Use of Microneedle Arrays for the Treatment of Second Degree Burns

BEE 4530 – Computer Aided Engineering: Applications to Biomedical Systems

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1. Executive Summary

Although a hypodermic needle inserted through the stratum corneum, the uppermost layer of skin, and into the tissue can deliver drugs effectively, it can lead to infection and be very painful. Transdermal drug delivery mediated by various microneedle technologies is a less painful method of drug delivery that also limits infection. Also, as with hypodermic needles, the microneedles successfully bypass the thick stratum corneum which is a limiting factor in transdermal drug delivery. One application of this technology is the delivery of pain medication to the skin of burn victims. A drug patch containing ibuprofen can be placed over an array of microneedles inserted into the patient's damaged skin. In this study, the drug concentration in the burn victim's dermis over time was modeled using COMSOL software. The effects of initial drug concentration in the patch and spacing between needles of the microarray were examined to develop an optimized model of drug delivery through second degree burns. Initially, a two dimensional model of a single microneedle inserted into the dermis was used to test assumptions made about drug diffusion through burnt skin. A three dimensional model was then constructed to examine the effects of microneedle spacing on the drug concentration profile. To determine the optimal setup, the average drug concentration in the burnt skin was measured while varying initial ibuprofen concentration in the patch and microneedle spacing. The results showed that the patch should contain a 0.4 mol/m^3 concentration for a two hour application with 100 micrometer spacing. The optimal microneedle spacing was found to be a nearly linear function of the patch drug concentration the manufacturer aims to use.

Key words: microneedles, diffusion, second degree burns, ibuprofen

2. Introduction

Hypodermic needles are currently the standard method of delivering medication transdermally. However, because the use of hypodermic needles can be painful and introduce infection, alternate modes of drug delivery have been developed. Drug patches are a painless alternative to hypodermic needles, but their drug delivery can be significantly limited by the stratum corneum, the upper layer of the skin. Microneedle arrays can be used in conjunction with drug patches to enhance drug delivery while also limiting a patient's risk of infection and discomfort. One application of this technology is the delivery of pain medication, like ibuprofen, to the skin of burn victims. To administer the ibuprofen to the burnt skin, an array of microneedles is inserted into the patient's skin and a drug patch is placed on top (Figure 1). The ibuprofen diffuses through the hollow microneedles and into the skin, which allows the drug to reach the burnt skin more quickly than with a drug patch alone. In order for ibuprofen to be an effective analgesic, its concentration in the dermis must be at least 30 mg/kg of body mass, which is the recommended dose for an adult. The concentration in the dermis, however, must remain under 100 mg/kg of body mass, which is the concentration at which ibuprofen becomes harmful [1]. Therefore, the initial ibuprofen concentration in the drug patch and the spacing of the microneedles in the array must be chosen to maintain an effective but harmless concentration of drug in the skin. This report presents a computer model of ibuprofen diffusion through a microneedle array that can be used to determine optimized microneedle spacing and initial drug patch concentration for delivery of ibuprofen to the dermis of a burn victim.

3. Design Objectives

We planned to use COMSOL to model the use of microneedles and drug patches for the treatment of second degree burns. The main objective of our model was to allow us to optimize the microneedle spacing in an array and the ibuprofen concentration of the patch. The following two dimensional (Figure 1) and three dimensional (Figure 2) models were used to achieve these goals.

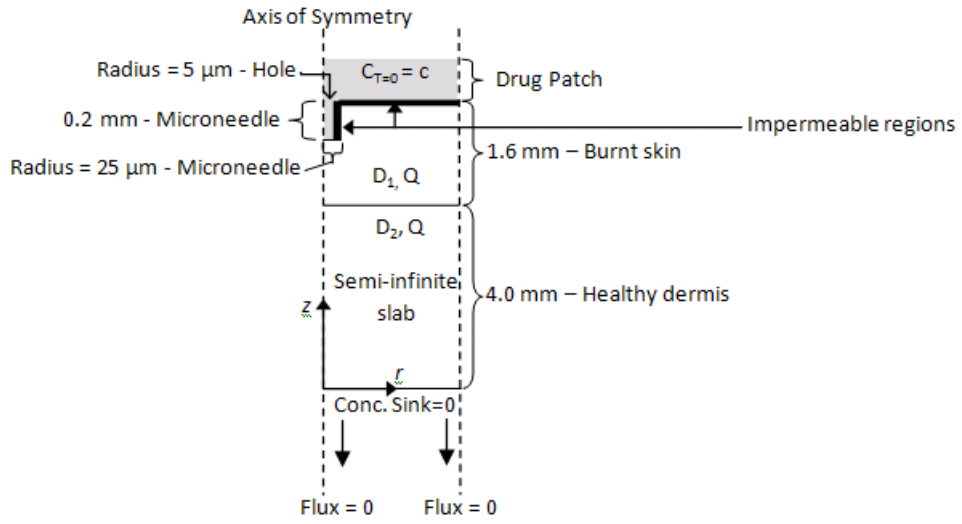


Figure 1- Schematic of two dimensional geometry for a single microneedle and the affected burnt skin.

Our initial goal was to model a single needle in two dimensions (Figure 1). We determined from existing literature [1] the ideal concentration of ibuprofen (30 mg of drug/kg of body mass) for localized use in the dermis. Then, we developed a transient model of the ibuprofen concentration at the burn area. This two dimensional model was used to quickly evaluate our geometry and validate our assumptions about the behavior of a single microneedle. It also allowed us to perform a sensitivity analysis and refine our parameters before moving forward to the three dimensional case.

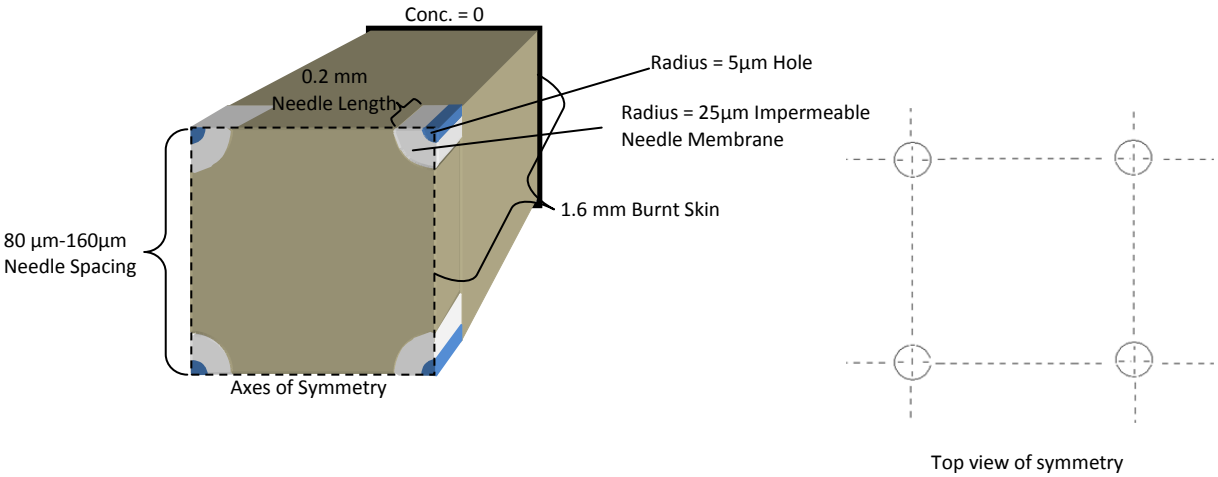


Figure 2- Three dimensional model of four microneedles in a square array implanted in the region of burnt skin for which these needles provide drug.

The objective of the three dimensional case was to account for the interaction of multiple needles in an array. The 2D case was the basis for the properties and assumptions used in the 3D case. With the three dimensional model, we varied the spacing between the microneedles and initial concentrations of ibuprofen in the drug patch in order to determine a scenario resulting in optimal ibuprofen concentration in the dermis.

4. Two Dimensional Design

Assumptions of 2D Design

Our 2D model (Fig.1) consisted of microneedles arranged in circular arrays as shown in Figure 3.

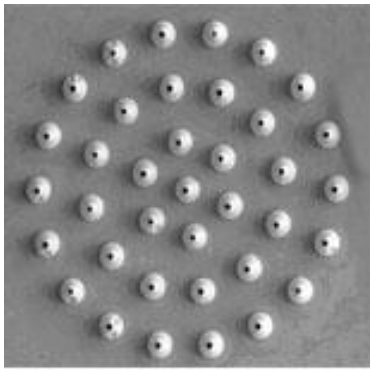


Figure 3- A circular microneedle array [2].

Due to the circular symmetry of this array, our 2D model assumed a flux of zero at each center point between two microneedles; we also assumed zero flux at the radial center of each microneedle. These assumptions are also present in our schematic (Fig. 1). We assumed drug transport by simple diffusion. Because microneedles are often flushed with water before a patch is applied, we used the diffusivity of ibuprofen in water in our set-up to model the movement of drug through the microneedle. In addition, we assumed that the blood acts as a concentration sink and provides a driving force for this diffusion. There is a silicon layer between the patch and the skin that serves to keep the microneedles in place and also prevents diffusion of ibuprofen from the patch into the skin. Therefore, we assumed no drug diffusion from the patch into the

skin between microneedles. As a final assumption, we used uniform physical properties of the burnt skin.

