The Effects of Applied Local Heat on Transdermal Drug Delivery Systems

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Executive Summary

Transdermal drug delivery systems have been developed over the past several decades and now include patches for birth control, nicotine addiction, and pain relief. The local application of heat can increase the diffusion coefficient of the drug in the skin and result in faster delivery of the drug and shorter time to reach a steady state concentration of the drug. While this procedure is desirable for some systems where a faster dose will aid in alleviating pain and/or symptoms, it can also be a cause of concern for some drugs. Fentanyl, a chronic pain relief drug, can cause accidental death by overdose. We report herein an analysis of the effects of various heating situations on transdermal fentanyl delivery based upon a model developed using COMSOL Multiphysics. The utilization of such a model allows for the determination of situations which may be potentially dangerous for fentanyl drug users, and enables the development of usage guidelines and safety mechanisms for transdermal delivery systems. Using the computer model, the following cases were simulated: no applied heat, ThermaCare heat pad, fever, and heating blanket. The heating blanket and ThermaCare heat pad simulations showed the most dangerous increases in fentanyl blood concentration above no-heat levels: about 180% and 100%, respectively, over 30 hours; by contrast, the patient fever model reported a 40% increase in fentanyl blood concentration. These simulations demonstrate the dangers of fentanyl transdermal pain patches when skin temperature is increased, and can be used to develop better patient guidelines for patch use and to improve fentanyl transdermal systems. Lastly, this computer model may be used to model other transdermal drug delivery systems for the improvement of patient guidelines and/or the development of new systems, thus decreasing the need for experimentation on subjects.

Key words: transdermal, drug delivery, fentanyl

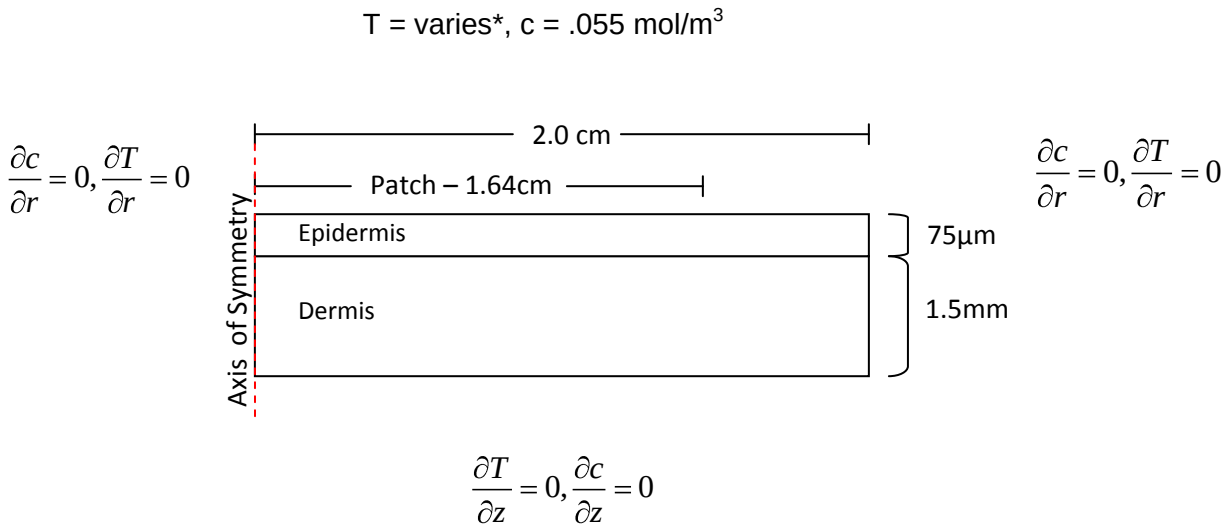
Introduction and Design Objectives

The increasing popularity and market of transdermal drug delivery systems, in the form of a skin patch, has resulted in several commercially available products ranging from birth control to nicotine addiction to pain relief. Such patches are designed to give an appropriate drug dose over a given time at body temperature. Directly applied heat or otherwise raised body temperature can increase the diffusivity of the drug from the transdermal system in the skin and result in a higher dose of drug over the same time, leading to potentially adverse effects. This report focuses on the effects of local heat applied when using a fentanyl pain patch. The fentanyl patch is of particular interest due to the fact that there have been numerous documented cases of accidental overdose when using the transdermal delivery system. Many of these overdoses were caused by perturbations of body temperature created by deliberate or unintentional heating of the body or the area with the patch.

While several drugs that are currently marketed as transdermal systems can cause adverse effects when a certain dose threshold is surpassed over a given time, fentanyl is of particular concern due to its potential lethal effects that can result from such an overdose. Fentanyl is

used as an analgesic and an anesthetic, typically in the operating room. First synthesized by Janssen Pharmaceutica (Belgium) in 1959, fentanyl is an opioid analgesic that is eighty times more potent than morphine. Transdermal delivery systems release the drug through the skin and into fat where it can then be released continuously over a longer period to treat chronic pain. However, even correctly designed patches may allow overdose when external heat is applied and increases the diffusivity of fentanyl in the skin. Incidents of such overdoses have been documented when patients applied heat to the patch area in order to treat an acute pain attack. The dangers of fentanyl overdose as a result of heat addition have been extensively documented. One published case reported respiratory failure in a patient undergoing surgery; the cause was found to be fentanyl overdose as a result of a heating blanket being put on the patient, who was wearing a fentanyl patch.[i] Additionally, the FDA has issued a warning regarding the potential for accidental fentanyl overdose when heat is applied to the patch, either directly or indirectly. The FDA notes that overdoses may result in dangerous side-effects, including respiratory failure, drowsiness, dizziness, nausea, confusion, anxiety, vomiting, itching, or even death.[ii]

Our simulation demonstrated a significant increase in fentanyl dosage when a heating blanket and ThermaCare heat pad were applied to the skin surface during the 30 hour time period analyzed (typical duration of patch use). Despite even detailed warnings prescribed with transdermal drug delivery systems, the risk of overdose when using a transdermal drug delivery system is still a concern. We propose the use of computer simulation of drug diffusion with varying heat application to develop better, quantitative guidelines that address the risks of elevated body temperature when using transdermal drug delivery systems and to design such systems with possible safety mechanisms to protect patients against overdose. The goal of this project is to model the Duragesic fentanyl transdermal[iii] delivery system using COMSOL Multiphysics. By developing a model of the transport properties of fentanyl through two layers of the skin (epidermis and dermis), the effects of local applied heat on the diffusion of fentanyl in the skin can be analyzed. Additionally, such a model can be used to determine guidelines for patients using the Duragesic patch. Such a model could also easily be used to examine other transdermal drug delivery systems including motion sickness and birth control. This report will guide the reader through the development of a computer model of fentanyl diffusion, beginning with the governing equations and physics from which the model was built. The model will be tested in four different scenarios, one in which a heating pad is applied (ThermaCare brand), one in which the patient has a fever (102º F), one in which a heating blanket (42º C or 107.6ºF) is covering the patient, and a control case in which no local heat is applied. By analysis of the results from these scenarios, the increase of drug delivery attributable to local applied heat will be determined. Through this analysis, guidelines for use of fentanyl patches and similar transdermal drug delivery systems in regard to local applied heat and safety concerns will be discussed in addition to possible design considerations.



