Microstructure Modeling of Controlled Release Drug Coatings

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Presented at the 15th International Coating Science and Technology Symposium,
September 13-15, 2010, St. Paul, MN [1]

Drug eluting coatings represent a relatively new class of combination medical products that incorporate controlled release technologies with more traditional devices to improve functionality and performance. The primary example is the drug eluting stent (DES), which has demonstrated a significant reduction in the rate of restenosis after angioplasty compared to bare metal stents. To manufacture a drug eluting coating, typically one or more layers of a solution of drug and polymer are cast, either by pipette or spray, on the device surface. Subsequently the solvent evaporates, leaving behind a composite of drug and polymer that can exhibit complex and intricate spatial variations in both chemical and physical composition. A number of recent studies have demonstrated the intimate relationship between materials and manufacturing conditions, the microstructure (morphology) of the drug-polymer composite coating, and drug release [1–3]. If these relationships can be elucidated and quantified, it should be possible to replace much of the current empiricism used in the selection of materials for drug eluting coatings and process design by a more directed approach, tailoring the design to obtain a desired release behavior.

To predict these relationships, we have devised a novel formulation, based on diffuse theories, to predict microstructure development during coating fabrication and the impact of microstructure on subsequent release kinetics [4–7]. The basic model for systems containing an arbitrary number of components, n, which may only assume an amorphous state and are specified by their respective volume fractions (composition), ϕ_i, can be given by:

$$\frac{\partial \phi_i}{\partial t} = \nabla \cdot \sum_{j}^{n-1} DA_{ij} \nabla \phi_j + \nabla \cdot DB_i \nabla \nabla^2 \phi_i. \tag{1}$$

In the equation, A_{ij} and B_i are dimensionless quantities that are functions of fundamental, system-specific thermodynamic quantities that include temperature, molar volumes of the components, and the interaction (χ_{ij}) parameters between components. The quantity D represents the kinetic contribution and is a function of the diffusivities of the pure components. The model enables us to predict the response of an arbitrary system over a wide range of environmental conditions and, therefore, provides facile means to rapidly assess new formulations or processing routes and reduce empiricism in product development. In fact, we have used the model to probe the impact of drug loading, solvent evaporation rate, drug–polymer affinity, relative solvent strength, and various spray cast parameters.

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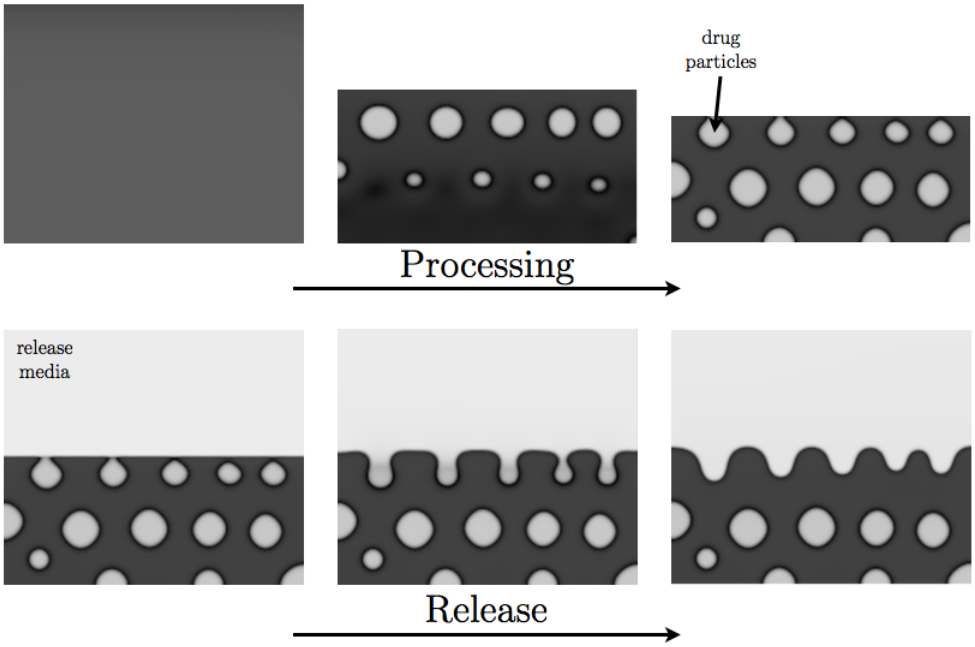

Figure 1: Example of model predictions of microstructure evolution during manufacturing and release

An example of the how the model can be used to predict microstructure evolution during both manufacturing and drug release is provided in Figure 1. The first row illustrates the development of microstructure during the coating process. Initially, the coating is applied as a homogenous mixture of drug and polymer dissolved in solvent. As the solvent evaporates, the system becomes more condensed and enriched in both drug and polymer. Eventually, the mixture becomes super-saturated and phase separation occurs, resulting in the formation of compact, drug–rich regions within a matrix of the polymer. This process continues until the vast majority of the solvent has been removed and the structure becomes essentially kinetically locked. To simulate release, the predicted structure is immersed in the release media and allowed to evolve using Eqn. 1 as shown in the second row of the figure. In this particular example, we assume that the release media does not swell or degrade the polymer. Thus, only drug near the coating surface can readily dissolve into the media. Based on the calculation illustrated in the second row, we can specify the amount of drug release as a function of time, *i.e.* the drug release profile.

