Veryst Engineering

Engineering Through The Fundamentals

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Transdermal Drug Delivery with Permeation Enhancer

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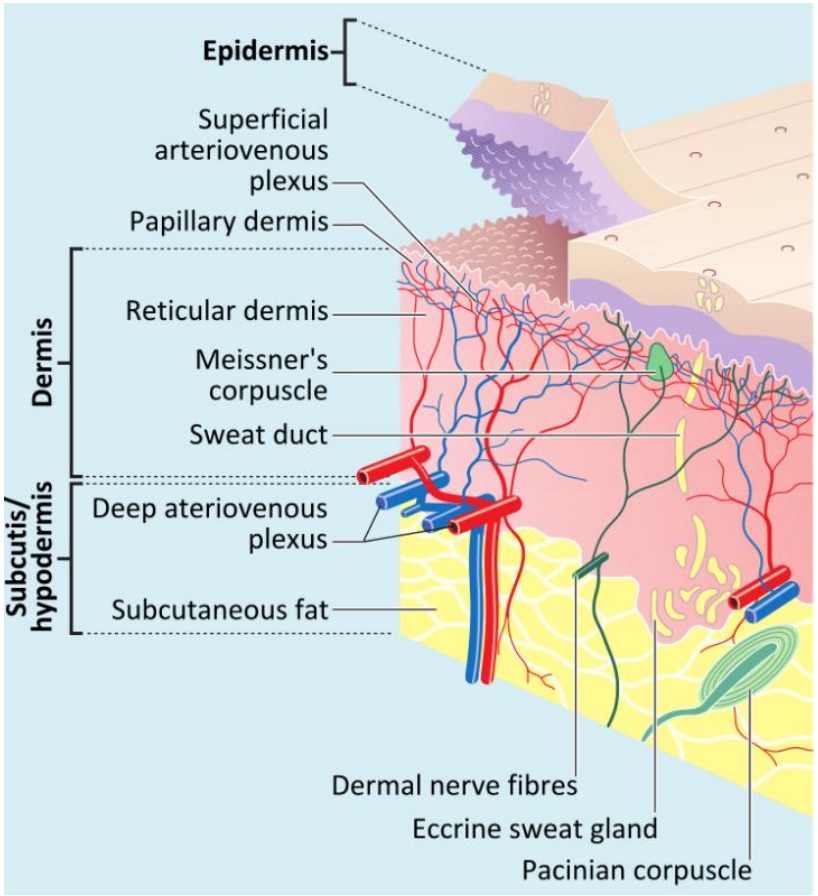
Introduction

- Transdermal drug delivery (TDD) is used to deliver drugs through the skin as an alternative to oral, intravascular and subcutaneous routes.
- TTD has less frequent dosing, it is not invasive, and it is simple to use.
- Skin is a very effective barrier and provides resistance to drug delivery.

Introduction

- There are two main 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 epdidermis 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.



From Wikipedia

Introduction

- The majority of drugs do not penetrate the skin at rates sufficient for healing except those whose molecule are small.
- To improve drug delivery through the skin, permeation enhancers are used.
  - Permeation enhancers are agents that alter the structure of skin so that sufficient drug delivery can be achieved.

Problem Description

- We developed an axisymmetric COMSOL Multiphysics model of drug diffusion from a patch to skin .
- The patch is an adhesive layer with the drug and enhancer.
- 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 of epidermal layer
- Initial conditions:
  - Drug and the enhancer are dissolved in the patch uniformly, while their concentrations are set to zero in the skin.

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

Transdermal Model

- The governing equations to be solved

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

- Continuity of normal flux of the drug and enhancer at the interface

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

- Partitioning happens at the interface when the equilibrium solubilities of a species is different in two materials.

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

Transdermal Model

- We captured the effect of an enhancer by assuming that diffusivity of the drug in the skin increases linearly with concentration of the enhancer

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

- Here, parameter μ determines the degree of enhancement of drug due to presence of enhancer.

Boundary Conditions

- 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 concentrations are set to zero there.