Patch size (circular) = 33.6 cm^3

*Temperature profile as given by Figure 4.

Figure 1. Schematic of system and skin with boundary conditions and appropriate geometry. The hypodermis layer was not included in the COMSOL model since fentanyl uptake occurs in the dermis. Not drawn to scale.

Model Design

In order to assess the effects of applied heat on transdermal drug delivery systems, COMSOL Multiphysics was used to create a simulation tool to evaluate these drug delivery systems in response to various methods of heating. The model geometry (Figure 1) encompasses two layers of skin (epidermis and dermis). A small section of skin outside the radius of the patch was also included in the model to determine the amount of lateral diffusion of the drug within the skin layers. The heating elements were modeled as covering the patch as well as the additional section of the skin on the side of the patch. The geometry and size of the fentanyl patch modeled was chosen after review of several common, commercially available fentanyl patches. The circular geometry of the path permitted the use of two-dimensional axisymmetric model to reduce computation. A constant concentration of fentanyl at the skin surface was used as the transdermal patch is designed to maintain a constant concentration over a period of 72 hours (length of time before patch should be replaced).

Our model is designed to report fentanyl blood concentration over time, based upon the ability of fentanyl to diffuse through human skin. The diffusivity of fentanyl in skin is given by the Arrhenius relation for diffusion, which relates diffusivity to skin temperature. It is this relation upon which the diffusivities of the epidermis and dermis layers in our model were based.

Our model was designed to match data from a study by Ashburn, et al., in which subjects were periodically tested for fentanyl blood concentration following application of a fentanyl patch. In

one experiment, subjects wore the patch for 24 hours without heat addition, and then one hour of heat from a heat pad (42º C) was applied to the patch, followed by five hours without heat. Our model was first compared with the experimental data for the 24-hour period in which no heat was added; our data is shown below on the right.

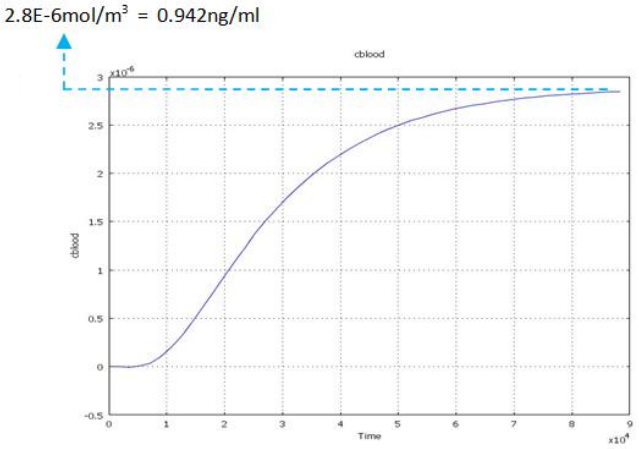


Figure 2. Comparison of model to experimental data: fentanyl blood concentration over 24 hours with no applied heat.

We multiply the model's blood concentration value of 2.8E-6mol/m^3 by the molecular weight of fentanyl (336.5g/mol) and divide by 10^{6}ml/m^3 to obtain a value of 0.942ng/ml. This value is very similar to the 0.9ng/ml recorded in the experiment[iv].

Our model further considers the effect of temperature on the diffusion coefficient for fentanyl in skin, which is given by the Arrhenius relation for diffusion. All else equal, the Arrhenius relation should account for any changes in diffusivity due to temperature; however, studies have shown that an increase in skin temperature from 32ºC to 40ºC can increase the cutaneous blood flow 10-15 times. This effect has been shown to dramatically increase the rate of drug flux into the bloodstream.[v] To account for this, a term was added to the diffusivity equation for the dermis layer to mimic the effects of increased blood convection on fentanyl diffusion. The term was designed to amplify changes in diffusivity resulting from increases in temperature. The general forms of the equations used in both the epidermis and dermis layers are given below:

Epidermis: $$D = D_0 e^{\left(-\frac{E}{RT}\right)}$$

Dermis: $$D = D_0 e^{\left(-\frac{E}{RT}\right)} + \overbrace{400(D_T - D_{33^\circ C})}^{\text{Added term}}$$

*Values of coefficients in the above equations may be found in the Appendix.

Previous experimental studies have suggested that the diffusivity of the dermis is 400 times that of the epidermis at body temperatures.[vi] By comparing our simulation to experimental data that included applied heat, it was determined that the difference in diffusivities between the epidermis and the dermis that was amplified 400 times when heat is applied instead of 400 times the diffusivity at body temperature. The multiplicative factor of 400 in the added term shown above was tailored to match experimental data. Our model's data is shown below.

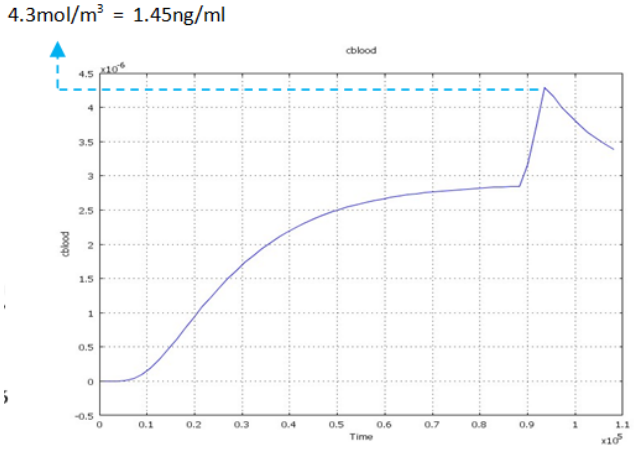


Figure 3. Comparison of model to experimental data: fentanyl blood concentration over 30 hours with one hour of applied heat at 24 hours.

The graph above shows blood concentration of fentanyl measured over a 30-hour period. Our model incorporated the same heating curve used in the experimental study[vii]. It was found that the aforementioned relationship yielded the greatest similarity between our model and the experimental study to which it was compared, with the peak values being the same.

In order to develop a temperature profile over time to model localized heat by a heating pad, we collected data on the temperature profile of skin surface temperature while using a common commercial instant heating pad (data shown below).

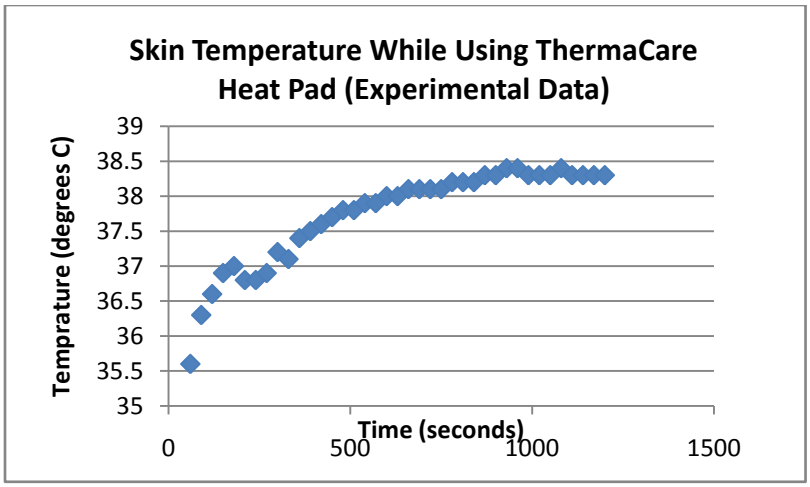


Figure 4. Skin temperature over time while using a ThermaCare heat pad on the arm (experimental data).

