Optimization of Transdermal Drug Delivery with Microcapsules

BEE 4530 - Computer-Aided Engineering:
Applications to Biomedical Processes

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1. Executive Summary

Research in transdermal drug delivery systems has gained much attention in the past thirty years. One of the biggest challenges in developing an effective system however, is getting past the tightly-structured outermost layer of the skin called the stratum corneum. While many different techniques to safely bypass the stratum corneum have been employed, one promising method of transdermal drug delivery is the use of drug-loaded microcapsules. Encapsulating the drug, as opposed to a non-encapsulated topical application, allows the drug to diffuse into hair follicles where drug release can occur in the deeper layers of the skin.

COMSOL was used to model the diffusion of drug through a hair follicle and into the skin layers, via microcapsules of inner radius 300nm and outer radius 350nm. The diffusion of microcapsules through the hair follicle, drug through the microcapsule shell, and drug through the skin layers was modeled using three transient diffusion equations that were solved simultaneously. The drug in microcapsules was modeled as emerging from a source, similar to a patch, above the hair follicle.

The COMSOL model was verified by comparing the time for the microcapsules to penetrate into the follicle, the time for the drug to diffuse out of the microcapsules, and the drug concentration in the dermis to literature values. It took 60-70 minutes for the microcapsules to be evenly dispersed throughout the follicle, which is supported by literature values.[1] The microcapsule released 75% of its encapsulated drug after 1.25 hours, which is comparable to a literature value of 70% release in 2 hours.[1] Additionally, the same source showed that drug release by the microcapsule was complete after 4 hours; almost all of the drug had left the microcapsule in 4 hours in our model. The drug concentration in the dermis in our model after 4 hours (0.0005 ug/mL) was lower than literature sources. However, our design only had drug-containing microcapsules applied directly above the hair follicle, when in reality, much more drug would be applied to the skin surface.[2] We showed that a slight variation of our design, using a thin layer of drug over the entire skin surface, greatly improves the value of drug concentration in the dermis. A sensitivity analysis was conducted to determine the significance of parameters on our model.

The solution from our design led to a slightly high release rate of the drug and a low final drug concentration in the skin, relative to literature values. This indicated that our model would best reflect the behavior of a potent drug requiring a fast release rate and a low dosage in skin. In order to obtain a more accurate solution, the simplifications in our design could be adjusted and the realistic complexities of actual skin could be added. While we only studied diffusion through one hair follicle, studying several hair follicles in a representative region of the skin could lead to changes in the final drug concentration achieved in the skin. Despite the many simplifications of our model, we were able to show that this microcapsule transdermal system is an effective method for bypassing the highly impermeable outer skin layer.

2. Introduction

2.1 Background

Drug delivery through the skin has been a rapidly growing area of research in the past thirty years. Compared to the conventional methods for drug delivery such as oral intake or injections, transdermal drug delivery has proven to have several advantages. Drugs administered transdermally avoid both degradation in the gastro-intestinal tract and the first-pass effects of the liver[3,4,5,6] , which are typical problems associated with oral delivery. Injections are painful, inconvenient, and invasive, which is not the case with transdermal systems.[7] Drug delivery through the skin allows for better control of dosage due to the impermeablility of the human skin[8], and longer release periods of the drug.[6] The transdermal systems are also noninvasive, can be self-administered, and are generally inexpensive[6], making them highly favorable over the conventional drug delivery techniques.

Transdermal drug delivery systems have become increasingly sophisticated over time. The first transdermal system that was approved in the United States in 1979 was the motion sickness patch delivering scopolamine. The nicotine patch was approved for use ten years later. Patch systems generally make up the first-generation transdermal delivery systems and are the most popular types of systems currently in clinical use.[6] Other non-patch first-generation systems are in the form of liquid spray, gel or other types of topical formulations.[6] The greatest limitation for first-generation systems, however, is the highly impermeable outermost layer of the skin called the stratum corneum.[6] Drugs delivered through the first-generation approach must therefore be of low molecular weight, lipophilic and highly effective at low doses.[6]

Second-generation transdermal delivery systems have also advanced clinical practice. The goals of these second-generation systems include increasing the permeability of the stratum corneum, improving transport through the skin by adding a driving force, and preventing injury to deeper tissues.[6] The greatest challenge has been finding the correct balance between increasing delivery rates, while preserving tissues from damage.[6] Some of the main techniques used to achieve these goals have been the addition of chemical enhancers, iontophoresis and noncavitational ultrasound.[6] Second-generation systems have mostly improved the delivery of small molecules.[6]

Lastly, the third-generation transdermal systems represent the most sophisticated system designs. These systems focus on targeting a stronger disruption of the stratum corneum while protecting deeper tissue layers.[6] Techniques used have included novel chemical enhancers, electroporation, cavitational ultrasound, microneedles, thermal ablation, and microdermabrasion.[9] These advanced methods are specifically relevant to macromolecule delivery; they are entirely excluded in first and second generation systems.[6] Third-generation

systems however, are usually more aggressive and a balance between effectiveness and safety must be acknowledged.

The advancements of transdermal systems have mainly worked to address the limitations of the skin. The greatest limitation is that the skin has poor permeability due to the structure of the stratum corneum layer of the skin.[10] Being able to effectively bypass this first layer is critical in expanding the applicability of transdermal drug delivery to larger molecules. While second and third generation systems have begun to address this, first-generation systems still prove to be the most clinically relevant systems. The complexity of second and third generation systems have introduced problems such as irritation and other safety concerns[10] which must first be overcome before their approval for widespread use.

For our project, we studied the advantages of using microcapsules for transdermal delivery. This method has attributes of both first and second generation systems. Drug-containing microcapsules are typically applied topically, like first generation systems, but the microcapsules are targeted to go into hair follicles, which allow the drug to bypass the stratum corneum layer. Unlike typical second generation systems, there is no chemical modification of permeability involved, and the stratum corneum also remains perfectly intact. Therefore, the use of microcapsules provides a method that causes less damage to the skin and also offers a vehicle for molecules too large to diffuse directly through the stratum corneum.

2.2 Design Objectives

The primary objective of our project was to provide a COMSOL model of transdermal drug delivery using drug-containing microcapsules. COMSOL Multiphysics is an engineering design software that uses finite element analysis to simulate heat, mass, and fluid transfers in physical systems. Our model was used to validate the effectiveness of microcapsules in comparison to the case with drug in non-particle form. Microcapsules would allow the transport the drug through a follicle and the release of the drug at deeper regions in the skin. Other objectives of our project were: 1) to determine the optimal initial concentrations and properties of drug-containing microcapsules needed to obtain a proper final drug dosage in the dermis skin layer; and 2) to verify the significance of follicles in transdermal drug delivery.

In COMSOL, we modeled three separate types of diffusion. The diffusion of microcapsules into a hair follicle was modeled using a patch-like applicator containing the initial amount of microcapsules. This applicator was placed above the follicle opening to mimic the diffusion of microcapsules located only in that specified area (disregarding microcapsules located in non-porous areas of the skin). Drug diffusion out of the microcapsules was modeled next, to follow the timed-release of the drug. A mass transfer governing equation was used, with diffusivity set to zero in each region of the skin, since this second diffusion was only used to track the change in concentration in the capsule over time. The last diffusion, the diffusion of drug into the skin layers, tracked the location of the drug after it left the microcapsule. These

three parts of our model satisfied the objective of obtaining a visual distribution of the drug in the epidermis and dermis skin layers.

Our design was meant to model a "general" transdermally delivered drug with properties based off of several sources of literature. Parameters, such as drug diffusivity in each of the skin layers or through the microcapsule shell, and initial conditions, such as drug concentration in the capsule or amount of microcapsules applied to the skin surface, can be varied to determine the behavior of a specific drug. However, much experimental data is needed as a validation step to accurately simulate the delivery of a specific drug, especially since the use of microcapsules is still novel to most drugs.

The stratum corneum, as well as the other skin layers, is mostly impermeable to microcapsules.[11] For our design, we assumed that drug-containing microcapsules do not enter the skin layers and only penetrate the skin through the hair follicles or pores. Also, microcapsules that enter the follicle do not all collect at the bottom.[11] For some, the hair strand/particles/oily medium within the follicle disrupts their path. Therefore, the mechanism of microcapsule transport was assumed to be diffusion driven by a concentration difference of microcapsules on skin surface and at the bottom of the pore, with an equal distribution along the length of the follicle at steady state. To further simplify our model, the release of drug was assumed to be consistent out of all microcapsules (same shell thickness, same release reaction) and the initial drug concentration within each microcapsule was constant.

