Design of a Transmucosal Patch for Fentanyl Delivery to Cancer Patients

Floris van Breugel
Ed Reznik
Nick Burnett
Simon Frid

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Executive Summary

Fentanyl is an analgesic that is about 80 times more potent than morphine. It is administered as a transdermal patch for chronic pain relief and as an oral transmucosal lozenge for breakthrough pain relief which is often experienced by cancer patients. The latter administration, under the brand Actiq® exploits the higher permeability of buccal mucosa to achieve a much faster onset. We developed a model of a transmucosal patch as an alternative to existing designs, in order to achieve faster pain relief, improved dosage efficiency, and greater pharmacokinetic control via an impermeable layer. We simplified the design in to 1D model with diffusion and a reaction rate, which simulates uptake fentanyl into the blood. After implementing the model in COMSOL, we calculated the pharmacokinetic profile of fentanyl in the plasma over time with first order linear non homogenous equation. Our resultant profile peaks at 20 minutes and matches Actiq®'s profile. A sensitivity analysis yielded that the plasma elimination rate of fentanyl, the epithelium diffusivity and the diffusivity, thickness and distance of the impermeable layer all had a significant affect on the time to peak. A second sensitivity analysis determined that the initial concentration and diffusivity, thickness and distance of the impermeable layer had the greatest influence on peak fentanyl concentration. In conclusion, we believe that a transmucosal patch is a viable design alternative for fentanyl delivery due to it's a rapid onset and the potential for diffusive control with the impermeable layer. Further exploration is recommended to evaluate

Key words: fentanyl delivery, cancer, pain relief

Introduction

Fentanyl is an analgesic that is about 80 times more potent than morphine, and shows great promise for fast-acting severe pain relief. Fentanyl is effective at plasma concentrations as low as 2ng/ml and undergoes rapid metabolism. It is commercially available as a transdermal patch and as an oral transmucosal lozenge under the names Duragesic® and Actiq® (Fig. 0), respectively. The transdermal patch focuses to relieve chronic pain, and therefore has a delayed effect which results in the accumulation of Fentanyl in the skin. Transmucosal delivery avoids these problems because of the higher permeability of the buccal mucosa as compared to the skin, yielding a 15-20 minute onset in Actiq®. Actiq® is primarily intended for breakthrough cancer pain relief, in which patients have developed considerable tolerance to existing analgesics. Despite Actiq®'s advantages, the lozenge delivery is poorly controlled as 75% of Fentanyl is lost to saliva. Since Actiq® is administered as a lozenge, the drug delivery is not easily controlled by the doctor. Additionally, the drug delivery is affected by changes in pH, temperature, and the amount of saliva. For this reason, we wish to model a mucoadhesive Fentanyl patch in order to obtain better pain relief, with greater efficiency and control.
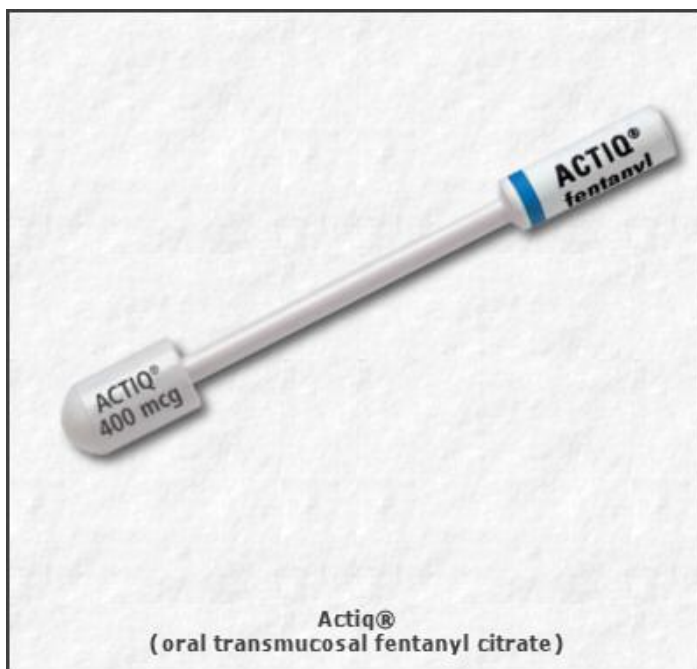

Figure 0. Actiq® lollipop.

Design Objectives

The purpose of our model is to evaluate the potential of a fentanyl transmucosal mucoadhesive patch as an alternative to the already existing transdermal patches and oral transmucosal lozenges. Our first design objective is to decrease the time for fentanyl to reach effective plasma concentrations. Faster delivery of Fentanyl would result in faster pain relief, which is a top priority among breakthrough cancer patients. As a result, patients would be able to conveniently obtain pain relief as necessary, without the need for sustained analgesic concentration in the plasma. Our second design objective is to increase the effective fentanyl plasma concentration for a given dosage. This objective aims to be a direct improvement on the 75% mass inefficiency of Actiq®. In addition, we anticipate an adhered patch would be less susceptible to the oral cavity uncertainties in temperature, pH, and amount of saliva, therefore improving overall control. Our final design objective is to determine the influence of an impermeable layer within the patch that can be used to control the diffusion of fentanyl. If we can manipulate the diffusivity or distance of the impermeable membrane to the tissue, we can

customize the pharmacokinetic profile without changing the concentration of fentanyl within the patch.