While Eqn. 1 accounts for much of the physics that will dictate microstructural evolution in these systems, in some cases it is necessary to extend the model to incorporate additional phenomena that may impact the coating structure that develops during manufacturing and/or the response of that structure when it is introduced into the release media. We have incorporated these extensions into the model for systems that exhibit crystallization, chemical bonding between components, and chemical reactions. Based on the extensions, we have examined the impact of using a drug with a tendency to crystallize in controlled release coatings. Further, we have probed effect of using block co-polymers (chemically bound) as well as biodegradable polymers (hydrolysis reaction) in the matrix and their influence on structure formation and release.

We have also validated that the model can be successfully used to predict microstructure evolution

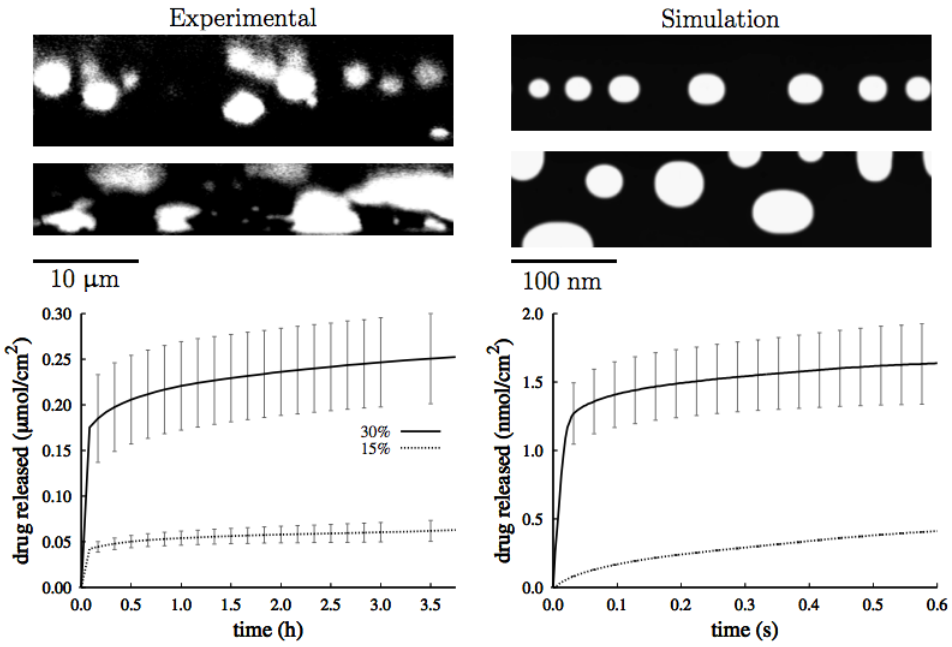

Figure 2: Comparison of experimental data from systems composed of tetracycline and styrene-isobutylene-styrene (SIBS) co-polymer and simulations conducted based on the model.

during manufacturing as well as the structural response after the coating is subjected to release media, *i.e.* drug release behavior. An example of the predictive capability of the model is provided in Figure 2. The figure illustrates a comparison of experimental data from systems composed of tetracycline and styrene-isobutylene-styrene (SIBS) co-polymer and simulations conducted based on the model. From top to bottom, the first column shows the relative tetracycline concentration (black to white = low to high concentrations) along typical two-dimensional slices through the coating thickness for systems with 15% drug, systems with 30% drug, and the elution curves obtained from these systems. The second column shows simulations results, based on the model under comparable conditions.

Note that due to computational restrictions, the length and time scales of simulations are small compared to the experiment. However, we find that simulations based on small, idealized systems are qualitatively consistent with the experimental observations. Further, we find that the results scale quite well. For example, if we take the average thickness of the experimental coatings in Figure 1 to be $15\ \mu\mathrm{m}$ and note that the simulated coatings are 100 nm thick, the experimental coatings are 150 times larger. Next, we recognize that the amount of drug release will scale proportionally to system size and the release time will scale proportionally to the square of the system size. So, if we scale the abscissa of the simulated release curves by 150^2 and the ordinate by 150, we find that simulated behavior can be essentially superimposed on the experimental observations of drug release.

While computational limitations exist, there is still great insight to be gained from predictions based on small-scale idealized systems, which can serve as a guide to reduce the amount of experimental effort required to optimize formulations for specific applications. Currently, the model

equations are solved using a tool developed at the National Institute of Standards and Technology known as FiPy[1] [8], which is an object oriented, partial differential equation solver written in Python. Using the FiPy framework, we have developed straightforward Python scripts that allow simulations based on the model to be routinely conducted on a standard workstation. Recently these scripts, collectively referred to as TheraPy, have been made publicly available[2].

Acknowledgements: The model and source code described in this abstract were developed in collaboration with James Warren, Jonathan Guyer, and Daniel Wheeler of the National Institute of Standards and Technology, as well as Chang-Soo Kim, currently at the University of Wisconsin Milwaukee. The experimental data were provided courtesy of Dinesh Patwardhan, Ken McDermott, Ji Guo, and Benita Dair of the US Food and Drug Administration.

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[2] http://matforge.org/redmine/projects/therapy/wiki