2.3 Schematic

In order to solve this problem using COMSOL, we made a 2D axisymmetrical model of a hair follicle in skin, with a drug source containing microcapsules directly above the follicle (Figure 1). The hair follicle was modeled as a cylinder with radius 35μm. The geometry was further simplified by considering the skin layers to be flat and even. Within the drug source, there are $7.4*10^{14}$ microcapsules/m^3, each with an initial drug concentration of 100,000g/m^3 within its core. Each microcapsule has an inner radius of 300nm and an outer radius of 350nm (Figure 2). The governing equations, boundary conditions, initial conditions, and material properties can be found in Appendix A.

This design focused on the effect of a hair follicle used as a pathway for microcapsules to diffuse into the deeper skin layer. Therefore, the drug source box was designed directly above the hair follicle. Also, the size of the each region was confirmed with the literature sources to apply the realistic dimensions. Microcapsules leave the drug source and enter the follicle, but they cannot diffuse into the epidermis or dermis. Microcapsules release drug as they diffuse into the follicle, and the drug diffuses through the skin layers with different diffusivities, causing them to move more easily through the dermis than the epidermis.

This design was successfully used to demonstrate the drug diffusion occurring through the hair follicle. However, it had some limitations of having only one hair follicle and only a partial drug source designed above the skin layer.

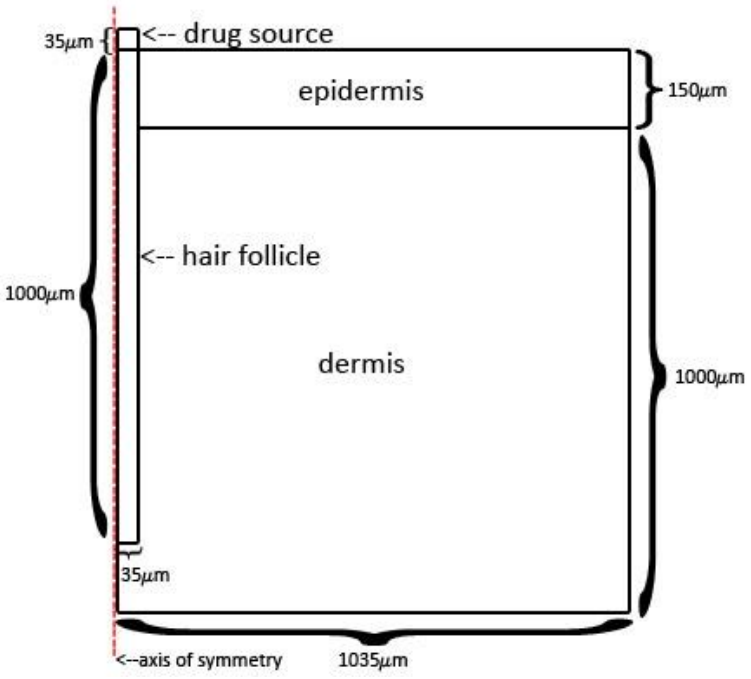


Figure 1: Schematic of skin and hair follicle showing the source containing drug-loaded microcapsules above the follicle. This model is 2D axisymmetrical.

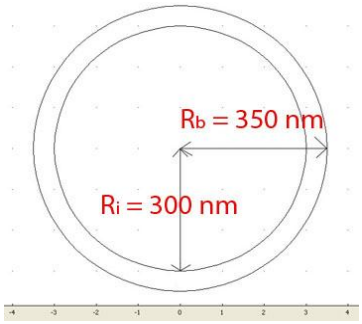


Figure 2: Dimensions of a typical microcapsule.

3. Results and Discussions

3.1 Solution and Qualitative Description

The COMSOL simulation of this project showed drug diffusion through the hair follicle, epidermis, and dermis, in a period of 4 hours. The surface plots of the concentration of both the microcapsules and drug in the skin layers showed that the microcapsules successfully aided in the distribution of the drug in the dermis layer.

The capsules were thoroughly spread out in the hair follicle but did not penetrate the skin layers, since we set the diffusivity of capsules in the skin at zero to follow our model conditions (Figure 3). The microcapsule concentrations at the lower right corner of the follicle showed that the concentration reached steady state after approximately 4000 seconds (Figure 4). In other words, the microcapsules were evenly spread throughout the follicle after 67 minutes of diffusion.

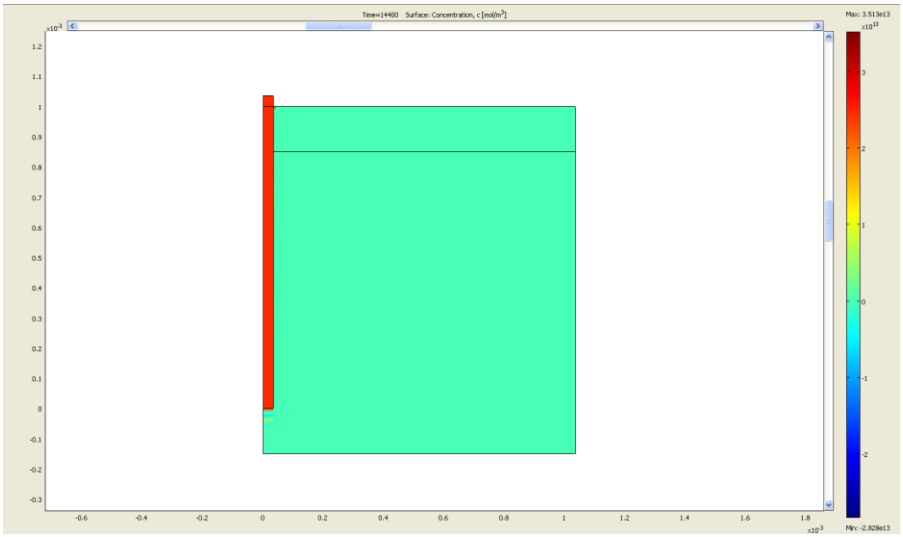


Figure 3: Surface plot of microcapsule concentration in the hair follicle region at time = 7,200 seconds = 2 hours. The capsules were thoroughly spread out in the hair follicle (red) but did not penetrate the skin layers (green).

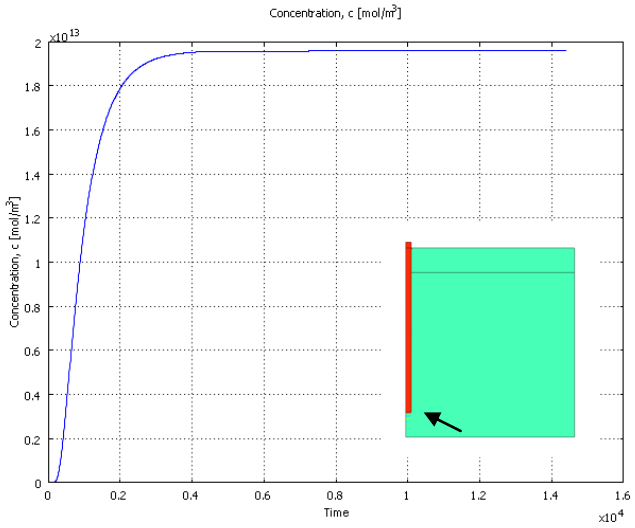


Figure 4: Microcapsule concentration at the lower right corner of the follicle, over a 4 hour period. The concentration reached steady state after approximately 4000 seconds.

The surface plot of the drug in the skin layers showed that the drug diffused more easily in the dermis layer than in the epidermis layer, which is consistent with the fact that the drug has higher diffusivity in the dermis than in the epidermis (Figure 5). The two surface plots (Figure 5 and 6) showed that more drug was concentrated around the hair follicle at two hours, and it diffused further out and away from the source of microcapsules and the hair follicle after four hours.

