Effect of Drug Loading and Polymer Chemistry on the Structure Formation of Drug-Polymer Coatings: Experiments and Simulations

Martin K. McDermott, Chang-Soo Kim, Dave M. Saylor, Dinesh V. Patwardhan, Steven K. Pollack

Food and Drug Administration, Center for Devices and Radiological Health, Office of Science and Engineering Laboratories, Division of Chemistry and Materials Sciences, 10903 New Hampshire Avenue, Building 64, Silver Spring, Maryland 20993

Introduction: The incorporation of drug within polymer matrices is commonly used as a way of controlling the rate of release of drug from a solid carrier inside the body. The amount of drug released is in part determined by the composite microstructure of the drug in the polymer matrix, which, in turn, is determined by processing variables. Drug-polymer coatings are typically fabricated by casting a solution of drug and polymer in a solvent. Drug particles form *in situ* in a polymer matrix as the solvent is evaporated. The microstructure of the drug [1] and polymer [2] will depend on the physical and chemical properties of the drug, polymer, and solvent, as well as on the processing environment. This study examines the effects of drug loading and polymer chemistry on drug and polymer microphase separation using computer modeling and experimental methods. The results will be used to quantitatively understand the relationships between processing, microstructure and release kinetics of drug from a polymer matrix.

Methods:

Experimental

A drug-polymer stock solution was made by dissolving poly(styrene-b-isobutylene-b-styrene) (SIBS) triblock polymer (SIBSTAR) with 15 or 30 % w/w styrene, Mw 100000 (Kaneka Texas Corporation, Pasadena, TX) and tetracycline drug (Assay > 98.0% (NT), Fisher Scientific) in tetrahydrofuran (THF) (Fisher Scientific). The solution solids concentration was 3 % w/v and contained various tetracycline concentrations. Filtered solutions were mixed with the polymer-THF stock solution to create the final THF/polymer/drug solution with a solids concentration of 1 % w/v. The solution was cast at room temperature in air. Atomic Force Microscope (AFM) scans of coating surfaces were obtained using a Molecular Force Probe 3D instrument manufactured by Asylum Research. AFM images were acquired in tapping mode using a silicone OMCL-AC240TS probe with a spring constant of 1-3 N/m. In addition, three dimensional images of the drug beneath the coating surface were collected with a Laser Scannng Confocal Microscope (LSCM)(model DMIRBE) manufactured by Leica Microsystems, GmBH, Wetzlar, Germany using a 100x oil immersion objective.

Simulation

A two-dimensional numerical model employing the Cahn-Hilliard diffuse interface theory has been developed to predict and mimic the experimental structure formation for drug-polymer (tetracycline-SIBS) coatings in controlled drug release applications. The model is based on quaternary systems consisting of tetracycline, poly-styrene, poly-isobutylene, and solvent to mimic the experimental system. The model can assume amorphous or crystalline states of drug and polymers. Initially, the model system started from a homogeneous mixture of the quaternary components. As solvent is removed from the system using an explicit evaporation scheme, structure development in the composite coating is computed based on the diffuse interface theory. Structural evolution of the systems with various drug loadings styrene weight fractions (in SIBS polymer) of 15 and 30 % were simulated.

Results: Computer simulations demonstrate that the computationally calculated structures are in good agreement with those from experiments. Both experimental and computational results indicate that polymer chemistry (styrene weight fraction in SIBS) as well as drug loading significantly influence the characteristics of structure formation. An example of composite images obtained from AFM is illustrated in Figure 1.

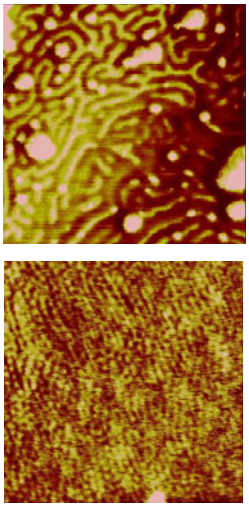

Figure 1. Example of 1 um x 1 um AFM images of poly(styrene-*b*isobutylene-*b*-styrene) (SIBS) triblock polymer: 15 w% styrene, Mw 100000 (top), 30 w% styrene, Mw 100000 (bottom)

Conclusions: The drug and polymer microstructure in solvent cast coatings for use in controlled drug release has been characterized by AFM and LSCM. A computational model has also been developed to predict the structure formation of the experimental coatings. Using the computer modeling and experimental results, the impact of manufacturing variables, such as drug loading, polymer chemistry and evaporation rate, on drug and polymer phase structure development can be predicted.

References

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