R6003

Mechanistic Nucleation and Growth Can Predict Nonlinear Dose-Dependent Precipitation of Enabled Formulations of Nimodipine in GastroPlus™

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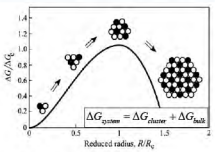
PURPOSE

Simulation of precipitation can be important for accurate prediction of the absorption of many oral formulations. Amorphous solid dispersions, salt forms, cocrystals, solutions, and nanoparticles all can exhibit various levels of supersaturation leading to crystallization *in vivo*. In this work, we model the precipitation of nimodipine solid dispersions across three doses with a mechanistic nucleation and growth (MNG) model as well as with first-order precipitation kinetics. We compare results from the MNG model with first-order precipitation to show the benefits of the MNG model with respect to accurate simulation of the nonlinear magnitude and rate of precipitation due to dose escalation.

METHODS

Classical Nucleation Theory seeks to mathematically describe the difference in Gibb's free energy between a solution of drug and the sum of the free energy of the crystal and solution phase after phase change or crystallization. Figure 1 is a description of the MNG equations used in GastroPlus™ as described by Lindfors L., J. Colloid. Interfac. Sci. 325, 404, 2008.



Molecules are in a constant state of collision with each other, forming clusters and then breaking apart. This process continues in order to keep the molecules in solution, until the free energy needed to keep them in solution becomes greater than that required to form the cluster. This difference in free energy determines the rate of formation of new clusters, known as nuclei. The net rate of precipitation is a combination of the formation of new nuclei and the growth in size of already formed clusters of nuclei.

Graph : Schmelzer, J. Non-Crystalline Solids 356, 2901, 2010

Nucleation Rate:

$$\frac{dN}{dt} = D_{mono} N_{Av} c^2 \left(\frac{k_B T}{\gamma}\right)^{1/2} \ln\left(\frac{c}{S}\right) \frac{R^*}{R^* + \lambda} * \exp\left(-ExpCorr \frac{16\pi}{3}\left(\frac{\gamma}{k_B T}\right)^3 \frac{v_m^2}{\ln\left(\frac{c}{S}\right)^2}\right)$$

Pre-exponential Term: Related to the frequency of molecular collisions and the rate of mass transport

Exponential Term: Related to the free energy change going from solution to a nucleus at a given size

D_{mono} = Diffusion coefficient of the monomer (cm^2/min)
N_A = Avogadro's number (6.02E+23 molecs/mole)
c = Concentration of free monomer (moles/cm^3)
k_b = Boltzman's constant (1.38E-21 cJoules/Deg. K)
T = 310° K
γ = Interfacial tension (Newtons/cm)

S = Solubility at the current pH
R^* = Critical radius (cm)
λ = Effective radius from Lindfors (cm)
ExpCorr = exponential correction factor
v_m = Molecular volume
= (V_m/N_A = XX cm^3/molec / 6.02E+23 molec/mole)

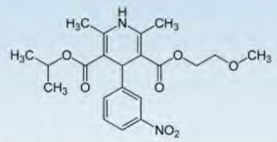
Growth Rate:

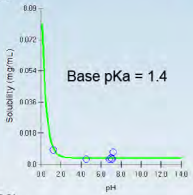
$$\frac{dX_{nc}}{dt} = 4\pi R_P^2 \frac{D_{eff}}{h}(S_b - C_b) \quad where \quad r_p = \left(\frac{4}{3\pi}\frac{X_{nc}}{\rho}\right)^{\frac{1}{3}}$$

X_{nc} = rate of particle growth
R_p = radius of particle
D_{eff} = effective diffusion coefficient of free and bile salt micelle drug
ρ = density
h = diffusion layer thickness
S_b = solubility in the bile micelle media
C_b = sum of the concentrations of free monomer and the bile micelle bound molecule

Figure 1: Mechanistic Nucleation and Growth (MNG) Model

The physiochemical properties of nimodipine utilized in the GastroPlus™ simulations are shown below.





- logP = 4.18 (Barbato, Eur. J. Med. Chem., 31, 311, 1996)
- Solubility pH 7.0 (µg/mL) = 3.86 (Yunzhe, Int. J. Pharmaceut., 359, 144, 2008)
- pKa = 1.4 (base) (fitted to solubility vs. pH profile obtained from Yunzhe 2008)
- Solubility FaSSIF pH 6.5 (µg/mL) = 11.9 (Fu, Colloids Surf. B, 109, 161, 2013)
- Caco-2 Papp (cm/s x 10^{-5}) = 6.04 (Agilent, Pub #5989-7668EN, 2007)
  Converts to human jejunal Peff = 3.12 x 10^{-4} cm/s
- CYP3A4 metabolism:
  Exp. 3A4 K_m = 36 µM (Liu, Acta Pharmacol. Sin., 21, 690, 2000)
  S+ 3A4 V_{max} = 65.4 nmol/min/nmol with ISEF 2.5 (AP 7.0)
- Fup_{human} = 2 % (Product Monograph Nimotop® Tablets)

A human physiologically based pharmacokinetic (PBPK) model (American male, 69 years, 68 kg) was employed to predict plasma profiles.

