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THREE-DIMENSIONAL MATHEMATICAL ANALYSIS OF THE DIFFUSION OF REACTIVE HORMONE FROM A TRANSDERMAL DRUG PATCH

Amin Etminan*, Yuri Muzychka
Department of Mechanical Engineering, Memorial University of Newfoundland (MUN), St. John's, NL, Canada
*corresponding author's email: aetminan@mun.ca

Abstract—The characteristics of percutaneous absorption have widely emerged as important in medical treatment and pharmacological purposes. Drug patches are an effective tool in medical care and criminal justice systems collecting specific doses of substances in a body through sweating and in delivering prescribed medicine into a body through the skin. This simple method has caused a high user-popularity of drug patches across a wide range of applications. In this study, two- and three-dimensional mathematical modellings of drug patch adhesives on human skin are investigated. As the governing equation, the Helmholtz equation has been solved using the separation of variables method along with the least-squares technique to properly obtain closure for non-homogeneous boundary conditions of the problem. The effects of the important parameters involving the number of terms, the Damköhler number, and the length of the computational domain on the concentration of the mass diffusion and its differential versus the depth of skin, are discussed in-depth for different planes on the skin and skin thickness depth. The results reveal that when the aspect ratio is increased, the two-dimensional problem is changed into a one-dimensional problem, particularly when $L \gg a$.

Keywords- drug patch; Helmholtz equation; least square; Maple; separation of variables.

I. INTRODUCTION

The importance of the permeability of human skin has emerged from the capacity of the skin to accumulate specific substances. Transdermal biotechnology is becoming an intriguing field of study due to its high potential in biomedical, and pharmaceutical applications [1]. These applications are a route of design and optimizing drug-delivery systems, wherein active drug components penetrate the skin layer for systematic distribution. Therefore, the relationship between the skin permeability and the molecular properties of drugs plays a vital role in pharmacological purposes. The history and the development of medicine transdermal delivery systems associated with a large number of drugs were overviewed by [1, 2] where the anatomy and physiology improvements of the skin were highlighted. Benson et al. [1] also reviewed the local and systematic transdermal drug-delivery methods focusing on the technologies, limitations, and benefits of adhesive patches.

The prominence of the drug penetration and the skin delivery system motivates researchers to describe its performance in detail. A vast variety of drug patches has been employed by both medical centres and people as a drug detector tool or a method of pain relief. A drug-test patch as a sweat collection device adheres to a person's skin like a band-aid. The inner part of the patch contacting the person's skin has an absorbent pad that soaks up perspiration. If there are drugs in a person's sweat, the patch absorbs those as well. So, when a drug-test patch is removed, it should contain samples of all the drugs the person took and sweated out while wearing the patch [3-6]. The majority of studies on drug penetration through the skin are clinically-oriented [5,6], and the physical and mathematical natures of this type of drug delivery have not been adequately investigated. The permeability of the skin has an essential role to pass or reject the molecules of a drug patch, which has been discussed and reviewed by Mitragotri et al. [7]. Mathematical frameworks along with the advantages and the limitations of a large number of modeling methods have been studied by [7].

The design of drug-test patches is crucial in ensuring controlled dosage and safety. Generally, a drug-test patch is worn for a week or more. To thwart efforts to conceal drug use, drug-test patches are designed so that once removed, they cannot be reattached. The patch is modulated to contain medication and is designed in such a way that the medication permeates the skin in a controlled fashion, attaining more steady levels of the drug in the body. It can be worn for as little as eight hours or as long as seven days, depending on the therapeutic indication. These patches are secured with adhesives, which are designed to adhere comfortably to the skin as long as indicated by a physician. Each patch also has a unique number that testing centres record when putting on the patch. Drug-test patches can be used to test for several different drugs, including marijuana, cocaine, opiates, amphetamines/methamphetamine, and phencyclidine [8]. When compared with other conventional delivery systems involving oral and injection, the drug-test patch delivery system offers certain advantages, such as easily used by the patient/caregiver, high bioavailability, low drug-drug interactions, steady drug delivery, and the possibility of visual monitoring by the caregiver, but its main disadvantage arises from the preventive role of the skin to let the medicine cross freely [9].