Problem Schematic

The cheeks of the oral cavity are lined with the buccal mucosa, see Fig. 1. The stratified squamous epithelium of the buccal mucosa is not keratinized. Keratinized epithelium contains lipids which significantly impede the layer's permeability to water and water soluble compounds. As a result, the buccal epithelium is more permeable than the epidermis and other keratinized epithelia. Underneath the epithelium is a think layer called the lamina properia. The buccal submucosa lies underneath the epithelium and lamina properia, and is rich in blood vessels.
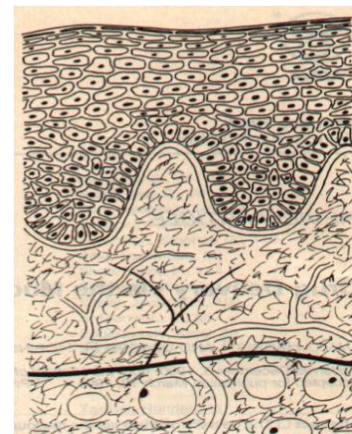
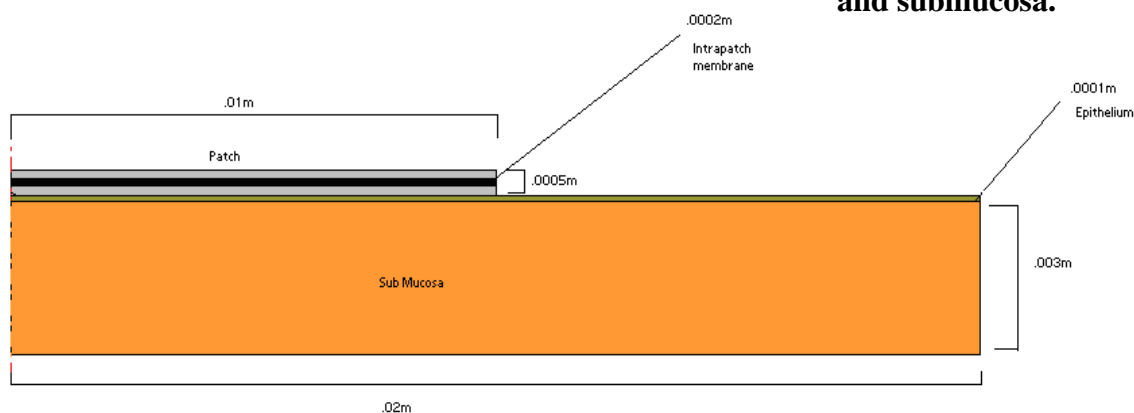**Figure 1. Schematic showing epithelium, lamina properia, and submucosa.**

Figure 2. Schematic of the patch, mucosa and their various dimensions.

A schematic of our proposed model of the transmucosal drug delivery is shown in Fig. 2. Fentanyl diffuses from the patch, through the epithelium and into the submucosa, where is enters systemic circulation. We chose to simplify our model by combining the lamina and submucosa because the geometry of the lamina was difficult to model and has very similar diffusive properties to the submucosa. The diameter of the cylindrical patch is 2cm, with a height of 0.5mm. The epithelium and submucosa are 0.1mm and 3mm respectively. In addition to the adhesive patch, epithelium and submucosa, we incorporate a 0.2mm impermeable membrane in the patch to examine the effect of controlled diffusion. Because the flow of fentanyl is predominately from the patch to the submucosa, we used a 1D model (experimentation with a 2D axi-symmetrical model is shown in the appendix). We modeled the mass diffusion of fentanyl taking into consideration the transient, diffusion and reaction terms as shown below:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + R \qquad (1)$$

where c is the concentration of fentanyl, D is the diffusivity of the layer and R is the reaction rate of fentanyl in the layer.

The diffusivity of mucoadhesive hydrogel patches is typically 10^{-7} m^2/s. In the presence of the impermeable layer, the diffusivity is changed to 10^{-11} m^2/s. Studies have shown that the diffusivities of the buccal mucosa epithelium and submucosa are $4*10^{-11}$ and 10^{-11} m^2/s respectively. The purpose of the reaction rate is to model the uptake of fentanyl into blood. Uptake of drugs into blood vessels is often modeled by 1st order reaction rates, with a reaction coefficient of ~1 for highly vascularized tissue, such as the submucosa. In order to approximate the complicated geometry of the epithelium and lamina properia, we included a reaction rate in the epithelium, albeit only 10% of the rate in the submucosa.

$$R_{Patch} = 0 \qquad R_{Epithelium} = -0.1\,c \qquad R_{Submucosa} = -c \qquad (3)$$

Since source and sink of fentanyl is the patch and the submucosa respectively, we treat our model as an isolated system. Our boundary conditions on the top of the patch and the bottom of the submucosa are both zero flux.

$$\left.\frac{\partial c}{\partial x}\right|_{Patch, x=0} = 0 \quad \text{and} \quad \left.\frac{\partial c}{\partial x}\right|_{Submucosa, x=.003} = 0 \qquad (2)$$

Actiq® is currently available in 200, 400, 600, 800, 1200 and 1600µg dosages. Given that the volume of our patch is $1.57 * 10^{-7}$ m^3 and fentanyl's molecular weight of 336g/mol, we can calculate our initial molar mass to match Actiq®'s dosages. Since we expect our patch to use less fentanyl than Actiq®, we chose an initial mass of fentanyl in our patch of 5 mol/m^3, corresponding to ~250µg dose.