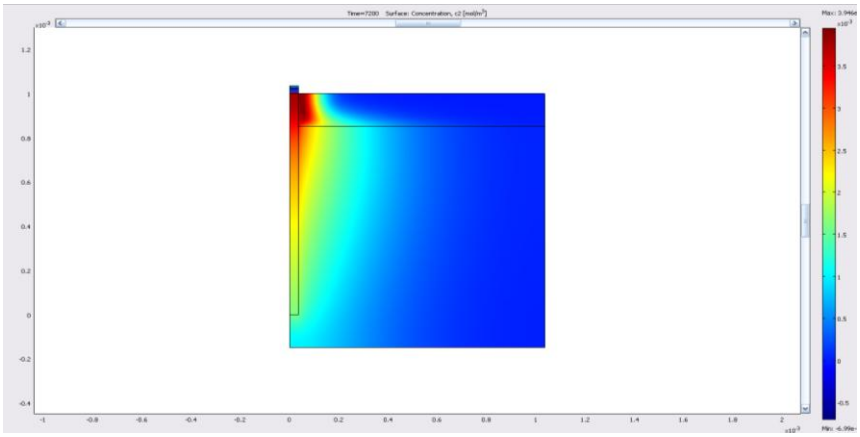


Figure 5: Surface plot of drug concentration in the skin layers after 2 hours. This concentration plot (red: high conc.,blue: zero conc) shows the movement of drugs diffusing into the dermis layer more than the epidermis layer via the hair follicle pathway. After 2 hours, the drug is still highly concentrated right belove the drug source box.

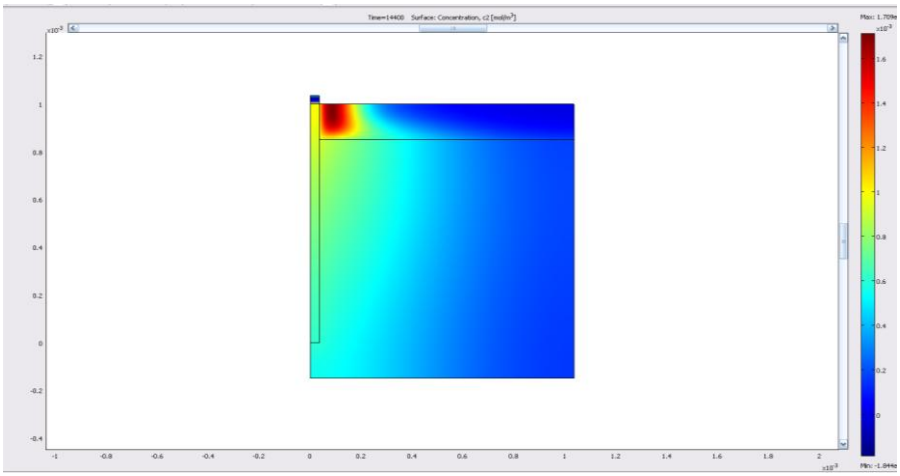


Figure 6: Surface plot of drug concentration in the skin layers after 4 hours. The concentration plot (red: high conc.,blue: zero conc.) shows that more drug is diffusing into the dermis layer to reach the steady state in the domain. After 4 hours, a small region next to the hair follicle in the epidermis layer becomes highly concentrated with drug (dark red), because the drug continuously flows out of the hair follicle, but does not diffuse further into the epidermis layer because of the low diffusivity.

In order to understand the process of drug diffusion out of the microcapsules and into the skin layers, we graphed the drug concentration at both the corner of hair follicle and the center of the dermis layer. Figure 7 shows that the concentration of drug near the hair follicle greatly increased within the first 2500 seconds and then started to decrease. This trend showed that once the drug was released from the microcapsules, it first accumulated by the follicle and then diffused into the skin layer. In both locations, the drug concentration slowly reached the steady state concentrations.

The concentration of the drug at the bottom of the follicle increased as the microcapsules moved down the pore and as more drug diffused out from the microcapsules. However, after a certain period of time, the concentration of the drug decreased, as it diffused into the dermis layer. The concentration of drug at the center of dermis region increased as more drug diffused out from the microcapsules and away from the follicle. Figure 7 shows that the concentration slowly increased at a point within the dermis layer, and will later reach a slight plateau. However, the amount of drug will eventually decrease as the drug diffuses deeper into the dermis skin layer (away from the follicle) or when the drug gets taken up into the bloodstream.

To examine the changes in the concentration of drug in the capsule, we plotted the concentration over time (Figure 8). The initial concentration of drug at the microcapsule core was 100 mg/ml. The graph shows that the drug concentration in the capsules fell below 25mg/mL after about 4,000 seconds. Therefore, approximately 75% of the drug in the capsule

diffused out after 67 minutes, the time at which it took diffusion of the microcapsules to reach steady state.

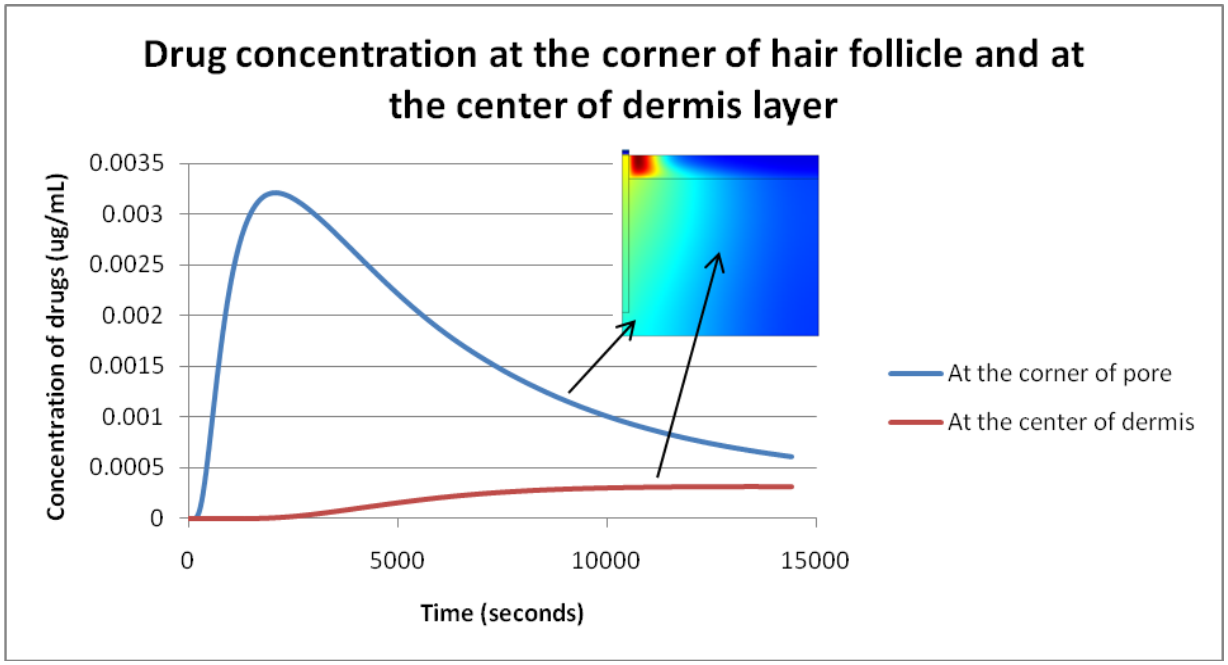


Figure 7: Drug concentration at the lower corner of hair follicle and at the center of dermis layer over a 4 hour period. The blue line shows how the drug accumulates near the hair follicle as it is released from the microcapsules, and the concentration decreases as it diffuses into the skin layer. The red line shows how the drug concentration in the center of dermis layer slowly reaches the steady state over time.

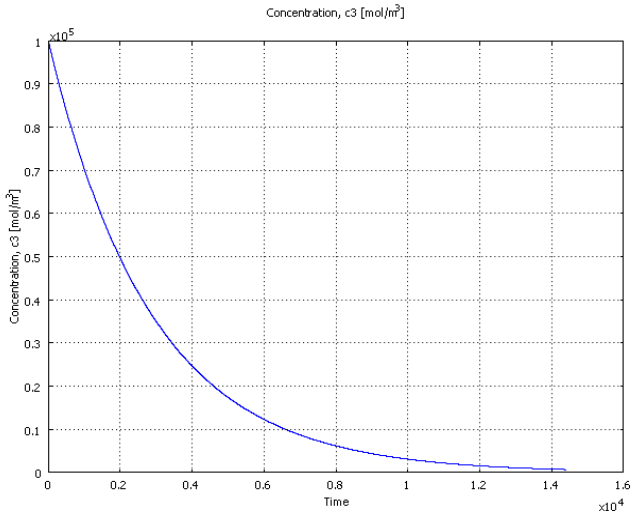
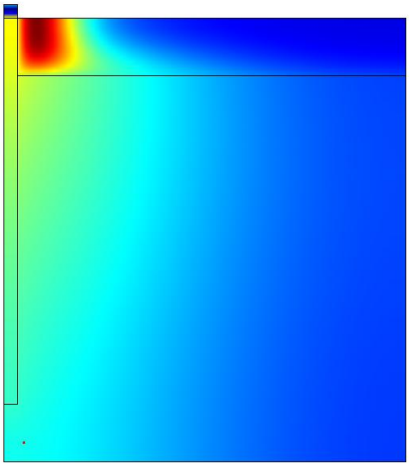


Figure 8: Drug concentration in the microcapsule analyzed over a 4 hour period. This graph shows that about 70% of the drug diffuses out of the microcapsules after one hour.

