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A numerical framework for drug transport in a multi-layer system with discontinuous interlayer condition

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ABSTRACT

Discontinuous boundary conditions arise naturally when describing various physical phenomena and numerically modelling such conditions can prove difficult. In the field of pharmaceutical sciences, two such cases are the partitioning of a compound between different materials and a flux rate membrane controlling mass transfer between materials which both result in a discontinuous jump in concentration across adjacent materials. In this study, we introduce a general one-dimensional finite element drug delivery framework, which along with diffusion, reversible binding and dissolution within material layers, incorporates the partitioning and mass transfer conditions between layers of material.

We apply the framework to construct models of experiments, which along with experimental data, allow us to infer pharmacokinetic properties of potential material for drug delivery. Understanding such material properties is the key to optimising the therepeutic effect of a targeted drug delivery system.

1. Introduction

For the treatment of localized diseases, therapuetic levels of medication need to be sustained in areas which can be hard to reach. Effective optimization techniques for targeted drug delivery require understanding of the various pharmacokinetic processes involved. Mathematical models that accurately describe these processes are a valuable tool in the estimation of the properties of potential drug carrying materials, which can subsequently be used to forecast the distribution within specific regions of the body during delivery.

In this paper, a numerical framework that incorporates the physical processes required to simulate various drug delivery systems is introduced. The framework presented is a one-dimensional, multi-layer model that is governed primarily by a diffusion-reaction equation, but also allows for two types of coupled secondary state, chosen independently within each layer. The secondary state is governed by either the Noyes–Whitney equation, as presented by Frenning et al. [1,2], or the two-phase mathematical model presented by Pontrelli and de Monte [3], for transdermal drug delivery. Our numerical model can be applied to the modelling of drug release from a delivery device to the target area with dissolution, absorption, and reversible binding taking place in any of various layers involved, both in the delivery device and target system.

One of the challenging aspects of numerical modeling in this context is accurately considering the interface conditions and the associated discontinuities in drug concentration that stem from both partitioning and interfacial resistance or surface barriers. This is a challenging subject that has been considered in the past by e.g. Hickson et al. [4] and Rim et al. [5]. Rim et al. constructed a finite element model for transdermal drug delivery, incorporating the effects of partitioning between layers. Their approach is based on decomposing a partition interface into two adjacent boundaries belonging to separate layers. A mixed method is employed, whereby cross boundary normal flux and concentrations at each boundary are modeled as independent variables. McGinty and Pontrelli [6] recently presented a drug release-absorption model based on finite differences that deals with discontinuities in concentration caused by interlayer mass transfer conditions which describe interfacial resistance. Their model is based on a special difference scheme developed by Hickson et al. [4]. The models developed by Hickson et al. and Rim et al. both contain a concentration discontinuity condition across the boundary. Gupta et al. [7] introduced a model characterizing transport of a lipophilic solute across the cornea with good comparisson with trans-corneal concentration profiles from experiments. Results exhibit the importance of incorporating the effects of partitioning and interfacial resistance between the epithelium, stroma and endothelium layers as well as at outer boundaries. Pimenta et al.

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[8] successfully determined the partition coefficient of poly-hydroxyethylmethacrylate and silicone based hydrogels in combination with three different drugs.

The work presented in this paper incorporates all the boundary effects mentioned above, including partitioning, mass transfer effects and flux continuity, into a finite element formulation that eliminates the need for additional variables or special schemes at the boundaries. The approach is based on a two step construction. First, the finite element scheme is constructed separately for each layer with arbitrary flux conditions at the outer boundaries of each one. Following that, the layer equations are assembled into a global scheme that ensures continuous flux between layers while at the same time satisfying the interlayer boundary conditions.

The capabilities of the numerical framework presented are demonstrated, and the importance of incorporating both partitioning and mass transfer effects is highlighted by constructing models describing different aspects of drug transport. The numerical framework is used to simulate three cases. First, we simulate an moxifloxacin impregnated intra-ocular lense in a Franz diffusion cell with three different thicknesses of lens material. The results are compared with experimental data. The second case models a two phase transdermal system developed by Pontrelli and de Monte [3]. The third case is a reevaluation of data presented in Snorradottir et al. [9], on transdermal drug delivery. Results show the importance of having interlayer conditions that include both partition and mass transfer effects and that the proposed framework can apply successfully to all the cases considered.

2. Model

The mathematical model presented below consists of two coupled partial differential equations, describing possible drug related physical processes taking place within a sequence of layers of different materials, along with general boundary conditions capturing possible cross layer mechanisms. The model is one-dimensional with respect to space.

2.1. Layer equations

Within a given layer α, of thickness H_α, demarked by points $x_{\alpha-1}$ and x_α, we model two variables, an unbound fluid state C_α and a bound secondary state S_α in terms of concentration (mg/cm^3), with the following set of coupled partial differential equations

$$\begin{aligned}\frac{\partial C_\alpha(x,t)}{\partial t} &= \frac{\partial}{\partial x}\left(D_\alpha \frac{\partial C_\alpha(x,t)}{\partial x}\right) - d_\alpha C_\alpha(x,t) - b_\alpha(S_\alpha(x,t), C_\alpha(x,t))\\ \frac{\partial S_\alpha(x,t)}{\partial t} &= b_\alpha(S_\alpha(x,t), C_\alpha(x,t))\end{aligned} \tag{1}$$

where D_α is the diffusion coefficient (cm^2/h), d_α is a decay coefficient within the layer, which may e.g. describe leakage or metabolic consumption (1/h). The term $b_\alpha(S_\alpha(x,t), C_\alpha(x,t))$ relates the binding and unbinding process. We use schematic diagrams, such as the one depicted in Fig. 1, to vizualize models. In order to describe the release from solid drug systems we let S_α signify the solid state and choose the Noyes–Whitney equation [10] to describe dissolution