Results

In order to achieve our design objectives we modeled the system in COMSOL (details in appendices), a finite element approach to modeling diffusive processes. Initially, the system only modeled the concentration of drug in the patch and tissue layers. However, this resulted in a simple solution where over time the drug reached a uniform concentration in the tissue. However, the submucosa (and to some extent the epithelium) is highly vascularized, and would quickly take up the fentanyl as it was diffusing. Therefore, a reaction rate in the submucosa (and a smaller reaction rate in the epithelium) was added to simulate uptake to the blood.

However, it is actually the concentration of fentanyl in the blood that is of interest. Pharmacokinetic data (and intuition) point to the fact that concentration in the blood approaches zero over time as the drug is metabolized and systemically removed. To accurately replicate this data, a first order differential equation was solved in COMSOL. This equation included terms that represented drug uptake to the blood and clearance/metabolism of drug in the blood. This is shown below.

Rate of change of fentanyl plasma concentration: **dc/dt** (mol/mL)	=	Rate of change of fentanyl plasma concentration due to adsorption: **f'** (derivative of output)	—	Rate of change of fentanyl plasma concentration due to elimination: **k · c** (1st order reaction rate)

The most apparent characteristics of the drug profile are the brief burst immediately following administration and the tapering tail following the burst. With our default values we achieved a peak time of 20min and a concentration of Fentanyl of 0.09 ng/mL (see Fig. 3). Depending on the dosage administered in the patch, the peak concentration in the burst increases proportionally. This peak is desirable because it provides pain relief to the patient by after only a few minutes. Once the drug concentration in the blood spikes, the patient receives pain relief and the tapering drug concentration will sustain the patient for several more hours.
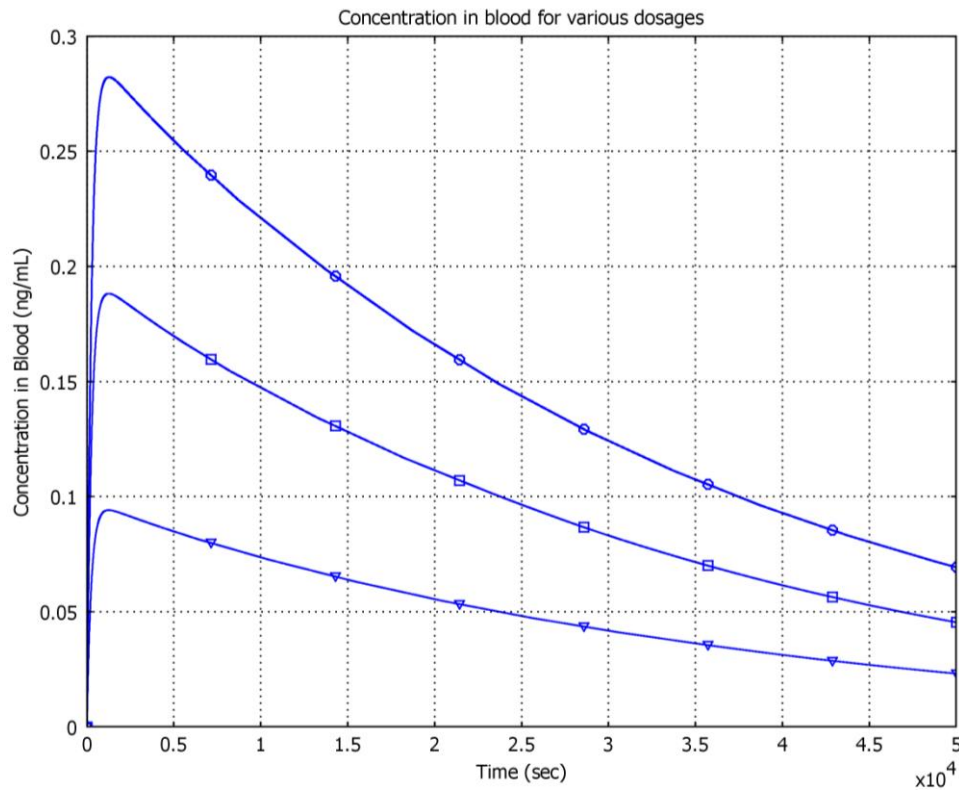
Figure 3. Drug concentration profile for varying initial concentrations (5, 10, 15 mol/m^3 corresponding to triangles, squares, and circles respectively).