3.2 Validation of the Design

In order to validate the benefit that microcapsules provide for transdermal drug delivery in porous skin areas, we compared our original design with the microcapsule source placed directly above the hair follicle to a design where the microcapsule source was placed above the epidermis. A point in the dermis layer below the follicle was chosen to compare the concentration change in the skin. As shown in Figure 9 and Figure 10, when the microcapsules were placed above the hair follicle, the drug diffused significantly more into the dermis layer after 4 hours than when the microcapsules were placed above the epidermis. The drug barely diffused into the epidermis layer when the capsules were placed above the skin surface.

Figure 11 depicts the concentration profile over time at a chosen point in the dermis skin layer. It shows a significantly lower drug concentration when the capsules are placed above the skin surface rather than directly above the follicle opening. The drug concentration range varied from 0.0015ug/mL to 0.0006ug/mL for the original design, whereas the concentration barely reached 0.0001ug/mL for the new design. This validates that the use of microcapsules for transdermal drug delivery in porous skin areas helps to achieve a higher concentration of drug in the dermis layer, along with a quicker diffusion of drug into deeper skin layers.



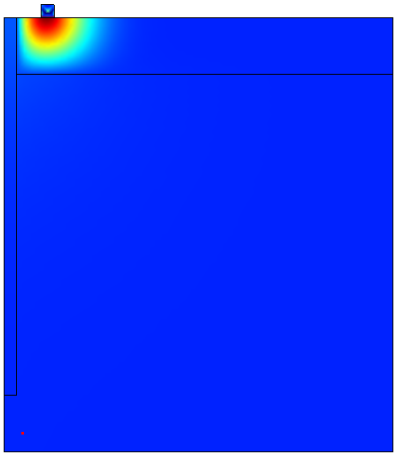


Figure 9: Surface plot of drug concentration in the skin layers analyzed over a 4 hour period, when the capsules are diffusing into the hair follicle. (left)

Figure 10: Surface plot of drug concentration in the skin layers analyzed over a 4 hour period, when the capsules are placed on the non-porous skin surface. (right)

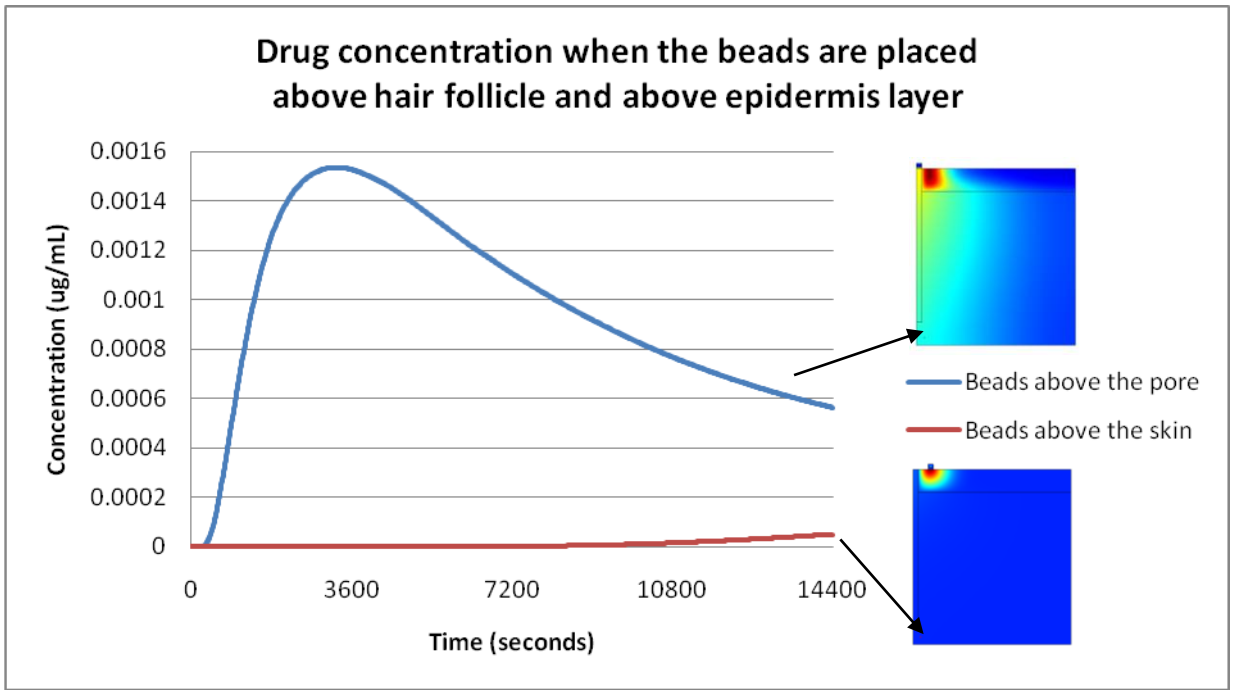


Figure 11: Drug concentration at a point below the follicle analyzed over 4 hour period for (a) when the capsules are diffusing into the follicle (b) when the microcapsules are placed on the non-porous skin surface.

3.3 Accuracy Check

An accuracy check of our design was conducted by comparing our results with results from related literature. In a pharmaceutical research article studying the follicular penetration of the drug adapalene from microcapsules,[1] it was found that follicular penetration was related to the length of application time, which supports the increasing follicular concentration of microcapsules as a function of time in our model. As mentioned before, the capsules reached steady state and were evenly distributed in the follicle after 4000 seconds, which is about 67 minutes (Figure 4).

In the same study, it was also shown that approximately 70% of adapalene diffused out of the microspheres in two hours. In our model, 70% of the drug diffused out in about one hour (Figure 8). Although there is a difference of an hour, this time value is dependent on the drug diffusivity out of the microcapsule shell. Our model had a faster release rate, which would be appropriate for a drug that does not need to be released at high dosage at deeper skin layers. Our drug was released from the microcapsule quicker and at shallower skin layers as compared to the adapalene study.

For our model, we began with 100mg/mL as the initial concentration of drug in the microcapsules. The drug in the skin layer reached steady-state concentration at 0.0005 ug/mL

after approximately 4 hours of diffusion (Figure 7). This range is lower than the recommended amount of epinephrine in skin, which is 1 ug/mL.[2] Once again, the effective concentration of the drug in the skin would vary with different drugs and different initial conditions. Our model appears to be most appropriate for a drug that requires a fast release rate but works in low dosages.

Considering the limitations of our model, this measure of final concentration could be made more accurate by adding realistic complexities of the skin to our simplified design. Also, the skin contains many hair follicles and pores that would allow drug to efficiently diffuse into deeper skin layers. In our model, we only looked at microcapsules entering through a single hair follicle. Considering that the drug concentration near the end of hair follicle reached a peak concentration of 0.0033ug/mL and then slowly decreased to 0.0005ug/mL as more drug diffused into skin layers, the steady state drug concentration would likely be higher in a region with multiple hair follicles.

For simplification purposes, we applied the microcapsules solely on top of the hair follicle. In a more realistic situation however, the drug will likely be applied throughout the skin surface rather than just over the hair follicles. A slight modification to our original design was done to test how having a thin layer of drug over the entire skin surface (in addition to direct application above the follicle opening) would affect the drug concentration in the deeper skin layers. This design resulted in an average concentration of 0.015ug/mL, a larger concentration value that more closely resembles the recommended concentration of epinephrine in skin (Figure 12, Figure 13). It is important to note however, that this model assumes that the drug in question is permeable to the stratum corneum. There would not be a difference in the concentration found in the skin if the drug was completely impermeable through the stratum corneum. In this case, the use of microcapsules as vehicles to bypass the stratum corneum becomes all the more important for effective drug delivery.