As observed in Figure 1, a patch is applied to the epidermal layer of the skin to deliver specific substances or to detect drugs

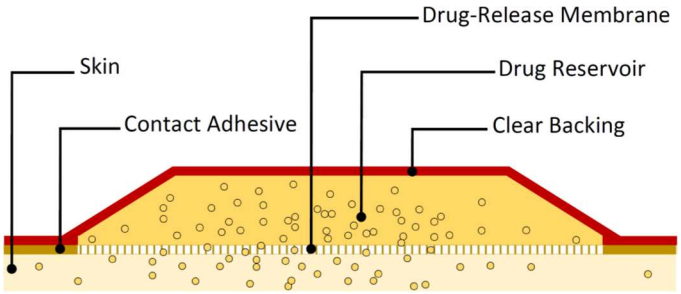

Figure 1. A schematic of a drug patch and its main components.

taken by the patient during the sweating process. Every patch has four important components: clear backing, drug reservoir, drug-release membrane, and contact adhesive. Two passive and active methods have been employed to enhance the rate of the penetration of the drugs via the skin. The passive method uses chosen enhancer materials, and micro- and nano-delivery systems to increase the rate and the depth of drug penetration effectively [10]. Conversely, the active method physically enhances drug delivery by using an external driving force, such as electrical (iontophoresis and electroporation), thermal (laser and radiofrequency thermal ablation), ultrasound, mechanical (microneedles), and velocity (jet injector) [10].

Several mathematical techniques have been proposed by researchers to model and analyze drug penetration through the skin. Guy and Hadgraft [11] applied Laplace transform approaches to obtain a mathematical expression for two extreme cases: short-time and long-time release rates, which are inaccurate around unit normalized time. Fernandes et al. [12] mathematically modeled and analyzed a transdermal drug-delivery system in the skin. They used Laplace transform approaches to describe Fickian diffusion equations as the governing equations of the problem. Their results revealed that an increase of the vehicle to the skin partition coefficient was achieved with a reduction of the drug-delivery rate. A comprehensive review has been conducted to recognize mathematical abilities for designing and optimizing biomaterials, particularly bio-erodible polymers in biomedical technologies and the drug-delivery process [13].

II. Problem Statement, Governing Equation, and Boundary Conditions

The transdermal or dermal delivery of drugs into the skin, and the collecting of specific substances through sweating by the use of drug patches are commercially and scientifically required to design and model optimized patches. This study aims to model a transdermal hormonal contraceptive patch and its diffusion of chemicals that pass through the skin layer. This problem has been simplified as described below and solved both numerically and analytically. The problem under consideration is transformed into a Partial Differential Equation (PDE), which has been solved analytically using the separation of variables method. Some simplifying assumptions considered are described as below:

1. The skin is modeled as a homogeneous layer without variations due to hair follicles, sweat glands, and area-specific thickness affecting diffusivity. Variations due to changing PH and water content are also not considered.
2. The considered patch is infinitely thin, allowing study of only the surface area of the patch.
3. It is presumed that the patch is in perfect contact with the skin, allowing for maximum diffusion of the drug into the skin.
4. Blood in the capillaries flows fast, letting it be assumed the drug concentration in the blood is zero at all times.
5. The concentration of the drug is kept constant over time and essentially constitutes an infinite sink, with an assumption of zero flux at the patch-skin interface.

The configuration of the problem is illustrated in Figure 2, where the dimensions of the computational domain are $2L \times 2L$ and t. The area of the drug patch on the $x - z$ plane is $2a \times 2a$ and its thickness is negligible. Regarding the geometrical details and the nature of mass transfer into/from the skin, the drug concentration, C_A, has a three-dimensional distribution and is a function of x, z, and y.

