COMSOL Simulation of Transdermal Toxin Expulsion via Adsorptive Dermal patch

Kwon J. Kwon*, Michael L. Hess, and Robert M. Polski
Andrews University, Berrien Springs, MI 49103
*Corresponding author: HYH312, Department of Engineering and Computer Science, Andrews University, MI 49103; hkwon@andrews.edu

Abstract: Mathematical skin models play an important role in fields such as transdermal drug delivery and assessment of dermal exposure to industrial chemicals. Extensive research has been conducted on modeling skin for transdermal drug delivery; however, little effort has been made to view the skin as a permeable layer to expel waste chemicals or toxins from the body. Activated charcoal has an extraordinarily large surface area and pore volume, making it suitable for a wide range of applications, including toxin removal. In this work, we focused on topical application of charcoal poultices or dermal patches that are used for expelling impurities through transdermal adsorption. We developed a two-dimensional computational skin model to evaluate removal of toxins through skin as diffusive and permeable layers. The results were compared with and without the aid of an adsorptive topical dermal patch or poultice. The result demonstrated that topical application of a highly adsorptive layer is an effective way of accelerating the toxin expulsion process.

Keywords: skin model, activated charcoal, adsorption, dermal patch.

1. Introduction

Human skin is a highly complex organ made of multiple composite layers, including the subcutaneous tissue, the dermis, and the epidermis. These layers contain ducts and pores that allow substances to pass into or out of the body[1]. The skin of aquatic animals is permeable, and excretory wastes pass out by diffusion. In terrestrial animals, the skin is less permeable, and excretory products pass out only through ducts and pores. Topical application of activated charcoal (AC) poultices and packs stimulate circulation, causes sweating that excretes toxins, and draws out impurities. Although it is clinically proven that these noninvasive treatments can help to rid the body of many different toxins and infections, it is generally reflected that such method lacks scientific explanation.

Mathematical skin models play an important role in fields such as transdermal drug delivery and assessment of dermal exposure to industrial chemicals. Extensive research has been conducted using the skin as a means of moderating and controlling drug delivery through transdermal adsorption[2]. Little effort has been made, however, to view the skin as a permeable layer to expel waste chemicals or toxins from the body. Activated charcoal possesses an extraordinarily large surface area and pore volume, making it suitable for a wide range of applications, including toxin removal[3,4]. In this work, we focused on topical application of charcoal poultices or commercial dermal patches that are used for cleansing the body by stimulating circulation and drawing out impurities thorough transdermal adsorption[5]. We developed a two-dimensional computational skin model to evaluate removal of toxins through skin as permeable layers. The simplified skin model consists of the epidermis, dermis, and hypodermis layers as diffusive layers and endotoxins of inflammation as a point source (Figure 1). The results were compared with and without the aid of an adsorptive topical dermal patch or poultice.

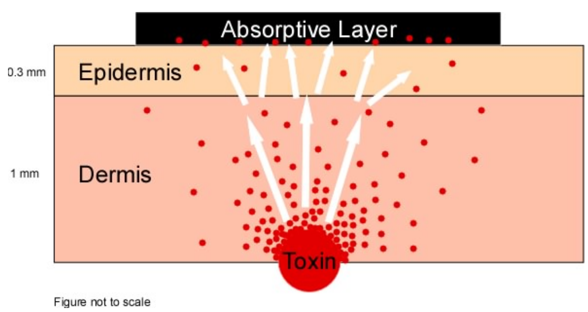

Figure 1. Schematic diagram of 2D multilayered skin, and a point source.

A few commercial AC dermal patches are commercially available at various AC compositions. Some of them were proven to be efficient in removing acute inflammations and poisons while providing the convenience of a non-stick patch (Figure 2). The focus of this paper is to understand transdermal toxin expulsion mechanisms with the aid of a highly adsorptive layer. Migration of molecules at the solid-solid interface can be limited[6], however, activated charcoal provides a vast surface area of interface to allow this process to work efficiently[4].

Figure 2. Images of commercial charcoal patch dermal application.

2. Mathematical models

2.1. Governing equations

We developed a 2-dimensional multilayered skin model that consists of epidermis, dermis, and hypodermis with a topical adsorptive layer. The skin is modeled as a homogeneous slab with a surface area that is larger than the thickness. Any variations in the thickness, diffusion across sweat ducts, hair follicles, any short pathways, and other surface defects are not considered. The therapeutic patch, attached to the skin, is infinitely thin. The skin layers were considered permeable, permitting toxins to diffuse and spread as microcirculation in capillaries carries the molecules. Despite the non-selective nature of the adsorptive charcoal patch, we focused on a single component of mass transport from a highly concentrated source. We modeled the mass transport by diffusion using the Fick's equation.

$$\frac{\partial c}{\partial t} = D\nabla^2 c$$

Charcoal adsorption of the toxin was modeled using the Langmuir adsorption theory, which specifies that when a toxin molecule occupies a site, no further adsorption can take place at that site[7].

$$c + s \underset{k_{des}}{\overset{k_{ads}}{\rightleftarrows}} c \cdot s$$

$$-\frac{dc}{dt} = \frac{dcs}{dt} = k_{ads}[c][s]_0(1-\theta) - k_{des}\theta$$

where c is toxin concentration (mg/m^3); s_0, available adsorption sites; and θ, adsorption capacity [mg/g] defined as follows.

$$\theta = \frac{[cs]}{[s]_0}$$

cs, adsorbed toxin sites.