Using a ThermaCare heating pad and a thermocouple the values of temperature over time at 30 second invervals for a total of 20 minutes were measured. This data was then applied to our model for interpolation of temperature over time. The ThermaCare heating pad is advertised to remain at its equilibrium temperature for at least eight hours which was also verified by our experimental study. Since our model analyzes drug delivery from the transdermal patch for six hours, the equilbrium skin surface temperature reached after 20 minutes was interpolated to the six hour time point. The experimental data used is subject to error of several forms, including movement of the thermocouple, uneven distribution of heating elements within the pad, and measurement error. ThermaCare heating pads develop uneven heating of the pad as a whole due to the fact that the pad consists of several heating elements interspersed throughout the pad, as opposed to a uniform distribution of heating elements. The experimental data was measured with the thermocouple against the skin in between two of these heating elements as opposed to directly touching a heating element.

Results and Discussion

The computer simulation described in this report was used to model fentanyl blood concentration in several situations in which elevated body temperature occurs. Drug uptake into the bloodstream does not begin until the drug reaches the vascular network in the dermis layer of the skin. To calculate fentanyl blood concentration, a function was written that integrated the total fentanyl flux through the bottom layer of the dermis. Fentanyl blood concentrations could then be compared to the control case (no heat) and described as percent increases (shown in Figure 9), which are more relevant for discussion given the numerous variables that dictate necessary, dangerous, and lethal fentanyl blood concentrations (age, weight, duration of fentanyl use, etc.) from patient to patient.

The computer model was used to simulate the concentration profile of fentanyl in the skin over 30 hours both with and without applied local heat, modeled with experimental data obtained from a ThermaCare heat pad, heating blanket temperatures, and elevated body temperatures resulting from fever. As seen in Figures 8-9, the continuous application of a ThermaCare heat pad increased the blood concentration of fentanyl by over 100% during the 30 hour time frame. The temperature increase of the skin surface produced by the ThermaCare patch (approximately 1.5 º C, see Figure 2) was determined to be a unsafe amount of localized heating for patients using the ThermaCare heat pad. Results from this simulation are relevant to numerous clinical cases where patients experiencing “breakthrough” pain apply heating pads to their fentanyl skin patches in order to obtain a higher dose more quickly. However, as demonstrated with this simulation, addition of a heating pad can drastically elevate fentanyl dose into the bloodstream and may result in the patient experiencing negative side effects and even death. Figures 5-6 describe two relevant simulations in regards to using a heat pad: ThermaCare heat pad applied at the beginning of patch use (where heating lasts 8 hours) and continuous application of a ThermaCare pad over the 30 hour use of the patch, respectively. The concentration profile of fentanyl in the blood is described by Figure 7 for the later case.

Patients who apply heating pads directly over the transdermal patch often do so to alleviate “break through” pain without understanding of the potential side effects that they may induce. Still other patients treat “break through” pain by applying multiple patches which multiplies fentanyl blood concentration by the number of patches applied. Despite manufacturer, physician, and FDA warnings about applied local heat and application of additional patches, many accidental overdoses have been documented, often resulting in death of the patients. This computer model could be used to developed more quantitative guidelines specific to individual patients (considering individual differences in the above mentioned variables that affect reaction to fentanyl doses; age, weight, duration of fentanyl use, etc.).

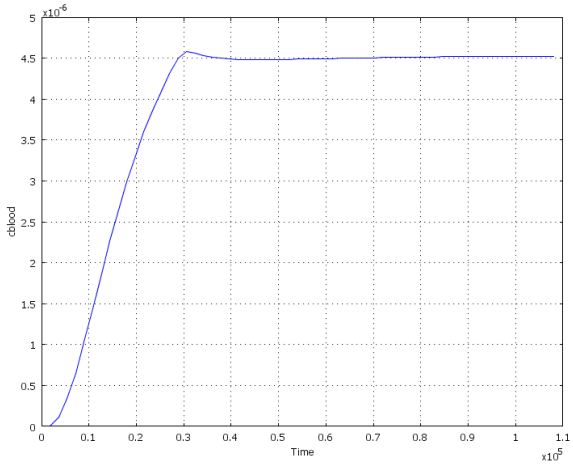


Figure 5. Fentanyl blood concentration over 8 hours when ThermaCare heat pad is applied at time zero (heat pad maintains equilibrium temperature for 6 hours). Blood concentration, cblood, is given mol/m^3. Time is given in seconds.

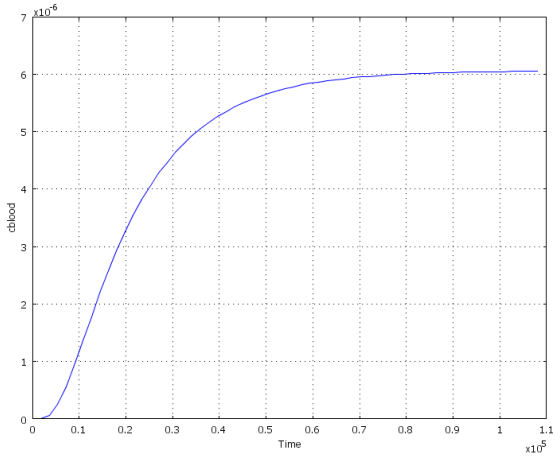


Figure 6. Fentanyl blood concentration over 8 hours while using ThermaCare heat pad continuously (over 30 hours). Blood concentration, cblood, is given mol/m^3. Time is given in seconds.

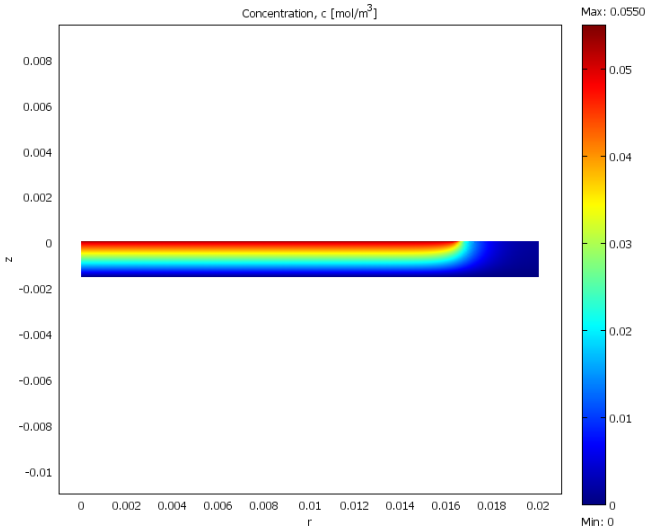


Figure 7. Fentanyl concentration profile after 30 hours in the epidermis and dermis when using a ThermaCare heat pad.