The transport phenomena of a gas, ion, and nonelectrolyte through the skin are accurately described and governed by Fick's second law of diffusion [14]. This law predicts the mass concentration change to time (unsteady situation) and position (steady situation) caused by mass diffusion. The drug concentration in the skin can be modeled as a partial differential equation called the Helmholtz equation, which represents a time-independent form of the wave equation as below:

$$\frac{\partial^2 C_A}{\partial x^2} + \frac{\partial^2 C_A}{\partial z^2} + \frac{\partial^2 C_A}{\partial y^2} - \frac{k''}{D_{AB}} C_A = 0 \qquad (1)$$

where C_A is the concentration of the diffusing species, k'' is the reaction rate, and D_{AB} is the mass diffusion coefficient.

The appropriate six boundary conditions are as follows:

x-direction,

$$\begin{cases} \frac{\partial C_A}{\partial x} = 0 & x = 0 \\ C_A = 0 & x = L \end{cases}$$

z-direction,

$$\begin{cases} \frac{\partial C_A}{\partial z} = 0 & z = 0 \\ C_A = 0 & z = L \end{cases}$$

y-direction,

$$\begin{cases} C_A = C_{A0} & y = 0 \quad 0 \le x < a \quad 0 \le z < a \\ \frac{\partial C_A}{\partial y} = 0 & y = 0 \quad a < x \le L \quad a < z \le L \\ \frac{\partial C_A}{\partial y} = 0 & y = t \end{cases}$$

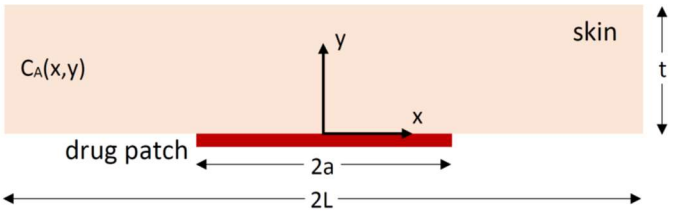

Figure 2. Schematic of the problem under consideration.

where C_{A0} is a constant mass concentration of the drug patch reservoir and t is the thickness of the skin layer.

As mentioned earlier, a zero-flux boundary condition has been applied at the contact surface between the patch and skin ($y = 0$), meaning that the drug can only diffuse upward through the skin layer. It is also assumed that the variation of the concentration of the drug along the y-direction of the contact area on the skin layer is zero. The problem is modeled in a steady-state and there is no variation versus time progressions for any parameters. Now, by substituting the dimensionless parameters $\phi = C_A/C_{A0}, X = x/t, Z = z/t, Y = y/t$ in (1), the dimensionless form of the governing equation will be obtained as below:

$$\frac{\partial^2\phi}{\partial X^2} + \frac{\partial^2\phi}{\partial Z^2} + \frac{\partial^2\phi}{\partial Y^2} - \frac{k"t}{D_{AB}}\phi = 0 \qquad (2)$$

where $Da = k"t/D_{AB}$ is a dimensionless group called the Damköhler number. This number represents the ratio of the chemical reaction to the diffusive transport rate and also has a significant role in the pattern of the drug distribution which will be discussed later. The value of the Da is highly problem-dependent but has a serious limitation in infinitely fast reactions, such as combustion, this is called the Burke-Schumann limit. An asymptotic analysis was carried out by Yu and Hunt [15] to establish a new method using non-Gaussian solute transport theory resulting in the differences between transport-limited and kinetic-limited chemical reactions. The present study assumes a range of the Da from 0.1 to 1 and its effects on the mass concentration.

