A New Predictive Model for Drug Release Based on Void Growth and Coalescence: A Continuum and Ensemble Approach.

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Statement of Purpose: The controlled release of small molecules, peptides, and proteins from polymeric particles has significant application within the overall drug delivery industry. The biodegradation of polyester nanoparticles and microparticles, and the simultaneous/sequential release of an entrapped drug, involves a complicated process of local polyester degradation that results in the formation, growth and coalescence of discrete voids within the particles. As the void structure develops and progresses towards the particle surface, pathways arise for drug diffusion/egress from the particle. The purpose of this study was to develop a novel model of the diffusion and release of drugs from biodegradable particles that implicitly accounts for the appearance, growth, and coalescence of voids within the polymer matrix.

Methods: The model considers the fate of tracer (drug or even polymer oligomer) within an ensemble collection of fabricated nano or microparticles. Each particle in the ensemble ends up with a tracer at a random position, which, in general, is different in each particle. The fate of the tracer is specified as a local probability density, $P(\vec{r},l,t)$, for finding the tracer at position $\vec{r}$ within a given particle, *l,* at time, *t*. The model also introduces a local induction time, $\tau(\vec{r},l)$, at every point within each particle, which represents the time required for the local polymer matrix to degrade sufficiently and allow local tracer diffusion. The local probability density is governed by an unsteady diffusion equation:

$$\partial P / \partial t = \nabla \bullet vD\nabla P$$

where D is an effective tracer diffusivity and v represents a "void function" governed by

$$v(\vec{r},l,t) = 0 \quad t \le \tau(\vec{r},l)$$

$$v(\vec{r},l,t) = 1 \quad t > \tau(\vec{r},l)$$

The tracer can only diffuse in void regions, but these regions grow and coalesce in time to ultimately allow tracer release. The fate of all tracers within the ensemble of L particles is governed by an ensemble probability density:

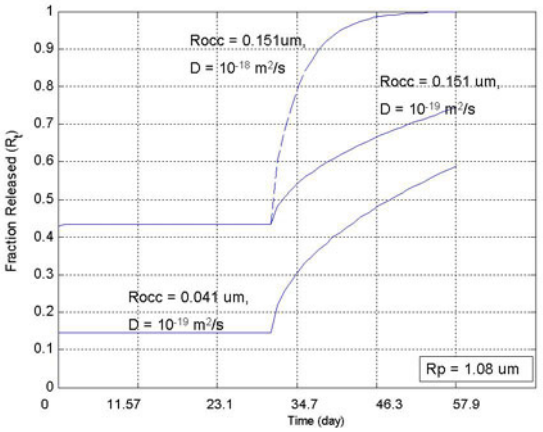
$$\overline{P}(\vec{r},t) \equiv L^{-1}\sum_{l=1}^{L} P(\vec{r},l,t)$$

which only needs to be determined and solved for a single canonical particle of volume, V. The tracer fractional release profile is then given by

$$R(t) = 1 - \int_V \overline{P}(\vec{r},t)\, dV$$

Results/Discussion: The model framework is general, but specific predictions require specifying an initial distribution of the tracer, as well as a distribution for the local induction time. In this application, in which the model is applied to double emulsion particles, the tracer was assumed to be within occlusions distributed randomly with no preferred location within any particle. We also assumed a normal distribution for the local induction time bounded by the limits of exponential degradation of amorphous versus crystalline regions of PLGA copolymer matrices.

Several drug release profiles predicted by the model for double emulsion particles with an average polymer Mw of 12 kDa and a diameter of 2.2 μm are shown below.



The drug release profiles exhibit several characteristic features that have been experimentally observed, including an initial release followed by a quiescent phase, and a later burst release which subsequently tapers off. The release profiles above varied according to the diffusivity of the tracer (D) and the radius of the occlusion in which the tracer initially resided (R_{occ}).

More specific comparisons and evaluation of the model against experimentally observed release profiles are presented in a companion abstract by our group at this meeting.

Conclusions: A new predictive model of drug release from an ensemble of biodegradable particles has been developed. The model employs a continuum description of tracer diffusion within discrete voids which develop, grow and coalesce with time distinctively within each particle. Initial predictions of drug release within PLGA microspheres appear promising. The model is being further evaluated and refined against experimental profiles of release for small molecules, peptides, and proteins.