Modeling and Simulation of the Local Tissue Response to the Long-acting Injectable Formulations

Azar Shahraz[1], James Mullin[2], Viera Lukacova[2]

[1]Simulations Plus, Inc. (current affiliation: Alnylam® Pharmaceuticals)

[2]Simulations Plus, Inc. 42505 10th Street West, Lancaster, California 93534, USA

AMERICAN CONFERENCE ON PHARMACOMETRICS

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

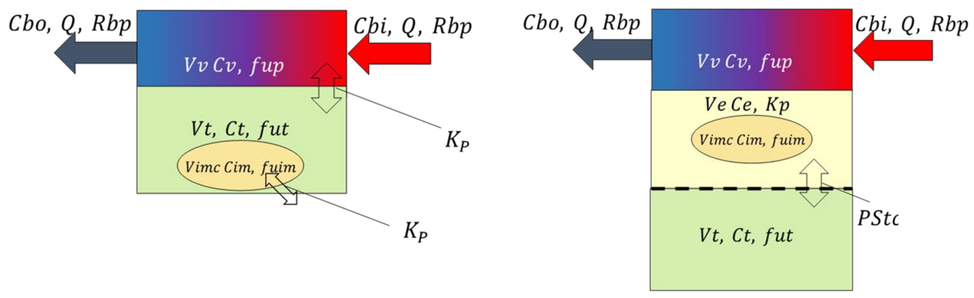
Objectives

Recently, long-acting injectable (LAI) drug formulations have attracted much attention for prolonged drug exposure from weeks to several months. However, the administration of foreign materials in the tissue can result in a variety of injection site reactions (ISRs), which have not been well characterized in the literature. The focus of the present work is to model consequences of localized chronic inflammation in tissue on drug diffusion and exposure caused by prolonged therapy with long-acting formulations.

Background

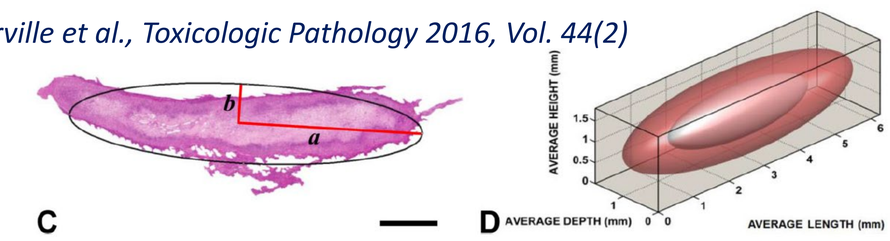
There are many hypotheses to describe the mechanism through which the immune response may affect the release of the drug from nano/microparticles[1,2]. One mechanism is the "walling off" effect of the immune cells caused by the chronic phases of inflammation, which may lead to formation of a fibrous capsule. This inflammatory rim surrounding the formulation depot can serve as a physical barrier for diffusion of drugs as well as acidic degradation products, increasing auto-catalyzed PLGA hydrolysis and also preventing drug diffusion away from the microparticles.

In this study, the tissue response triggered by the parenteral injection is modeled as an inflammatory rim surrounded the formulation depot. The outer layer of this immune cell layer (ICL) is in direct contact with the tissue compartment in the perfusion-limited tissue model or extracellular compartment in the permeability-limited tissue model as shown in figure below. .

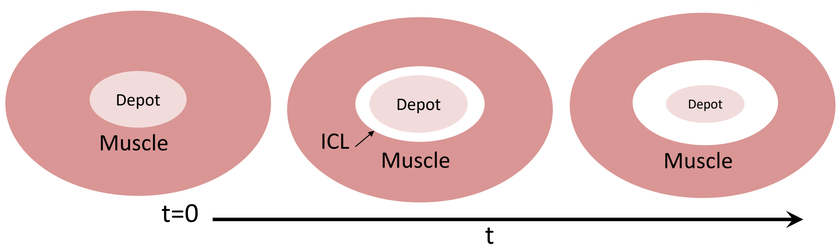


We characterized the dynamics of the ICL mainly based on the in vivo study performed by Darville et al.[2] to determine the local histopathological and immunological alterations generated by the IM injection of PP-LAI and polystyrene (PS) nano-/microsuspensions in the rat.

Darville et al., Toxicologic Pathology 2016, Vol. 44(2)



Schematic representation of the dynamic courses of cellular infiltration within the depot



Method

To account for slow diffusion of API through the ICL, the layer is divided into five (5) sublayers. The model accounts for the API diffusion through ICL with time-varying thickness and nonspecific tissue binding.