Results from 2D Analysis

The two-dimensional model was solved completely, independent of the three dimensional case. The mesh convergence, sensitivity analysis and further details of the 2D solution are available in the appendix. Here, however, our discussion will focus on those results which influenced the following 3D design. Our two dimensional model showed that there was no drug diffusion through the healthy dermis over the range of initial drug concentrations used. In addition, our 2D sensitivity analysis (Figure 19) showed that our model was not sensitive to the diffusivity of Ibuprofen through the healthy dermis, which allowed us to get rid of this subdomain in the 3D model and move the concentration sink to the bottom of the burnt dermis.

In order to determine what regions of our 3D model needed the finest mesh, we looked at a plot of the Ibuprofen concentration generated at an early time of 100s (Fig. 4).

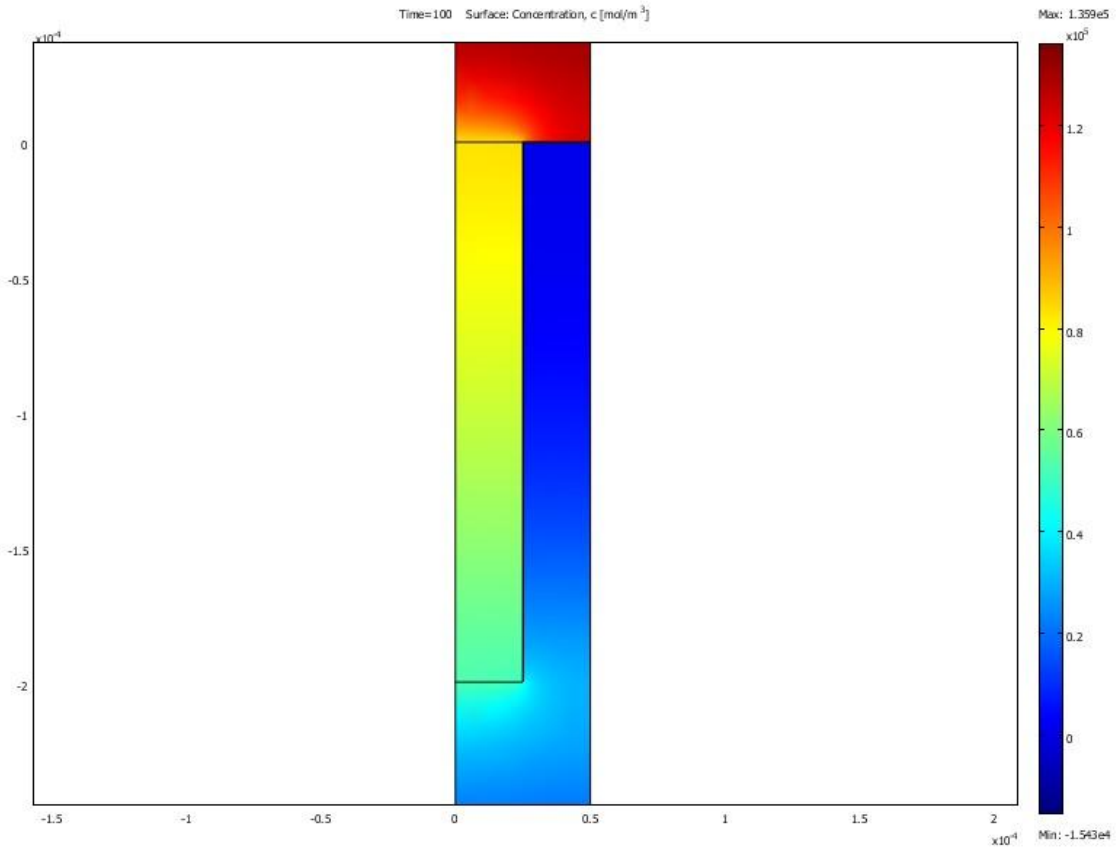


Figure 4 - Ibuprofen distribution in the needle tip and burnt skin at 100s.

This graph shows that the region of greatest change was in the burnt dermis located near the microneedles. Therefore, we made a finer mesh in this region of the burnt dermis for the 3D model.

Another finding in the 2D model which allowed simplifications to be made to 3D design was showing that the Ibuprofen concentration profile over time had little variation at different points within the needle (Figure 5).

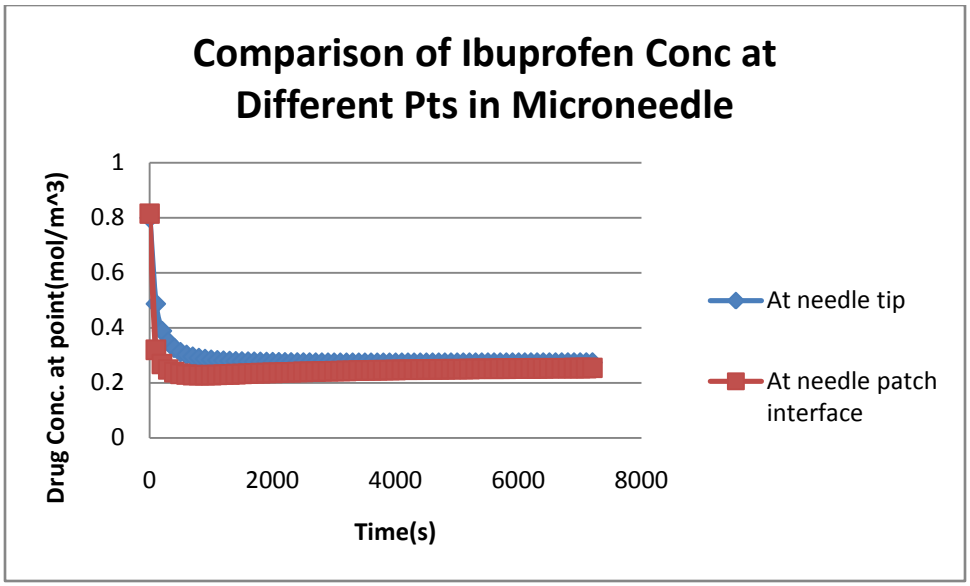


Figure 5- Comparison of Ibuprofen concentration over time at 2 points in the microneedle. The represents our justification for replacing the physical patch and needle with a boundary condition in the 3D model.

The data in Figure 5 shows that diffusion from the patch through the microneedle to its tip is not influencing the concentration profile at the interface between the microneedle tip and the target skin. Because the patch and needle properties did not alter the concentration profile, it was unnecessary to build, mesh, and compute these parts of the geometry in 3D. Instead, the 2D model was used to obtain the concentration profile at the needle tip (as seen in Fig. 5) and apply this function as a boundary condition at the needle tip in the 3D model.

5. Three Dimensional Design

Geometry and Governing Equations

The governing equation of our problem was the mass transfer equation in Cartesian coordinates. There was no reaction or convection, so only the transient and diffusion terms were included. As follows:

$$\frac{\delta C_A}{\delta t} = D_{AB}\left(\frac{\delta^2 C_A}{\delta x^2} + \frac{\delta^2 C_A}{\delta y^2} + \frac{\delta^2 C_A}{\delta z^2}\right)$$

The equation was applied to a three dimensional model of an array subset of four needles (Fig. 2), as previously discussed. Modeling of an entire array could be estimated by tiling these components; thus it was not necessary to analyze an array of the size that would be manufactured.

We also took full advantage of the symmetry of our situation. The dashed lines in Figure 2 show the four existing axes of symmetry. Because the model can be tiled to achieve a larger array, only a quarter of each of the four needles needed to be meshed and evaluated. These observations greatly reduced our computation time as did some astute observations.

As mentioned in discussion of the 2D results, one of the more crucial changes from our 2D model to the 3D model was to replace the physical representation of the patch and needle center with a needle-tip boundary condition. This varying boundary condition was found from the 2D model which was run with all the appropriate constants and the drug concentration at the needle tip was recorded as a function of time. The main reason for implementing a three dimensional model was to perform spacing studies. Therefore, it was crucial that all data collected from the 2D setup for use in the 3D model reflected the correct distance between needles. The concentration at the needle tip as a function of time was found in 2D models of a 50um needle-to-needle spacing as well as its 30% larger counterpart. These profiles are shown in Figure 6.