Finally, Fig. 4 shows our final drug profile across the patch. The scale of the y-axis is extremely small, indicating that after 50000 seconds (13.9 hours), there is essentially no drug left in the patch. This is excellent, because it indicates that little or no drug is left in the patch.
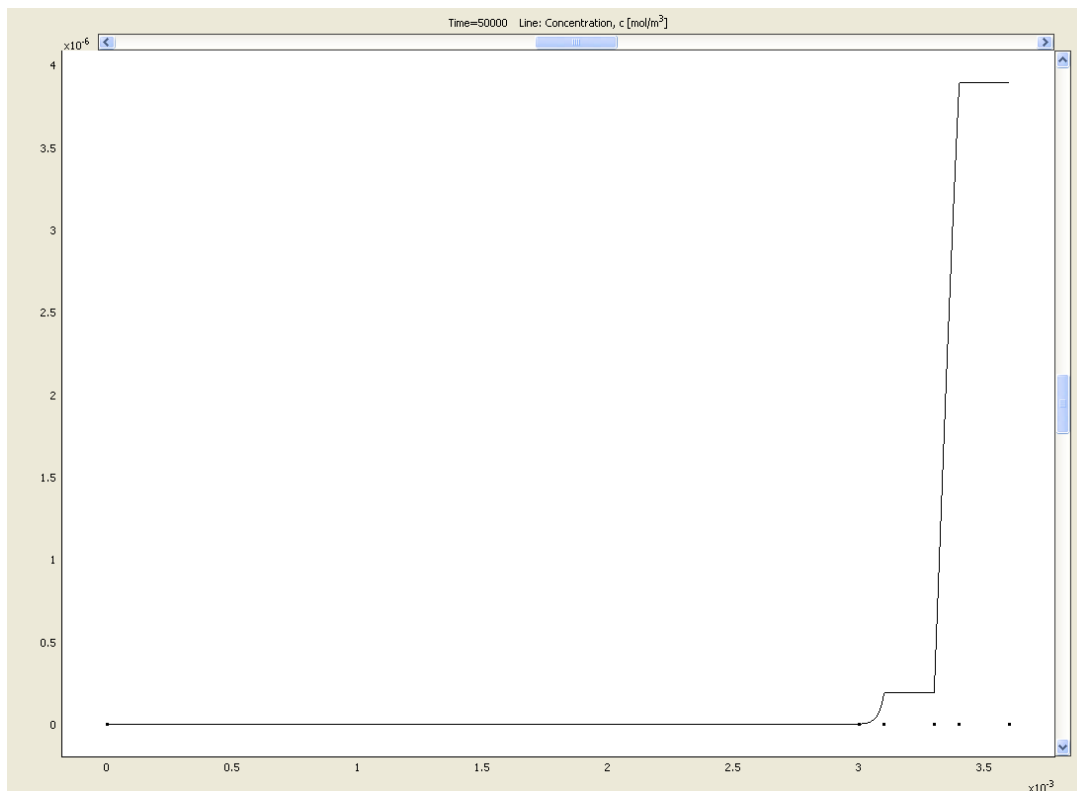
Figure 4. COMSOL model after t=50000s (13.9hrs). Note that the total concentration of the drug left in the system is nearly zero, this is because it has all been wicked away by the blood (as modeled by the reaction constant).

Sensitivity Analysis

In evaluating our model, several parameters were identified as candidates for sensitivity analysis based on their significance in the model formulation. These parameters include:

♦ Diffusivity of the epithelium
♦ Reaction rate in the submucosa
♦ Reaction rate in the epithelium
♦ Clearance rate (elimination rate constant) in the blood
♦ Initial Concentration
♦ Diffusivity of the impermeable layer
♦ Thickness of the impermeable layer
♦ Location of the impermeable layer in relation to the epithelium

These eight parameters were evaluated on their impact on two metrics: *time* to peak blood concentration and *peak blood concentration* itself. Results from the sensitivity analysis are shown in Fig. 5 and Fig. 6. In each case, the parameter being evaluated was increased and decreased by 20% of its initial value. The sensitivity analysis considered two types of parameters: design parameters (those relating to the qualities of the patch, such as barrier diffusivity) and system parameters (those relating to the qualities of the patient, such as epithelial diffusivity).

Time to peak concentration is the more important of the two metrics because it directly determines how quickly patients experience pain relief. The three system parameters that affect time to peak concentration most significantly are clearance rate in the blood, epithelium reaction rate, and diffusivity in the epithelium. Qualitatively, it makes sense that these three parameters would have an impact on time to peak concentration. Changes in clearance rate in the blood determine how quickly blood can eliminate drug that accumulates systemically in the body. Lower clearance rates imply that more of the drug can accumulate before the rate of clearance overcomes the rate of accumulation, and so lower clearance rates yield higher time for peak concentration (and higher clearance rates yield smaller time to peak concentration).

Similarly, the reaction rate and diffusivity in the epithelial layer influence the time to peak blood concentration. This is an intuitive result: the epithelial layer acts as the primary barrier to diffusion of the drug into the submucosa (where most of the drug is taken up into the blood). Thus, reducing the time that drug resides in the epithelial layer as well as increasing the amount that is taken up in this layer, will increase the *rate* at which drug reaches the blood.
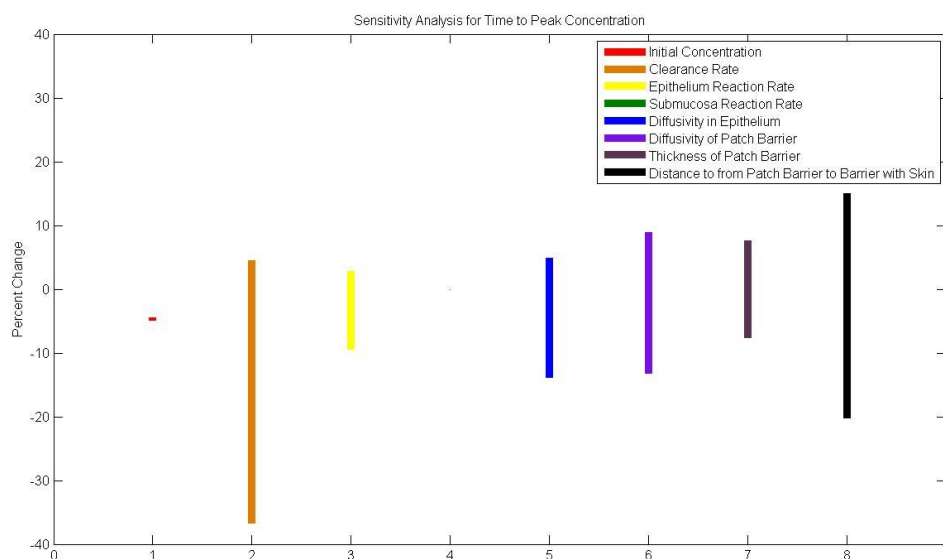