To define the fast initial dissolution of a solid dispersion that occurs in an enabled formulation due to excipients and formulation, a single Weibull function was fit to the lowest dose, where precipitation is low (time scale = 0.3, shape = 1). This is the "spring" in Figure 2.

The precipitation or "parachute" in Figure 2 was calculated using either a mechanistic nucleation and growth model or first-order precipitation kinetics. This treatment of the "spring and parachute" is shown graphically in Figure 2.

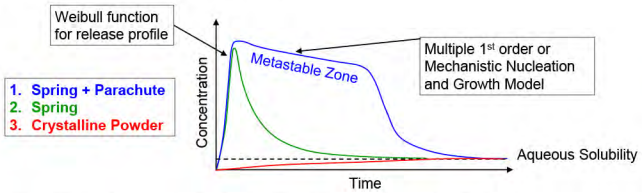
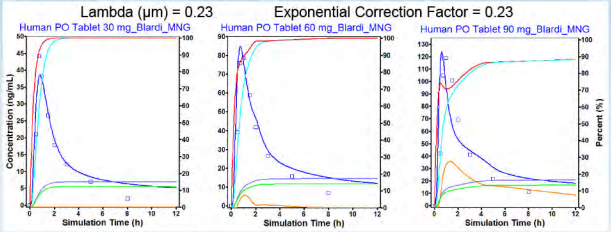


Figure 2: Schematic diagram of "Spring and Parachute"
Brouwers, Pharm. Sci., 98, 2549, 2009

RESULTS

To evaluate the precipitation models, simulated plasma concentration-time profiles for 30, 60, and 90 mg doses of nimodipine were compared to published clinical results from Blardi, Clin Pharm & Ther, 72, 556, 2002.

(a) Mechanistic Nucleation and Growth



(b) First Order Precipitation

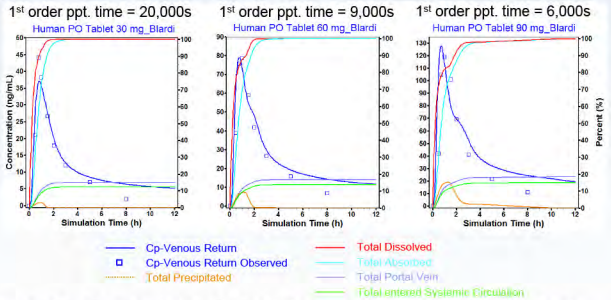


Figure 3: Comparison of precipitation models for 30, 60, and 90 mg doses of nimodipine.
(a) Mechanistic Nucleation and Growth Model
(b) 1st Order Precipitation Model

	30 mg				60 mg				90 mg			
	First-Order		MNG Model		First-Order		MNG Model		First-Order		MNG Model	
	Obs.	Sim.	Obs.	Sim.	Obs.	Sim.	Obs.	Sim.	Obs.	Sim.	Obs.	Sim.
% Fa		100		100		100		100		99.7		88.2
% F		12.27		12.25		13.68		14.1		15.1		13.5
Cmax (ng/mL)	44.15	37.1	44.15	38.5	78.63	78.95	78.63	84.9	119.1	127.6	119.1	124
Tmax (h)	0.75	0.84	0.75	0.84	1	0.76	1	0.75	1	0.72	1	0.6
AUC 0-t (ng-h/mL)	98.62	131.2	98.62	131.1	213.6	291.7	213.6	300.7	320.9	477.7	320.9	425.7
MNG Supersaturation Ratio at Nucleation				N/A				13.14				13.4
MNG Max Radius of Nuclei Duodenum (um)				N/A				6.1				4.7

Table 1: Summary of pharmacokinetic parameters

CONCLUSIONS

- Simple first order precipitation methods have proven to be useful in understanding *in vivo* precipitation, but the rate of precipitation must be adjusted for different doses such that the model can't be used to extrapolate effectively.
- The mechanistic nucleation and growth theory provides a more detailed understanding of the impact of chemistry and formulation on *in vivo* performance. It also allows for prediction of nonlinear dose-dependence of enabled formulations (with a single set of parameters).

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