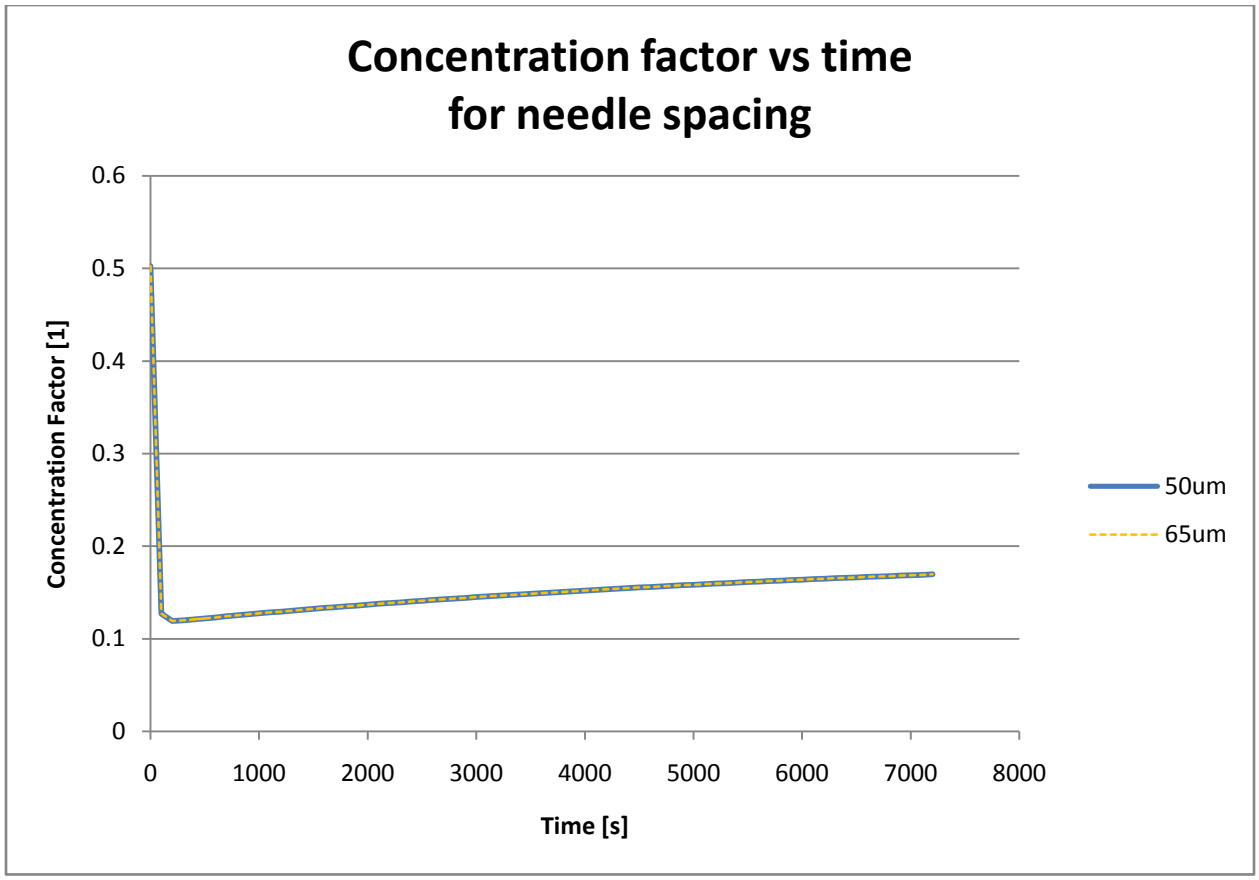


Figure 6- Shows the concentration factor vs. time profile for two different spacing, the 50 and the 65um.

As one may notice, the two spacings produce a nearly identical concentration factor profile that varies only by roughly 1%. Thus, it is not necessary to build a 2D corresponding to every 3D spacing desired to acquire a concentration boundary condition. The Ibuprofen concentration profile at the needle tip of a single 2D spacing was applied to all 3D studies. This approach to the 3D needle tip concentration boundary condition greatly simplified the amount of input work required to run the necessary simulations.

The other parameter we were varying was the initial drug concentration in the patch. It was, therefore, important to also demonstrate how changes in the patch's drug concentration at a single spacing altered the concentration profile at the needle tip. A plot of concentration factor versus time for different patch concentrations shows the linearly relationship between initial concentration in the patch and concentration profile at the needle tip.

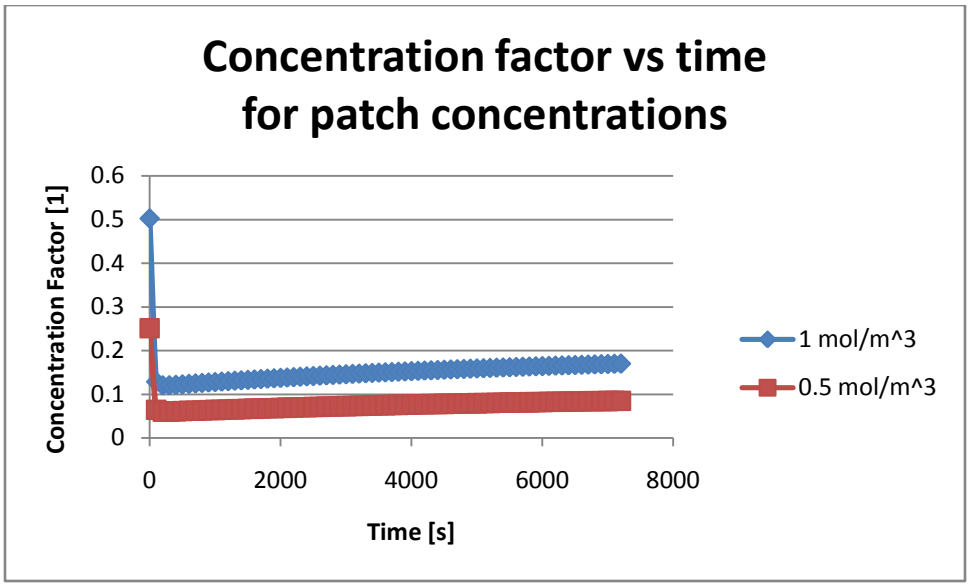


Figure 7 – This plot shows the concentration factor vs. time for different patch concentrations for the 50um needle spacing.

Looking at the Figure 7 it becomes apparent that the value of the concentration factor curve is directly related and proportional to the initial patch concentration. In the example given in Figure 7 it is apparent that the 1 mol/m^3 is twice as large in magnitude as the 0.5 mol/m^3 curve.

Mesh Plot

Our mesh used free mesh triangular elements, and a maximum element size was specified for each subdomain. The subdomains with the most drug diffusion were most finely meshed. The subdomains and their corresponding maximum element sizes are tabulated below in Table 1.

Table 1:

Subdomain	**Maximum Element Size (m)**
Top portion of burnt skin	2×10^{-5}
Middle portion of burnt skin	2×10^{-5}
Bottom portion of burnt skin	5×10^{-5}
Impermeable needle wall	5×10^{-3}
Needle tip	2×10^{-3}

The mesh in the area near the needle tips is also shown in Figure 8. As Table 1 indicates, the mesh varies from very fine in areas of great interest, namely the burnt skin nearest the microneedles, to fine in the lower burnt region.

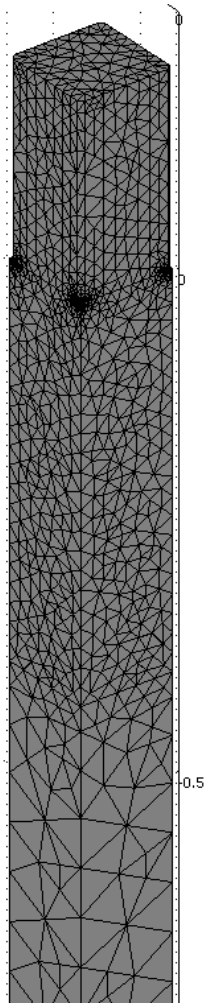


Figure 8 - The mesh of a 3D section of burnt skin varying in number of mesh elements relative to the microneedle proximity.

Results of 3D Modeling

The resulting contour plot of the drug distribution after 2 hours using the three dimensional model is shown in Figure 9.

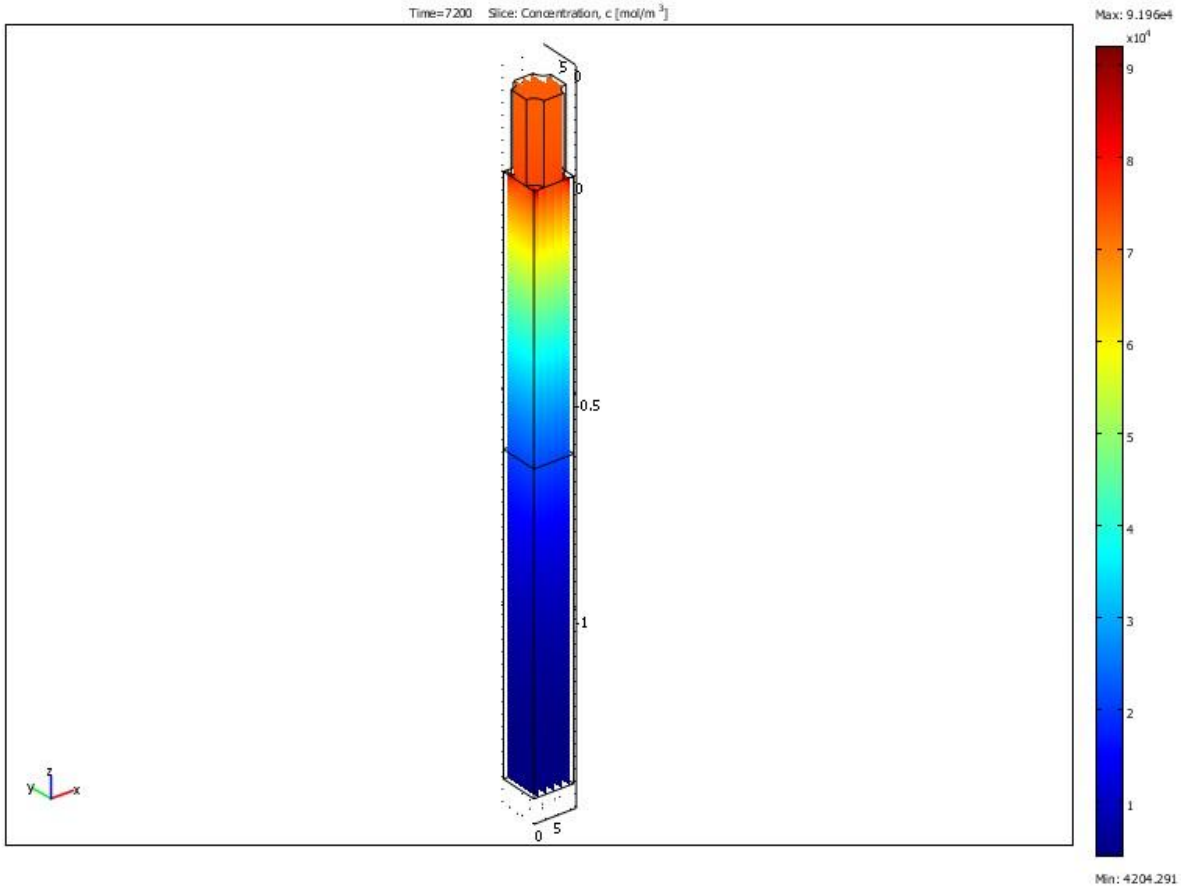


Figure 9 - Results after two hours of low concentration drug diffusion into burnt skin using 3D model.