Figure 5. Sensitivity analysis plot for important system variables, and their effect on time to peak. Each variable was tested at +/- 20% of the default value, and results are shown as percent change from the default time to peak.

A large effect was also observed as our three system parameters were altered. These results are critical, as they indicate that the time to peak may be controlled by the design of our impermeable barrier. The parameter which had the greatest affect on time to peak concentration was distance of the patch barrier from the epithelium. This is an extremely desirable result, because in terms of manufacturing difficulty, the parameter which is easiest to modify is the placement of our patch barrier. By increasing the distance between the barrier and the skin, we can reduce the time to peak concentration. Similarly, by the reducing the distance, we can increase the time. In addition, the thickness of the barrier has an effect on time to peak concentration. Increased thickness prolongs the time to peak, while decreased thickness reduces the time to peak.

The actual peak concentration is another metric we used in our sensitivity analysis. Initial concentration has the single greatest impact on actual peak concentration, but this is expected as increasing the dosage will naturally increase the peak blood concentration. None of the other parameters tested seemed to significantly affect the actual peak concentration. Aside from the clearance rate, the rest of the parameters relate to the rate of flow of drug into the blood, rather than the amount of drug itself. Thus, it is expected that these parameters would affect time to peak concentration more than actual peak concentration.
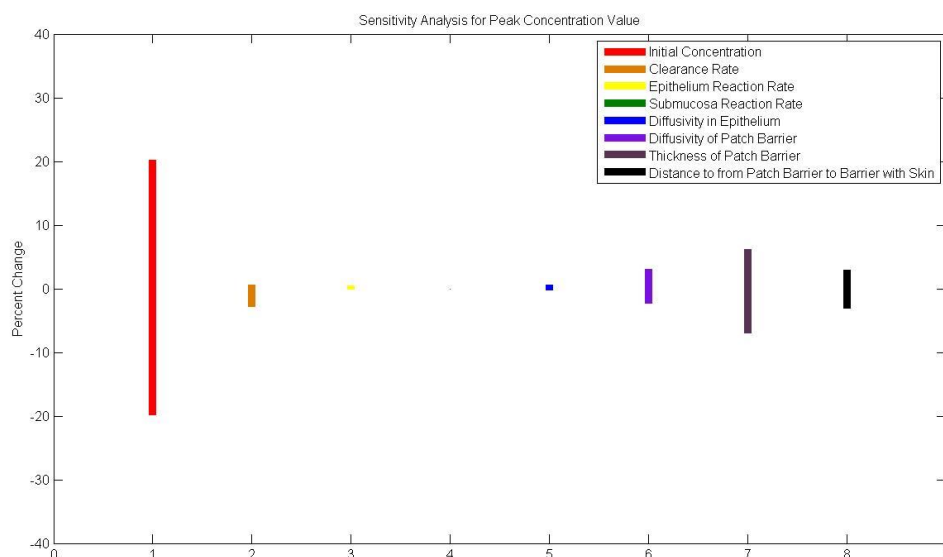

Figure 6. Sensitivity analysis plot for important system variables, and their effect on peak concentration. Each variable was tested at +/- 20% of the default value, and results are shown as percent change from the default peak concentration.

The system parameter that affected the peak concentration most significantly was the thickness of the patch barrier. As the patch barrier's thickness is reduced, a smoother, more constant blood concentration profile is achieved. Conversely, if the barrier's thickness is increased, a sharper blood concentration profile with a more pronounced peak is produced.