In addition to simulating the increase in fentanyl dose to a patient using a ThermaCare heat pad over different durations of time, this computer model was also used to simulate a patient with a fever (modeled at 102º F) and a patient whose patch is covered by a heating blanket. As seen in Figures 8-9, the elevated body temperature of a patient with a fever resulted in a 40% increase of fentanyl in the bloodstream. This simulation can be related to many clinical cases during which the patient becomes ill while using fentanyl skin patches. Since these patches are used continuously (replaced every 36 to 72 hours depending on the patch), illness of a patient could very well affect the dose of fentanyl that they receive through the duration of the illness. This results of this simulation make it apparent that both manufacturers and physicians should

include such cases when instructing patients on the use of fentanyl pain patches for enhanced safety.

Another case of interest was that of application of a heating blanket (modeled to maintain a constant temperature of 42 °C or 107.6 °F).[viii] As seen in Figures 8-9, the application of a heating blanket placed over the patient resulted in the highest increase of fentanyl blood concentration of the heating situations considered in this study with a 180% increase of fentanyl blood concentration when compared to the no heat case. Heating blankets placed over patients using fentanyl patches can lead to very dangerous situations. In one such documented case, a heating blanket was placed over a patient in the hospital. The applied heat resulted in a spike in fentanyl blood concentration that caused the patient to go into respiratory failure. Fortunately, in this particular case, the patient's physicians realized the cause and promptly removed the heating blanket and the patient recovered from the incident.[ix] Documented clinical cases similar to this incident not only stress the potential dangers of fentanyl pain patches when heat is applied, but also stress the importance of building a simulation that can model and predict such dangerous heating situations.

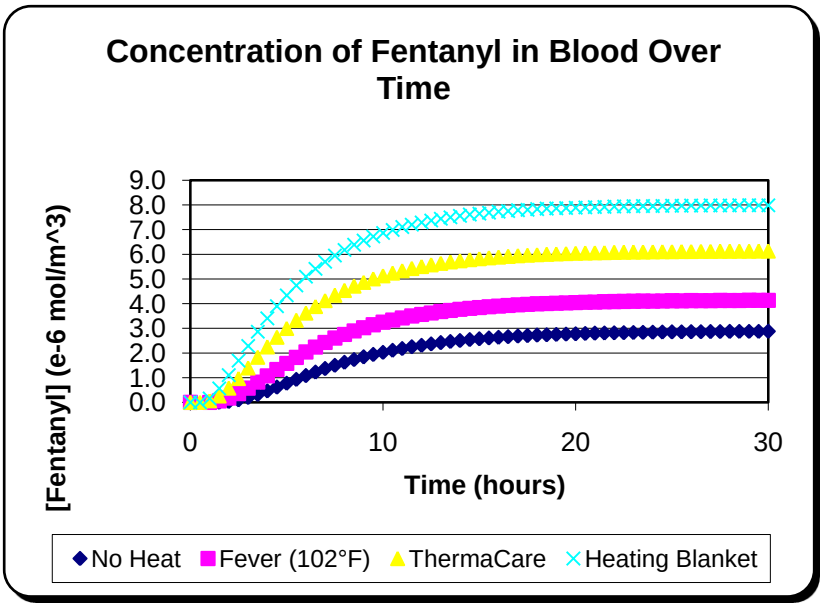


Figure 8. Comparison of fentanyl blood concentration over time with no heat, fever, ThermaCare heat pad, and heating blanket simulations.

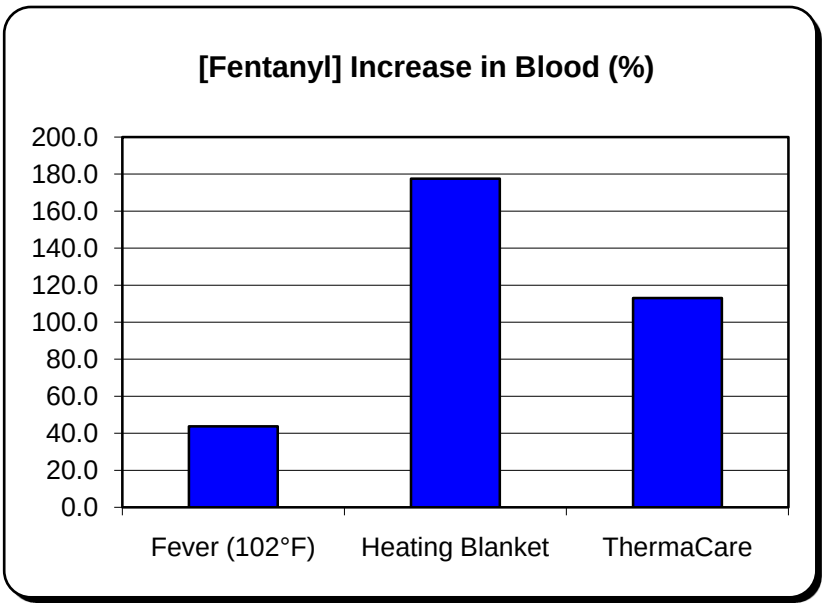


Figure 9. Increase in fentanyl blood concentrations in different heating situations (fever, heating blanket, and ThermaCare heat pad. Increases are reported as percent increases as compared to the simulation with no applied heat.

Sensitivity Analysis

Our sensitivity analysis with respect to a decrease and increase in conductivity, specific heat, and density values yielded no major change in the values of average concentration and temperature. The average concentration was calculated at the end of the simulation (6 hours, or 21600 seconds); however, temperature of the entire area converges to a single value at this time point. Therefore, a point where there was the largest gradient in temperature throughout the depth of the region of interest was chosen for the sensitivity analysis (400 seconds). Sensitivity analyses of the various parameters involved (thermal conductivity, density, and specific heat of the drug) were performed according to their likely ranges of variation as reported in the literature. No significant changes in either skin temperature or drug concentration were observed for such variations. Fifteen percent variability for thermal conductivity (k) and 5% variability for density (ρ) and specific heat (c_p) were chosen given these observed ranges as reported in the literature.[x] The sensitivity analysis with respect to temperature is seen in Figure 10. As shown in Figure 10, +/-15% variability in thermal conductivity (k) nor +/-5% variability in density (ρ) and specific heat (c_p), respectively, caused a significant deviation in the calculated average temperature at the 400 second time point (approximately 310K). Figure 11 illustrates the sensitivity analysis for concentration. As displayed in Figure 11, +/-15% variability in thermal conductivity (k) nor +/-5% variability in density (ρ) and specific heat (c_p), respectively, caused a significant deviation in the calculated average concentration at the 6 hour time point (approximately 1.85 mol/m^3).