The toxin was modeled as originating from a point source beneath the dermis, lasting several hours for an acute case or lasting consistently for a long term exposure. On the active reaction surface, the boundary condition couples the reaction for the substance c.

$$\mathbf{n} \cdot (-D\nabla c) = k_{ads} c \cdot s_0\,(1-\theta) - k_{des} cs$$

2.2. Implementation in COMSOL

The diffusion and reaction models were implemented into COMSOL using the physics of transport of dilute species and weak PDE equations.

The geometry contains multiple skin layers whose interface was applied with continuity boundary conditions via identity pairs.

Since the model deals with a phenomenon in a 2D domain coupled to another phenomenon occurring only at the sensor surface 1D boundary, the PDE mode with weak form in the boundary was added[8]. The weak form equation for the surface reaction is derived as follows:

$$0 = \int_{\Omega} v\,(k_{ads}c - k_{des}cs - \frac{\partial cs}{\partial t})dA$$

Where v is an arbitrary function on the domain Ω. The weak boundary equation for the upper surface was implemented in COMSOL multiphysics using the *test* function: *test(cs)*(*k_{ads}**c-*k_{des}**cs -*cs_t*)*.

A non-equidistant mesh was assigned to the near reaction boundary to describe the depletion of the substance more accurately as shown in Figure 3. The mesh used in the model yielded 10689 degrees of freedom. The transient diffusion-reaction model was simulated for 5-15 hours as indicated at an interval of 10 seconds.

The obtained result was processed to obtain the integrated surface concentration for remaining toxin concentrations in the skin layers.

The impurity removal rate can vary depending on charcoal types, impurity types, pH, etc.[9]. For this model, we used best approximated values from literature[9,10]. Values that were used are in the Appendix Table 1.

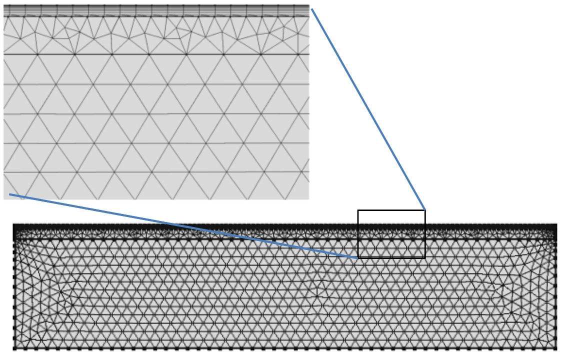

Figure 3. Non-equidistant mesh near the reactive boundary layer

3. Results

3.1. Depletion boundary layer

In developing the reaction-transport model, the first objective should be to determine whether the investigation is concerned with only reaction kinetics or with coupled reaction and transport phenomenon. A good theoretical indicator is estimating the Damkholer number that is defined as follows.

$$Da = Lk_{ads}s_0/D$$

The Damkholer number for this model is estimated to be O(100) indicating that the reaction rate is significantly faster than that of diffusion. This means the overall reaction is limited by diffusion and concentration of the toxin is depleted near the surface where the reaction occurs. As shown in Figure 4, a mass transfer boundary layer is formed near the reactive surface. This indicates that the process is transport limited. The formation of the transport boundary layer is more distinctive as the reaction rate increases.

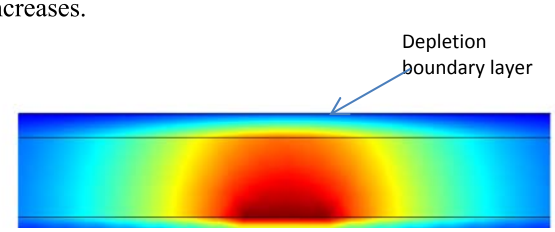

Figure 4. Near the reactive surface, concentration of toxin is depleted because reaction rate is much faster than that of mass transport.

3.2. Kinetics of adsorption

For a short term source that lasts a couple hours, the molecular diffusion through microcirculation clears off the toxin eventually even without a topical patch. We investigated if the adsorptive topical patch could accelerate this process. With the topical application of the adsorptive charcoal patch, the time to remove the remaining toxin was reduced significantly, as shown in Figure 5. Since the AC adsorptive capacity and reaction rate varies depending on the source of AC, we have simulated for high and low values of possible reaction rate. For 90% removal, the patch reduced the removal time by over 70% for highly reactive AC. The result demonstrated that dermal application of high adsorptive layer can effectively draw out impurities from approximately 1mm-deep skin layers. Thus far there have been reports on considering a permeable skin layer as a route to deliver drugs in to the body[1,2]. Here we show that internal body impurities can be expelled out via transdermal delivery.

