One Compartment Model for Dermal Absorption

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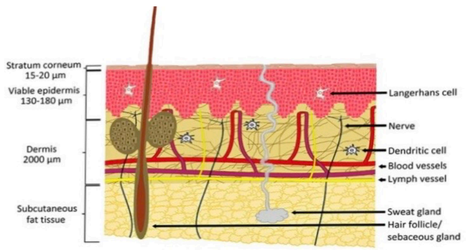
Background

Background: Transdermal drug delivery (TDD) is a method used to deliver a therapy into systemic circulation across the skin. Transdermal therapeutic administration is common practice in response to chronic inflammatory skin disease. However, subtherapeutic outcomes are prevalent without known cause. This is largely due to inter- and intraindividual variability of drug absorption through the skin. It is known that the inherent skin membrane function poses unique challenges to effective systemic drug delivery. Diffusion, metabolism, and other skin biophysics profiles and their contributions to drug response have yet to be fully elucidated.

Problem: The use of computational and predictive modelling poses potential to assist drug developers and clinicians in determining the most effective drugs for a given patient with their unique biological profile. Given the intricacies of biological interplay, it is important to determine which biological factors are the most predictive for drug delivery efficacy.

Why this model?: This one compartment model is used to simply illustrate the relationship between varied simulated rate constants and drug concentrations of the drug donor and acceptor as it relates to time.



Ailkani et al., Pharmaceutics 2015

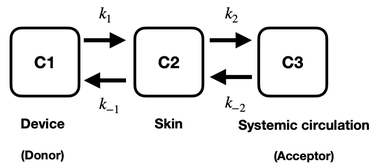
Anatomy of the skin.

Methods and Materials

1. We adapted a one-compartment model schematic to demonstrate the rate of forward and reverse flow between device, skin barrier, and systemic circulation.
2. Developed code in coding software, X Code to simulate a reaction diffusion equation of transdermal drug delivery.
3. Developed and plotted experimental parameters to simulate rates of transfer between compartments

Programming language: C++
Coding Software: X-Code
Coding Device: MacBook Air

One-Compartment Model



This schematic represents the rates of transfer of a drug compound in a one-compartment model of the skin. *C* denotes the average concentration of a compound in the compartment (device, skin, etc). *k* denotes the rate of transfer between compartments.

Ordinary Differential Equations (ODEs)

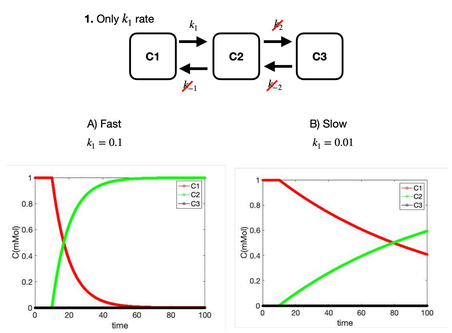
$$\frac{dC_1}{dt} = (C2 * k_{-1} - C1 * k_1)$$

$$\frac{dC_2}{dt} = C1 * k_1 + C3 * k_{-2} - (C2 * k_2 + C2 * k_{-1}))$$

$$\frac{dC_3}{dt} = (C2 * k_2 - C3 * k_{-2})$$

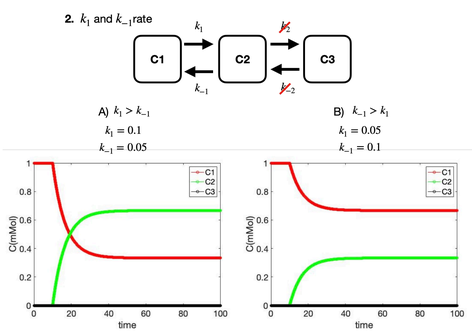
Ordinary Differential Equations (ODEs) are derived to represent the change in the amount if solute in different compartments over time. These equations represent the first order pharmacokinetics in the one compartment skin model.