Addition of a Diffusive Barrier in the Patch

In order to custom tailor the curve of the patch we considered adding a barrier with a lower diffusivity inside the patch. As seen in Fig. 7, addition of this layer reduces the peak value, increases time to peak, and reduces the steepness of the curve. While these results may contradict our initial objectives of increasing time to peak and the peak concentration, they provide important information for future designs. The ability to alter the shape of the blood concentration profile adds a significant amount of control over how the drug is administered. By decreasing the peak concentration, greater dosages can be administered and higher concentrations can be maintained, for prolonged periods without resulting in patient overdose.
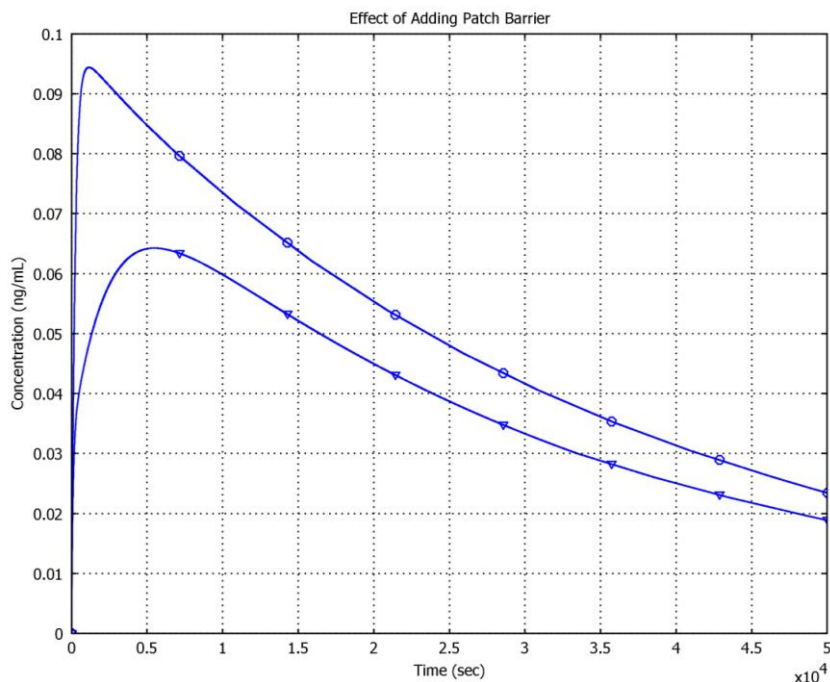
Figure 7. Profile with patch barrier (triangles) and without (circles).

Qualitative Interpretation

As the simulation starts the drug diffuses from the patch and into the epithelial layer. This layer has the lowest diffusivity of all layers in the system, and therefore serves as the rate-limiting layer in the process of drug absorption. As diffusion brings the drug into the submucosa, uptake to the blood occurs in both the epithelium and submucosa. Once in the blood, the drug is subject to a first order elimination reaction. Both the concentration and elimination rate of the drug increase until the peak concentration value is reached. The concentration steadily declines thereafter due to a reduced amount of drug left in the patch and a correspondingly high elimination rate. The result is the concentration profile with a peak immediately following administration and then a long tapering tail.

Discussion on Realistic Constraints

Our model was designed to simulate a buccal mucosal patch for the administration of fentanyl. In accordance with our design objectives, we sought to deliver the drug quickly to the patient and efficiently (without loss of drug to systemic metabolism). In this way, we could provide immediate relief to the patient and eliminate waste from administered dosages.

In this context, there are several issues to discuss relating to the implementation of our design. Because fentanyl is intended for patients with extremely severe chronic pain, it is a benefit that our blood profiles exhibit a characteristic shape of an immediate peak followed by a long, gradual decay. In this way, patients receive a quick burst of relief that will help them overcome a burst of pain and sustain them for several hours. Unlike other drugs, the tapering effect

reduces the likelihood that patients will abuse our patch because they will only experience a brief "high."

From a manufacturing standpoint, our mechanism of delivery offers a more efficient method for administering drug to a patient. Data from the current formulation of Actiq® estimates that 75% of drug is lost to the saliva. However, the buccal mucosal patch is adhesive and prevents a great deal of salivary loss. Thus, less of the drug needs to be included in the same formulation in order to trigger the same response in the patient.

In addition, the implementation of a low diffusivity layer can alter the blood concentration profile. This could allow the drug to remain in the system longer without risking the health of the patient. This also enables physicians to customize their prescriptions based on a patient's particular qualities and needs. Such customization and precise control is not possible with the current Actiq® lozenge.

Conclusion and Recommendations

From the results of our model, it is reasonable to conclude that a buccal mucosal patch is a viable alternative to current products for delivery of fentanyl. In comparison to the current Actiq® delivery system, our patch reduces drug loss to the saliva and is a hands-free alternative to a lozenge. Conversely, our design faces several challenges. First, it may be uncomfortable to some patients. Secondly, since only computer simulations have been completed to date, no method of adhesion to the buccal mucosa has yet been determined.

Using our computer simulation as a guide, we plan to use experimentation and clinical trials to definitively assess the viability of our design. Our sensitivity analysis will be essential in steering experiments towards the optimal design by highlighting the most sensitive and significant parameters. Finally, experiments will clarify how assumptions made in the model actually affect the final results.

Based on our results and corresponding sensitivity analysis, we now have a better idea of the most significant parameters of our design. Keeping this in mind, we suggest designing the patch with an array of high diffusivity barbs that could increase the rate of the initial rise in concentration. By bypassing the layer of lowest diffusivity, the drug can be diffuse into the submucosa faster, and therefore be taken up into the blood faster. When dealing with breakthrough cancer pain, the rate at which pain relief occurs is a vital aspect. It has also been shown that applying heat to the patch and surrounding tissue could increase diffusivity, so perhaps recommending that patients consume hot tea after placing the patch in their mouth would also increase drug efficacy.

Appendices:

APPENDIX A: Values Used

Detailed diagram, governing equations, boundary conditions, and initial conditions provided in the problem schematic section earlier. Below is a table detailing system parameters along with sources used to find them.

Parameter	patch	impermeable membrane	epithelium	submucosa
Initial Concentration	5 mol/m^3	5 mol/m^3	0 mol/m^3	0 mol/m^3
Source		Calculations shown below		
Diffusivity	10^-7 m^2/s	10^-11 m^2/s	4*10^-11 m^2/s	10^-11 m^2/s
Source	7-9	7-9	7-9	7-9
Reaction Rate Coefficient	0	0	-0.1	-1
Source	7-9	7-9	7-9	7-9

Table A1

The initial concentration of our patch was based on the Actiq® dosages. We used a default dosage of ~250µg, which can be calculated to be 5 mol/m^3 using fentanyl's molecular weight of 36g/mol and our patch volume of $1.57 * 10^{-7}$m^3.

