Simulation of *in vitro* Dissolution and Degradation of Orntide-loaded PLGA Microspheres

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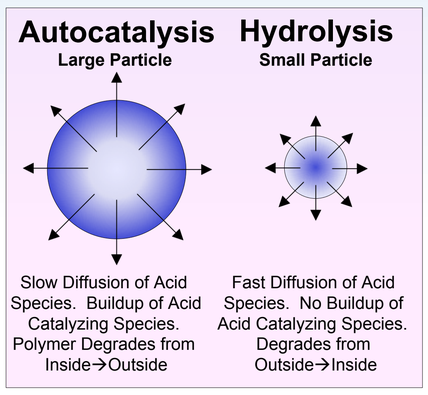
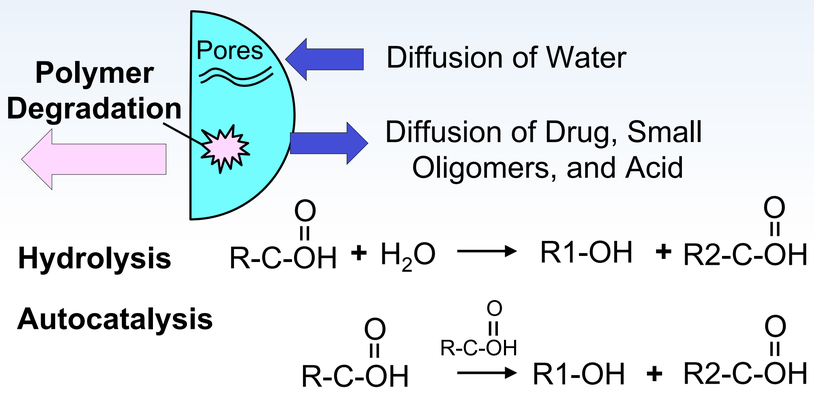
Introduction

An *in vitro* dissolution model has been developed to describe the drug release from orntide-loaded PLGA microspheres. Literature data for the degradation rates of various PLGA polymers obtained from literature were used to parameterize the *in vitro* dissolution model to predict the differences in drug release from PLGA microspheres with varying lactic acid/glycolic acid (LA/GA) ratios. We then assessed the ability of the model to predict new formulations with different LA/GA ratios using published data for orntide-loaded PLGA microspheres.

Methods

A model describing drug release from PLGA microspheres was extended from previous work within the simulation software DDDPlus™ Version 5.0 (Simulations Plus, Inc., Lancaster CA.) with funding support from the U.S. FDA (grant 1U01FD005463-01)[1]. The model accounts for diffusion of drug, soluble oligomers, and free acid through a spherical PLGA particle (Figure 1). The diffusion coefficient varies with position and time according to an exponential function of PLGA molecular weight. The differential equations are solved via the method of lines, using second-order finite differences.





$$\frac{\partial C_i}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D(r)\frac{\partial C_i}{\partial r}\right) + R_i \qquad \frac{\partial C_D}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D(r)\frac{\partial C_D}{\partial r}\right) + k_{diss}(S - C_D)\left(\frac{C_{ND}}{C_{ND,o}}\right)$$

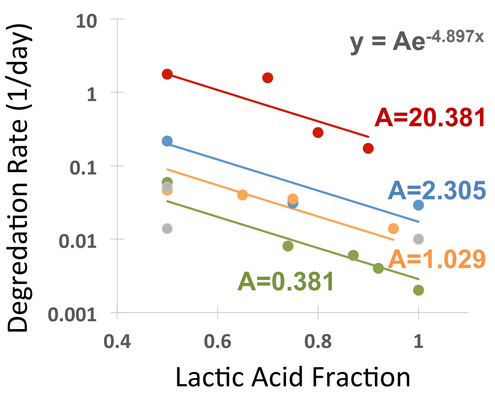
$$\frac{\partial C_{ND}}{\partial t} = -k_{diss}(S - C_D)\left(\frac{C_{ND}}{C_{ND,o}}\right) \qquad D(r,t) = D_o \times e^{-A\times\left(\frac{MW(r,t)}{MW_{ref}}-1\right)}$$

Where *i* = Drug, Small Oligomer, Water, and Free Acid

C_D	Concentration of free drug in matrix
C_{ND}	Concentration of undissolved drug in matrix
R	Rate of degradation
S	Solubility
$D(r,t)$	Diffusion coefficient – radial/time dependent
D_o, A	Initial diffusion coefficient and exponential diffusion constant
$MW(r,t), MW_{ref}$	Molecular weight in particle and reference

Figure 1: PLGA/Drug Diffusion and Degradation Model

To predict drug release across formulations with varying LA/GA ratios, an exponential correlation between PLGA degradation rate and LA fraction was built from literature data (Figure 2). While literature sources reported different absolute values for degradation rates of polymers with the same LA/GA ratio, the dependence of degradation rate on the LA/GA ratio was similar across different sources. It was theorized that this functionality could be applied globally for different polymer/drug systems.



