Transdermal Drug Delivery with Permeation Enhancer

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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. To improve drug delivery through the skin, permeation enhancers are used. We developed an axisymmetric COMSOL Multiphysics model of drug diffusion from an adhesive patch to skin. We captured the effect of the enhancer by assuming that diffusivity of the drug in the skin increases linearly with concentration of the enhancer. We validated our simulation by comparing with experimental measurements, in which the drug is fentanyl and the enhancer is lauryl pyroglutamate.

Keywords: Transdermal drug delivery, Epidermis, Skin, Diffusion.

1. Introduction

Transdermal drug delivery (TDD) is used to deliver drugs through the skin as an alternative to oral, intravascular and subcutaneous routes. TTD has advantages compared to the other delivery methods. It has less frequent dosing, it is not invasive, and it is simple to use. While there are many advantages to TDD, skin is a very effective barrier and provides resistance to drug delivery. There are two main layers in skin: epidermis and dermis (see Figure 1). Drugs must pass through the two sublayers of the epidermis to reach the micro circulation of the dermis. The upper-most epidermis 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 if their molecules are small enough. To improve drug delivery through the skin, permeation enhancers are used. Permeation enhancers are agents that alter the structure of the skin so that sufficient drug delivery can be achieved. Previous studies captured the effect of enhancers by setting the diffusivity of a drug to be a function of the concentration of the enhancer. For example, in Ref. [1], it is assumed that diffusivity of drug increases linearly with concentration of enhancer; and in Ref. [2] it increases as a hyperbolic function of enhancer concentration.

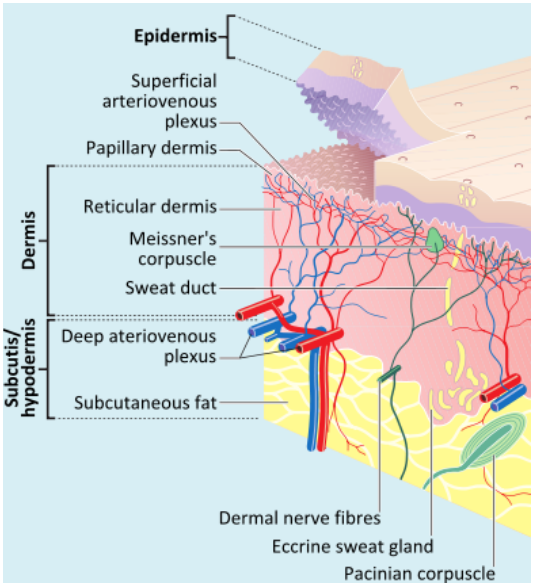

Figure 1 Skin layer (from Wikipedia)

3. Use of COMSOL Multiphysics Software

We developed an axisymmetric COMSOL Multiphysics model of drug diffusion from an adhesive patch to skin (see Figure 2). For initial conditions, we assume the drug and the enhancer are dissolved in the patch uniformly, and their concentrations are set to zero in the skin. The simulated patch has typical dimensions with radius of 0.9 cm and thickness of 50.8 µm. Thickness of the skin is considered 50.8 µm, which is a reasonable thickness for the epidermis layer.

Figure 2 Schematic of the model, with contour plot showing normalized initial drug concentration

The 1-D version of the governing equations to be solved are given as follows:

$$\frac{\partial C_i^K}{\partial t} - D_i^k \frac{\partial^2 C_i^K}{\partial x^2} = 0 \qquad i = 1,2$$
$$K = p(patch),\ s(skin)$$

where c_1^p and c_1^s are concentrations of the drug in the patch and skin, respectively, and c_2^p and c_2^s are concentrations of the enhancer in the patch and skin. D_i^p and D_i^s are diffusion coefficients of the patch and skin where subscript i is 1 for drug or 2 for the enhancer.

The following equation is required to satisfy the continuity of normal flux of the drug and enhancer at the interface of the patch and skin:

$$D_i^p \frac{\partial C_i^p}{\partial x} = -D_i^s \frac{\partial C_i^s}{\partial x} \qquad i = 1,2$$

Besides the above equations, a condition describing partitioning of drug and enhancer across the interface is needed. Partitioning happens at the interface when the equilibrium solubilities of a species is different in two materials. This results in discontinuity of the species across the interface as shown below:

$$\frac{C_i^S}{K_i^S} = \frac{C_i^p}{K_i^p} \qquad i = 1,2$$

where K_i^S and K_i^p are equilibrium distribution of a species (drug or enhancer) in patch and skin relative to a common reference material.