1. Only k_1 rate



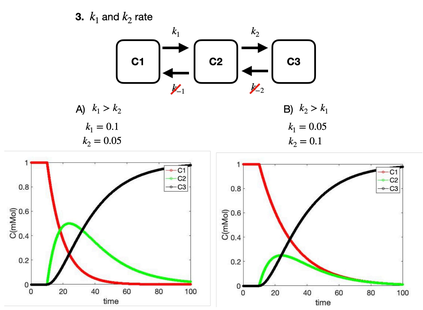
Only k_1 rate was observed in the deployment of this model in two scenarios: fast and slow. Experimental values of 0.1 and 0.01 were assigned to this model. The graphical outputs display the concentration of drug compound between the compartments over time.

2. k_1 and k_{-1} rate



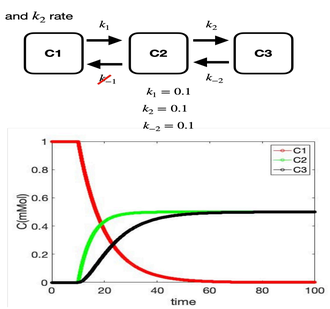
In this model deployment, only the forward and reverse rates between the the device and skin (k_1 and k_{-1}) were observed. We explored two rate scenarios: $k_1 > k_{-1}$ and $k_{-1} > k_1$. Experimental values of 0.1 and 0.05 were assigned to this model. The graphical outputs display the concentration of drug compound between the compartments over time.

3. k_1 and k_2 rate



Only the forward rates (k_1 and k_2) from the device to skin to systemic circulation were observed in this model deployment in two scenarios: k_1 and k_2. Experimental values of 0.1 and 0.05 were assigned to this model. The graphical outputs display the concentration of drug compound between the compartments over time.

4. k_1 and k_2 rate



In this model deployment, the forward rates, k_1 and k_2, and reverse rate, k_{-2}, were observed in this model deployment. All rates were assigned the experimental value of 0.1. were assigned to this model. The graphical output display the concentration of drug compound between the compartments over time.

Discussion and Future Directions

This model was suitable to simplistically explore the pharmacokinetic properties of transdermal drug delivery. This one-compartment model, however, possesses multiple limitations that will drive further research questions and project design in the future. Given the multifactorial nature of the interplay between biological characteristics, therapy characteristics, and therapeutic response it is appropriate to employ multidimensional and data-based modelling frameworks. We plan to use a multimodal multiscale approach including atomistic scale modeling to allow quantitative determination of the impact of underlying biophysical properties of skin. Atomistic scale modeling are computational models that mimic complex systems by accounting for the most fundamental and constituent parts of a system. Skin parameters that vary between individuals may alter the efficacy of transdermal drug delivery. Hence, we will use an atomistic representation of the biological components of the Epidermal and Dermal skin layers to test the effect of the following parameters on drug diffusion through the layers. Membrane composition will be varied, including fatty acid composition, thickness, hydration state and pH. Testing the impact of each of these parameters on the rate of diffusion across the skin layers will allow us to develop a function scale reaction diffusion model of transdermal drug delivery. This model can then be used as a high throughput screening tool to optimize drug deliver for specific drugs. For example, we can add additional hydration, or organic solvent mixtures into the model to determine the impact on transmural delivery time. Future model expansion can include incorporation of inflammatory elements and other various perturbations such as acute fibroblast migration to represent injury. We will validate the skin model by evaluating our model against published known drug efficacies such as clonidine, fentanyl, and topical tacrolimus.

Acknowledgements

I would like to acknowledge the guidance and expertise of various members in the Clancy lab, especially Dr. Colleen Clancy and Gonzalo Hernandez-Hernandez. I would also like to acknowledge the support from leadership in the ARC-MD program. Lastly, I would like to thank the support and sponsorship of the Association of Black Women Physicians (ABWP) whose generosity has enabled me to secure resources to support my learning of the intersection of technology and medicine.

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