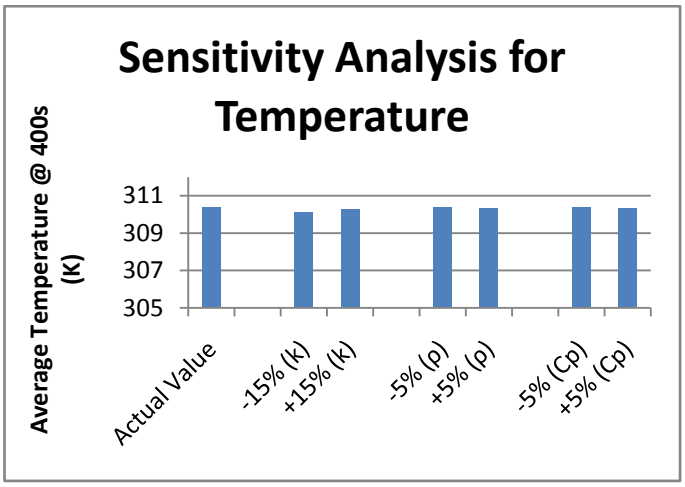


Figure 10. Sensitivity analysis for temperature. Thermal conductivity (k) was varied by 15%, while density (ρ) and specific heat (c_p) were varied by 5%. Average temperature was calculated at the 400 second time point.

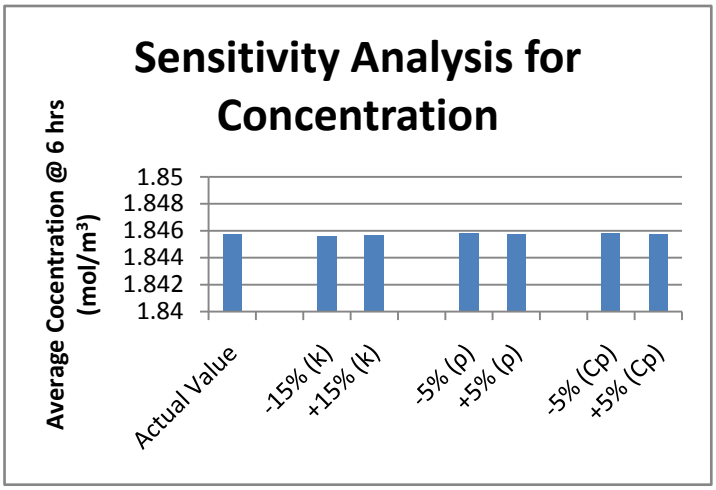


Figure 11. Sensitivity analysis for concentration. Thermal conductivity (k) was varied by 15%, while density (ρ) and specific heat (c_p) were varied by 5%. Average concentration was calculated at the six hour time point.

Accuracy Check

An accuracy check was performed to assess the validity of our model using a completely separate study (results given below). Model data shown below is similar to that in the literature. The input parameters for the model were modified to simulate the diffusion of scopolamine through human skin as explored by Rim et al.[xi] Our simulation is compared to that of the published study with no applied heat and constant diffusivity in both cases. This accuracy check verifies the data produced by the no heat model where diffusivity is constant against experimental data through the epidermis.

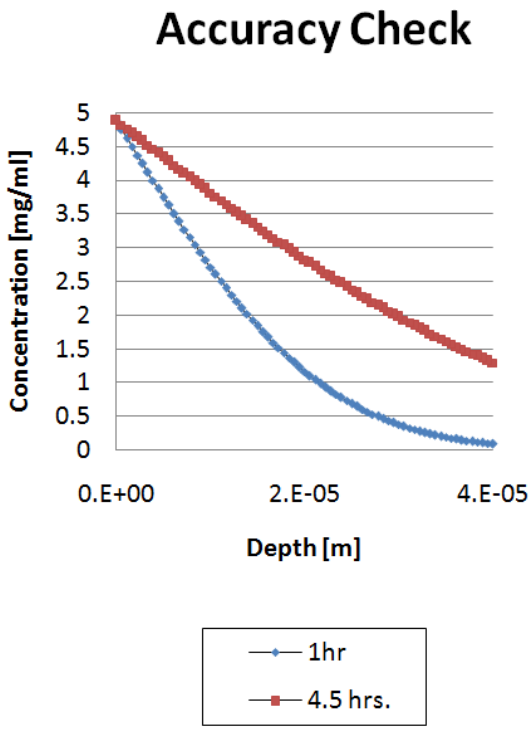


Figure 12. Scopolamine concentration profile for initial concentration of 4.4 mg/ml at different times. The diffusion is from an infinite vehicle.

Our model was verified for accuracy using data from the study by Ashburn, et al. for an experiment that was separate from the data used to calibrate our model (see “Methods”). The study used for verification of our model recorded blood concentration of fentanyl over a 30-hour period following application of a fentanyl patch, with heat applied during the first four hours, and then again for one hour at the 24-hour mark. (Note that the experiment upon which our model was based did not include heating for the first four hours, and was conducted with a separate subject population.)

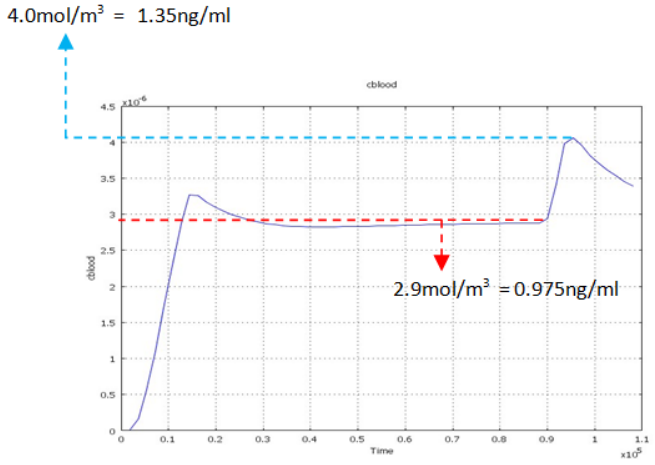


Figure 13. Comparison of model to experimental data: fentanyl blood concentration over 30 hours with early applied heat (first four hours) and one hour of applied heat at 24 hours.[xii]

It is readily observed that the general form of the concentration curve generated using our model very closely resembles that of the experiment: a peak occurs at the end of early heat addition (4 hrs), followed by a trough period which culminates in a second spike at the beginning of the final heating period (24 hrs). Comparing our peak values of 1.35ng/mL to 1.15ng/mL and trough values of 0.975ng/mL to .65 ng/mL, it becomes evident that the model's data closely resembles the experimental data: both trough and peak values are within the correct orders of magnitude and are within 50% of actual values.

It should be noted that the model data reports slightly higher fentanyl blood concentrations overall, compared to experimental data. We acknowledge that our model does not take into account the effects of drug degradation, which becomes a factor in fentanyl blood concentration at the timescales with which our model is concerned. Furthermore, our model is designed such that all fentanyl diffusing through the bottom of the dermis layer is reported in blood concentration. Both of these limitations existing in our model would account for slightly higher blood concentrations being reported than are found in the experimental study.