Coupling between a drug and a permeation enhancer causes nonlinear diffusion from the patch to skin, which increases drug diffusion. We captured the effect of the enhancer by specifying that diffusivity of the drug in the skin increases linearly with concentration of the enhancer:

$$D_1^S = D_0^S + \mu\, C_2^s$$

Here, parameter μ determines the degree of enhancement of drug due to presence of enhancer. Diffusion coefficient of the enhancer in the patch, D_2^p, does not have a significant impact on the drug delivery, therefore we set it equal to D_2^S. (see Ref. [1]). All the values of parameters that we used in this study are in Table 1.

The drug and enhancer do not transport through the top or the sides of the dermal patch. Therefore, we used zero flux boundary condition for the drug and enhancer at those locations. The lower boundary of skin is acting as a sink for both drug and enhancer, therefore their concentration is set to zero at that boundary.

4. Results

We compared calculated normalized concentrations of the drug in three cases: without the enhancer and with the enhancer with two different initial enhancer concentrations. Initial enhancer concentrations are 0.8 g/cm^3 and 0.12 g/cm^3. Initial drug concentration is 0.06 g/cm^3 in all three cases.

Figure 3 shows normalized concentrations of the drug when the initial concentration of the enhancer is 0.12 g/cm^3 and without the enhancer. The enhancer reduces concentration of the drug in the patch and increases it in the skin.

Figure 3. Normalized drug concentration after 60 hours. Top figure without enhancer, Bottom figure with enhancer. Initial enhancer concentration is 0.12 g/cm^3

Figure 4 shows the normalized drug concentration at different times along the thickness of the patch and skin. Z-coordinate between 0 and 50.8 μm is in the skin domain; Z-coordinate greater than 50.8 μm is in the patch domain. Drug concentration is discontinuous across the interface due to the partitioning. Enhancer reduces concentration of the drug in the patch.

Figure 5 compares normalized flux of the drug through the bottom boundary of skin domain to dermis for the three mentioned cases. The figure shows that the enhancer is significantly increasing the flux, as expected. Our results also show that drug flux increases when the initial concentration of enhancer increases in the patch. Note that

normalized fluxes have small values of order 1 nm/s. This is due to the effectiveness of skin resistance to drug delivery.

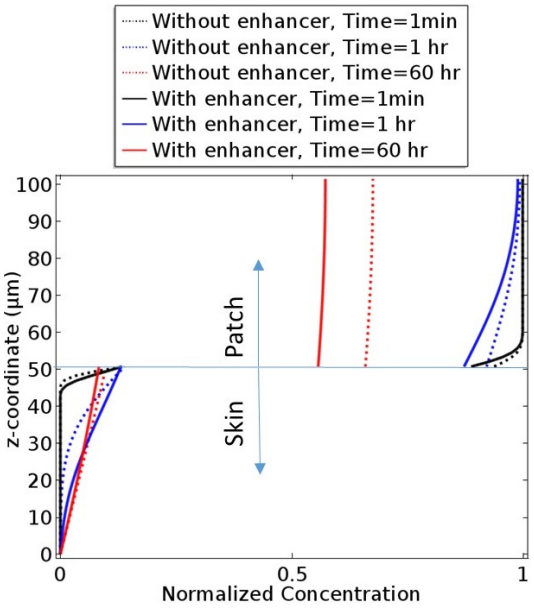

Figure 4. Normalized drug concentration at different times along the thickness of the patch and skin

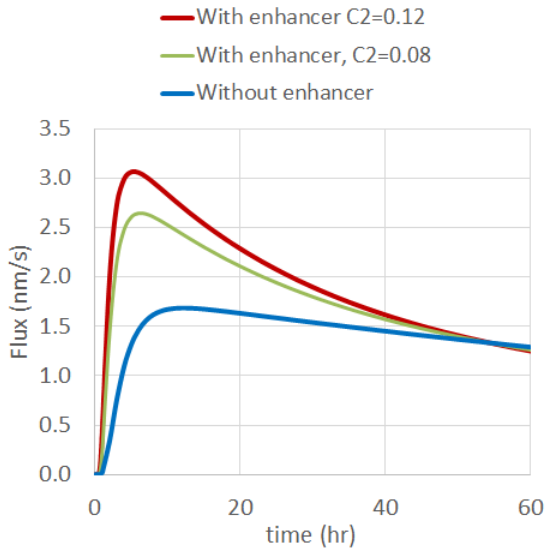

Figure 5. Variation of normalized drug flux to skin versus time

5. Discussion

We validated our model with the experimental drug flux values reported in Ref [1]. The drug, in this case, is fentanyl, and the enhancer is lauryl pyroglutamate (LP). Figure 6 shows experimental and calculated fluxes, with and without enhancer. The initial fentanyl concentration is 0.06 g/cm^3 and the enhancer (LP) concentration is 0 or 0.12 g/cm^3.

