**A New Predictive Model for Drug Release Based on Void Growth and Coalescence: Training and Verification**

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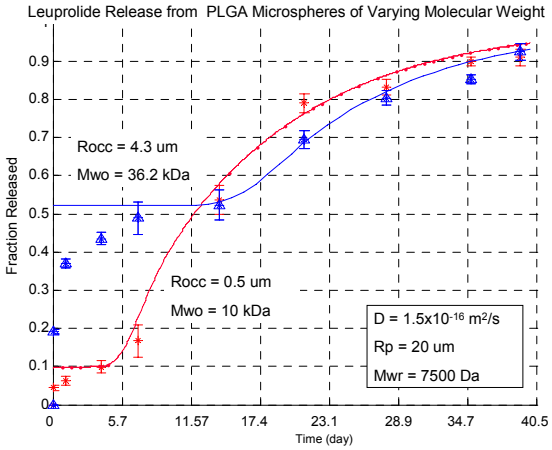
**Statement of Purpose:** The development of polymeric matrices to control the release of small molecules, peptides and proteins has created an industry valued at over 100 billion dollars. Lupron Depot ® and other controlled release vehicles developed by this industry have changed daily therapies into quarterly treatments. In these vehicles a therapeutic agent is encapsulated by a polymer matrix which degrades over time, gradually releasing the drug. Developing controlled release therapies, however, requires months of tedious experiments to target the desired drug release profile. The ability to predict drug release from polymer matrices using a priori parameters would dramatically reduce the time and expense associated with developing new controlled release therapies by virtually eliminating the need for exploratory, in vitro drug release experiments. Using ensemble analysis, a new continuum model was developed based on the growth of voids in a polymer matrix with the explicit goal of predicting drug release entirely from a priori values. In this abstract, we demonstrate a model that, for the first time, predicts release from poly(lactide-co-glycolide) (PLGA) nanoparticles and microspheres using readily available, a priori parameters.

**Methods:** Ensembling, a modeling technique which uses a system of probabilities to describe the average behavior of a series of vector events, was used to analyze release from PLGA microspheres. The resulting model for drug release based on the growth of voids bears resemblance to Poisson's equation and was implemented in one dimension using the finite element analysis program, Comsol Multiphysics®. (Comsol Inc., Burlington MA.) To initialize computation, uniform distribution of drug was assumed. Values for the average particle radius ($R_p$), the radius of drug filled occlusions ($R_{occ}$) and drug diffusivity ($D$) were also needed to define the model system.

The formation of voids in the polymer matrix has been well documented and can be related to variability in the polymer crystal structure. (2) In a degrading PLGA matrix, lamellar amorphous and crystalline regions develop. The prior have an inherently higher degradation rate and subsequently eroded first, leaving behind voids. To determine the fraction of polymer matrix occupied by voids, degradation data was gathered for amorphous and crystalline PLGA and formulated into a degradation rate distribution ($kCw$) based on variability in the lamellar size data. This distribution then was used to calculate the time required for the polymer matrix, of known initial molecular weight ($Mw_o$), to reach a molecular weight ($Mw_r$) where voids large enough to allow the passage of drug were formed.

Release profile data was collected from a number of sources to serve as a means of comparison for model predictions. If not initially available for predictions, model parameters, such as $Mw_r$ and $D$, were acquired by training the model on one data set and carrying out the prediction on another data set to check the validity of the acquired parameter.

**Results/Discussion:** The predicative capability of the model was tested for release agents ranging from small molecule drugs to large globular proteins and viruses. A sample prediction for the release of leuprolide acetate, the active agent in Lupron Depot®, is shown below.




Values for $Mw_o$, $R_p$ and $R_{occ}$ were published with the data.(3) Drug diffusivity and the $Mw_r$ were set for the low molecular weight case and applied to the higher. This figure illustrate how the model accurately predicts the volume of the initial burst, the duration of the lag phase, the onset of the secondary burst and the subsequent rate of release. This is just one example of the model's predictive capability. Equally accurate predictions were made for the release of other small molecules, peptides, protein and even virus.

**Conclusions:** A model was created which predicts release from 50:50 PLGA microspheres using readily attainable parameters. The model predictions have been validated for agents ranging from small molecules to viruses. As it stands, the model can be used to target the formulation parameters required to generate a desired release profile for a given drug, a process that would take months to accomplish experimentally. Thus, the model can serve as a powerful tool for the inexpensive and rapid development of a wide array of new therapies.

**References**

1. Zong XH. *Macromol.* 1999; **32:** 8107-8114.
2. Luan X. *JCR.* 2006; **110:** 266-272.