Drug elution kinetics and structure of absorbable matrix coatings

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Introduction:

In vivo, site-specific release of a therapeutic drug is commonly controlled by incorporating the drug with a solid polymer matrix. Typically, drug aggregates form in situ as the solvent evaporates from the substrate that has been coated with drug-polymer solution. The kinetics of drug release are related to the composite microstructure of the drug-polymer matrix, which in turn is controlled by processing variables, and the physical and chemical properties of the drug, polymer, and solvent. This study examines the early release kinetics of the drug from an absorbable coating material and the composite microstructure.

Methods:

A drug-polymer stock solution was made by dissolving tetracycline (TC) and poly(lactic-glycolic-acid) (PLGA) in tetrahydrofuran (THF). 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 using two different evaporation rates.

Dissolution

Sample coupons were individually placed in the elution chambers of a 400-DS Dissolution Apparatus VII (Varian, Palo Alto, CA). Eluted drug samples were collected at the end of various pre-selected time points within the first two days. The concentrations of drug in the eluted samples were measured using in-house TC-standards and a HPLC with 474 scanning fluorescence detector (Waters, Milford, MA). Analysis of TC was performed using the method of Vienneau et al. [1].

Microscopy

Surfaces of the coatings were imaged using a Molecular Force Probe 3D atomic force microscopy (AFM) (Asylum Research). Images were acquired in tapping mode using a silicone OMCL-AC240TS probe with a spring constant of 1-3 N/m. In addition, 3D images of the drug beneath the coating surface were collected with a Laser Scanning Confocal Microscope (LSCM) (model DMIRBE Leica Microsystems, GmBH, Wetzlar, Germany), using a 100x oil immersion objective.

Results:

Experimental observations indicate that polymer chemistry as well as drug loading significantly influences the characteristics of structure formation as well as drug elution. A typical AFM image and an elution profile are provided in the figure below.

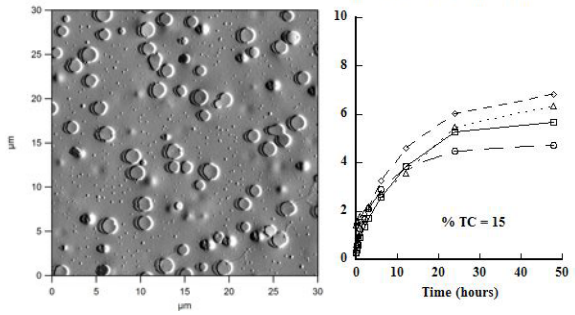

Figure 1. Representative data for PLGA (85:15) coatings with 15% tetracycline: AFM image (left) and corresponding elution curves (right) for selected copolymer ratios and solvent evaporation rates: 50:50 PLGA (75 mg/h (- -◊ - -) and 20 mg/h (····Δ····); 85:15 PLGA (75 mg/h (—□—□—) and 20 mg/h (—○—○—)).

Conclusions:

The initial elution rates have been characterized for both fast and slow cast evaporation rates. In addition, the drug and polymer microstructures in solvent cast coatings for use in controlled drug release have been characterized by AFM and LSCM. Using these data, we have elucidated the impact of manufacturing variables, such as drug loading, polymer chemistry and evaporation rate, on drug and polymer phase structure development, as well as the impact of phase structure and polymer chemistry on the subsequent drug elution kinetics.

Reference:

[1] D.S. Vienneau, C.G. Kindberg, J. Pharm Biomed. Anal. 16(1) (1997) 111-117.