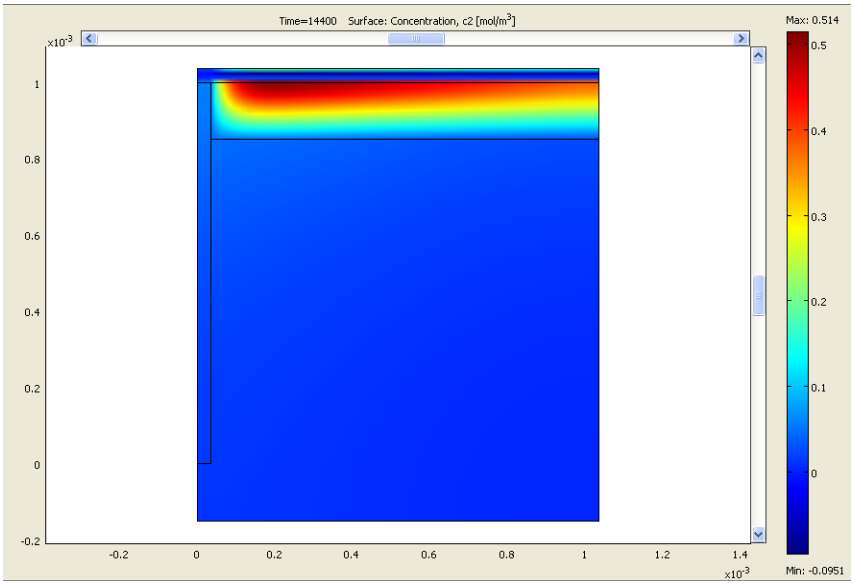


Figure 12: Surface plot of drug concentration with the thin drug layer over the skin surface, analyzed over a 4 hour period. A slight modification of having a thin layer of drug in the design resulted in an average concentration of 0.015ug/mL, significantly larger than that of the original design, which was 0.0005ug/mL.

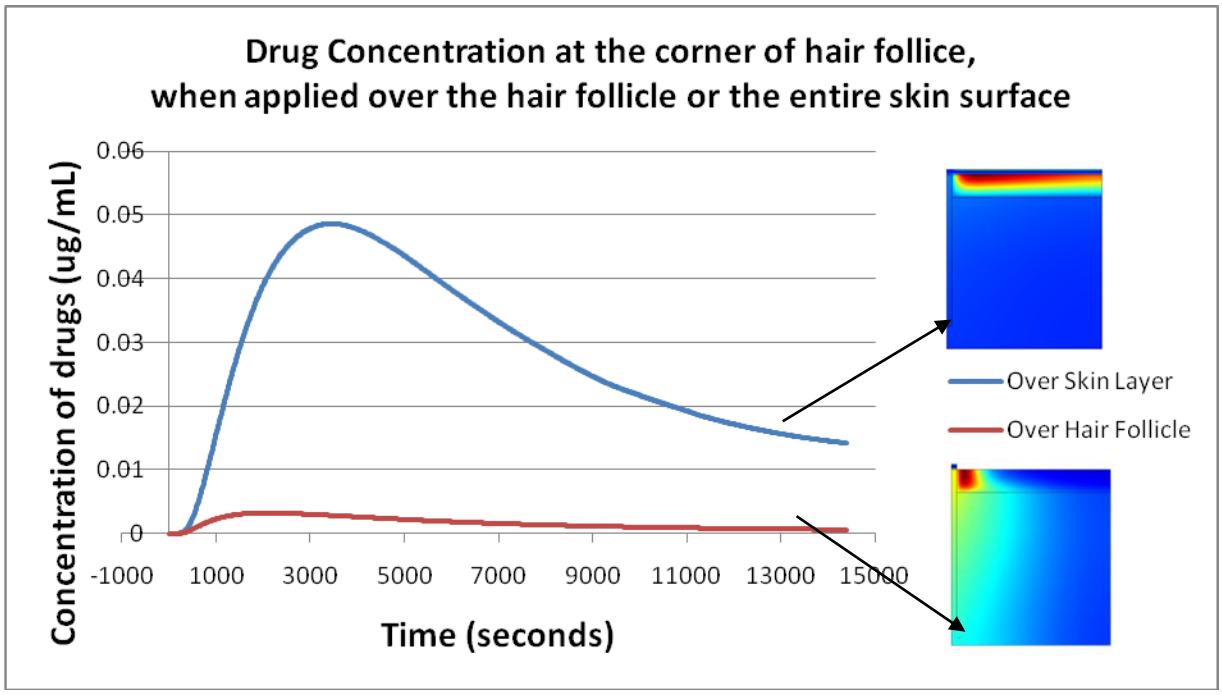


Figure 13: Drug concentration for the two scenarios: (1) when microcapsules are only placed directly over the hair follicle (as a small drop) and, (2) when microcapsules are placed over the entire skin surface (as a thin layer).

3.4 Sensitivity Analysis

Since our design objective was to model the behavior of a "general" transdermally delivered drug, the parameters used for our COMSOL simulation were estimates of values found in related literature. Sensitivity analyses were done on drug and microcapsule properties to determine how the final result, calculated as the total amount of drug delivered to the different skin layers after 4 hours, would change in response to varying parameters and initial concentrations. These sensitivity analyses are essential in identifying the inputs that contribute the most variability and potential error, while also serving as a reference for future researchers who wish to implement our design experimentally with a chosen drug of interest.

For our simulation, using the input parameters shown in Appendix A, we obtained $9.74*10^{-13}$ grams of drug in the dermis skin layer, and $1.06* 10^{-12}$ grams of drug in the epidermis and dermis skin layers combined, after 4 hours of microcapsule application. These values were obtained using a subdomain integration for drug concentration at 4 hours (14400 seconds) for the specified skin layers, and are shown in Figure 14 as the two gray dotted lines. Our values chosen for the diffusivity of drug through the follicle, 2.5e-10 m^2/s, and the diffusivity of microcapsules through the follicle, 2.2e-10 m^2/s, were good estimates. Although these parameters were not found in literature and were approximations, the sensitivity analyses show that the total amount of drug in the dermis starts to plateau at those values. The red and blue plots in Figure 14 show that there is no significant change in the total amount of drug with diffusivity values above $1.0*10^{-10}$ m^2/s, but the total amount exponentially decreases below $1.0*10^{-10}$ m^2/s.

A second sensitivity analysis showed the total amount of drug in the dermis after 4 hours is very sensitive to drug diffusivity through the epidermis. When the drug diffusivity through the epidermis was increased, the drug concentration in the dermis layer decreased, most likely due to an accumulation of drug in the epidermis layer and less distribution to the lower dermis layer. As shown in Figure 14 as the green plot, our value of $3.30*10^{-13}$ m^2/s is found in a region where the drug amount constantly changes with changes of this diffusivity parameter.

Similarly, our value of $1.20*10^{-11}$ m^2/s for drug diffusivity through the dermis skin layer also lies in a varying region; an increase in drug diffusivity through the dermis layer produced a decreasing drug amount in the epidermis and dermis layers as shown in Figure 14 as the purple plot. However, this trend is not as significant as the trend for drug through epidermis. A drug with better diffusivity values through the dermis are more easily distributed to the skin.