The results show a decreasing concentration as one moves further from the needle tips as expected.

6. Sensitivity Analysis

Sensitivity analysis was performed to gauge the effect of error in the chosen parameter values on the optimization and its final solution. The sensitivity analysis for both models was conducted at a time of two hours and measured through changes in the average concentration of the drug in the burnt skin segment. The variables that were analyzed included initial drug concentration, diffusivity of drug in the needle, diffusivity of drug in the burnt dermis, and diffusivity of drug in the healthy dermis. The 2D model also examined sensitivity of the average concentration to the diffusion coefficient in the patch, a factor that was eliminated in the 3D model. Furthermore the 3D model lacks the healthy skin section present in the 2D model. All testing was done at the initial drug concentration of 0.2 mol/m^3. The results of the sensitivity

analysis in the two dimensional case are available in Figure 19. The three dimensional model responds to changes as shown in Figure 10.

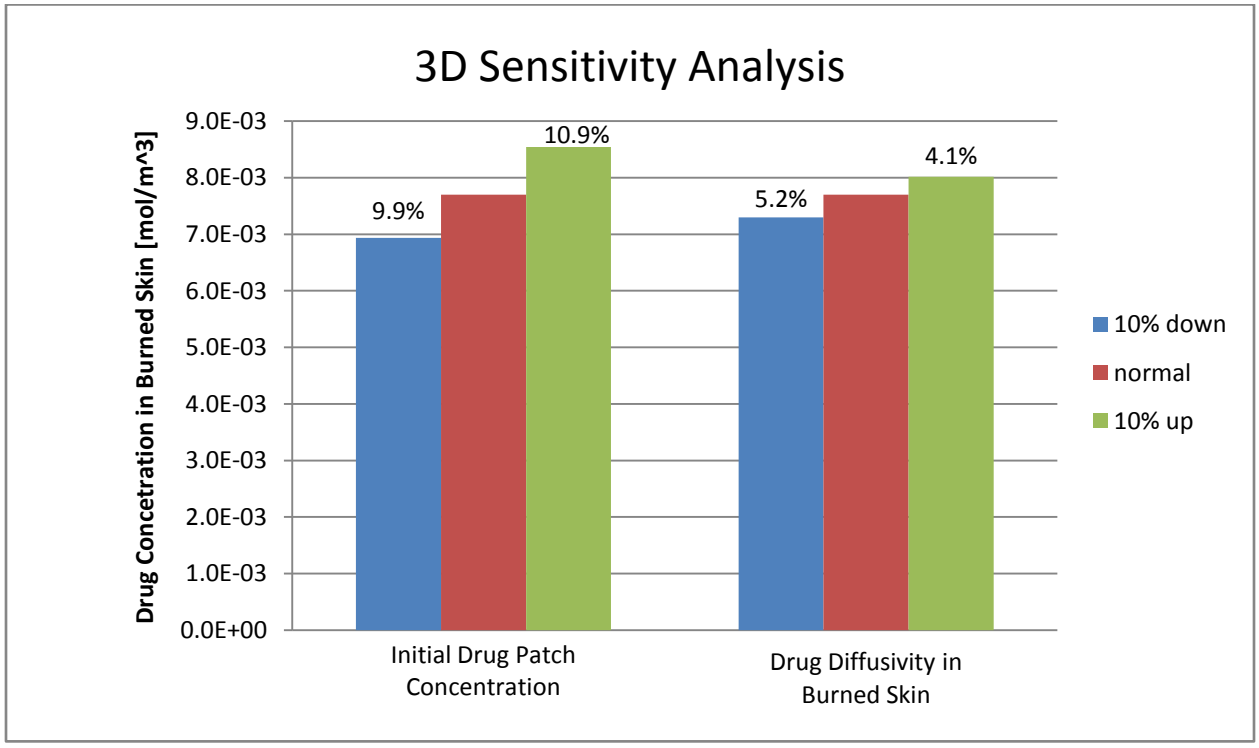


Figure 10 - Graph of sensitivity analysis of the 3D model showing the amount of change in the model outcome following a 10% increase or decrease in a single parameter value.

The results of the 3D sensitivity analysis are, for the most part, in near correspondence with those of the 2D sensitivity analysis. This assures that the assumptions taken to produce the 2D model were reasonable and had minimal effects on the accuracy of the solution. The drug concentration at the needle-patch boundary has the greatest effect on average burnt skin drug concentration. Variability in this factor on the magnitude of 10% caused a change of roughly 9-10% in both the 2D and 3D model.

The diffusivity of drug through the needle as well as the patch showed a moderate effect on the average burnt skin drug concentration in the 2D model and were evaluated at around 4 and 5% respectively. The 3D model lacked both a needle as well as a patch component.

Burned skin diffusivity changes showed a modest change of roughly 5% in relation to 10% shifts in diffusivity for the 3D model. This is of concern since this is not in agreement with the

2D model where this variable effect stood at a mere 0.5%. We believe that this is due to the fact that the 3D model does not have a patch or an actual needle space. In the 2D model the patch and the needle is given an initial concentration and a unique diffusivity. This creates an environment where both of these model spaces have an effect on the actual concentration felt by the burnt dermis. In the 3D model, however, the modulation of the concentration is completely placed on the burnt dermis as the patch was completely removed while the needle was reduced to a simple slice for computational feasibility.

The effect of diffusivity of the healthy skin variability showed a very small effect on the final solution. This effect was calculated to be near 0%, further validating the removal of this component from the 3D model.

7. Optimization of Design

To select the optimal design, we determined the relationship between average ibuprofen concentration in the burnt skin after 2 hours, simulated initial drug concentration in the patch, as well as needle spacing. Optimization was done using the 3D model for a more realistic answer that encompasses needle-needle interaction and diagonal spacing not handled by the 2D model. The results, obtained with COMSOL, are shown in Figure 11, which shows the average drug concentration in the burnt skin section as a function of both needle spacing and initial patch concentration.

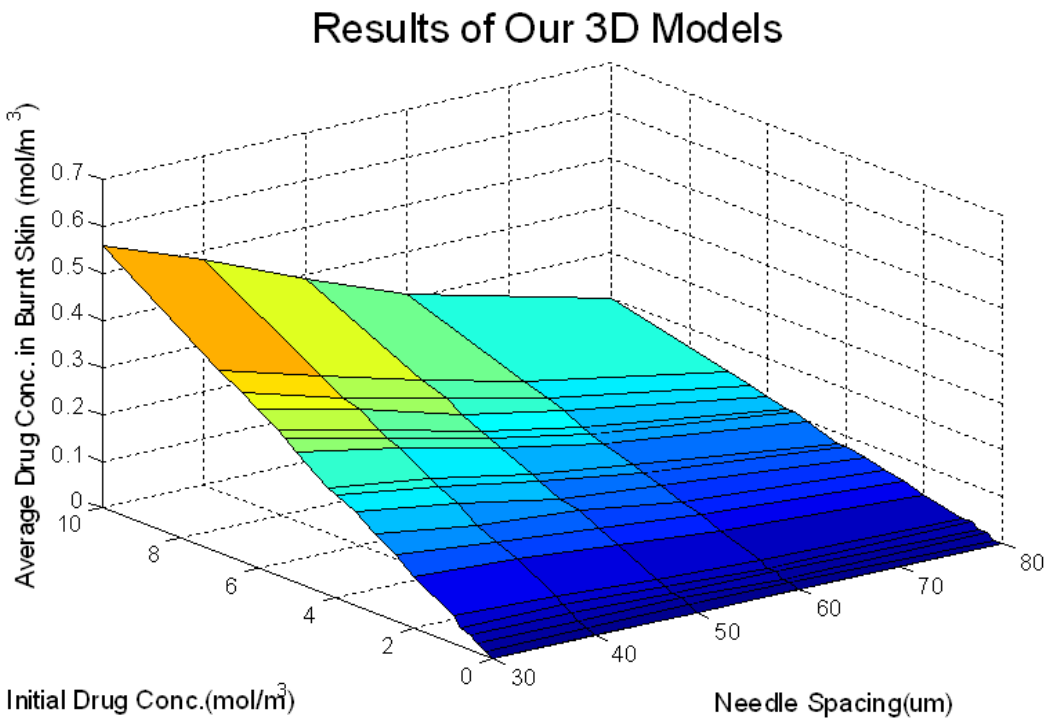


Figure 11 – Plot showing the interaction of initial Ibuprofen concentration in the patch and needle spacing, and the resulting average Ibuprofen concentration in the burnt skin.

As one may notice the model exhibits an almost linear response to both needle spacing and initial patch concentration. This makes sense since all of the components to the diffusivity equation are linear and varying needle spacing influences the amount of the drug sink/source in a completely linear matter.