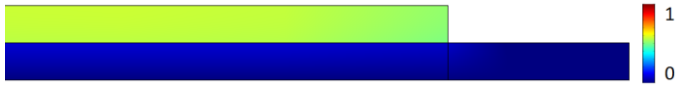
Schematic of the model, with contour plot showing normalized initial drug

Results

- We compared calculated normalized concentrations of the drug with initial concentration of 0.06 g/cm^3 in three cases:
  - Without the enhancer
  - With initial enhancer concentrations of 0.8 g/cm^3
  - With initial enhancer concentrations of 0.12 g/cm^3

Without enhancer

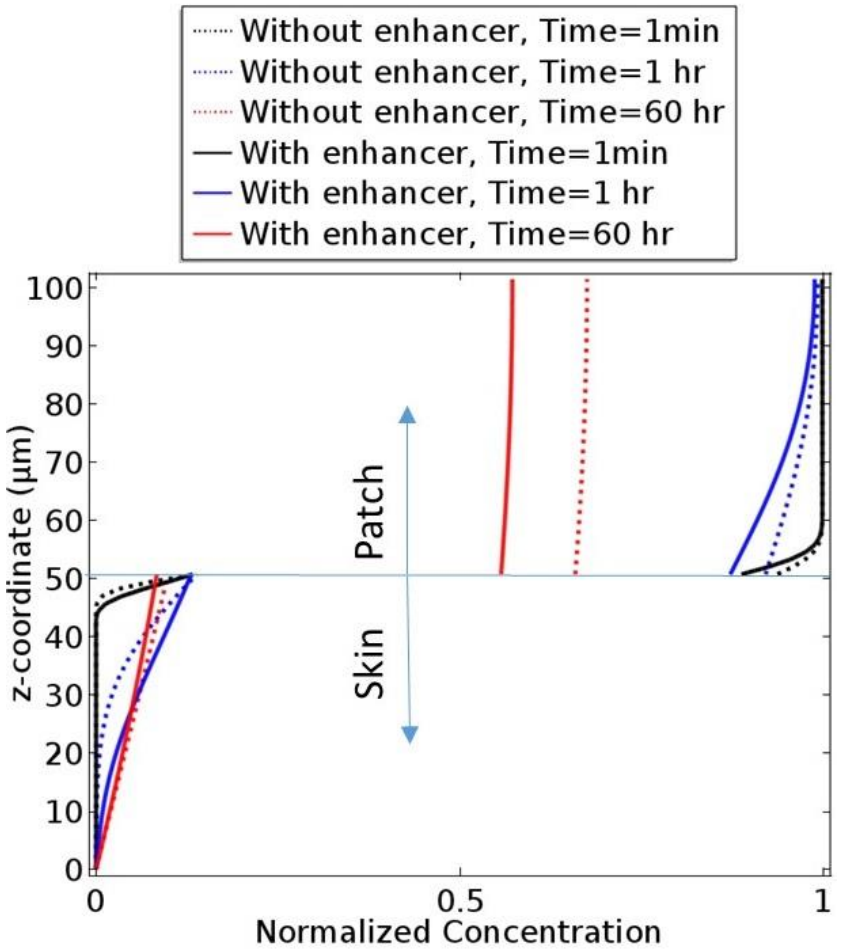
With initial enhancer concentrations of 0.12 g/cm^3



Normalized drug concentration after 60 hours

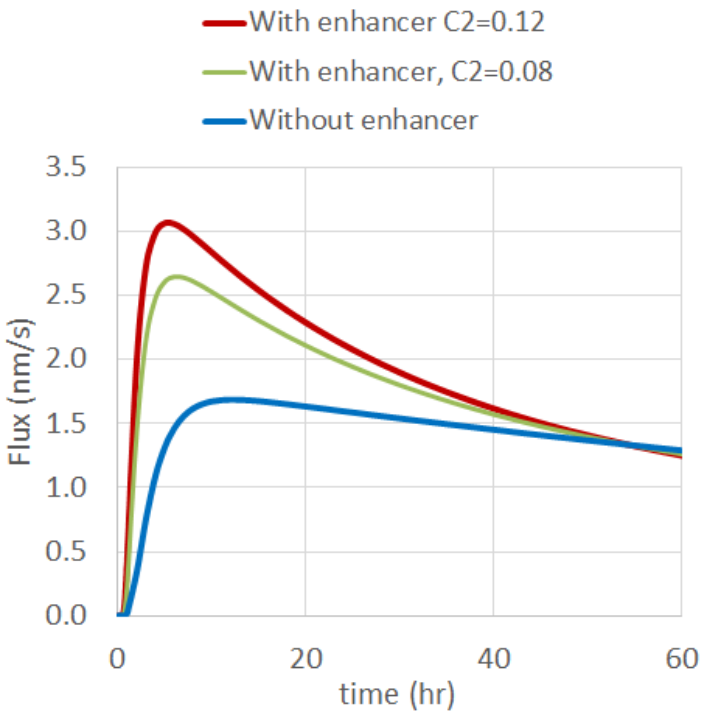
Drug Concentration

- Normalized drug concentration at different times along the thickness of the patch and skin.
- Drug concentration is discontinuous across the interface due to the partitioning.
- Enhancer reduces concentration of the drug in the patch.