Other Parameters	Values	Source
Plasma volume	2.7 L	
elimination rate constant	0.0003	5

Table A2

dimensions	thickness
patch above membrane	0.15 mm
impermeable membrane	0.2 mm
patch below membrane	0.15 mm
epithelium	0.1 mm
submucosa	3 mm

Table A3

APPENDIX B: Computational Methods

Initially we modeled the system using a 2D axis-symmetric model, Fig. A1, and showed that it could be accurately represented by a much simpler 1D model, mesh shown in Fig. A2. The 2D axis-symmetric model consisted of our patch, impermeable layer, epithelium and the submucosa, all with equivalent depth and diffusivities to our current model. The epithelium and submucosa that was modeled had a radius twice that of the patch. We found upon running the simulation that diffusion in the radial direction was negligible and the system could be treated as a 1 dimensional model.
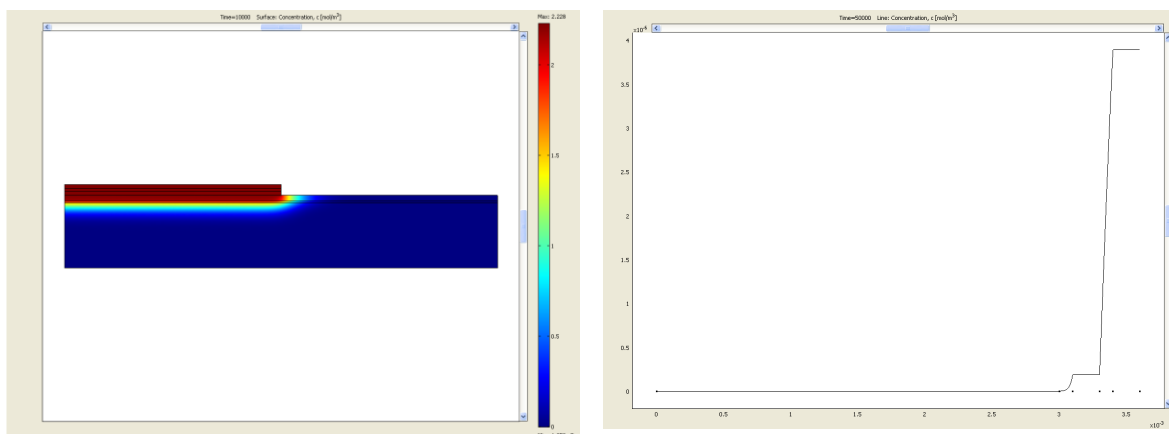

Figure A1. 2D and 1D computational models after being run in COMSOL.

The 1D model we implemented in COMSOL consisted of a non-uniform mesh with a minimum element size of 0.000001m in the most critical region with a mesh element growth rate of 1.1 (see plot below).
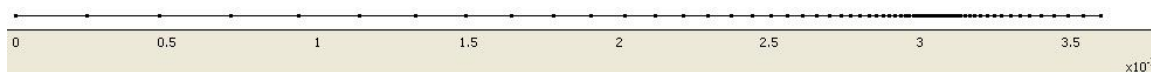

Figure A2. Nonlinear mesh of the model system, dimensions in meters.

Using COMSOL's finite element method with a time step of 5 seconds we solved the governing equations with the associated boundary conditions discussed above. The tolerance was 0.01 and the absolute tolerance was set to 0.001 (the default values). In order to solve for the pharmacokinetic drug profile shown in the results we used COMSOL to integrate a differential equation based on the diffusion model and a first order reaction rate as described in the results section.