A model of this sort provides the design team with all sorts of combinations of spacing and initial concentration that would effectively cause the desired average concentration in the burnt skin. The target concentration of ibuprofen in the burnt skin after 2 hours was an average of 0.20 mol/m^3, while the maximum recommended dosage was roughly 0.66 mol/m^3. This close difference between the two boundaries forced us to seek an average rather than a minimum concentration of 0.20 mol/m^3 because that latter case resulted in greatly too high values at the patch-skin boundary that experiences the greatest amount of flux. A sample profile can be observed in the Figure 21, which shows the concentration difference as a factor of roughly 12.5 of concentration at the patch/burnt skin boundary versus burnt/healthy skin boundary. Accordingly for this specific model setup establishing an minimum concentration of 0.20 mol/m^3

would result in a maximum concentration of 2.5 mol/m^3, grossly above the maximum recommended dosage.

To measure the effect of spacing on the drug transport we evaluated the 3D model at a variety of needle spacing. To quantify the effect of spacing we obtained a vertical drug concentration profile across the burnt skin section and calculated its standard deviation. The standard deviation is a measure of the compactness of the values across the distribution. Thus by minimizing the standard deviation across this burnt skin distribution we were maximizing uniformity across the section. This would allow the designers to place higher concentrations in the patch and thus achieve higher minimum concentrations while staying below the maximum recommended concentration. The results of this optimization can be observed in Figure 12, below.

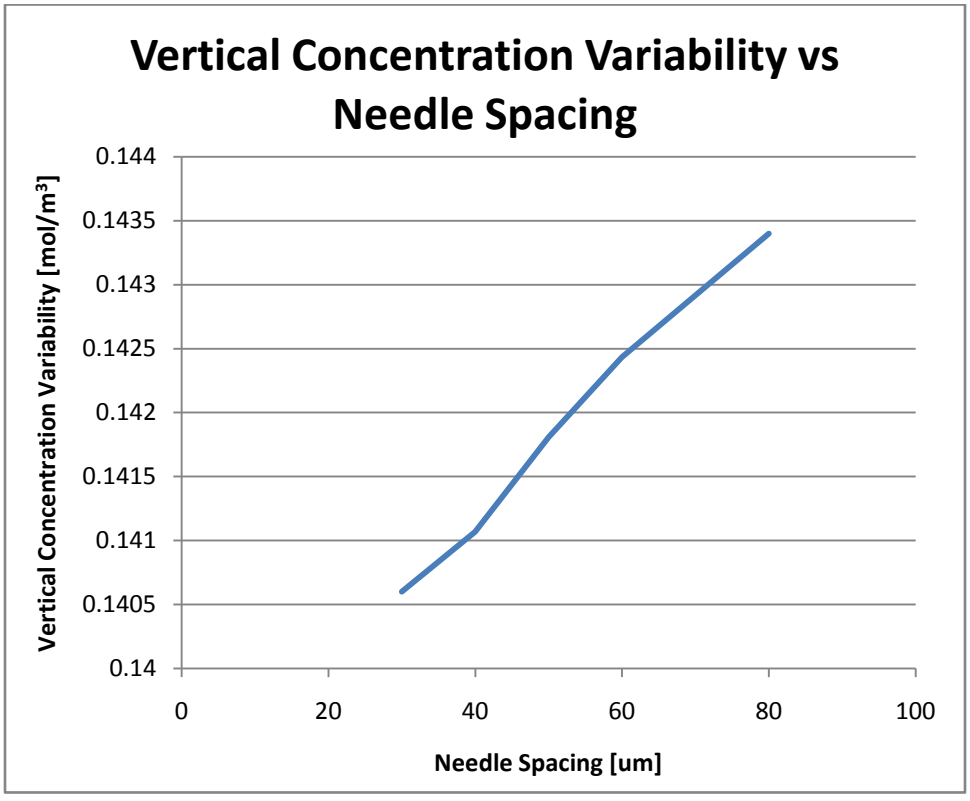


Figure 12 - Shows the relationship between the needle spacing and vertical concentration variability in the burnt skin section of the 3D model. All values shown are those of optimal setups yielding average 0.20 mol/m^3 concentrations for each spacing.

As one can clearly see there is a very strong linear relationship between needle spacing and vertical variability in the burnt skin section. Using an objective function that maximizes uniformity across the model, we would end up with a theoretical spacing of 0, which is the physically common sense solution that we did not see at the forefront of objective design for this project. The real and practical answer is that the optimal spacing will depend on application and the desired results. Increased needle spacing ensures less discomfort to the end-user, but has the disadvantage of less uniform concentration diffusion. It is up to the designer and the medical objective in question to figure out proper tolerances and spacing needs.

We can, however, comment on the ideal patch drug concentration versus needle spacing relationship. Figure 13 shows the relationship that we discovered during our simulation.

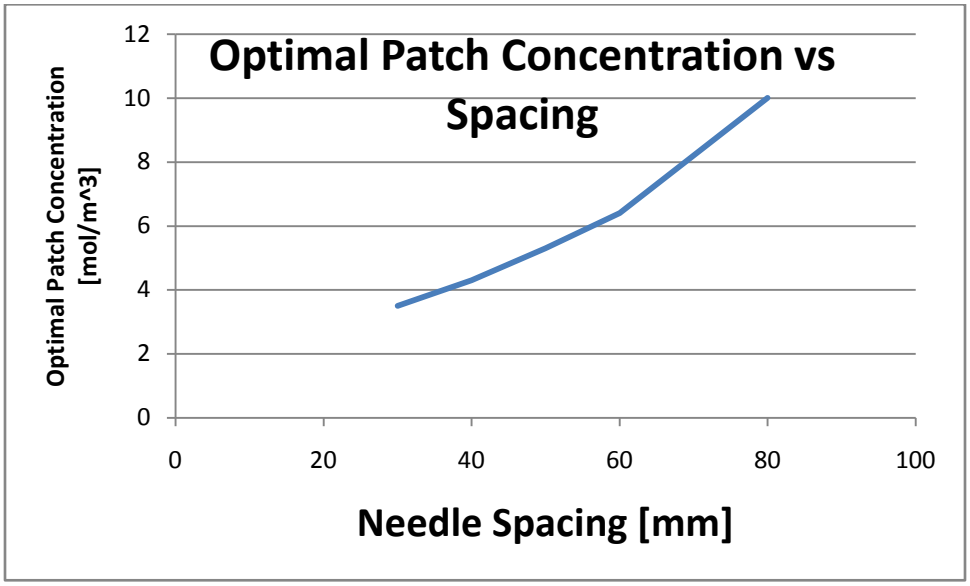


Figure 13- Shows the optimal patch concentration of ibuprofen as a function of needle spacing.

As one may observe the optimal concentration of the drug in the patch varies very much linearly with needle spacing. This is an intuitively correct solution since by adding inter-needle distance we are adding linearly as much drug sink as source. The only potential limiting factor in this observation is that the needle size remains the same and now has to transport a larger quantity of drug. This, however, is a non-issue since the needle diffusivity is much larger than the either patch or burnt skin diffusivity. Thus it flows from this observation that needle flow limitations are not the bottleneck and the graph in Figure 13 fully agrees with the common sense interpretation of the situation.

8. Accuracy Check

Research through current publications does not indicate that values have been found for ibuprofen concentration in skin using a microneedle array. However, transdermal drug delivery applications have been researched in other ways that may be compared to our application.

The model that we have chosen to verify our setup is a published study regarding the delivery of BSA to rat skin via a microneedle array of spacing 200um, initial patch concentration of 6250 ug/cm^2, and diffusivity of 315.8 ug/cm^2/hour [3]. Using this information we were able to modify our model in terms of design and parameters while keeping the same fundamental setup shared with our own model. While the experimental and modeling representations of drug depletion from a patch result in some difference after long times, we are concerned mainly with the 4 hour period in which Ibuprofen is typically administered. Figure 14 shows our results of this time period which follow the same trend in the experiment over this timeframe.

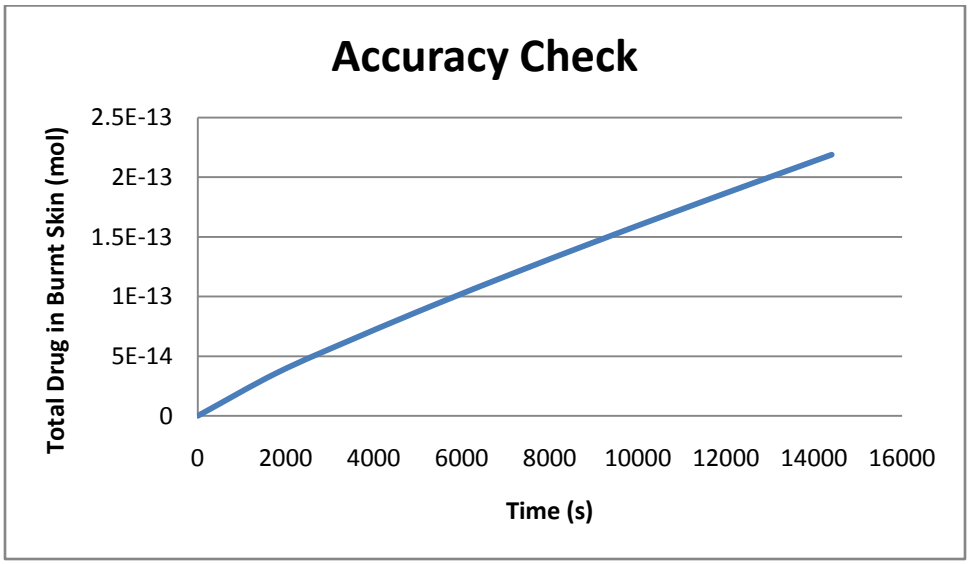


Figure 14 – Plot for accuracy check which shows the same trend of drug present in burnt tissue versus time as the experimental setup.