- *ICL* unbound *concentration:* $C_{1,u}^{ICL} = C^{Dep}$
- *ICL total concentration at the interface with depot:*

$$C_{1,t}^{ICL} = K_p^{ICL/Dep}\, C^{Dep}$$

- *Mass balance equation for API in ICL at interface with the depot:*

$$\left(\frac{V^{Dep}}{K_p^{ICL/Dep}} + V_1^{ICL}\right)\frac{dC_{1,t}^{ICL}}{dt} = -\frac{Diff}{h_1^{ICL}} \times SA \times \left(C_{2,u}^{ICL} - C_{1,u}^{ICL}\right)$$

- *API diffusion through the ICL :*

$$\frac{dC_{j,t}^{ICL}}{dt} = \frac{Diff}{\left(h_j^{ICL}\right)^2} \times \left(C_{j-1,u}^{ICL} - 2C_{j,u}^{ICL} + C_{j+1,u}^{ICL}\right)$$

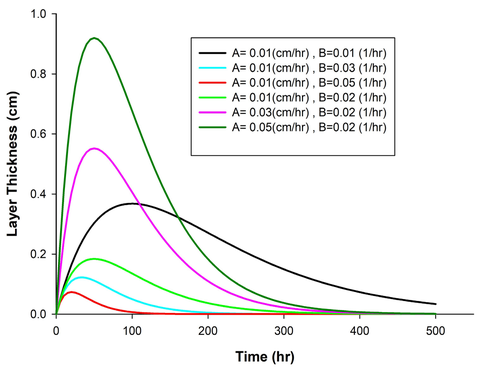
- *The mass balance in the last sublayer (j=5) which is in contact with tissue or extracellular compartment can be written as (X= tissue or extracellular) :*

$$\left(V^x K_p^{x/ICL} + V_5^{ICL}\right)\frac{dC_{5,t}^{ICL}}{dt} = -\frac{Diff}{h_5^{ICL}} \times SA \times \left(C_{5,u}^{ICL} - C_{4,u}^{ICL}\right)$$

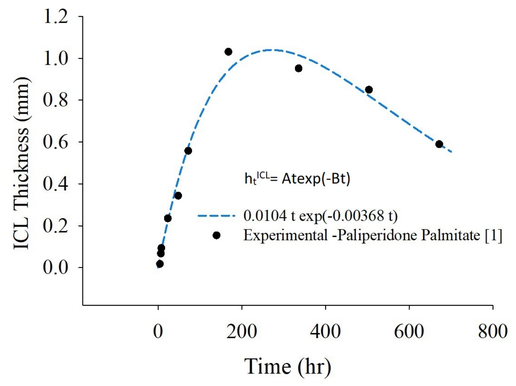
- *The thickness of the ICL layer at any time :*

$$h_t^{ICL} = \sum_{j=1}^{5} h_j^{ICL} = Atexp(-Bt)$$

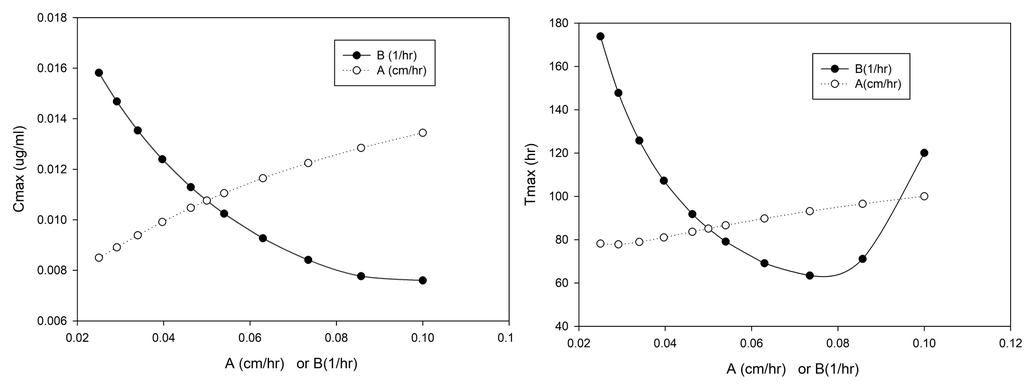
Results



The effect of parameter A and B on the dynamics of the immune cell layer.



The dynamics of infiltrated cell layer after a single intramuscular administration of paliperidone palmitate long-acting injectable in the rat



The effect of thickness parameters on Cmax and Tmax after single intramuscular administration of paliperidone palmitate long-acting injectable in the rat.

References:

The work was done under funding from the FDA (grant 1U01FD005463-02)

[1] Darville N, et al., Toxicologic Pathology 2016, Vol. 44(2)

[2] Doty A C, Doctoral Dissertation, University of Michigan 2015