Mesh Convergence

In order to test the accuracy of our mesh, we did a mesh convergence analysis using constant mesh sizes, shown in Fig. A3. We chose to check the time of the peak concentration, as that is the value we are most interested in. Due to the complicated dynamics of this nonlinear system the mesh convergence oscillates a few times before settling down. In order to dramatically reduce the computation time that would be required to achieve accurate results we used a nonlinear mesh, where the elements are smallest in the most critical areas. Around the epithelium layer we have a minimum mesh size of 0.000001m and a growth rate of 1.1. This resulted in accurate mesh convergence (as seen by the pink square in our plot), with a total of only 198 mesh elements. Due to our simplified linear model, we are able to get accurate results with very short simulation times. Based on the mesh convergence results we can conclude that our results are independent of the mesh characteristics.
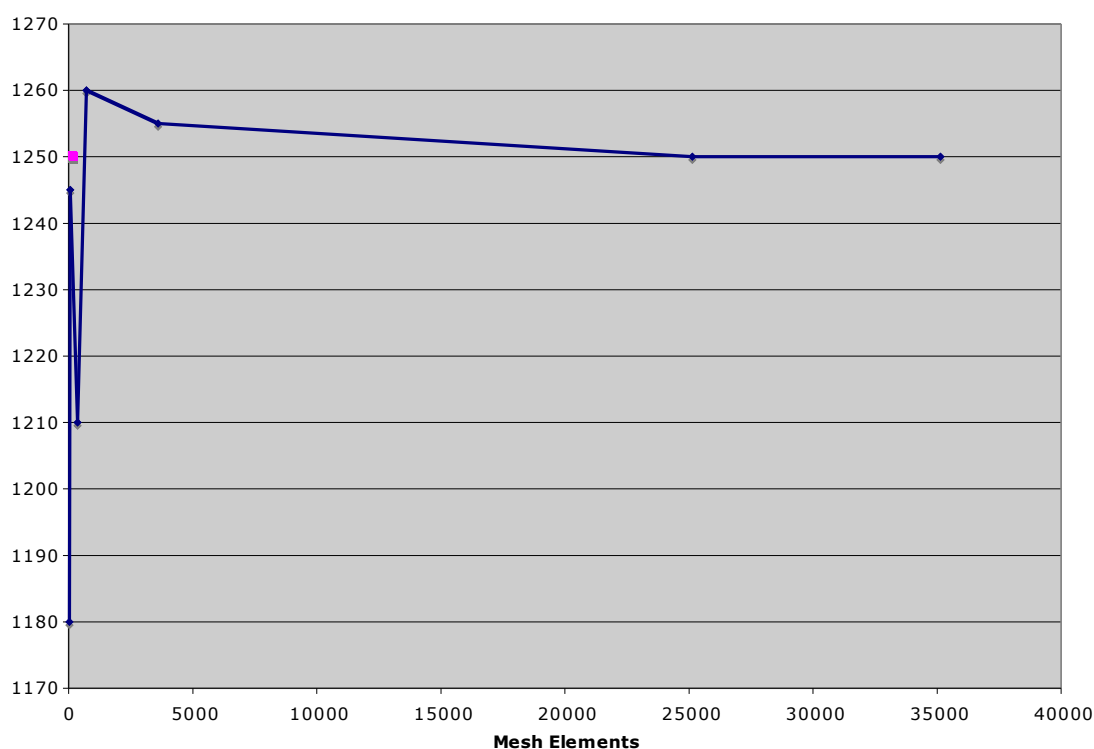

Figure A3. Mesh convergence plot. Note the oscillations before the mesh finally converges after 25,000 elements. Using a non-uniform mesh of 198 elements we were able to achieve similar accuracy in much less time.

Accuracy Check

In order to check the accuracy of our model we compared the results to the experimental results published by Actiq®, reproduced in Fig. A4, which uses the same active ingredient fentanyl. The Actiq® approach consists of a lollipop impregnated with the drug that the patient puts in their mouth until they get the desired pain relief. In Fig. A4 the effect of the drug is seen for various dosages. In our model we plotted the concentration profile in the blood over time for initial concentrations equal to 5, 10, and 15 mol/m^3, as seen earlier in Fig. 3.

While the exact concentrations do not entirely match, the general shape of the curve is the same, and the peak times and values are within an order of magnitude of the Actiq® system. The two systems are different, so one would expect there to be some discrepancies. The similarities, however, suggest that our model should be within the range that we can begin doing conservative, careful clinical trials to further validate its accuracy.
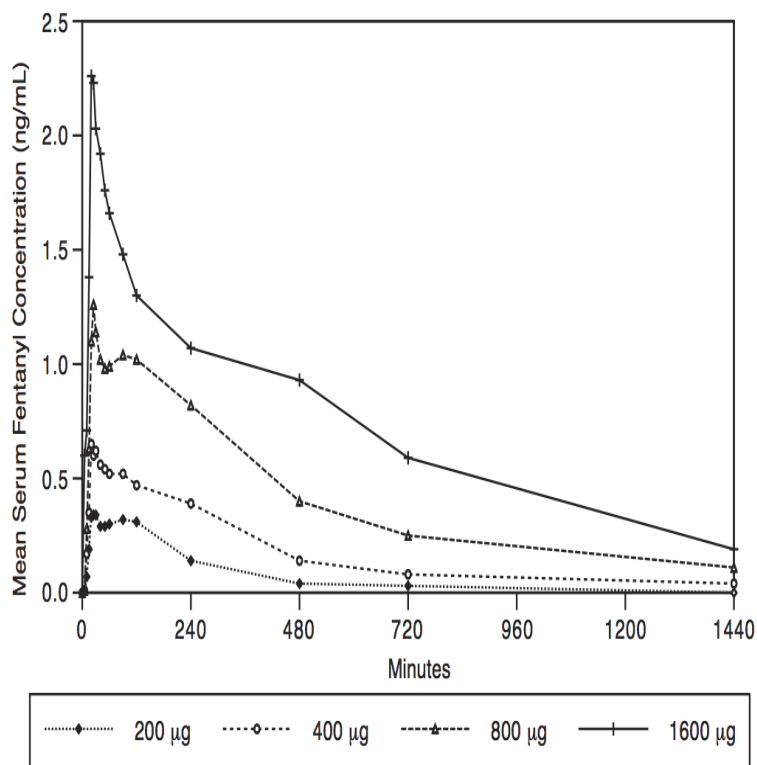
Dosage (mcg)	Concentration (mol/m^3)
200	3.786037706
400	7.572045692
600	11.3580834
800	15.14409138
1200	22.71613708
1600	30.28818277

Table A4. Comparison of drug dosages and equivalent initial concentrations for our patch based on our patch volume (see diagram).

Figure A4. Drug concentration profiles for varying dosages of Actiq®, adapted from Actiq.com

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