It is also interesting to note that both the 2D model and the 3D model showed nearly identical concentrations under identical model setup. This trend can be observed in the sensitivity analysis portion and mainly Figure 10 and 19.

9. Conclusion

Microneedles can be effectively used to increase drug transport from a drug patch through the epidermis without causing infection or discomfort in the patient. A three-dimensional model of ibuprofen through burnt skin was created to examine the effects of initial drug patch concentration and microneedle spacing on the drug concentration profile in the dermis. The results of this optimization can be viewed in Figures 12 and 13. This model and these results can be used for design of ibuprofen microneedle systems as well as other drug systems since the fundamental physics remain the same. Needle spacing remains a factor that has to be determined *in situ* and will vary for different applications.

10. Design Recommendations

Our model of drug diffusion through burnt skin could be improved to make a more realistic three-dimensional model of transdermal drug delivery to burn victims. One of our biggest challenges was finding the input parameters needed for this model. For some parameters, such as the diffusivity of ibuprofen through burnt skin, we estimated the values based on available data for similarly sized and structured molecules. Because, according to the sensitivity analysis, the model is most sensitive to the diffusivity of ibuprofen through the burnt skin, it would be very important to have an accurate value for this parameter. Therefore, future models should strive to find more accurate input parameters.

Our model examines simple drug diffusion through the burnt dermis without the use of a pharmacokinetic model for the behavior of the drug in the skin. However, our setup could be made more realistic by including a pharmacokinetic model such as the one seen in Al-Qallaf's model of transdermal drug delivery: $V_b \frac{dC_b}{dt} = \left(\frac{dQ}{dt}\right) S_a - K_e C_b V_b$ [4]. In this model K_e is the elimination rate constant from the blood compartment, dQ/st is the penetration rate of drug through the skin, S_a is the surface area of the microneedle array, V_b is the volume of distribution in the blood, and C_b is the drug concentration in the blood [4]. While we were unable to implement this model because we could not find the necessary pharmacokinetic constants for ibuprofen, we would recommend that future models consider including pharmacokinetic behavior of the drug in the skin.

Finally, the model could be improved by incorporating drug diffusion into the bloodstream. When performing our accuracy check, it was difficult to find research papers that discussed the desired concentration of ibuprofen in the dermis of a patient. Instead, research papers discuss drug concentration in the bloodstream. Therefore, for the purposes of data validation and verifying accuracy, it would be an improvement on our model to include the bloodstream in the geometry.

11. Realistic Constraints

Microneedle arrays can be successfully used as a less painful alternative to hypodermic needles in many applications. They are also able to enhance transdermal drug delivery from a drug patch. However, there are some realistic constraints that could prevent microneedle arrays from becoming the standard tool of transdermal drug delivery. Because this method of drug delivery involves both a drug patch and a microneedle array, it may be more work to produce than hypodermic needles. Additionally, because microneedles are a relatively new technology and are more structurally complicated than hypodermic needles, it likely costs more to manufacture these arrays. Therefore, it could be difficult to convince healthcare providers to use microneedle arrays and not hypodermic needles. Indeed, healthcare providers and patients would have to be taught the potential advantages of microneedle arrays (such as a lower risk of infection and less discomfort for the patient) before they could replace hypodermic needles. Additionally, there would still be applications where hypodermic needles would be preferable, such as IVs and blood drawing.

12. Appendix A: Mathematical Statement of Problem

Governing Equation: Mass transfer equation in cylindrical coordinates

$$\frac{\delta C_A}{\delta t} = D_{AB}\left(\frac{\delta^2 C_A}{\delta x^2} + \frac{\delta^2 C_A}{\delta y^2} + \frac{\delta^2 C_A}{\delta z^2}\right)$$

Boundary Equations:

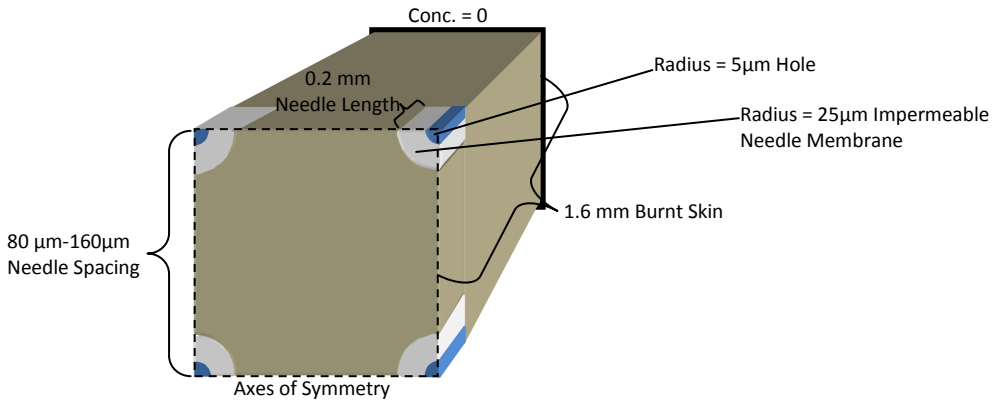
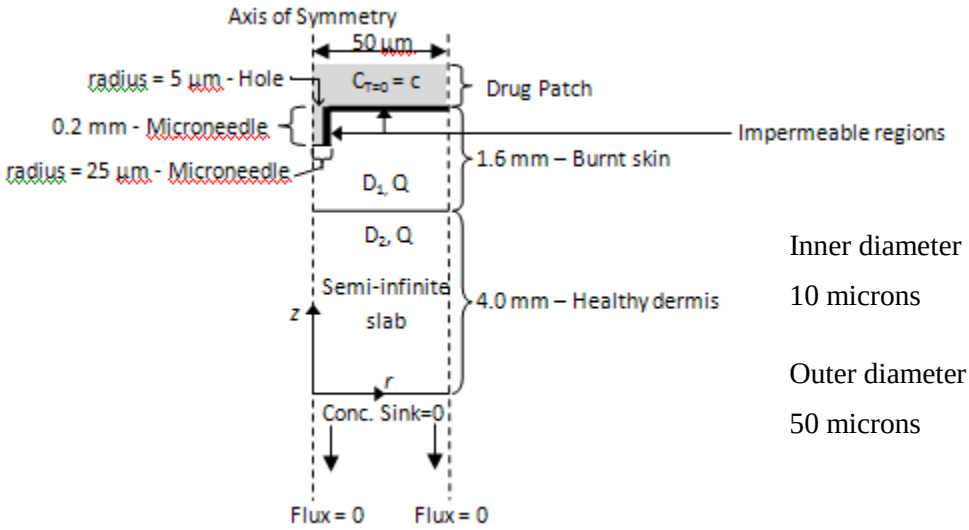


Figure 15- Three dimensional model of four microneedles in a square array implanted in the region of burnt skin for which these needles provide drug.

Layer	Initial Concentration
Microneedle Tip	54370-163110 mol/m^3
Burnt Dermis	0 mol/m^3

The initial microneedle tip concentration was varied between 54370 mol/m^3 and 163110 mol/m^3 during the optimization process.

13. Appendix B: 2D Schematic and Results



Inner diameter of the tip of the microneedle: 10 microns

Outer diameter of the tip of the microneedle: 50 microns

Figure 16- Schematic of two dimensional geometry for a single mirconeedle and the burnt skin it affects.

Governing Equation: Mass transfer equation in cylindrical coordinates

$$\frac{\delta c_A}{\delta t} = D_{AB}\left(\frac{1}{r}\frac{\delta}{\delta r}\left(r\frac{\delta C_A}{\delta r}\right) + \frac{\delta^2 C_A}{\delta z^2}\right)$$

Initial Conditions:

Layer	Concentration
Drug Patch	54370 – 163110 mol/m^3
Microneedle Tip	0 mol/m^3
Burnt Dermis	0 mol/m^3