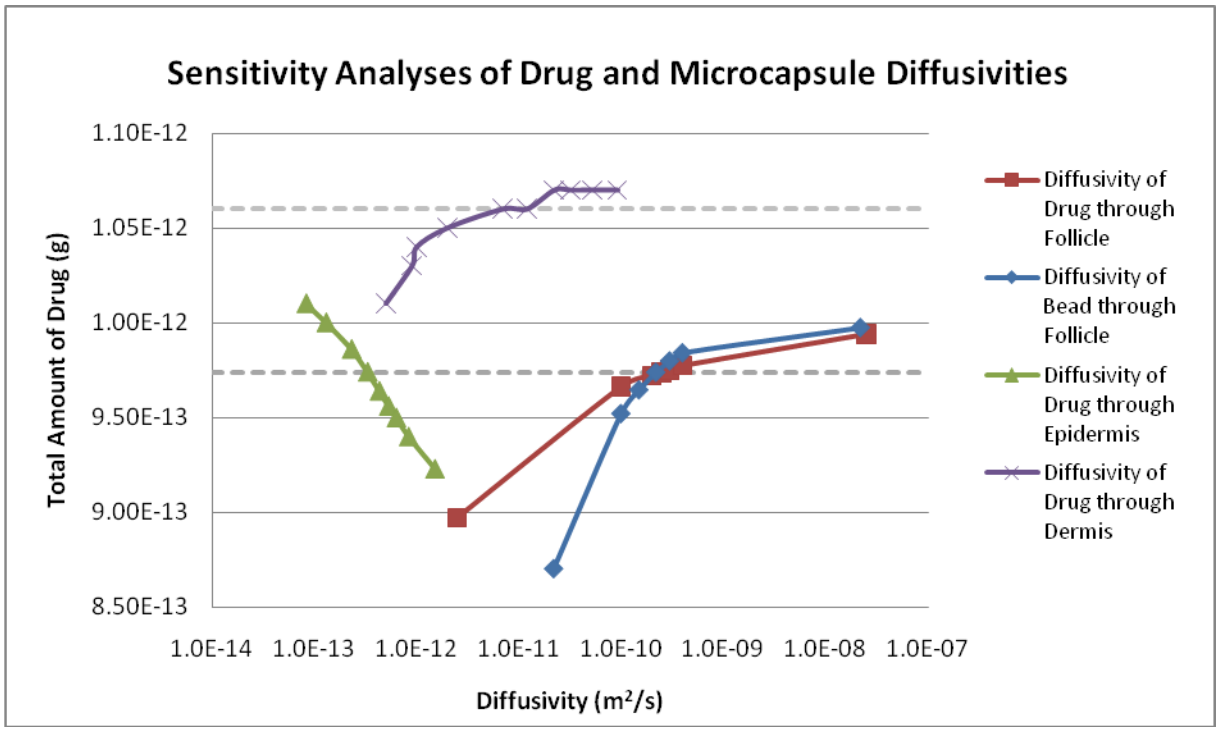


Figure 14: Sensitivity analysis for four diffusivity parameters: (1) drug diffusivity through follicle, (2) microcapsule diffusivity through follicle, (3) drug diffusivity through epidermis, (4) drug diffusivity through dermis. For (1)-(3), the total amount of drug in the dermis layer was used for analysis. The green line (3) shows the reduction in the total amount of drug in the dermis layer, since diffusivity of drug through the epidermis layer is increasing, causing more drug to diffuse into the epidermis and less into the dermis. For (4), the total amount of drug in both the epidermis and dermis layers was used for analysis. The two dotted gray horizontal lines indicate the values we obtained for total amount of drug in dermis layer (lower gray line) and total amount of drug in epidermis and dermis layers (upper gray line).

The sensitivity analysis conducted for initial concentration of drug within a microcapsule shows that the amount of drug in the dermis layer after 4 hours increases linearly with an increase in this initial condition (Figure 15). The results of this analysis can be useful for researchers hoping to obtain a specific dosage of drug in the dermis layer after a specific application time.

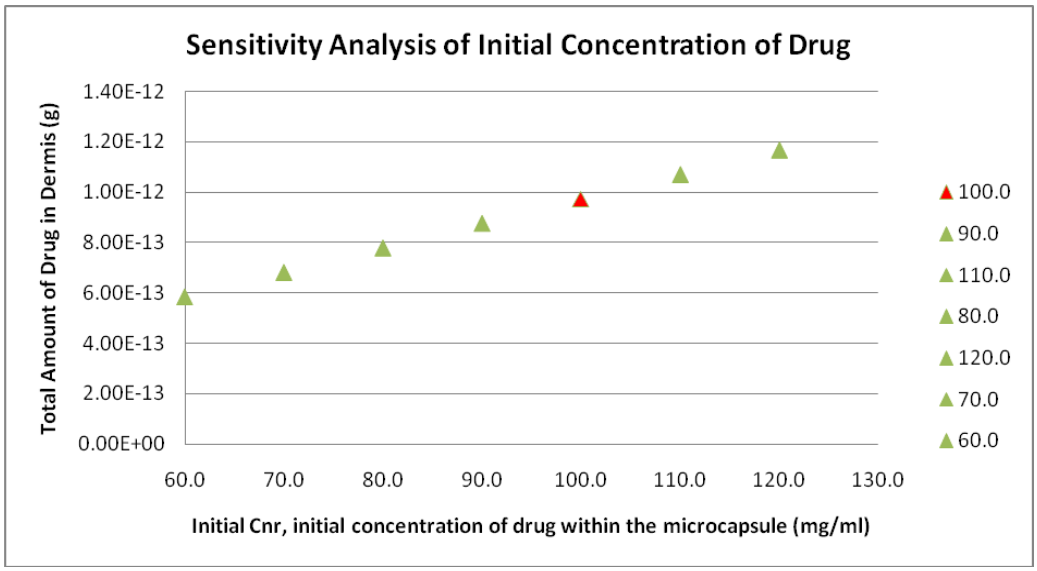


Figure 15: Sensitivity analysis for the initial concentration of drug within the microcapsule, using total amount of drug in the dermis layer for analysis. The value we used in our design is in orange.

In the sensitivity analysis done for drug diffusivity out of the microcapsule, Figure 16 shows that our value of $1.50*10^{-18}$ m^2/s (obtained from literature[11]) is the optimal value. This diffusivity value incorporates properties of the microcapsule shell and its interaction with the contained drug and is responsible for the "timed-release" of the drug. With this optimal value, microcapsules were best able to keep the drug contained until they bypassed the epidermis skin layer, thereby releasing most of the drug in deeper regions of the skin and obtaining the greatest amount of drug in the dermis layer at 4 hours after microcapsule application.

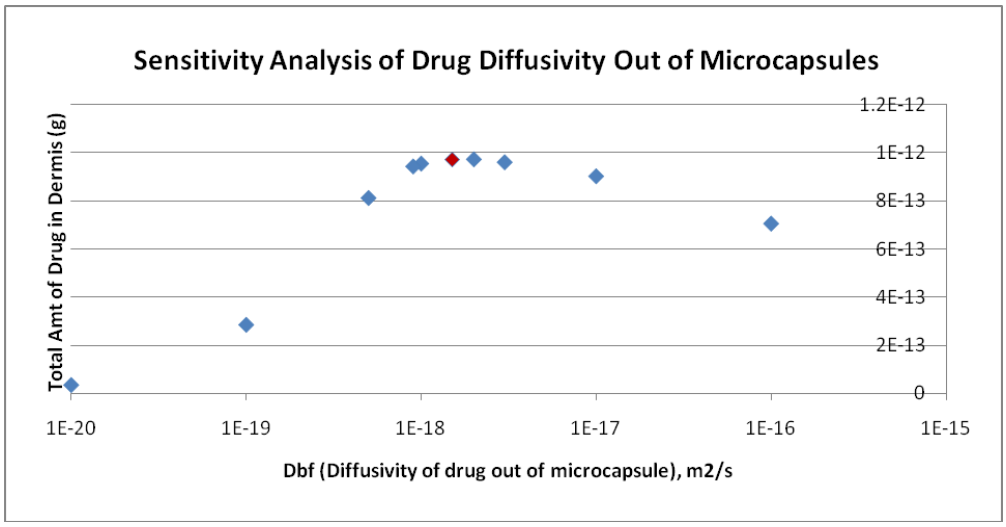


Figure 16: Sensitivity analysis for drug diffusivity through the microcapsule shell, using the total amount of drug in the dermis layer for analysis. The value we used in our design is in red.

4. Conclusion

4.1 Goals

Our goal in this project was to test the effectiveness of using microcapsules for transdermal drug delivery. One of the major challenges in the current state of research that we addressed was the problem of getting a drug past the stratum corneum layer of the skin. We also aimed to determine the relationship of initial drug concentration and skin layer properties with the final steady-state drug concentration in the dermis. In summary, this project aimed to verify the significant role of hair follicles in drug delivery.

In our model, we studied the diffusion of drug-loaded microcapsules in a single hair follicle. To verify that drug diffusion into the skin is, in fact, more efficient via the follicular pathway utilized by the microcapsules, we ran a problem in COMSOL with the microcapsule source placed on the skin surface (Figure 10). From this experiment, we were able to confirm that drugs are able to diffuse faster into the skin with the use of microcapsules in hair follicles. We can therefore conclude that hair follicles, in combination with microcapsules used as vehicles, play a significant role in efficient drug delivery. This is, therefore, an effective method for bypassing the highly impermeable stratum corneum layer.

