Development of Silica Release Model for Intraocular Injections

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Introduction

This poster reviews the development of a numerical framework within DDDPlus™ (Version 6.0, Simulations Plus, Inc.) to simulate the degradation and drug dissolution/release from silica matrix formulations within a flow-through apparatus that simulates physiologically relevant flow and volume of the vitreous. The proposed mathematical model is then used to describe the degradation of silica particles as well as drug release from vancomycin and bupivacaine.

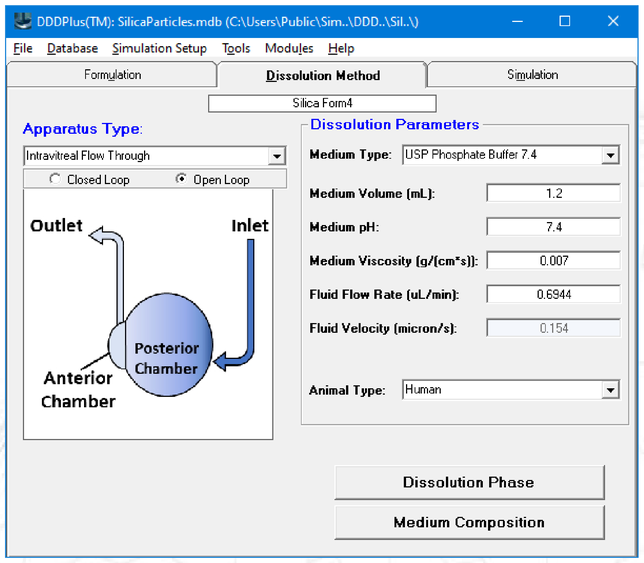


Figure 1: DDDPlus Intravitreal Dissolution Model

Methods

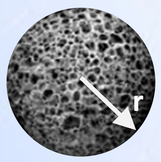
The silica release model is a multiphase mathematical model consisting of a solid silica and a fluid-filled pore phase. The model accounts for all relevant kinetic and transport processes, including reversible mass action kinetics for silica hydrolysis; diffusion of water, drug, and free silica; and tracking of solid and pore phase volume fraction, as shown in Figure 2. Models were created for spherical and cylindrical geometry. Partial differential equations for kinetics and diffusion are solved using the method of lines within the commercial software package DDDPlus™. The method of lines discretizes the spatial equations into a system of time-dependent odes that are solved with a stiff ODE solver.[1] The model was evaluated with literature data for the degradation of silica microparticles without drug with various particle sizes, as well as formulations of bupivacaine and vancomycin.[2,3]

Fluid-Filled Pore Phase Dissolved

$$\phi\frac{\partial C_{d,d}}{\partial t}=\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\phi D_d}{\tau}\frac{\partial C_d}{\partial r}\right)+k_{diss}\left(C_{sat}-C_{d,d}\right)\frac{C_{d,u}}{C_{Od,u}}$$

$$\phi\frac{\partial C_{s,d}}{\partial t}=\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\phi D_s}{\tau}\frac{\partial C_{S,d}}{\partial r}\right)+R_{s,d}$$

$$\phi\frac{\partial C_W}{\partial t}=\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\phi D_w}{\tau}\frac{\partial C_w}{\partial r}\right)-2R_{s,d}$$



Solid Phase Undissolved

$$\frac{\partial C_{d,u}}{\partial t}=-k_{diss}\left(C_{sat}-C_{d,d}\right)\frac{C_{d,u}}{C_{od,u}}$$

$$\frac{\partial C_{s,u}}{\partial t}=-R_{s,d}$$

$$R_{s,d}=k_{f,s}SC_{s,u}C_w^2-k_{r,s}SC_{s,d}$$

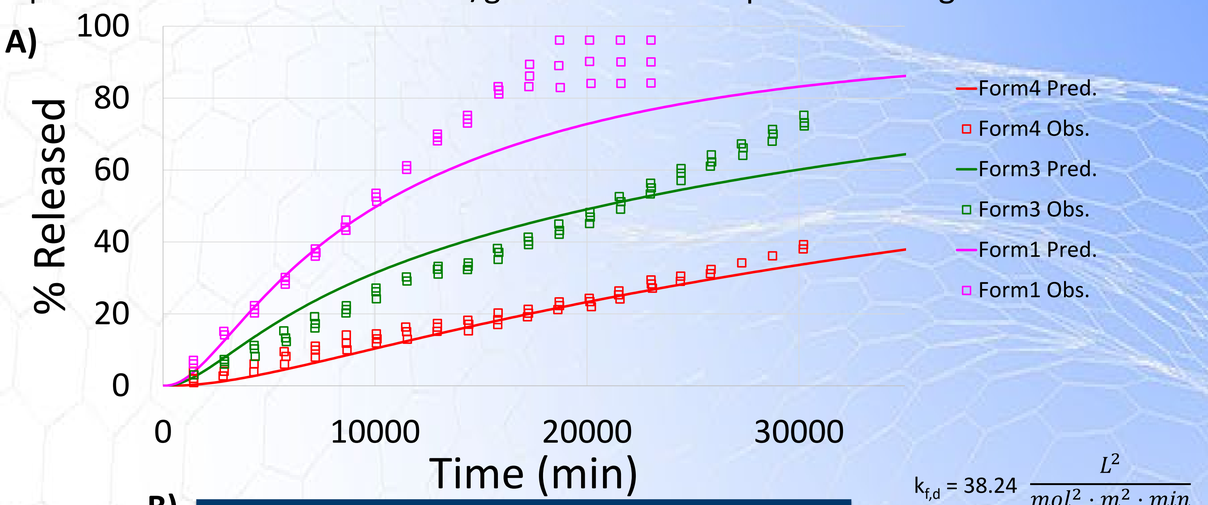
$C_{s,d}, C_{s,u}$	Concentration of dissolved/undissolved silica	s	Specific surface area
$C_{d,d}, C_{d,u}$	Concentration of dissolved/undissolved drug	ϕ, τ	Porosity and tortuosity
$C_{od,u}$	Concentration of initial undissolved drug	$R_{s,d}$	Rate of silica degradation
C_{sat}	Solubility	$k_{f,s}, k_{r,s}$	Forward/reverse silica degradation rate
C_w	Water concentration	r	Radius
D_d, D_s, D_w	Diffusion coefficient drug, silica, and water	t	Time

