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Morphology of Drug Eluting Coatings on Stents

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Introduction

A significant advance in the treatment of cardiovascular disease, drug eluting stents combine a cylindrical steel mesh (stent) with a drug/polymer coating. The stent keeps weakened blood vessels open, and the polymer coating elutes a drug which prevents re-blockage of the vessel due to scar tissue formation (restenosis). Challenges arise in the formulation of the coating since it must be thin and conformal, incorporate a high concentration of drug, control the rate of drug release, and also withstand the severe deformations of the metal cage upon insert into the blood vessel. Here we apply multiple techniques to probe coating morphology from the microscale to the nanoscale: light, infrared, Raman, scanning electron, and scanning probe microscopies.

Experimental

Stents were coated with a mixture of the drug dexamethasone in poly(alkyl methacrylate) polymers. By changing the drug concentration from 5 to 43 wt% and the alkyl chain length of the poly(alkyl methacyrate) from poly(ethyl methacrylate) to poly(octadecyl methacrylate), a broad range of coating morphologies were created. In addition, coatings of dexamethasone mixed into blends of short and long alkyl chain length poly(alkyl methacrylates) were also examined. Darkfield light microscopy reveals coating cloudiness and polarized light microscopy reveals drug crystal formation. Optical interferometry quantified coating roughness and thickness along and around the stent, and infrared microscopy confirmed coating composition uniformity along the stent. High-resolution scanning confocal Raman microscopy images the distribution of drug within the polymer and blend coatings, and images multi-layer coating thickness and morphology. Scanning electron and scanning probe microscopies image the distribution of drug at the surface of the coating. In particular we exploit digital pulsed force mode (DPFM) imaging to decipher the surface composition of the coatings at the nanometer scale.

Results

Upon increasing the concentration of dexamethasone, or increasing the alkyl chain length of the poly(alkyl methacrylate) polymer, a transition from clear transparent coatings to cloudy coatings to coatings with crystallized drug domains occurs. Remarkably, changing coating process parameters shifts the transition from clear to crystalline coatings dramatically. The characterization methods show that the clear coatings exhibit a homogeneous mixing of drug into polymer, the cloudy regions correlate with regions enriched in dexamethasone, and the crystalline regions contain pure dexamethasone. Coating morphology correlates with drug elution rates: the amount of "burst" (drug released in the first 24 hours) increases as the degree of mixing decreases (clear → cloudy → crystalline). In addition, coatings of dexamethasone incorporated into blends of poly(butyl methacrylate) (PBMA) and poly(lauryl methacrylate) (PLMA) exhibit interesting morphologies within the coating and at the coating surface. Raman microscopy indicates dexamethasone preferentially partitions into poly(butyl methacrylate). Raman images reveal the degree of mixing of

dexamethasone and the two polymers along with the morphology of any top-coating layers applied (FIG 1). The DPFM scanning probe images reveal complex layering of dexamethasone and the two polymers at the surface of dexamethasone/PBMA/PLMA coatings (FIG 2).

