527f Effect of Rbcs on Dispersion in Tissues and Inclusion of Dispersion in Pharmacokinetic Models

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Physiologically-based pharmacokinetic models usually assume that each tissue is a well-mixed compartment; however, some researchers have shown that models which include dispersion describe drug distribution more adequately. We develop a PBPK model that includes dispersion of drug as it traverses the capillaries. In the model, each tissue compartment is represented as a collection of Krough tissue cylinders. The long time limit of the dispersion coefficient, D*, is derived by using a multiple time scale approach along with a regular expansion in the aspect ratio of the capillary. Previous attempts to determine the dispersion coefficient in the capillaries neglected the presence of the red blood cells and also assumed that the Biot number (Bi), which characterizes the permeability of the capillary walls to the solute of interest, is O(1). We extend the analysis to include cases in which the Biot number is small. Additionally, we include the presence of red blood cells (RBCs) in the capillaries.

In blood flow through the capillaries, the capillary diameter is smaller than the size of the RBCs. Consequently, the RBCs must deform in order to flow through the capillaries. Plasma fills the space between successive RBCs, and there is an extremely thin layer of plasma between the RBCs and the capillary wall. Blood flow inside the capillaries is similar to plug flow; however, the region between successive RBCs is kept well-mixed by a pair of counter-rotating vortices that convect with the flow. We develop a model that describes the capillary as having regions of equally spaced RBCs and regions of plasma in between the RBCs. This model is used to derived D* for the case of O(1) Bi. In this case, the dispersion of the drug arises due to molecular diffusion, interfacial mass transfer resistance, and convective flow. The dependence of D* on physiological and drug-dependent parameters is investigated, and D* is incorporated into two pharmacokinetic models – a single tissue and blood compartment model and a whole-body PBPK model. In the limit of vanishing tissue thickness and also for the case when the drug does not partition into the tissue, the dispersion coefficient becomes equivalent to the effective diffusion coefficient because of the well-mixed characteristics of the capillary blood in the presence of RBCs. In the limit of infinite plasma in the capillary and negligible amounts of RBCs, the dispersion coeffiecient is identical to the expression for a radially well-mixed capillary region.

We also develop a model for both large and small Bi which neglects the RBCs in the capillary. In the absence of RBCs, the results for the case of O(1) Bi match those obtained by previous researchers. For the case of O(ε) Bi, where ε is the ratio of the capillary radius and the length, the average mass transfer equations for the capillary and tissue regions are coupled and do not simplify to a simple convection-dispersion form.