Figure 2: Silica Degradation and Drug Release Mathematical Model

Results

With a single set of degradation and diffusion parameters, the model predicted the degradation of spherical silica particles with diameter between 15 – 40 μm, specific surface area ranging from 19 – 390 m^2/g, initial pore diameter from 10 – 100 nm, and pore volume of 0.67 – 1.02 mL/g. The result is depicted in in Figure 3.

A)



B)

Formulation	1	2	3	4
Particle size (um)	15	15	25-40	15
Pore diameter (nm)	10	30	50	100
Surface area (m^2/g)	390	108	48	19
Pore Volume (mL/g)	1.02	0.83	0.67	0.8

$$k_{f,d} = 38.24\ \frac{L^2}{mol^2\cdot m^2\cdot min}$$

$$k_{r,d} = 0.04158\ \frac{1}{m^2\cdot min}$$

$Ds = 1.0982E^{-13}\ cm^2/s$

Figure 3: A) Percent Released vs. Time for Silica Particle Degradation with Model Parameters for Formulations Shown in Table B

The model was applied to two drug formulations for bupivacaine and vancomycin, as shown in Figure 4. The silica degradation was available for vancomycin-loaded microspheres, and these were used to fit the degradation kinetics and free silica diffusion coefficient. The same degradation parameters were able to predict silica degradation in both formulations but with different diffusion coefficients for each API.

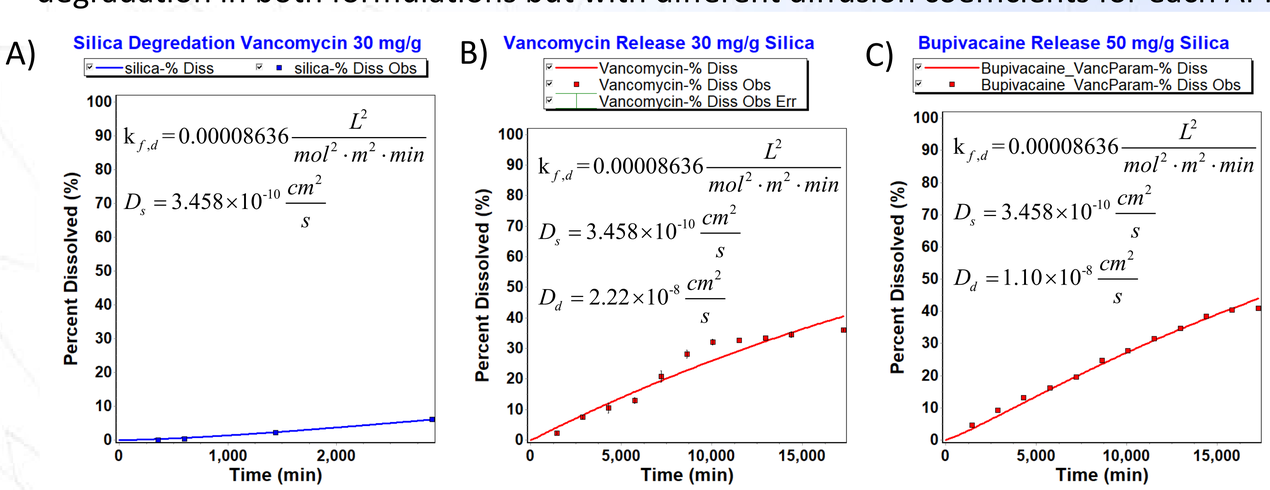


Figure 4: A) Silica Degradation for Vancomycin Formulation of 30 mg/g Silica, B) Vancomycin Release from 30 mg/g Silica Using Parameters from Formulation (A), and C) Bupivacaine Release for 50 mg/g Silica Using Same Silica Degradation and Diffusion Parameters from (A)

Conclusion

The mechanistic silica degradation and release model is a useful tool in predicting degradation of particle size and specific surface area variants. Additionally, it provides insight into the release of vancomycin and bupivacaine. The model allows for parameter sensitivity analysis providing useful insight into key formulation parameters like particle size, degradation rate, and porosity. Additional validation of the model is ongoing, so any necessary future improvements will be evaluated.

References

1. Crank, John. The mathematics of diffusion. Oxford university press, 1979.
2. Sun, et al., Drug delivery 27.1 (2020): 703-711.
3. Radin, Biomaterials 30.5 (2009): 850-858.