Results of 2D Design

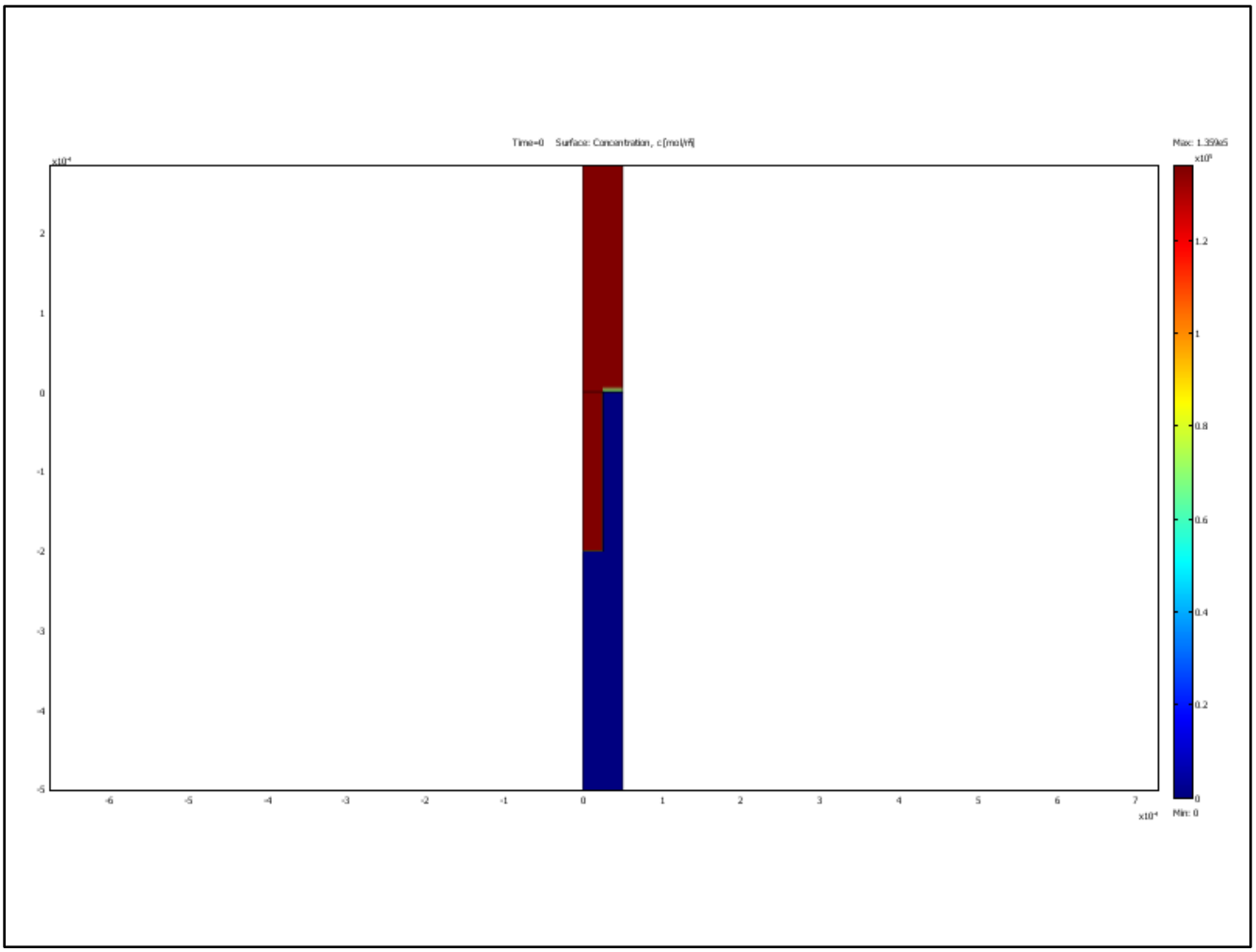


Figure 17- Initial conditions for 2D case. Contour plot for 2D schematic at time = 0 seconds and C_o = 14375 mol/m3.

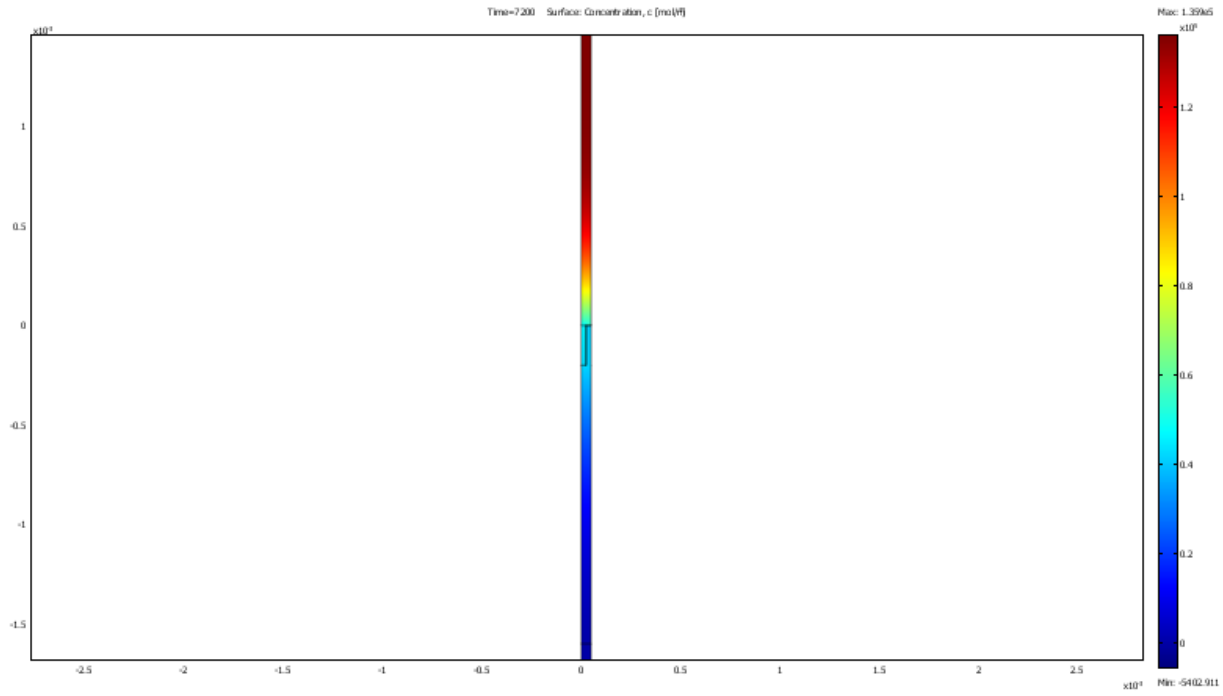


Figure 18- Contour plot for 2D schematic at time = 7200 seconds and C_o = 14375 mol/m3.

2D Sensitivity Analysis

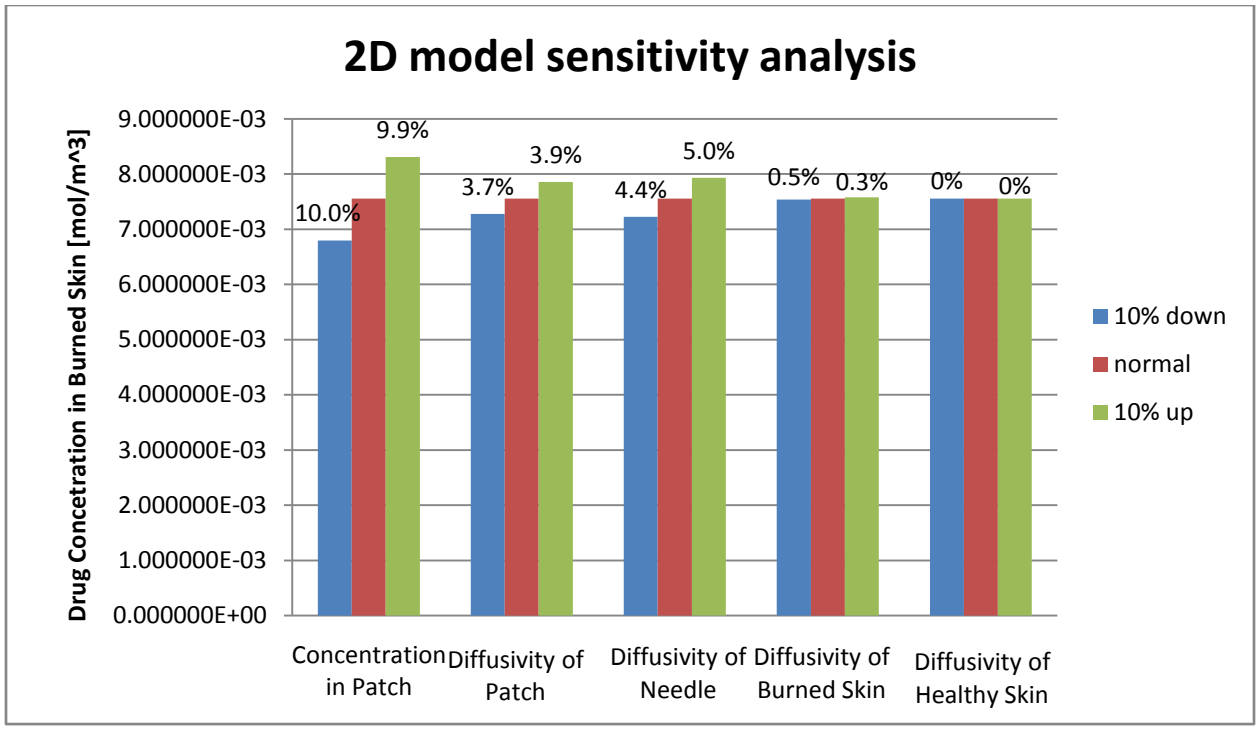


Figure 19- Graph of sensitivity analysis of the 2D model showing the amount of change in the model outcome following a 10% increase or decrease in a single parameter value.

14. Appendix C: Mesh convergence

2D Mesh

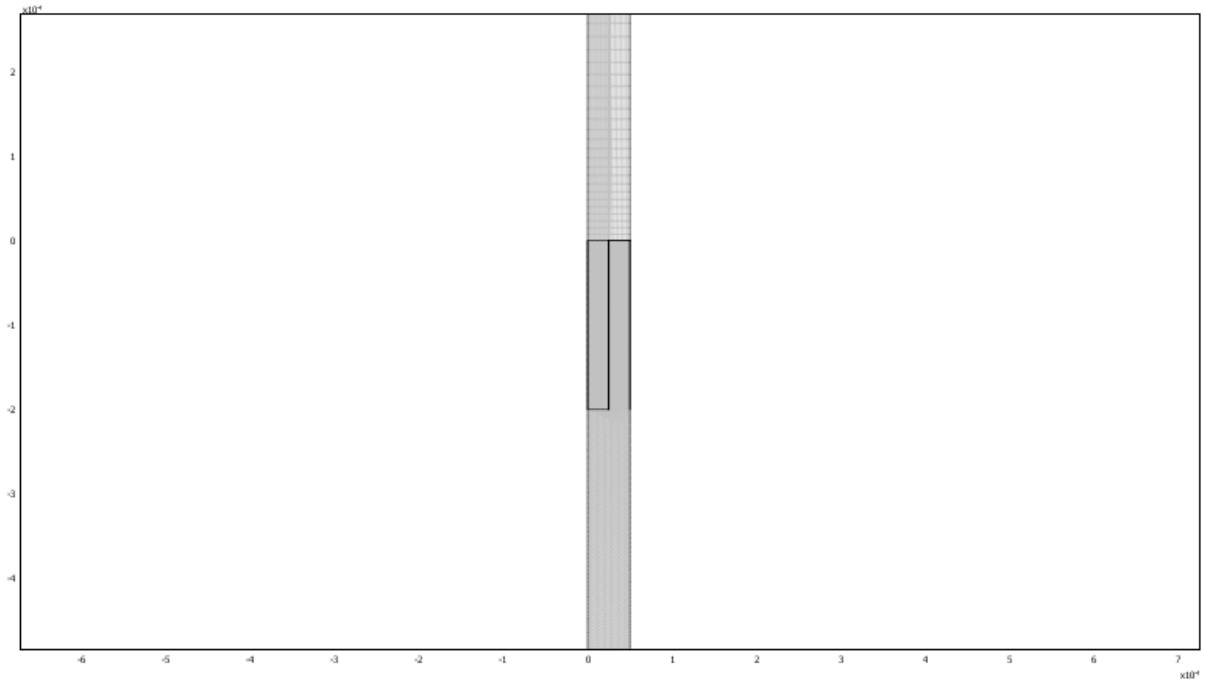


Figure 20- Mesh distribution for 2D model. Mesh is rectangular and specified by edge.