III. Mathematical Analysis

The separation of variables, also known as the Fourier method, is one of several methods for solving ordinary and partial differential equations, in which algebra is used in rewriting an equation so that each of two or more variables occurs on each side of the equation. After providing the homogenous and non-homogenous boundary conditions, an analytical solution using the Fourier method can be applied to (2). Here, the governing equation (2) is linear and five out of six boundary conditions are homogeneous. Therefore, (2) can be considered as a product of three one-variable functions as below:

$$\phi(X, Z, Y) = \Psi(X)\,\Lambda(Z)\,\Phi(Y) \qquad (3)$$

Now, by rewriting all the terms in (2) regarding the separation of variables introduced by (3) and dividing both sides by $\Psi\Phi$, the new form of the governing equation will be:

$$\frac{\Psi"}{\Psi} + \frac{\Lambda"}{\Lambda} + \frac{\Phi"}{\Phi} - Da = 0 \qquad (4)$$

After substituting the first five boundary conditions one-by-one, the general solution of (4) is:

$$\phi(X, Z, Y) = \sum_{m=1}^{M}\sum_{n=1}^{N} G_{nm}\cos(\lambda_n X)\cos(\gamma_m Z)\left[\cosh(\beta_{nm} Y) - \tanh(\beta_{nm})\sinh(\beta_{nm} Y)\right] \qquad (5)$$

where, $\lambda_n = (2n-1)\frac{\pi}{2}\frac{t}{L}$, $\gamma_m = (2m-1)\frac{\pi}{2}\frac{t}{L}$, and $\beta_{nm} = \sqrt{\lambda_n^2 + \gamma_m^2 + Da}$.

Then, by applying the 5th mixed boundary conditions over two specific regions at $Y = 0$ would be resulted in:

From the 1st region over $0 \le X < a/t, 0 \le Z < a/t$:

$$\sum_{m=1}^{M}\sum_{n=1}^{N} G_{nm}\cos(\lambda_n X)\cos(\gamma_m Z) - 1 = 0 \qquad (6)$$

From the 2nd region over $a/t < X \le L/t, a/t < Z \le L/t$:

$$\sum_{m=1}^{M}\sum_{n=1}^{N} G_{nm}\,\beta_{nm}\tanh(\beta_{nm})\cos(\lambda_n X)\cos(\gamma_m Z) = 0 \qquad (7)$$

Now, using the least-squares method described by Rencher and Christensen [16], the integrations of (6) and (7) over appropriate regions lead to:

$$I_{MN} = \int_0^{a/t}\int_0^{a/t}\left[\sum_{m=1}^{M}\sum_{n=1}^{N} G_{nm}\cos(\lambda_n X)\cos(\gamma_m Z) - 1\right]^2 dX dZ + \int_{a/t}^{L/t}\int_{a/t}^{L/t}\left[\sum_{m=1}^{M}\sum_{n=1}^{N} G_{nm}\,\beta_{nm}\tanh(\beta_{nm})\cos(\lambda_n X)\cos(\gamma_m Z)\right]^2 dX dZ \qquad (8)$$

After computing (8) using the software Maple 2017 software, the unknown G_{nm} coefficients in (5) can be provided supporting the solution to be completed. To simplify the solution, the same numbers of truncation terms in the series and eigenvalues are assumed; $N = M$.

IV. Discussion

Reactions typically occur in a series of multiple reaction steps. In general, the contributions of all steps result in an overall reaction rate. Chemical reactions are always coupled with mass transfer since the reactants have to travel to the location where the conversion takes place in a drug patch reservoir and the products have to penetrate into the human's skin. In this study, the drug mass comes out from the reservoir part of the patch and penetrates into the skin in all directions. According to the common and real dimensions of drug patches in the market, the geometrical details of $a = 0.02$ m, $L = 0.1$ m and $t = 0.01$ m are considered (see Figure 2). The physical meaning of numerical simulation can help researchers develop a more in-depth understanding of a problem. Therefore, it would be beneficial to have a brief discussion of the problem later, when $Da = 0.1$ and $N = 100$.

