

## Mathematical Modeling of Bi-phasic Mixed Particle Drug Release from Nanoparticles

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**Statement of Purpose:** Biodegradable polymeric nanoparticles (NPs) are widely considered as a vehicle for the controlled administration of drug in implant application as it is suitable for a) protein/peptide encapsulation, b) sustained release, c) high drug loading, etc. It is very important to tailor a local release profile of the drug(s) that is commensurate with temporal sequence of the pathogenesis of disease and the effectiveness of the selected drug based upon the targeted biological processes [1]. Nanoparticle design variables, such as drug release rate and particle degradation rate, depend on both process-dependent and process-independent variables. The main objective is to determine the dependence of design variable on process-independent parameters such as particle size, molecular weight (MW) and the mixing ratio of particle population of different size. To that end, we developed a mathematical model for mixed particle drug release and compare it with *in vitro* release data to demonstrate feasibility.

**Methods:** In constructing the mathematical model for the mixed particle drug release from NPs, we assume that the dispersed drug phase contributes to two discrete modes of drug transport within the particles [1]. These are: (I) the fast mode, which is the release of drug from a highly percolated structure of drug phase within the polymer, and (II) the slow mode, which is the release of the drug from a non-percolated, polymer-encapsulated phase of the drug. Drug transport from the polymeric matrix is therefore governed by [2]

$$\begin{aligned} \frac{\partial C_I}{\partial t} &= D_I \left( \frac{\partial^2 C_I}{\partial r^2} + \frac{2}{r} \frac{\partial C_I}{\partial r} \right) \\ \frac{\partial C_{II}}{\partial t} &= D_{II} \left( \frac{\partial^2 C_{II}}{\partial r^2} + \frac{2}{r} \frac{\partial C_{II}}{\partial r} \right) \end{aligned} \quad (1)$$

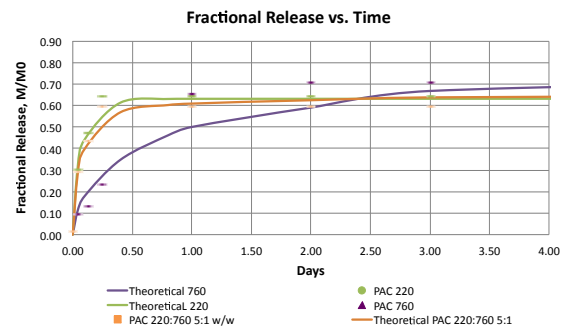
Assuming perfect sink condition and a uniform initial drug concentration, the following analytical solution can be derived to describe the resulting biphasic release rate in the polydisperse case:

$$\begin{aligned} \frac{M}{M_0} &= \sum_i \alpha_i f_i \left\{ 1 - \sum_n \frac{6}{n^2 \pi^2} e^{-\frac{n^2 \pi^2 D_I t}{R_i^2}} \right\} \\ &+ \sum_i \alpha_i (1 - f_i) \left\{ 1 - \sum_n \frac{6}{n^2 \pi^2} e^{-\frac{n^2 \pi^2 D_{II} t}{R_i^2}} \right\} \end{aligned} \quad (2)$$

The model contains three parameters that need to be determined before it can be used in a predictive capacity: the two effective diffusivities ( $D_I$  and  $D_{II}$ ) associated with each mode of drug release, and fraction of drug in slow phase  $f_i$  at the initial time ( $t=0$ ). Additionally, the drug release can be tailored by mixing different sizes of NPs in the polydisperse case, providing two additional design parameters:  $R_i$ , the size of the  $i^{\text{th}}$  NP in the mixture and  $\alpha_i$ , the fraction by weight of the  $i^{\text{th}}$  NP in the formulation.

On the experimental side, spherical NPs of 2 different sizes, 220 nm and 760 nm, were prepared from biodegradable 50:50 PDLGA. Single emulsion technique (W/O) was used to encapsulate Paclitaxel with 50:50 PDLGA at drug-polymer ratio D:P = 1:9 w/w. *In vitro* drug release was performed in 0.1 % Tween 20 in phosphate buffer at pH 7.4 for the monodisperse case as well as polydisperse case where one of the samples was a mixture of 1:5 w/w of 760 nm and 220 nm.

**Results:** Fig. 1 shows an initial burst of drug release from the NPs before reaching a plateau for all three cases considered. Our model closely captures this bi-phasic nature of the drug release. As the particle size increases, the release rate (the slope of the release profile) decreases. Quite expectedly, in the mixed particle case considered, the release profile mimics that of the particle size that makes up a larger proportion (by weight) of the mixed formulation. Mass transport parameters fit the 220 nm and mixed particle population (220:760 nm) experimental release data very well (Fig. 1). However the predictive power of the biphasic analytical mass transport equation (Eq. 2) falls short for the longer time points data of the 760 nm particle size. This could be due to different concentration gradient of very hydrophobic drug such as Paclitaxel between 220 nm and 760 nm sizes.



**Fig. 1:** Fractional drug release (“M/M0”) over time for i) 220 nm, ii) 760 nm and iii) a mixture of 1:5 w/w of 760 nm and 220 nm particles; and comparison with corresponding model prediction (“Theoretical”).

**Conclusions and Future Work:** Our bi-phasic mixed particle model closely captures trends in experimental data in both monodisperse and polydisperse case. Size-dependent release rate is observed for NP from the same formulation. Mixed particle population does indeed provide additional degree of freedom to control release rate. The model can be used to predict drug release at earlier time points. Mathematical model inclusive of absorption phenomena and various concentration gradient at  $t = 0$  need to be studied.

### References:

- Hossainy SFA, Prabhu S. Journal of Biomedical Materials Research Part A. 2008;87A(2):487-93.

2. Crank, J. The Mathematics of Diffusion. Oxford, Clarendon Press, 1975.