Conclusions and Design Recommendations

The motivation in undertaking this particular study was to assess the dangers of deliberate or accidental addition of heat to skin patches containing fentanyl. It is evident from our findings that the addition of heat by either a heating pad or heating blanket dramatically increases the rate of drug delivery from a patch applied to the skin. Given the myriad factors involved in prescribing the proper dose of fentanyl to a patient (including body weight, size, gender, amount of pain, response to side-effects, length of time having taken fentanyl or other related drugs, and other factors), as well as the many known side-effects and acknowledged toxicity of the drug, the importance of maintaining the prescribed dosing is realized. Our findings reported herein

indicate that the addition of heat to a fentanyl skin patch might increase the rate of drug delivery well into the toxic range for certain patients. We further extrapolate from our findings that heat addition of any kind, such as from exercise (which may or may not be relevant considering the nature of the patient's ailment), use of a sauna, or a particularly hot day, might similarly increase the rate of fentanyl drug delivery well above the tolerable dosage. However, most of such cases are not as relevant to discussion as most fentanyl patients are not undertaking such activities given the nature of the conditions that require fentanyl prescription. Since both the activities and prescription requirements can be quite variable from patient to patient, the development of this simulation could greatly benefit the manufacturer and physician by being able to give the patient more individualized, quantitative guidelines for safe use of their prescribed fentanyl skin patch.

The negative side effects that are caused by high levels of fentanyl blood concentration pose a greater danger with patches that are manufactured to provide higher doses over time. Given the numerous factors that govern a patient's needed dose of fentanyl, physicians can prescribe patches that vary in their intended drug flux or prescribe the use of multiple patches simultaneously. All simulations in this study were modeled with a "low dose" patch (25 µg/hr). However, by running many simulations it was determined that a patch that provided 80µg/hr of fentanyl would approach the lethal blood concentration of fentanyl when coupled with a ThermaCare heating pad. Patches designed to deliver 80µg/hr are currently available for patients needing higher doses. As seen in Figure 14, addition of a ThermaCare heat pad causes the blood concentration to approach $2.0*10^{-5}$ mol/m^3 over the 30 hour use period (lethal fentanyl blood concentration for most patients is $2.077*10^{-5}$ mol/m^3).[xiii]

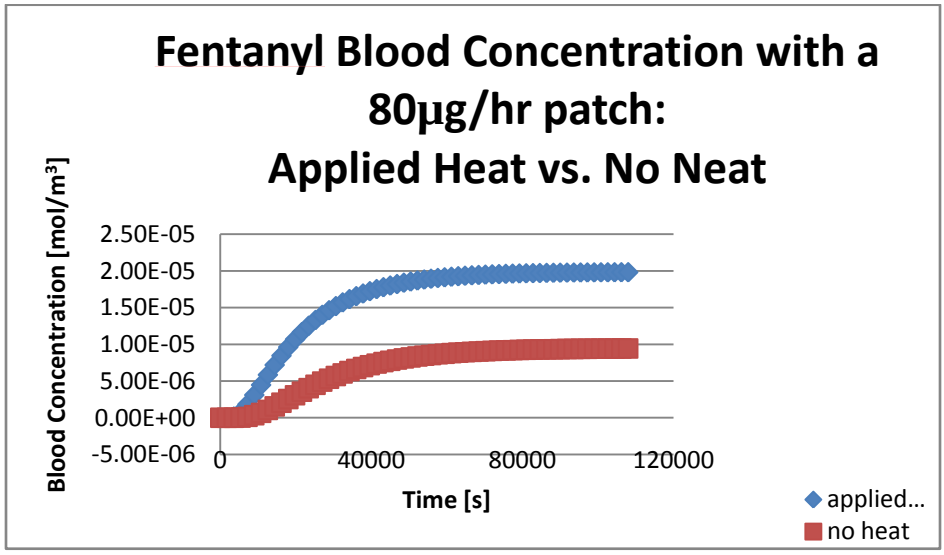


Figure 14. Fentanyl blood concentration for 80µg/hr patch with and without applied heat by a ThermaCare heat pad.

In addition to using this simulation for providing such guidelines, a computer simulation could be used to experiment with potential designs without as much experimentation with subjects. The

development of a transdermal delivery system for fentanyl that protected patients against possible overdose is a potential goal of future simulation studies. Despite the packaged warnings from both the companies that market the fentanyl patches and warnings from the FDA, overdoses still occur and are often lethal. Accidental overdoses have also taken the lives of several children who placed used patches from the trash on themselves. The development of a patch where patients are required to apply heat to the patch in order to obtain the necessary dose of fentanyl over time is a possible design that could eliminate such accidental overdoses. A drawback to such a design could present the problem of insufficient dose, however, which would be another parameter that would need to be analyzed in the severity of effect on the patient through clinical studies. Additionally, the cost of such a system would likely discourage any company from producing such a product, given the cost of a heat pad. For example, the ThermaCare heat pad used in this study (maintaining temperature for up to 8 hours) costs approximately three dollars. Such a system would be financially impractical in addition to the inconvenience posed to the patient. Reusable heat pads (such as those placed in the microwave) could solve the financial constraint of a heat-required system, however, the inconvenience and potential discomfort that the patient would experience when using the system may discourage its development. Given the number of heat pads available on the market, manufacturability would not be a concern for implementing this system. The drawbacks, as stated previously, would lie in the economic and user convenience and comfort, for a system with increased safety.

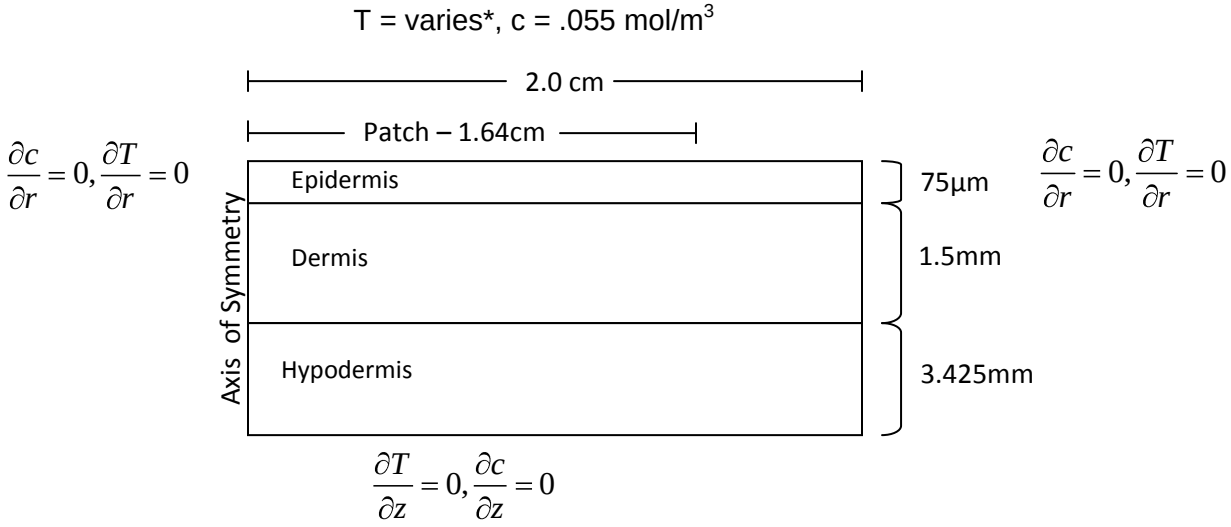
While any redesign of the fentanyl patch would require animal and/or human clinical studies, the use of computer simulation as modeled in this report would drastically reduce experiment time and cost in such an endeavor. Patches that contain small needles that direct fentanyl directly into the capillary network in the dermis could potentially be designed in order to lessen the possible effects of heating on drug diffusion in the epidermis and dermis and thereby improve the safety of the patch. Patches of this design would likely incur a greater cost to the manufacturer, but such an economic constraint could provide greater safety associated with the product. Despite the safety gained by reducing the effects of potential heating, such a design could raise other ethical questions since it would be easier to abuse by fentanyl addicts and would not improve the safety issue of children mistaking fentanyl skin patches as stickers and placing them on their bodies, resulting in overdose.