We also examined the relationship between the initial drug concentration in the microcapsules, and the skin layer diffusivity properties, on the final drug dosage achieved in the dermis, through a series of sensitivity analyses. Changes in the diffusivity properties of the skin layers greatly affected the final drug concentration in the skin. We found that increasing the diffusivity values of the dermis and follicle led to higher final concentrations, which was expected. We learned, however, that this was not the case for increasing the diffusivity of the epidermis, where we found a decrease in the final drug concentration. When the initial concentration of drug in the microcapsule was varied, we found that the final concentration in the skin was directly correlated to the initial concentration in the microcapsule. These relationships would be very useful for optimizing drug concentration values for a specific drug.

4.2 Improving the Design

Our model provided a simple but comprehensive understanding of drug diffusion through microcapsules and hair follicles. In order to obtain a more accurate solution however, the many simplifications in our design could be adjusted and the realistic complexities of actual skin could also be added. While we only studied diffusion through one hair follicle, studying several hair follicles in a representative region of the skin could lead to changes in the final drug dosage achieved in the skin. We also modeled the hair follicle, epidermal layer, the dermal layer and the stratum corneum (as a boundary condition), as straight blocks. Real skin contains many sub-layers within the epidermis and dermis and has more curvatures in structure. Different sub-layers are likely to vary in diffusivity. Skin also contains other components such as pores, sweat

ducts, glands, nerves, blood vessels, muscles, and fat tissue which could all affect the diffusion of drug throughout the skin.

Lastly, our model assumed that the size of drug molecule is small enough to diffuse into the epidermis layer, but big enough to have some difficulties when diffusing all the way to the dermis layer. This is important to note when comparing topical drug application and microcapsule application because some drug molecules are physically too large to pass through the skin layers at all. Although we specified the boundary condition representing the stratum corneum as zero flux, we still had some diffusion of drug occur which would only be relevant to cases where the drug particles were somewhat permeable to the stratum corneum. If we could specify a drug particle size, our solution could reflect situations that would occur depending on the drug size.

Despite the many simplifications of our model, we were still able to simulate and draw important conclusions of the transport of drug through the skin in this microcapsule transdermal system.

4.3 Difficulties

During the course of our project, we faced several difficulties in achieving our goals. The first challenge was in capturing the complex diffusion processes occurring in real skin in our design. Our problem was unique because it involved two separate diffusion processes, the first being the diffusion of microcapsules into the follicles and the second being the simultaneous diffusion of drug out of the microcapsules. With the help of our professor and teaching assistants, we were able to derive suitable governing equations to model these two diffusion processes. In COMSOL, we actually used three diffusion equations, where the last equation kept track of the drug concentration changes inside the microcapsules.

Another difficulty we faced was finding realistic property values. Since this was a problem we anticipated, we researched many different diffusivity values reflecting behaviors of many different drugs. Due to the varying amount of information available for different drugs, we decided not to choose a specific drug and went forward with values that appeared most common and reasonable for a general drug model. This however, led to other minor problems which were discovered during our accuracy check and validation. We found that our design conditions led to a slightly high release rate of the drug and a low final drug concentration in the skin. This indicated that our model would best reflect the behavior of a potent drug requiring a fast release rate and a low dosage in skin.

4.4 Realistic Constraints and Design Recommendations

Aside from the limitations in our model resulting from simplifications in the design, we must also consider other realistic constraints such as manufacturability, ethical, and health and safety issues. In terms of manufacturability, there are currently many transdermal systems in the form of patches available to the public.[6] Given the efficiency of drug delivery that transdermal systems offer, they would be more cost effective to manufacture, since drug would not be wasted as much as in other delivery methods. The ease of application of the drug would also contribute to the feasibility of producing transdermal systems, since medical professionals would not be needed. Ethical concerns in transdermal drug delivery systems could arise if animal testing is used. Established ethical practices will need to be carefully applied to this system in order to ensure that codes are not violated.

Lastly, health and safety concerns are the most important constraints in transdermal drug delivery research. Aside from tightly controlling the drug release rates, the best way to monitor safe administration of the drug would be education of proper use. For example, if certain external or internal conditions may alter drug release rates, it is important for manufacturers to address these warnings. In this way, responsibilities must be balanced between the manufacturer and user. Our model did not have significant realistic constraints, which additionally makes transdermal drug delivery systems a favorable method for drug delivery.

This design is recommended for those who are interested in studying the microcapsule drug delivery system for the practical use. Since this project was designed to study the delivery of any "general" drug, when the design is used for one specific drug, the new sets of parameters (especially diffusivities) must be accurately chosen for the drug of interest to obtain satisfying results for analysis. This model simulation would be very useful for obtaining a target final drug dosage in skin layers. However, one must be aware that there are limitations to our design and this could be improved by adding necessary variations into the design. The size and location of drug source box or the number of hair follicles in the design can be changed to apply the model to the real situations and obtain accurate results. The number of follicles can be considered based on the application location of the drug. It is also recommended to avoid the use of this model, and any transdermal drug delivery system, for open wounds or mucosal linings.

5. Appendix A: Mathematical statement of the problem

Governing Equations

Diffusion of microcapsules - mass species equation with transient and diffusion terms:

$$\frac{\partial C_b}{\partial t} = D_b \frac{\partial^2 C_b}{\partial x^2}$$

Diffusion of drugs – mass species equation with transient and diffusion terms, with an added "generation" term that actually represents drug leaving the microcapsule core:

$$\frac{\partial C_d}{\partial t} = D_d \frac{\partial^2 C_d}{\partial x^2} + \frac{C_{NR} - C_d}{\frac{r_b - r_i}{4\pi r_i r_D D_d}} \cdot C_b$$

Equation for drug concentration in the core – mass species equation with transient term, with an added "generation" term that actually represents drug in the microcapsule core.

$$-\frac{4}{3}\pi r_i^3 \frac{\partial C_{NR}}{\partial t} = \frac{C_{NR} - C_d}{\frac{r_b - r_i}{4\pi r_i r_D D_d}}$$

Variables:

C_b= number of microcapsules / cm^3
D_b= diffusivity of microcapsules
C_d= concentration of drug
D_d= diffusivity of drug in skin layers
C_{NR}= concentration of drug in the core of microcapsule
r_D= radius of microcapsule outside
r_i= radius of microcapsule inside

Boundary Conditions

All interior boundaries were considered continuities for both the diffusion of microcapsules and the diffusion of drug. However, material property differences account for changes in diffusivity from region to region. All exterior boundaries were considered to have the condition flux = 0, as they were either far from the source or interfacing with air.

Initial Conditions

The initial concentration of microcapsules ($C_{b,0}$) in the drug source was calculated based on the outer radius of the microcapsule, and assuming close packing of the microcapsules, as $7.4*10^{14}$

microcapsules/m^3. The initial concentration of the drug in the core of the microcapsules ($C_{NR,0}$) was determined based on common drug concentrations. Many topical drugs claim to have a 0.01% mass/volume drug formulation. If the microcapsule formulation were to be equivalent, the same mass of drug would be present, but it all would be contained in the microcapsule cores, which is a much smaller volume. A basic mass balance was done, to find an initial concentration in the core, of 100,000g/m^3.

Input parameters

The following input parameters are listed with the reference that was used to decide on the parameter. The full references can be found at the end of this document.

Table 1: Diffusivity, Microcapsule Sizes and Its Sources

Constant	**Value**	**Reference**
Diffusivity, drug in microcapsule shell	$1.5 * 10^{-18} m^2/s$	Yow 2009
Diffusivity, drug in epidermis	$3.3* 10^{-13} m^2/s$	Dalby 2001
Diffusivity, drug in dermis	$1.2* 10^{-11} m^2/s$	Filer 1994
Diffusivity, drug in hair follicle	$2.5*10^{-10} m^2/s$	Frum 2007
Diffusivity, microcapsules in hair follicle	$2.2*10^{-10} m^2/s$	Sonavane 2008
Diffusivity, microcapsules in skin	$0\ m^2/s$	Assumption
Microcapsule outer radius	350 nm	Yow 2009
Microcapsule innter radius	300 nm	Yow 2009

6. Appendix B: Solution Strategy

Solver

We solved our problem with COMSOL using the direct finite element method because our schematic was simple enough to not require the use of an iterative method.

