process time alone can induce differences in bulk release of almost a factor of two and typical non-uniformities of $\pm 30\%$ during the initial periods of release. Because these substantial variations may have deleterious clinical ramifications, it is critical that both the system microstructure and the control of that microstructure are considered to ensure the device will be both safe and effective in clinical use. Published by Elsevier Ltd. on behalf of Acta Materialia Inc.

Keywords: Controlled drug release; Diffuse-interface; Phase-field theory; Microstructure; Dissolution

1. Introduction

A popular method of controlling drug release is to incorporate the drug into a polymer matrix, which acts as a diffusion barrier, thus slowing the rate of drug release. Recently, this method of drug delivery has been used in the form of coatings on medical devices, most notably in drug eluting stent applications, with remarkable results [1–3]. Since the 1990s angioplasty in conjunction with bare metal stents have been used as scaffolding to prop open and support a blood vessel (e.g. coronary artery), respectively, for patients with cardiovascular disease. In about 30% of the cases, the human body response is in form of scar tissue called restenosis, resulting in renarrowing of the blood vessel. The presence of minute quantities of cytotoxic or cytostatic drug reduces proliferation of smooth muscle cells (restenosis) to the point that fewer than 10% of patients exhibit restenosis. This reduction is important for patient quality of life and for managing the costs of cardiac disease.

The drug–polymer coatings are routinely fabricated by dissolving a mixture of drug and polymer into a solvent. The solvent then evaporates, leaving a system consisting of essentially only drug and polymer. Depending on the

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[1] D.V.P. wishes to dedicate this paper to the memory of Professor J. Larry Duda (Pennsylvania State University, Department Chemical Engineering, 1936–2006).

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materials (drug, polymer and solvent) and the environmental conditions during manufacturing, the remaining material system may exhibit complex composite structures. In other words, instead of a homogeneous mixture of drug and polymer throughout the system, the system will typically separate into drug- and polymer-rich phases. Further, the distinct phases present in the composite system are either in an amorphous or a crystalline state. Thus, the microstructure of these systems can consist of intricate spatial variations in both chemical and physical (structural) states. The underlying microstructure that evolves during manufacturing will, in turn, have a significant impact on the kinetics of drug release. For example, it has been demonstrated in one system that inducing more phase separation by altering the polymer chemistry substantially increases the amount and rate of drug released [4]. Furthermore, it has also been shown that increasing the size and number of distinct drug-rich regions increases the amount and rate of drug released [5]. Thus, it is recognized that both the type of materials and environmental conditions will influence the composite microstructure that evolves during manufacturing and, consequently, the drug release kinetics. However, the relationships between processing, structure and release kinetics are not well understood, let alone quantified.

Previous studies, which have focused mainly on the impact of structure on bulk drug release and not local variations in release or the effect of processing on structure, have been limited experimentally to a few isolated systems [4–6]. Theoretical efforts, reviewed recently in Ref. [7], have focused primarily on empirical models [8,9] and mean-field approaches [5,10] that do not explicitly consider the underlying microstructure of the drug delivery system. To address these issues, we have developed a generally applicable theory for the evolution of microstructure in drug–polymer–solvent systems. The theory, which can be applied to any specific combination of material species over a wide range of environmental conditions, consists of a set of partial differential equations (PDEs) that govern the evolution of the chemical constituents (drug, polymer and solvent) expressed as field variables. Further, the PDEs also govern the evolution of an order parameter field, the phase field, that specifies the local degree of crystallinity. The PDEs describe the evolution of these fields, which, in turn, describe the microstructure of the system. To illustrate the application of the PDEs, we have conducted calculations to predict the evolution of microstructure in a hypothetical, yet characteristic, material system during both manufacturing and drug release. Based on these calculations, we have assessed the relationships between processing, microstructure and drug release in the representative system.

In this manuscript, we describe the development and application of a phase field theory for the evolution of microstructure in drug–polymer–solvent systems. In the following section, we present an overview of the derivation of the model equations. We also assign the material-specific parameters in the equations based on a representative material system and describe the calculations conducted to elucidate the relationships between processing, microstructure and release kinetics. Next, we illustrate the outcome of the calculations, which is followed by a discussion of the results. Finally, we provide a brief overview in the Section 5.

2. Materials and methods

2.1. Overview

The application of diffuse-interface theories to predict the evolution of microstructural phenomena has become increasingly popular in recent years (for a recent reviews on the subject see Refs. [11,12]). These methods, which are based on two well-known continuum equations, the Cahn–Hilliard [13] and Allen–Cahn [14] equations, have been employed to predict the formation of solidification structures in both pure [15] and alloyed [16,17] metals. Recently, they have also been extended to molecular systems to predict the behavior of ternary amorphous polymer, solvent and non-solvent systems [18–20]. Here, we build on these concepts to develop a predictive theory for the evolution of microstructure in controlled drug delivery systems that consist of drug, polymer and solvent, which can assume both amorphous and crystalline states. We do, however, ignore the presence of homophase interfaces (i.e. crystallographic orientation is neglected) and potential crystallographic anisotropies in interface energy and mobility. By neglecting crystallographic orientation, evolving homophase structures will coalesce instead of impinging to form grain boundaries. Further, strong interface energy or mobility anisotropies will give rise to faceted, elongated structures. By omitting these phenomena, predicted structures will be restricted to smoothly varying, equiaxed shapes. However, we do not expect these phenomena to have significant influence on the overall spatial distribution and state of the drug within the polymer matrix, and therefore on the release kinetics. Inclusion of these additional phenomena, while formally straightforward, adds significant complexity to the current model, and would only give rise to relatively small perturbations in the predicted evolution of the microstructure. These phenomena are therefore neglected in this preliminary study. Finally, we note that the PDEs only characterize diffusive transport and ignore other transport mechanisms, such as fluid flow.

To derive the equations governing structural evolution in these systems, we start by postulating a functional form for the free energy as a function of the field variables that describe the system, which includes corrections to the standard homogeneous free energy that account for the presence of internal interfaces in the system. Based on this expression, we can then specify the equations that govern the evolution of those field variables, and therefore the system, in such a way that the free energy of the system is minimized as a function of time. This includes the presence of

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