Given the numerous negative side effects of fentanyl overdose and their severity, the addition of heat to such skin patches is realized given the number of health issues, accidental deaths, and suicides caused by these patches every year. However, other drugs that are currently available in transdermal delivery systems could potentially be enhanced by applied heat where a faster dose is necessary. Scopolamine, a drug used to treat motion sickness, is on such drug. In order to be effective, the drug must reach a given steady state concentration in the blood at least an hour before the motion sickness would set in. Since many consumers do not always plan ahead or anticipate motion sickness, a design that allowed a faster delivery would be beneficial for such a system. However, scopolamine, similarly to fentanyl, can have adverse effects on some people when too high of a dose is given too quickly, though not as severe as those of fentanyl (side effects of dizziness and nausea). Therefore, such a design would need to implement safety mechanisms as well as packaged warnings. Another proposed possibility

for heat and diffusion coupled transdermal drug delivery is for emergency contraception, currently available in pill form, but advantageous when the dose of drug is administered faster to the bloodstream. Again, as mentioned previously, the development of such a system would invariably require numerous clinical studies, but the use of a computer simulation model would expedite the design and experimental process of such systems. Lastly, it should be noted that there is ethical concern when designing systems that require heating to be most effective. This is due to the fact that advertisement of such a system may lead consumers of other transdermal drug delivery products to believe that applied heating is beneficial to their own system, which may not in fact be the case, such as that of fentanyl, and could lead to misconceptions that promote abuse of these patches and result in negative side effects and/or death.

Given the potential dangers associated with fentanyl, a computer simulation of its diffusion and therefore delivery into the body can be an important asset for both manufacturer and physician. Simulations can provide manufacturers and physicians the necessary tools to provide patients with quantitative guidelines in hopes of improving the safety of transdermal fentanyl delivery systems. The reduced time of experimentation granted by a simulation benefits the company by reducing costs and time to development, as well as a means to test newly conceived designs or safety implements for the system before manufacturing them. As stated previously, this simulation may also be used to assess the safety and feasibility of using applied heat with other transdermal drug delivery systems.

Appendix A: Mathematical Statement of the Problem



Patch size (circular) = 33.6 cm^3

*Temperature profile as given by Figure 4.

Figure 15. Schematic of system and skin with boundary conditions and appropriate geometry. The hypodermis layer was not included in the COMSOL model since fentanyl uptake occurs in the dermis. Not drawn to scale.

Initial Conditions:

T_{tissue}=37ºC

C_{tissue}=0 mg/cm^3

Governing Equations:

Heat Transfer: $\rho c_p \frac{\partial T}{\partial t} = k\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial T}{\partial r}\right)+\frac{\partial^2 T}{\partial z^2}\right]$

Mass Transfer: $\frac{\partial c}{\partial t} = D\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right)+\frac{\partial^2 c}{\partial z^2}\right)$

Arrhenius Relation: $D(T) = D_0 e^{-(E/RT)}$

Table 1. Input Parameters[xiv]	
Density (ρ)	1000 kg/m^3
Thermal Conductivity (k)	
Epidermis	0.21 W/(m·K)
Dermis	0.37 W/(m·K)
Heat Capacity (c_p)	
Epidermis	3181.82 J/(kg·K)
Dermis	2846.15 J/(kg·K)
D isotropic	
Epidermis	3.61e-11*exp(-50/(0.90078*T)) m^2/s
Dermis	3.61e-11*exp(-50/(0.90078*T)) + 400*(3.61e-11*exp(-50/(0.90078*T)) -3.61e-11*exp(-50/(0.90078*306))) (T) m^2/s
Reaction Rate (R)	0 mol/(m^3·s)
[Fentanyl] at Interface	0.055 mol/m^3

Appendix B: Solver, Time Stepping, Mesh, and Mesh Convergence Analysis

Solver

Both the Mass and Heat Diffusion solvers in COMSOL were used for the simulations presented in this report. The Direct (UMFPACK) linear system solver was used.

Time Stepping

Over the 30 hour simulations presented in this report, time steps were taken every 1800 seconds. Time steps taken by solver were set to Intermediate. Times stored in output were specified times.

Mesh Convergence

In order to determine that the solution is independent of the mesh, a mesh convergence was completed. The number of mesh elements was varied while calculating the average concentration and average temperature. These values were then plotted in order to view the number of mesh elements where the average concentration and average temperature converged to a value. By completing the mesh convergence, it was determined that 3000 mesh elements is optimal for the model in regards to computing time.

As displayed by Figures 18-20, temperature values are accurate for all of the experimental meshes, but for the concentration, the average concentration converges for the mesh with approximately 4500 elements (Figures 16 and 21) . However, after computing the concentration profile over the time frame of interest, it was concluded that the greatest variation in concentration was in the epidermis region. Therefore, separate mesh convergences were performed for subdomains 2 and 3, the dermis and the epidermis, respectively. The final mesh (Figure 22) was chosen for subdomains 2 and 3 separately at the mesh element number where both the average concentration and temperature converged to one value.

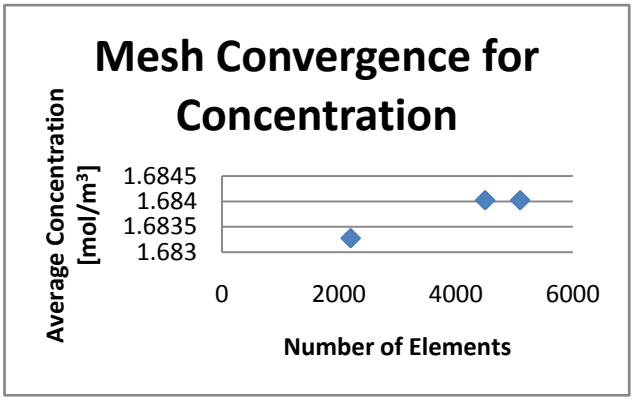


Figure 16. Mesh convergence for concentration for all three subdomains (hypodermis, dermis, and epidermis).