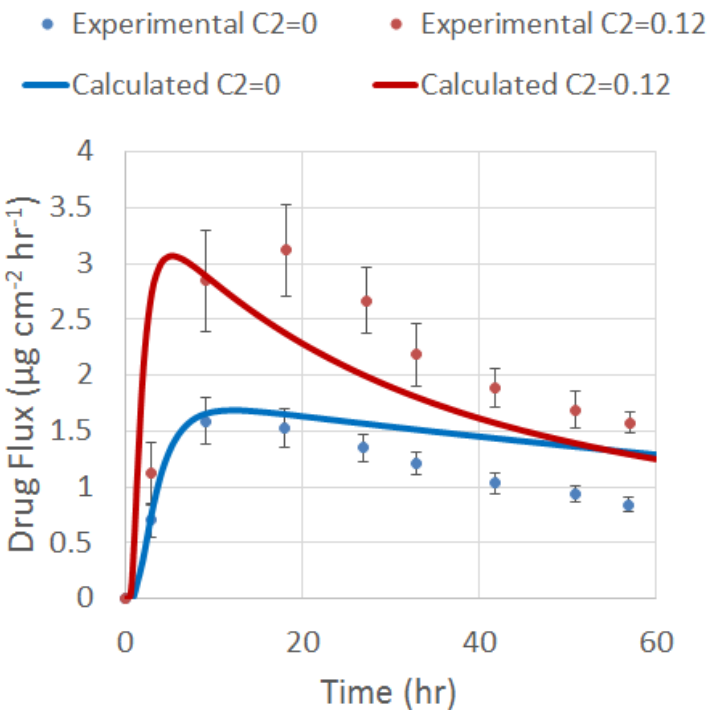
Drug Flux

- Normalized flux of the drug through the bottom boundary of skin domain to Dermis for the three mentioned cases.
- Enhancer is significantly increasing the flux as expected.
- Drug flux increases when the initial concentration of enhancer increases in the patch.
- Normalized fluxes have small values of order 1nm/s. This is due to the effectiveness of skin resistance to drug delivery.



Comparison with Experimental Data

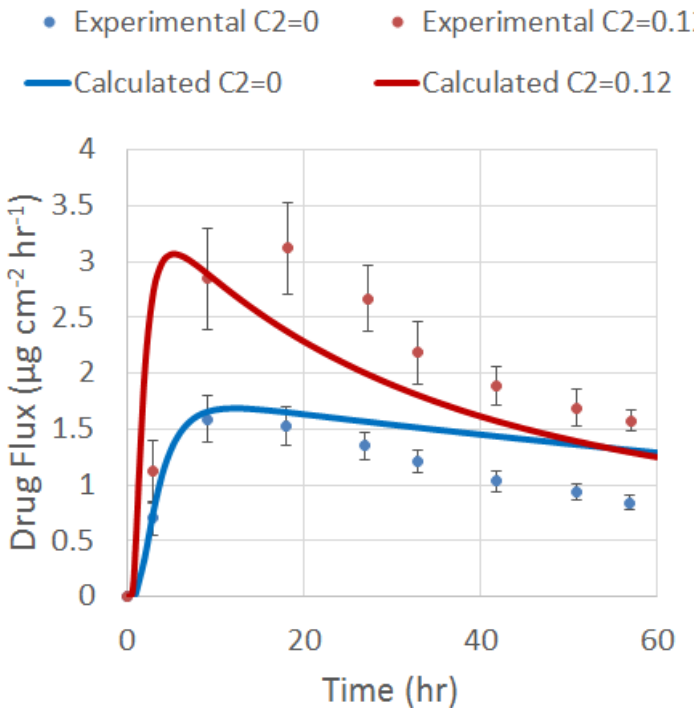
- We validated our model with the experimental drug flux values in Ref. [1]
  - Drug is fentanyl and enhancer is lauryl pyroglutamate
- Calculated flux
  - Predicts the experimental maximum flux value and its increase with the enhancer concentration correctly



Initial drug concentration is 0.06 g/cm^3 and the enhancer (LP) loading is 0 or 0.12 g/cm^3

Discussion

- Does not predict measured experimental flux accurately over a long time
  - The experimental data show time dependency in diffusivity coefficient.
  - Effect of hydration on diffusion characteristic in the patch is not clear.
    - The patch used in the experiments has an occlusive backing causing water retention



Initial drug concentration is 0.06 g/cm^3 and the enhancer (LP) loading is 0 or 0.12 g/cm^3

Summary

- We developed two domain layer to simulate the transdermal drug delivery method.
- We assumed that diffusivity of the drug in the skin depends linearly on the enhancer concentration.
- 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 does not match the experimental data over a long time.
  - We identified several potential reasons.
- Further studies are needed to evaluate effect of hydration of the patch and other processes that affect diffusion in the skin.

Reference

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