For the 2D model, a mesh convergence analysis was performed and resulted in the following mesh at the converged point.

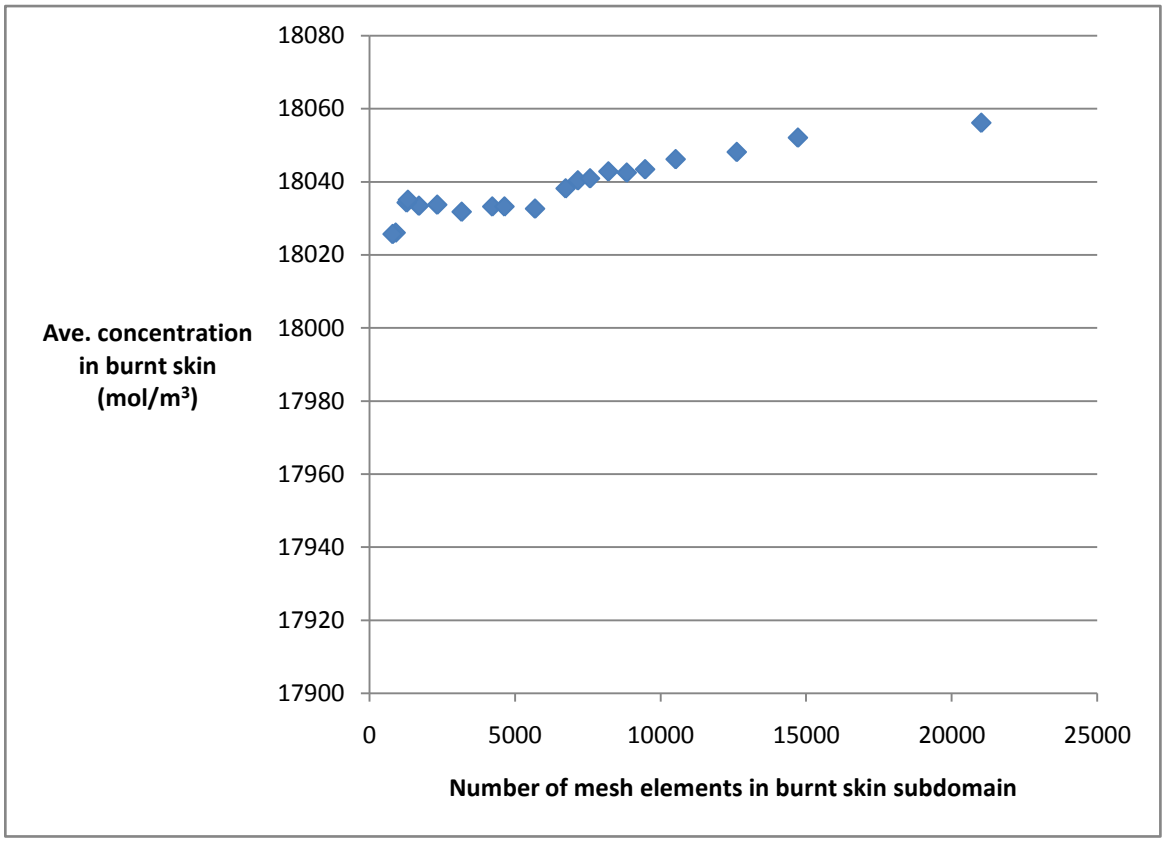


Figure 21 - Average ibuprofen concentration in burnt skin vs. # of mesh elements.

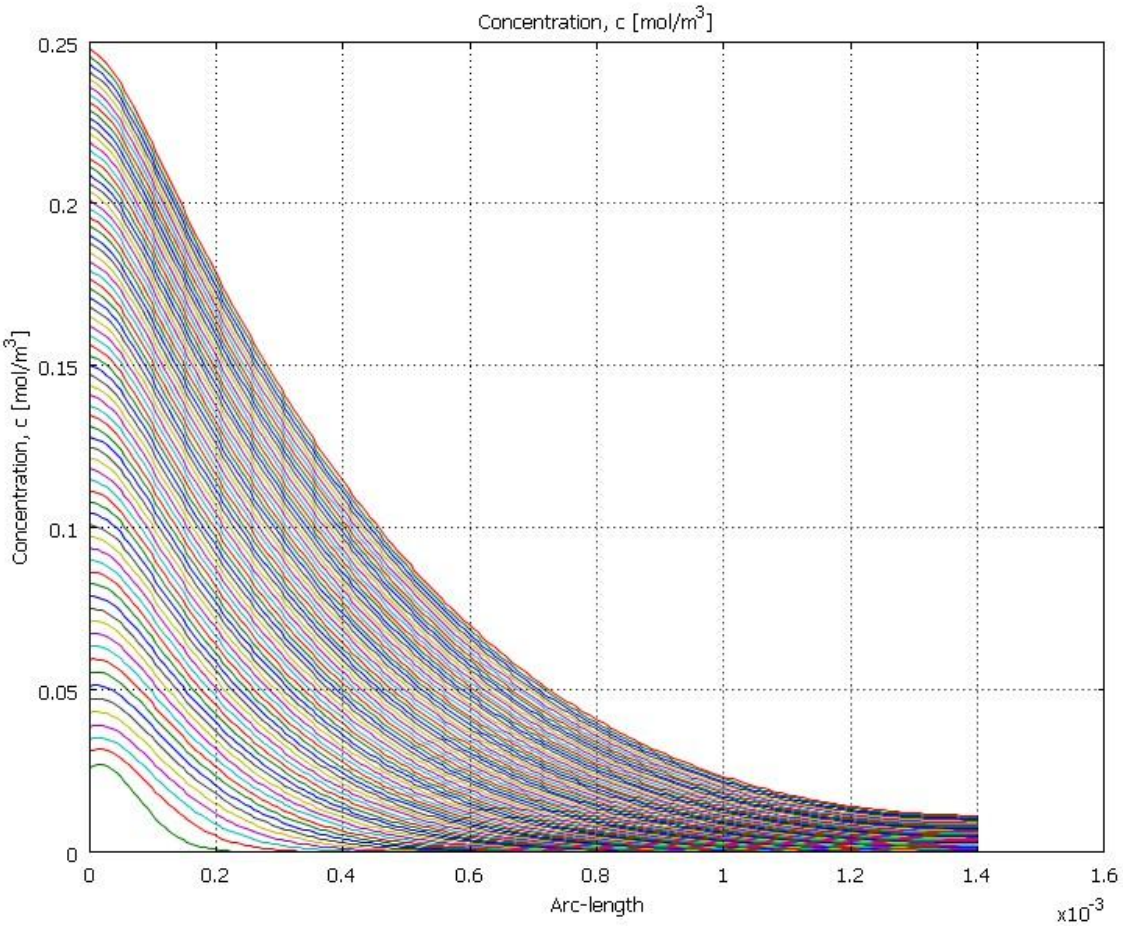


Figure 22- Sample vertical concentration profile for drug diffusion in the 3D model. Setup shown is for the optimal concentration of the 80um needle spacing and at the center line of the burnt skin area. Average concentration shown is 0.20 mol/m^3.

The average drug concentration in the burnt skin starts to converge around 22000 mesh elements at 1806 mol/m^3. A large number of mesh elements is required for convergence. One reason for this large value is that compared to the depth of the skin, the length and width of the needle are relatively small. Also, because the drug is expected to diffuse, the concentration in the needle tip is quite large. Since a large concentration of drug diffuses out of a small area, the surrounding area is very dynamic and requires a fine mesh.

3D Model Mesh

The 3D model used the maximum amount of elements allowed by the computer's memory to solve the schematic created. Therefore, the mesh could not have been further refined.

15. Appendix D: Physical Constants

Table 2: Physical Constants

Constant	Value	Source
Diffusivity of patch reservoir	1 E -11 m^2/s	Datta, A. and Rakesh, V [4]
Diffusivity of ibuprofen in water	7.3E-10 m^2/s	Feng, H. and Bellantone, R. [3]
Diffusivity of ibuprofen in burnt epidermis	3.056E-11 m^2/s	Sharif, B. et al [5]
Diffusivity of ibuprofen in healthy dermis	5.34638889E-15 m^2/s	Herkenne, C. et al. [6]

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