$$b_\alpha(S_\alpha(x,t), C_\alpha(x,t)) = -A_{0,\alpha}k_\alpha\left(\frac{S_\alpha(x,t)}{S_\alpha(x,0)}\right)^{2/3}(c_{s,\alpha} - C_\alpha(x,t)) \tag{2}$$

where $k_{d,\alpha}$ is the dissolution rate coefficient of solid drug (cm/h), $c_{s,\alpha}$ is the solubility of the drug (mg/cm^3), $A_{0,\alpha}$ is the initial surface area of the solid drug per unit volume (cm^2/cm^3), where the drug particles are assumed implicitly by the model to retain their shape as the drug dissolves such that the surface area is proportional to the volume to the power of 2/3 [11]. Initial concentrations of bound drug $S_\alpha(x,0)$ and unbound drug $C_\alpha(x,0)$ must be specified in each layer. Expression (2) can be made linear with respect to the secondary state variable by introducing a new dependent variable $\widehat{S}_\alpha(x,t) = S_\alpha^{1/3}(x,t)$ as is done in [9]. Then (1) becomes

$$\begin{aligned}\frac{\partial C_\alpha(x,t)}{\partial t} &= \frac{\partial}{\partial x}\left(D_\alpha \frac{\partial C_\alpha(x,t)}{\partial x}\right) - d_\alpha C_\alpha(x,t) + k'_\alpha \widehat{S}_\alpha(x,0)\widehat{S}_\alpha^2(x,t)(c_{s,\alpha}\\ &\quad - C_\alpha(x,t))\\ \frac{\partial \widehat{S}_\alpha(x,t)}{\partial t} &= -\frac{k'_\alpha}{3}\widehat{S}_\alpha(x,0)(c_{s,\alpha} - C_\alpha(x,t))\end{aligned} \tag{3}$$

where $k'_\alpha = k_\alpha A_{0,\alpha}/S_\alpha(x,0)$ is the effective dissolution rate (cm^3/[mg h]). The presentation of the finite element approximation and the time stepping procedure in this paper is based on the assumption that the secondary state equation is linear with respect to the secondary state variable, as well as the primary state equation being linear with respect to the primary state variable. Note that Eq. (3) and the modification after Eq. (4) both satisfy this assumption. The binding and unbinding process can be in the form of a two-phase equation

$$b_\alpha(S_\alpha(x,t), C_\alpha(x,t)) = -k_1 S_\alpha(x,t) + k_2 C_\alpha(x,t) \tag{4}$$

where k_1 and k_2 are unbinding and binding rate coefficients (1/h), respectively. In some applications it is appropriate to assume a conservation condition for binding by replacing the k_2 coefficient with $k'_2(S_{max,\alpha} - S_\alpha(x,t))$, where $S_{max,\alpha}$ denotes the density of binding sites [6]. In this case the model is non-linear and the present finite element method has to be modified by linearizing the equation in an appropriate way.

2.2. General boundary conditions

Between layers we define general interlayer boundary conditions with which we are able to describe the combined mechanisms of partitioning and mass transfer rate.

A partition between layers, occuring at x_α, describes a concentration discontinuity in equilibrium determined by the ratio P_α, refered to as the partition coefficient (dimensionless). The ratio controls the jump in concentration on one side of an interface proportionally with respect to the concentration of the other side. The mass transfer coefficient K_α (cm/h) controls the flux resistance across the interface possibly due to a thin diffusion barrier. For interlayer boundary point x_α, we have

$$\begin{aligned}&-D_\alpha \frac{\partial C_\alpha}{\partial x}\bigg|_{x=x_\alpha^-} = -D_{\alpha+1}\frac{\partial C_{\alpha+1}}{\partial x}\bigg|_{x=x_\alpha^+}\\ &= K_\alpha(C_\alpha(x_\alpha,t) - P_\alpha C_{\alpha+1}(x_\alpha,t))\end{aligned} \tag{5}$$

Low K_α slows the rate at which the ratio of concentration difference between the layers approaches the ratio P_α. Sometimes it may be more appropriate to express the right-hand side of (5) as

$$K'_\alpha(P'_\alpha C_\alpha(x_\alpha,t) - C_{\alpha+1}(x_\alpha,t))$$

This can be realised by setting $K_\alpha = K'_\alpha P'_\alpha$ and $P_\alpha = 1/P'_\alpha$. When needed we shall refer to K and P as the layer α / layer $\alpha+1$ mass transfer and partition coefficients respectively and refer to K' and P' as the layer $\alpha+1$ / layer α mass transfer and partition coefficients. For simplicity, we may refer to the flux at x_α as J_α. Alternatively, we can express (5) as

$$K_{\alpha-}C_\alpha(x_\alpha,t) - K_{\alpha+}C_{\alpha+1}(x_\alpha,t) \tag{6}$$

and refer to $K_{\alpha-} = K_\alpha$ and $K_{\alpha+} = K_\alpha P_\alpha = K'_\alpha$ as the left and right rate coefficients at $x = x_\alpha$, cf. (4). At outer boundaries x_0 and x_N we define general outer boundary conditions in a similar manner

$$\begin{aligned}-D_1\frac{\partial C_1(x,t)}{\partial x}\bigg|_{x=x_0} &= K_0(C_{b,0} - P_0 C_1(x_0,t))\\ -D_N\frac{\partial C_N(x,t)}{\partial x}\bigg|_{x=x_N} &= K_N(C_N(x_N,t) - P_N C_{b,N})\end{aligned} \tag{7}$$