Time Stepping

We used a constant time step of 10 seconds, for a period of four hours, or 14,400 seconds. This was a sufficient amount of time for most of the drug to leave the microcapsules and to diffuse throughout the dermis.

Tolerance

We used COMSOL's default values of 0.01 for relative tolerance and 0.0010 for the absolute tolerance.

Mesh / Mesh Convergence

For mesh convergence, we used mapped mesh for our computational domain. After reaching 800 mesh elements, the average concentration of drug in the dermis layer converges to $2.92*10^{-4}$ g/m^3. For mesh convergence, we used mapped mesh for our computational domain. The graph shows that after reaching 800 mesh elements the average concentration of drugs in the dermis layer converges to $2.92*10^{-4} g/m^3$(Figure 17 and Table 2). We decided to use 812 mesh elements of mapped mesh for our computation.

Table 2: The number of elements and average concentration of drug in dermis after 4 hours

Number of elements	Total amount of drug in dermis [grams]	Average concentration of drug in dermis [grams/m3]
72	1.53E-12	4.55E-04
255	1.11E-12	3.30E-04
420	1.03E-12	3.05E-04
812	9.80E-13	2.92E-04
2650	9.81E-13	2.92E-04

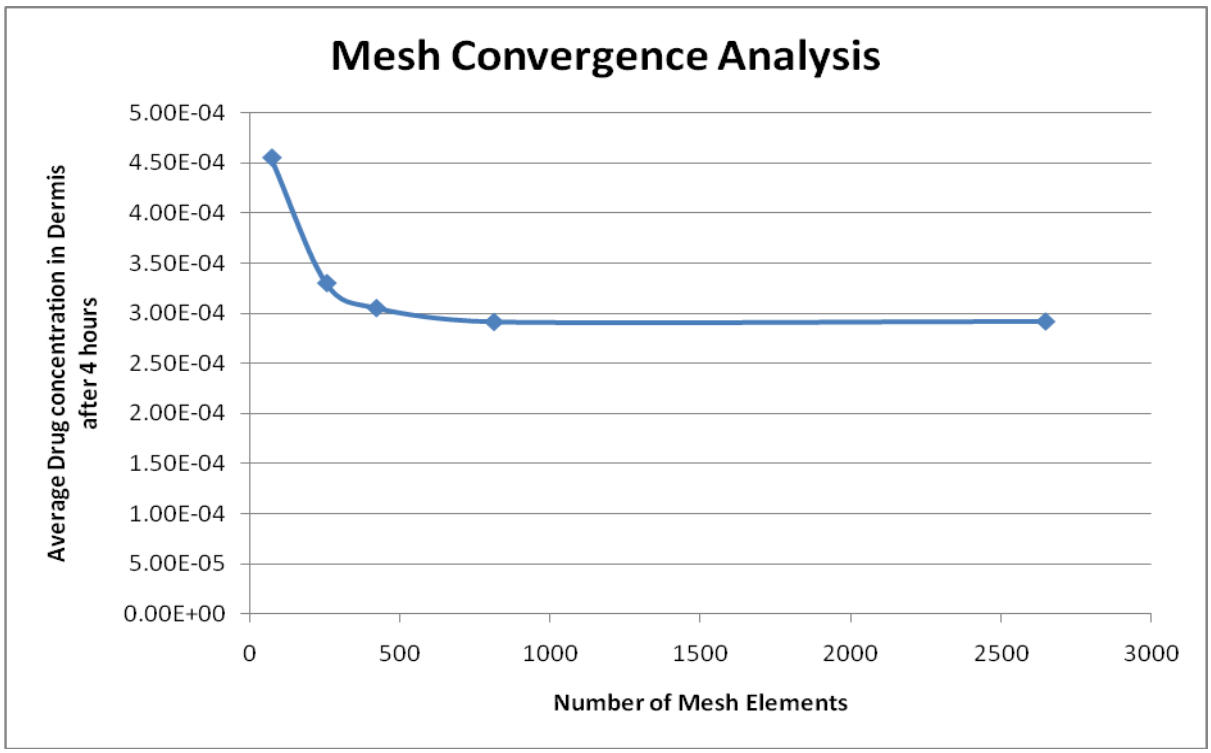


Figure 17: The mesh convergence analysis on the concentration of drug in the dermis region vs. number of mesh elements.

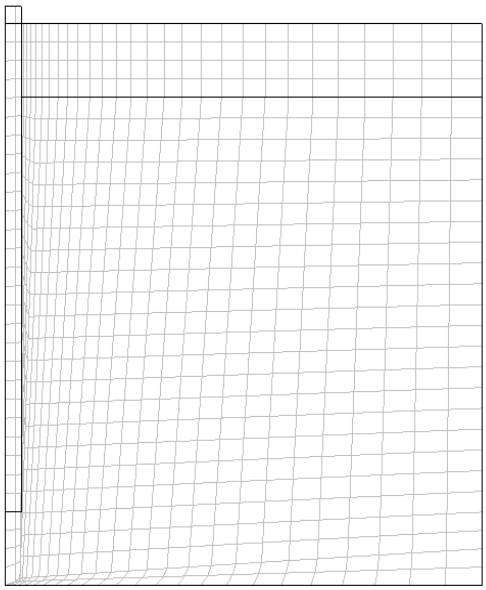


Figure 18: The final mapped mesh of the computational domain with 812 mesh elements

7. Appendix C

References

1. Rolland A, Wagner N, Chatelus A, Shroot B, Schaefer H. Site-specific drug delivery to pilosebaceous structures using polymeric microspheres. *Pharmaceutical Research*. 1993; 10(12): 1738-1744.

2. Newton D, McLeod G, Khan F, Belch J. The effect of adjuvant epinephrine concentration on the vasoactivity of the local anesthetics bupivacaine and levobupivacaine in human skin. *Regional Anesthesia and Pain Medicine*. 2004;29(4):307-311.

3. Hadgraft J, Guy RH, Eds. *Transdermal Drug Delivery: Developmental Issues and Research Initiatives*; Marcel Dekker: New York, 1989.

4. Smith EW, Maibach HI, Eds. *Percutaneous Penetration Enhancers*; CRC Press: Boca Raton, FL, 1995.

5. Amsden BG, Goosen MFA. Transdermal delivery of peptide and protein drugs: an overview. *AIChE Journal*. 1995; 41: 1972-1997.

6. Prausnitz MR, Langer R. Transdermal drug delivery. *Nature biotechnology.*2008; 26(11): 1261-1268.

7. Miller MA, Pisani E. The cost of unsafe injections. *Bull. World Health Organ*. 1999; 77: 808–811.

8. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. *European Journal of Pharmaceutical Sciences.* 2001; 14: 101–114.

9. Arora A, Prausnitz MR, Mitragotri S. Micro-scale devices for transdermal drug delivery. *Int. J. Pharm*. 2008; 364(2): 227-236.

10. Henry S, McAllister DV, Allen MG, Prausnitz MR. Microfabricated microneedles: a novel approach to transdermal drug delivery. *Journal of Pharmaceutical Sciences.* 1998; 87(8): 922-925.

11. Yow HN, Wu X, Routh AF, Guy RH. Dye diffusion from microcapsules with different shell thickness into mammalian skin. *European Journal of Pharmaceutics and Biopharmaceutics*. 2009; 72: 62-68.

12.Dalby, Richard. Dec. 10, 2001. Transdermal Drug Delivery. School of Pharmacy, University of Maryland, Baltimore. Accessed on March 16, 2005: http://www.pharmacy.umaryland.edu/faculty/rdalby/Teaching%20Web%20Pages/Transdermal%20Drug%20Delivery.pdf

13. Filer CW, Allen GD, Brown TA, et al. Metabolic and pharmacokinetic studies following oral administration of 14C-famciclovir to healthy subjects. *Xenobiotica*. 1994**;** 24(4):357-68.

14. Frum Y, Bonner MC, Eccleston GM, Meidan VM. The influence of drug partition coefficient on follicular penetration : In vitro human skin studies. *European Journal of Pharmaceutical Sciences.* 2007; 30: 280-287.

15. Sonavane G, Tomoda K, Sano A, Ohshima H, Terada H, Makino K. *In vitro* permeation of gold nanoparticles through rat skin and rat intestine: Effect of particle size. *Colloids and Surfaces B: Biointerfaces*. 2008; 65: 1-10.