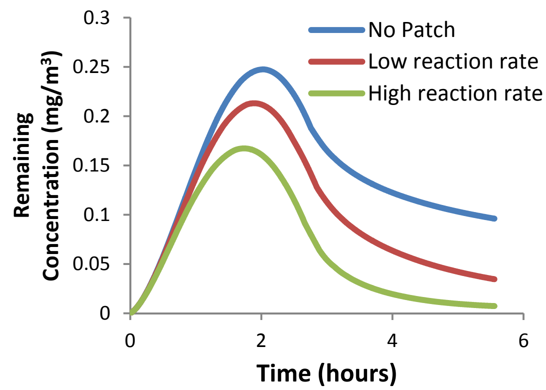

Figure 5. Concentration versus time over short term exposure of sources. The point source was appointed as waveform that last only about 2 hours.

We also examined the result of a long-term exposure of a constant point source. Figure 6 shows the simulated data for a long-term toxin application and remaining concentration in skin. The data show that adsorption of toxins at the beginning is reasonably fast and asymptotically reaches a maximum. With no patch available, the toxin slows accumulates in the skin over time posing a potential danger. With application of highly adsorptive patch, the toxin can be efficiently removed and maintained at a saturated, manageable level. Depending on its reaction rate constant, the saturation values are different.

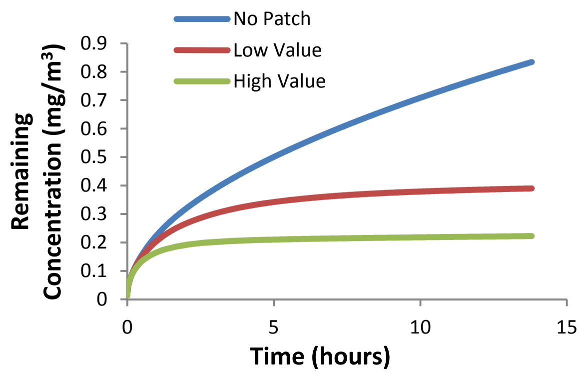

Figure 6. Concentration versus time over long term exposure of sources. The point source was applied as a rectangular function that lasts over 15 hours.

The results indicate that having an adsorptive layer produced a significant decrease in concentration over time compared to the case of no adsorptive layer.

3.3. Effect of activated charcoal composition

Commercial activated patch composition varies greatly depending on the product. A charcoal poultice, made with activated carbon powders and minimal delivery agent, possesses the highest AC composition providing high efficiency but is very hard to handle and leaves residues in skin. Most commercial products contain AC ranging 1%~15% compared to the AC poultice. Figure 6 show that AC is extremely efficient to adsorb and remove impurities at even a relatively low AC dose in the product. At 10%, the removal rate is approximately 60% of its maximum capacity. The result shows 10-20% AC composition provides the most efficient toxin removal rate. The result also demonstrates that a commercial AC patch that contains relatively low content can also be used to remove impurities efficiently.

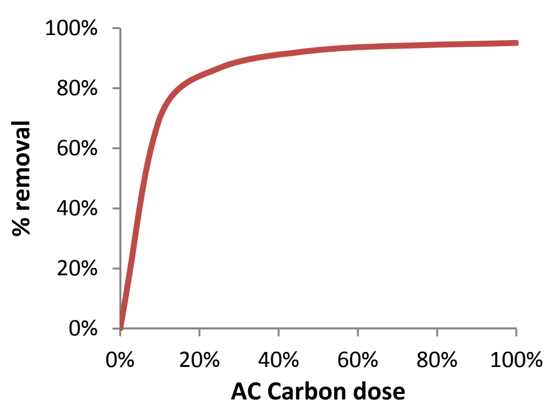

Figure 6. Effect of AC dose on the toxin removal.

4. Conclusions

This study represents what is, to our knowledge, the first attempt to create a mathematical model to account for transdermal delivery of an internal substance out to the skin with the aid of a topical application of adsorptive layers to draw out impurities. For many years, we have known of the efficacy of dermal application of activated charcoal only clinically, but a scientific model or explanation has been lacking. Developing an in-vitro experimental model that can verify the model is in progress. Although several assumptions were used to make the otherwise complex model simple, the model successfully showed how the concentration of a toxin in the skin can be reduced significantly faster with an external, topical adsorptive patch. The COMSOL model allows flexibility in shaping geometry, so this work can also be expanded to study different geometry and structures of skin models for higher utility.

5. References

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7. Appendix

Table 1: Values used for the simulation

Parameters	Values	References
D epidermis D dermis	10^{-6} [cm^2/s] 10^{-5} [cm^2/s]	[11]
Kads Kdes	0.07~0.3 [1/min] 0.0001 ~0.0003[1/min]	[4]
Source concentration	10~40 [mg/L]	[3]
Adsorption capacity	4.7~18.8[mg/g]	[9]