Literature Source
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Figure 2: PLGA Degradation Rate vs. Lactic Acid Fraction

Orntide microsphere *in vitro* dissolution data with PLGA containing 50%, 75%, 85%, and 100% LA monomers were obtained from literature[2]. The *in vitro* experiments were performed with 20 mg of particles in 0.1 M Phosphate Buffer at pH 7.4 utilizing a dialysis method in 45 mL buffer.

Drug loading ranged from 10-18% and particle size (D50) ranged from 3–7 μm across formulations. The drug and formulation properties were entered as initial and/or boundary conditions in the model. The dissolution and degradation parameters were fitted to a single formulation (85% LA). Release rates of other formulations were then predicted (not fit) utilizing the PLGA degradation rate function derived from literature data (Figure 2).

Results

The mean absolute error (MAE) of the predicted dissolution was 8.6% for predicted formulations with 50%, 75%, and 100% LA. The formulation with 85% LA used to fit the dissolution model had a MAE of 2.6%. The observed and predicted dissolution profiles are shown in Figure 3. The degradation rate function derived from literature data provided a reasonable estimate of polymer degradation.

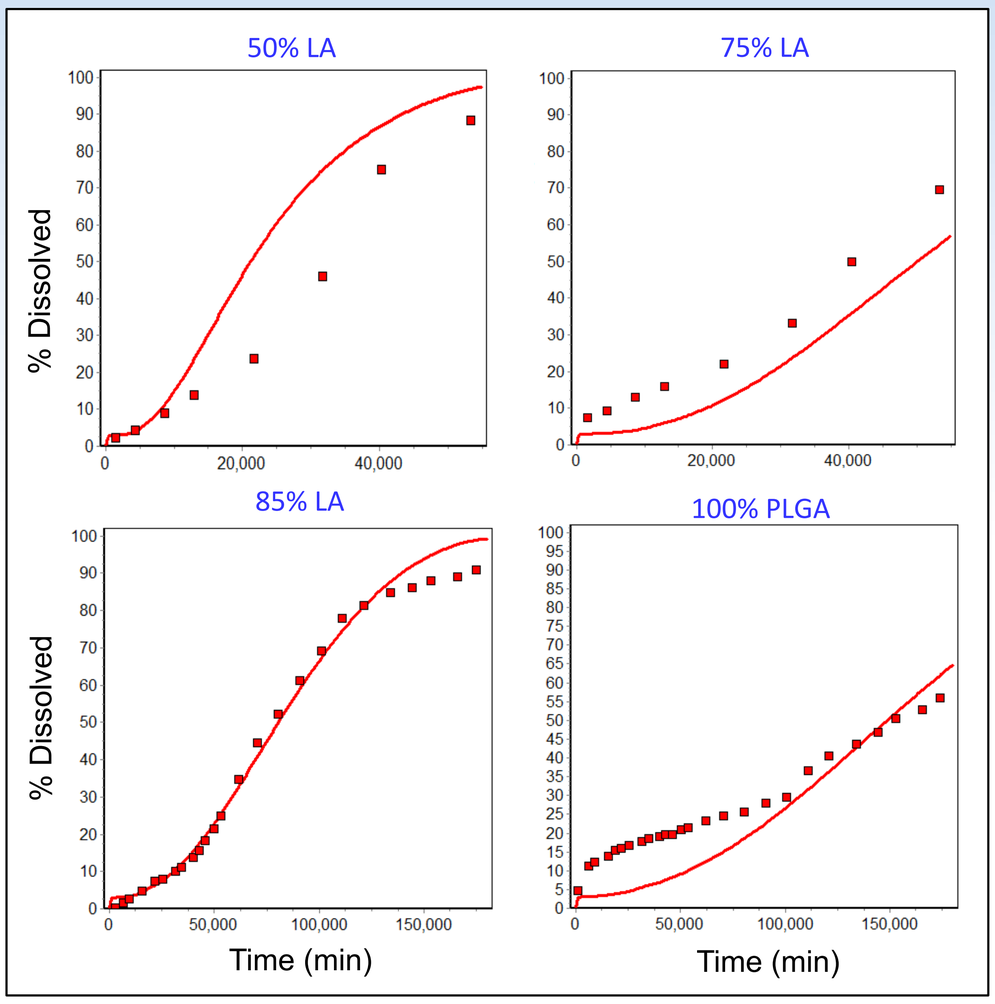

Figure 3: Observed (points) and Simulated (lines) Orntide Dissolution Profiles.

However, the variation in burst release of the 75% and 100% formulations was not well-predicted. Variation of drug distribution within the particles can be nonuniform[3], and is one likely cause of the deviations for the 75 and 100% PLGA particles. Furthermore, the degradation rate for the 50% LA formulation was overpredicted. Degradation rates were predicted based on pure polymer measurements. An interaction between drug and polymer could also affect the degradation rate and was not accounted for in the current model. Lastly, compositionally identical particles with the same particle size yield different dissolution rates based on manufacturing process differences[4]. Further study is required to understand these additional mechanisms for polymer degradation and drug release.

Conclusions

Utilizing experimental degradation rate data for pure PLGA polymers, a model was developed that can extrapolate drug release from PLGA microspheres with varying LA/GA ratios, The predictive capability of the *in vitro* dissolution model was demonstrated using orntide as model compound.

References

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