Transdermal Drug Delivery with Permeation Enhancer

A. Kermani[1], N. Elabbasi[1]

[1]Veryst Engineering, Needham, MA, USA

Abstract

Transdermal drug delivery (TDD) is used to deliver drugs through the skin as an alternative to oral, intravascular and subcutaneous routes. While there are many advantages to TDD, skin is a very effective barrier and provides resistance to drug delivery. There are two important layers in skin: epidermis and dermis. Drugs must pass through the two sublayers of the epidermis to reach the micro circulation of the dermis. The upper most skin layer, stratum corneum, has the highest resistance to diffusive transport into the skin. This layer is a barrier to approximately 90% of transdermal drug applications. Therefore, the majority of drugs do not penetrate the skin at rates sufficient for healing except those whose molecules are small. To improve drug delivery through the skin, permeation enhancers are used.

Permeation enhancers are agents that alter the structure and dynamics of skin to allow sufficient drug delivery. Previous studies captured the effect of enhancers by setting the diffusivity of a drug to be a function of the concentration of the enhancer. Diffusivity of drug increases with concentration of enhancer linearly in Ref. [1], and hyperbolically in Ref. [2].
We developed an axisymmetric COMSOL Multiphysics® software model of drug diffusion from a patch to skin (Figure 1). The patch is an adhesive layer with the drug fentanyl and enhancer lauryl pyroglutamate. This study replicates the experimental and numerical studies reported in Ref. [1].

Diffusion equations govern delivery of the drug and enhancer in the patch and skin. Continuity of normal flux and also partitioning of the drug and enhancer at the interface of the patch and skin is required. Partitioning happens at the interface when the equilibrium solubilities of a species is different in two materials. Continuity of normal flux and partitioning imposes Neumann and Dirichlet boundary conditions simultaneously at the interface.
Coupling between the drug and the permeation enhancer causes nonlinear diffusion from the patch to skin, which increases drug diffusion. We captured the effect of the enhancer by assuming that diffusivity of the drug in the skin increases linearly with the concentration of the enhancer, Ref[1].

Figure 2 compares normalized concentrations of the drug in two cases: with and without the enhancer. The enhancer reduces the concentration of the drug in the patch and increases it in the skin. Figure 3 compares normalized flux of the drug through the bottom boundary of skin domain. The figure shows that the enhancer is increasing the flux. Our

model accurately predicts the experimental drug flux values reported in Ref. [1]. Our result also shows that drug flux increases when the initial concentration of enhancer increases in the patch.

In summary, we chose a two-domain layer to simulate TTD. We could impose Neumann and Dirichlet boundary conditions simultaneously at the interface with COMSOL Multiphysics. Based on experimental data, we assumed that diffusivity of a drug in skin depends linearly on enhancer concentration. The obtained drug flux profile, which matches the experimental data, demonstrates the modeling capability and potential of the discussed formulation in studying TTD.

Reference

1. J. Rim, P. Pinsky, W Osdol, Finite element modeling of coupled diffusion with partitioning in transdermal drug delivery, Annals of Biomedical Engineeringm 2005, Vol 30, 1422-1438.

2. R. Mantiz, W. Luncht, K. Strehmel, R. Weiner, R. Neubert, On mathematical modeling of dermal and transdermal drug delivery, J. Pharm. Sci. 1999, Vol 87, 873-879.

Figures used in the abstract

Figure 1: Schematic of the model, with contour plot showing normalized initial drug concentration.

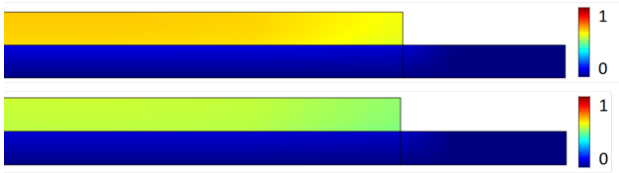

Figure 2: Normalized drug concentration after 60 hours. Top figure without enhancer, bottom figure with enhancer.

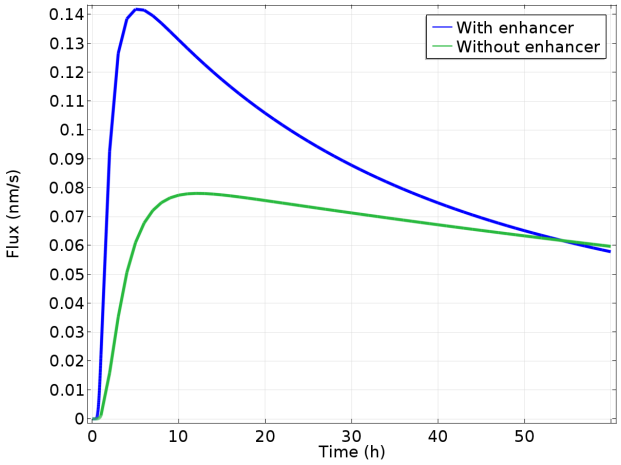

Figure 3: Normalized flux of drug.

Diffusivity of drug fentanyl in patch	3.16E-6(cm^2/hour)
Diffusivity of drug fentanyl in skin	1.08E-6(cm^2/hour)
Diffusivity of enhancer lauryl pyroglutamate in patch	7E-6(cm^2/hour)
Diffusivity of enhancer lauryl pyroglutamate in skin	7E-6(cm^2/hour)
Ratio of equilibrium distribution of fentanyl	0.15
Ratio of equilibrium distribution of enhancer lauryl pyroglutamate	0.15
Degree of enhancement	1.8E-4(cm^5/g/hour)
Initial concentration of drug fentanyl in patch	0.06(g/cm^3)
Initial concentration of drug fentanyl in skin	0
Initial concentration of enhancer lauryl pyroglutamate in patch	0.12(g/cm^3)
Initial concentration of enhancer lauryl pyroglutamate in skin	0

Figure 4: Parameter values.