27W0200

Development of an *in vitro* Mechanistic Model that Describes Drug Release from Risperidone Long-Acting Injectable Microspheres

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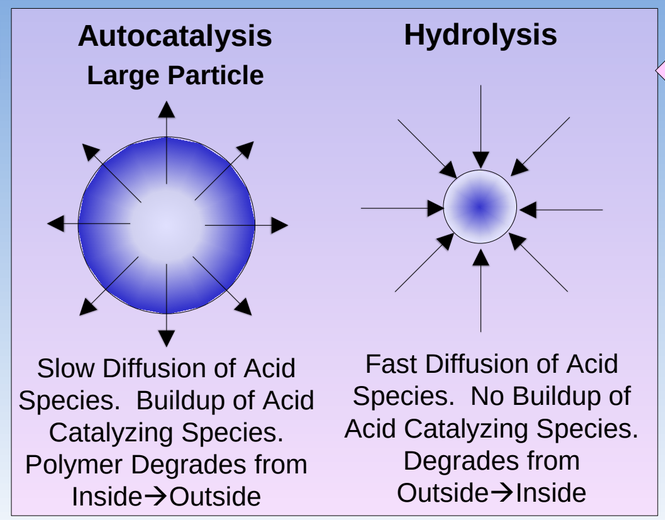
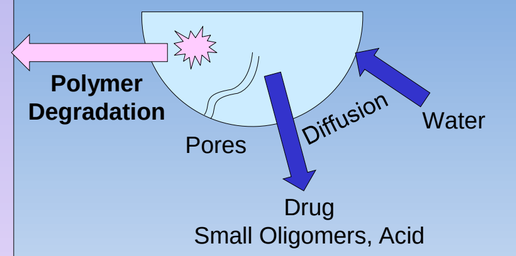
PURPOSE

Dissolution of long-acting injectable (LAI) microspheres *in vitro* is an important topic with relevance in many therapeutic areas from antipsychotics, antibiotics, and cancer, to drug abuse deterrence. Typical LAI formulations dissolve over the course of weeks to months. This extended time period makes *in vitro* measurements of drug release time-prohibitive and expensive. To address this concern, temperature-accelerated *in vitro* experiments and mechanistic modeling of drug release from microspheres is an active area of research, with the hope it will lower costs and accelerate the formulation development process. In this work, we present a mechanistic model for drug release from PLGA microspheres that includes diffusion (of drug, small oligomers, water, and free acid), hydrolysis, and autocatalysis degradation mechanisms in a spherical geometry. The *in vitro* model has been implemented within the DDDPlus™ (Dose Disintegration and Dissolution) software platform and serves as a foundation to build upon as we develop an *in vivo* model for dissolution and absorption of LAI microspheres within the GastroPlus™ software.

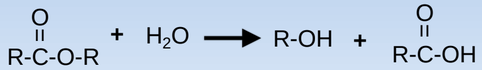
METHOD

An *in vitro* model for release of drug from LAI microspheres was developed in DDDPlus 5.0 (Simulations Plus, Inc.) with funding support from the U.S. FDA (grant 1U01FD005463-01). The model takes into account the full spatial concentration gradients of drug, water, carboxylic acid end-groups, and soluble oligomers within spherical degrading polymer dispersions. The polymer molecular weight is calculated vs. time based on the reaction/degradation rates at each radial position within the particle. As the molecular weight decreases within the particle and water accumulates, the matrix will begin to become more rubbery and diffusion will increase markedly as it gets closer to its glass transition temperature. To account for this process, the diffusion coefficient is calculated based on the polymer molecular weight and is a function of position within the particle. The model is described in Figures 1 and 2. The model is solved using a finite difference approximation and the Method of Lines.