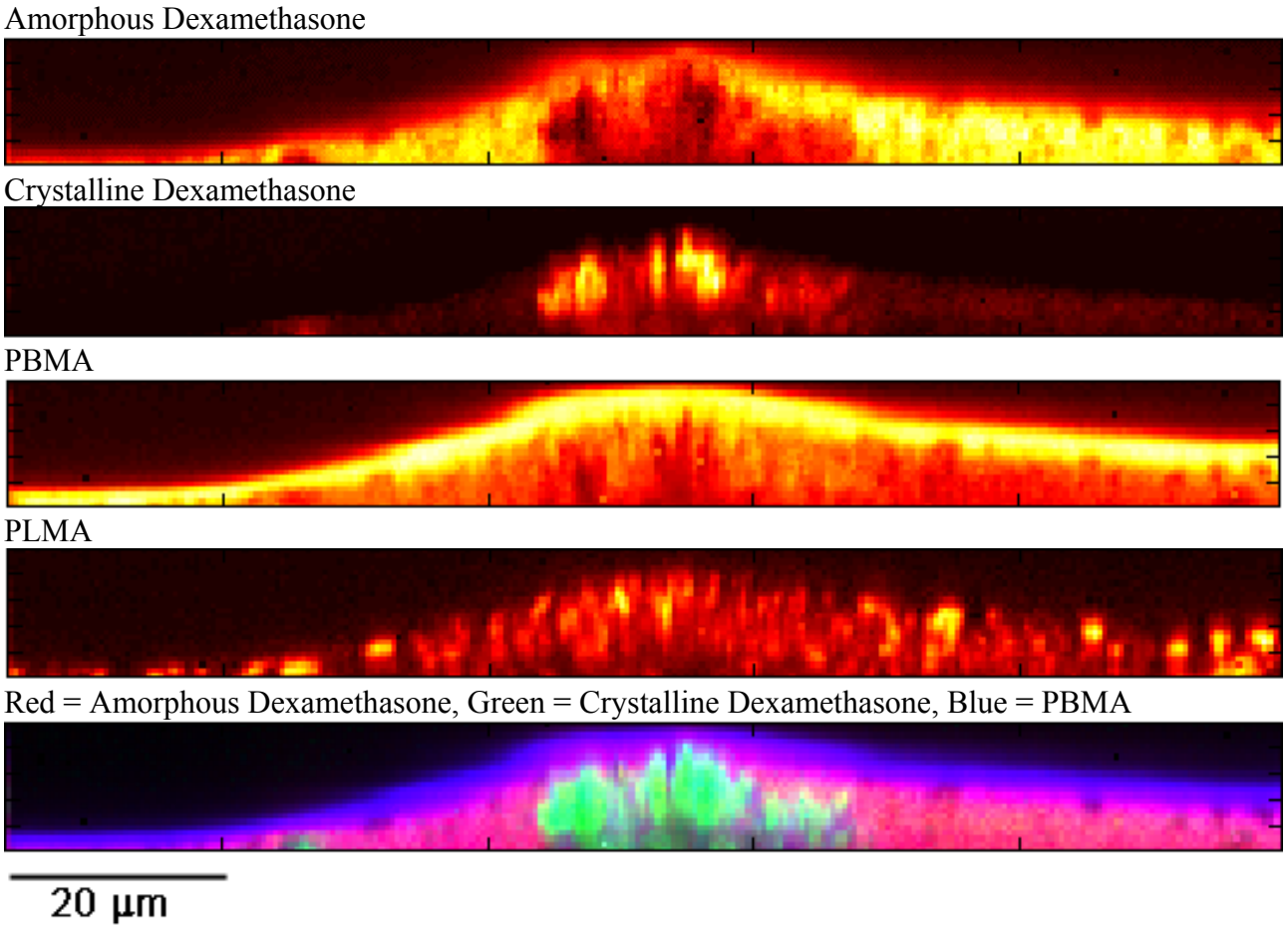

FIG. 1. Cross-sectional Raman images of the distribution of dexamethasone within blend coatings of PBMA and PLMA with a PBMA top-coating.

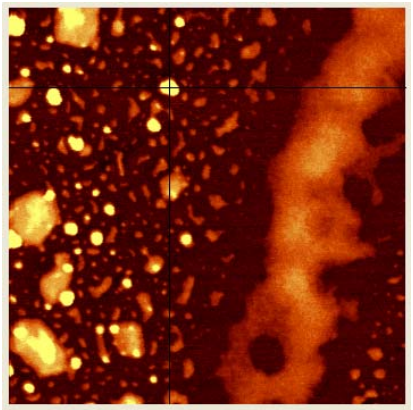

FIG. 2. DPFM scanning probe image of tip adhesion to coating surface of dexamethasone in PBMA and PLMA (43.5/43.5/13 by wt.): bright spots = PLMA, dark regions = dexamethsone

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