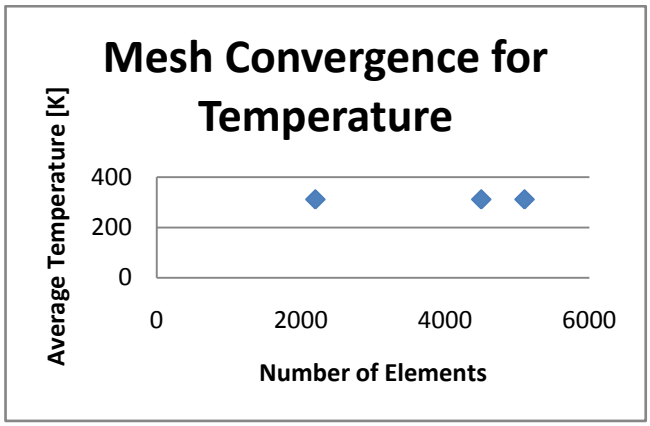


Figure 17. Mesh convergence for temperature for all three subdomains (hypodermis, dermis, and epidermis).

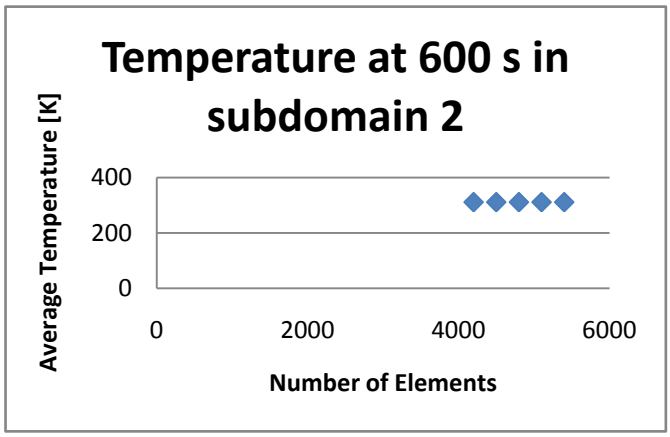


Figure 18. Mesh convergence for temperature in subdomain 2 (dermis) after 600 seconds.

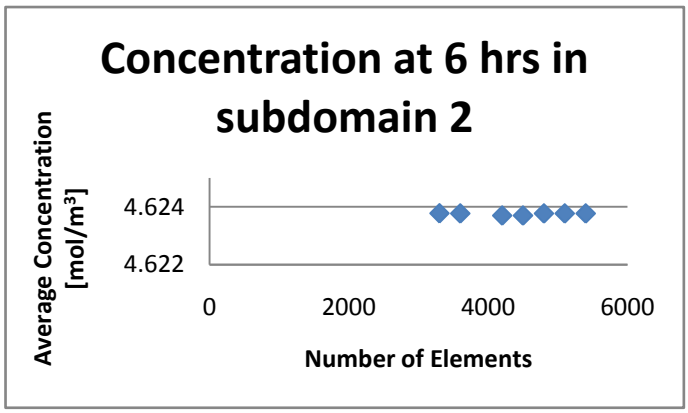


Figure 19. Mesh convergence for concentration in subdomain 2 (dermis) after 6 hours.

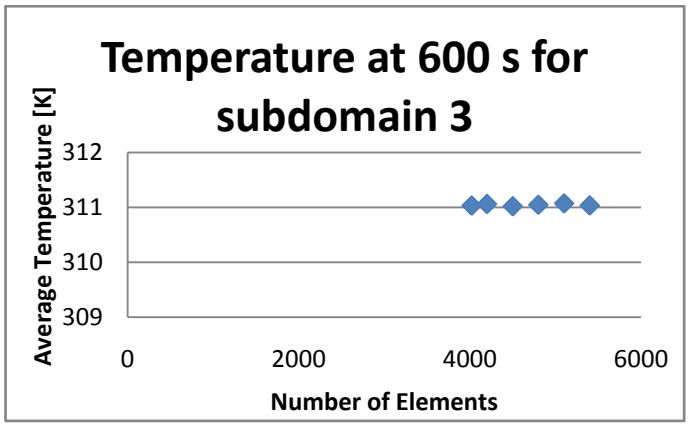


Figure 20. Mesh convergence for temperature in subdomain 3 (epidermis) after 600 seconds.

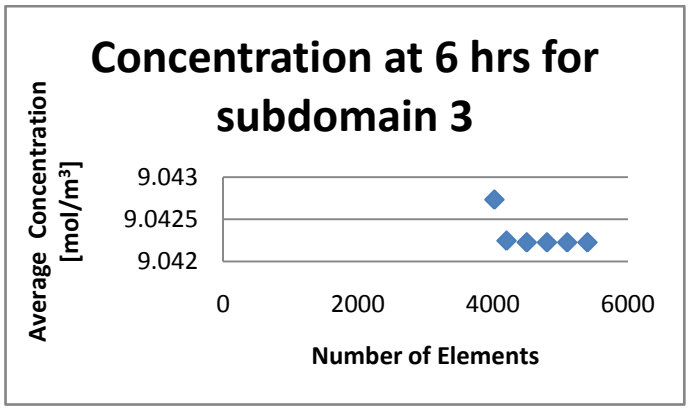


Figure 21. Mesh convergence for concentration in subdomain 3 (epidermis) after six hours.

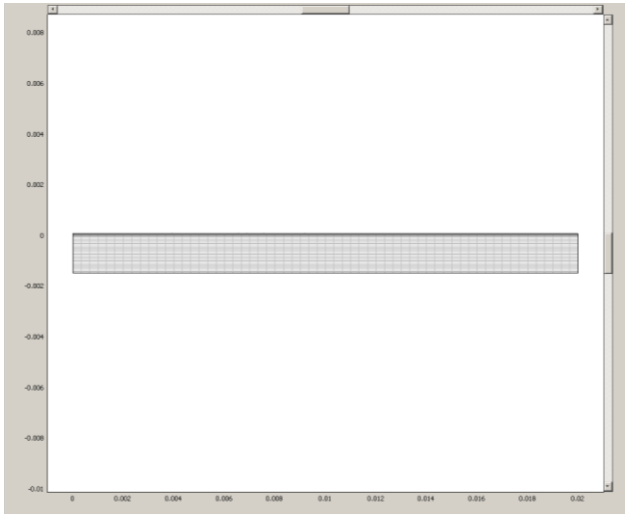


Figure 22. Final mesh containing a total of 3000 rectangular elements.

Appendix C

Diffusivity of Fentanyl:

$P = KD/\Delta x$, where:

P = permeability; D = diffusivity; K = partition coefficient; Δx = thickness of diffusion layer

$K = C_p/C_s$, where:

C_p = concentration in polymer; C_s = drug solubility in pure water

$D = D_0e^{(-E/RT)}$, where:

D_0 = pre-exponential factor; E = activation energy of diffusion; R

= universal gas constant; T = temperature, Kelvins

Experimental data and known constants:

$P_{37ºC} = 16.8x10^3 cm/hr$[xv]

$C_s = 0.122 mg/mL$[xvi]

$C_p = 0.2968 mg/mL$

$\Delta x = 1.575 mm$

$E = 50 kcal/lbmol$

$R = 0.90078 kcal/lbmol \cdot K$

$T = 310 K$

From calculations:

$K = 2.433$

$D = 3.02x10^{-11} mol/m^3$

$D_0 = 3.61x10^{-11} mol/m^3$

Appendix D: References

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