Hydrolysis



Autocatalysis

$$\frac{\partial C_i}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D(r)\frac{\partial C_i}{\partial r}\right) + R_i$$

$$\frac{\partial C_{ND}}{\partial t} = -k_{diss}\left(S - C_{ND}\right)\left(\frac{C_{ND}}{C_{ND,o}}\right)$$

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

$$D(r,t) = D_o \times e^{-A\times\left(\frac{MW(r,t)}{MW_{ref}}-1\right)}$$

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
A, D_o	Diffusion vs. molecular weight parameters
$MW(r,t), MW_{ref}$	Molecular weight in particle and reference

Figure 1: Model Equations (Constant-pH Rate Law)

In addition to the model in Figure 1 for constant internal particle pH kinetics, an additional model which assumes a variable internal pH was developed. This model assumes the free acid generated from the degradation of the PLGA matrix dominates the internal pH and thus the pH-dependent rate can be calculated as shown in Figure 2.

k	Rate Constants	LE, SE	Large/Small Oligomer
CA	Free Acid	K_a, K_w	Equilibrium Constants

$$COOH \Leftrightarrow COO^- + H^+ \qquad K_a = \frac{[H^+][COO^-]}{[COOH]} \qquad [H^+] = \sqrt{K_a[COOH] + K_w}$$

$$R_{CA}(r,t) = kC_{LE}(r,t)C_{CA}(r,t)C_W(r,t)$$

Constant-pH Rate Law For Autocatalytic Hydrolysis

$$R_{CA}(r,t) = kC_{LE}(r,t)\sqrt{K_a C_{CA}(r,t) + K_w}\,C_W(r,t)$$

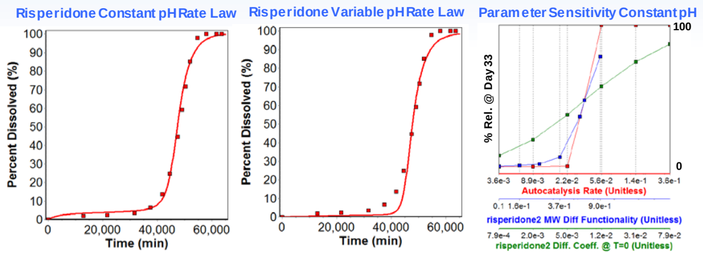
Variable-pH Rate Law For Autocatalytic Hydrolysis

Figure 2: Rate Laws Available for Computation of Microsphere Degradation

To prove that the mathematical formulation can reproduce the complex nature of PLGA microsphere release rates, we applied the model to calculate the release of the Risperidone (Consta™) LAI formulation. Data for the release profile was obtained from the literature.[1] Models were fit by optimizing the exponential diffusion parameters, dissolution constant, and autocatalysis rate (A, D_o, k_{diss}, and k) vs. the release profile. Then, predictions were made using parameter sensitivity analysis to look at effects of diffusion and degradation.

RESULTS

Both models accurately reproduced the highly sigmoidal *in vitro* drug release profiles of commercial risperidone PLGA microspheres, with R^2 values greater than 0.97. Multiple different assumptions for the polymer degradation rates, internal particle pH, and pH-dependent solubility all provide reasonable simulations for the observed risperidone *in vitro* dissolution profile. These models can be used with parameter sensitivity analysis to explore likely variability of risperidone release around model inputs for diffusion and reaction. However, more experiments are required to validate the exact mechanisms that dominate or contribute to risperidone release.



CONCLUSION

Several models for drug release from PLGA microspheres have been developed, implemented in DDDPlus 5.0, and used to describe the *in vitro* dissolution of LAI risperidone microspheres. These models account for most mechanisms reported in the literature for diffusion and degradation within PLGA microspheres. Additional work is ongoing to determine the exact nature of the mechanisms and how the *in vitro* model predicts the concentration of other microsphere constituents, including PLGA, soluble oligomers, acid end groups, and porosity vs time.

REFERENCES

1. Rawat, Int. J. Pharm., 2012, 32, 115-121
2. Ford-Versypt, Dissertation, U. Of Illinois Champaign, 2012.

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