Surfactant-like enhancers such as LP are known to enhance drug diffusivity. The model predicts the experimental maximum flux value and its increase with the enhancer concentration. However the model does not capture the broad peak and rapid decay of the flux very well.

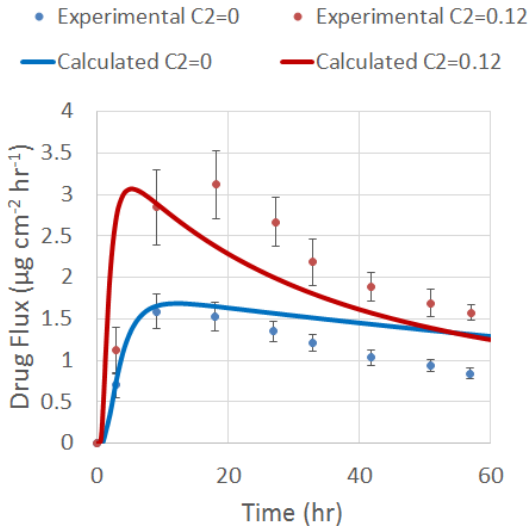

Figure 6. Experimental and calculated drug flux to skin

Our analysis do not predict measured experimental flux accurately over a long time. We suspect that the Fickian diffusion model may not be able to capture the physics of transdermal drug delivery over a long period of time (see Ref. [1]). Even if the Fickian model is the suitable, the experimental data show time dependency in the diffusivity coefficient. Therefore the mathematical model used here and the assumption of diffusivity varying linearly with enhancer concentration might be too simple to capture all aspects of drug diffusion, especially over a long period of time.

We assumed sink boundary condition at the bottom boundary of the skin next to the dermis.

This boundary condition is not very accurate since solubility of LP enhancer is not significant in the skin. The other extreme boundary condition of the enhancer is zero flux at the bottom boundary of the skin. This boundary condition increases concentration of the enhancer in the skin since the enhancer does not leave the system. This in turn increases the diffusivity of the drug and its flux. We recommend further investigations to characterize the correct boundary condition of the enhancers in future studies.

In this analysis we also did not consider the effect of hydration as its effect on the diffusion characteristics of the patch is not clear. The skin samples are stored fully hydrated before the experiments. Once the experiment starts and the patch is placed on the skin, its hydration level gradually increases and the patch starts to swell. This changes effective concentration of the drug and enhancer in the patch. This effect is not considered in this study.

All of the above mentioned simplifications can contribute to the shortcomings of the proposed method in capturing the characteristics of the experimental data over a long time.

6. Summary

We developed a two-layer model to simulate transdermal drug delivery with drug enhancers using COMSOL Multiphysics. COMSOL enabled us to easily set up continuity of fluxes, partitioning of the scalar concentration at the interface, and coupling of the diffusion coefficient of the drug and the enhancer concentration. Based on experimental data, we assumed that diffusivity of the drug in the skin depends linearly on the enhancer concentration. We validated our model with experimental data. The obtained drug flux profile, which matches the experimental data, demonstrates the modeling capability and potential of the discussed formulation in studying transdermal drug delivery.

The calculated flux did not match the experimental data over a long time. We identified several potential causes. Further studies are needed to evaluate effect of hydration of the patch and other nonlinear processes that affect diffusion in the skin.

7. References

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

8. Appendix

Table 1: Parameter values

D_1^p	Diffusivity of drug fentanyl in patch	3.16E-6 (cm^2/hour)
D_0^s	Diffusivity of drug fentanyl in skin	1.08E-6 (cm^2/hour)
D_2^p	Diffusivity of enhancer lauryl pyroglutamate in patch	7E-6 (cm^2/hour)
D_2^s	Diffusivity of enhancer lauryl pyroglutamate in skin	7E-6 (cm^2/hour)
K_1^S $/K_i^p$	Ratio of equilibrium distribution of fentanyl	0.15
K_2^S $/K_2^p$	Ratio of equilibrium distribution of enhancer lauryl pyroglutamate	0.15
μ	Degree of enhancement	1.8E-4 (cm^5/g/hour)
Initial C_1^p	Initial concentration of drug fentanyl in patch	0.06 (g/cm^3)
Initial C_1^s	Initial concentration of drug fentanyl in skin	0
Initial C_2^p	Initial concentration of enhancer lauryl pyroglutamate in patch	0.12 (g/cm^3) or 0.08 (g/cm^3)
Initial C_2^s	Initial concentration of enhancer lauryl pyroglutamate in skin	0