Different values of the truncation parameter, N, in the series of mathematical solutions control the accuracy of the results. The highest fluctuations of 6% happen for $N = 10$ at the central region of the contact area, which requires the calculations to use more terms in the series. When the required truncation in solution increase up to $N = 100$, the variations of the mass concentration on the contact area are changed into a semi-uniform trend, satisfying the 5th boundary condition of the problem (as expected). As N increases, the mass concentration distribution shows a steadier behaviour around $\phi = 1$ and its fluctuations decrease up to 40%, and 92% in the side and central

regions of the contact area, respectively. Additionally, in the side regions of the patch, the value of drug concentration is less than the appropriate amount of ~ 1 which disappears as the truncation increases. Consequently, the required truncation terms of series in the following calculations have been assumed $N = 100$ to generate more accurate results due to converging to a solution satisfying the boundary conditions.

As mentioned earlier, the Damköhler number relates a chemical reaction rate to the convective transport phenomena. The effects of the Da on the mass concentration distribution along the whole length of the skin are illustrated in Figure 3. As is shown, an increase in the Da causes stronger fluctuations, in particular over the side regions of the contact area $(-2 \leq X \leq +2)$. On the other hand, an increase in the Da reduces the mass diffusion in regions out of the contact area. It means that the mass diffusion is highly in the depth of the skin indicating an approximate one-dimensional problem. According to the nature of low-speed drug penetration, the value of the Da is assumed 0.1 for the following simulations. This assumption indicates an equilibrium condition where the diffusion happens much faster than the reaction rate.

Figure 4 shows the influence of an increase of L on the mass concentration distribution at the contact surface $(-2 \leq X \leq +2)$. A more elongated computational domain not only highlights the contribution of the second term in equation (8) to the drug diffusion pattern but also enhances the domain of mass diffusion fluctuations. As is displayed, the mass diffusion is concentrated on the central region of the patch by increasing L. Besides, the two-dimensional mass distribution changes to the one-dimensional distribution when $L \gg$ a particularly. In fact, the mass diffusion in side-direction is much lower than the in-depth direction due to the infinite length of the L compared to the limited length of the drug patch.

The distributions of the drug diffusion and the mass flux in skin thickness are shown in Figure 5. As is expected, the values of mass concentration and mass flux decrease by going into the skin thickness. The fluctuating distribution of the mass concentration at the skin surface disappeared in the depth of the skin and the distribution shows a parabolic profile that accredits the appropriate predictions of the least-square method. Its flux approaches zero on the surface far enough from the contact area that the 5th boundary condition is satisfied as well.

The contour of the mass concentration at $Y = 1$ is displayed in Figure 6. As is seen, the highest value of the drug mass concentration is located at the centre, where its value is ~ 0.93. The parabolic mass distribution can be easily found in the skin thickness.

V. Conclusions

Transport problems involving mass transfer through devices and surfaces have abounded in the field of microfluidics. It is challenging to select the appropriate model to characterize device performance as devices vary greatly in geometries and operation ranges. In many applications, it is not possible (or simply not desirable) to operate under conditions that yield a mass transfer boundary layer. In this research, two- and three-dimensional drug mass diffusion of an adhesive patch on the skin are numerically analyzed. The results show that when the truncation parameter increases, the variation of mass concentration at the contact area between the patch and the skin experiences a uniform distribution satisfying the 5th boundary condition. The oscillations at the edges of the patch are associated with singularities in derivatives of the solution at the boundary transition points. These are typical of such mixed boundary value problems. The Damköhler number also has a significant impact on the variation of the drug mass concentration and its flux in the skin thickness, where the rates of chemical hormone reaction and the diffusion of the drug are important. Furthermore, by increasing the Da, the values of both considered variables are reduced gradually. Finally, an increase in the aspect ratio changes the two-dimensional problem into a one-dimensional problem. Several validated surface response methodologies have been designed to deliver drug through the skin as a practical implementation of this analytical research.

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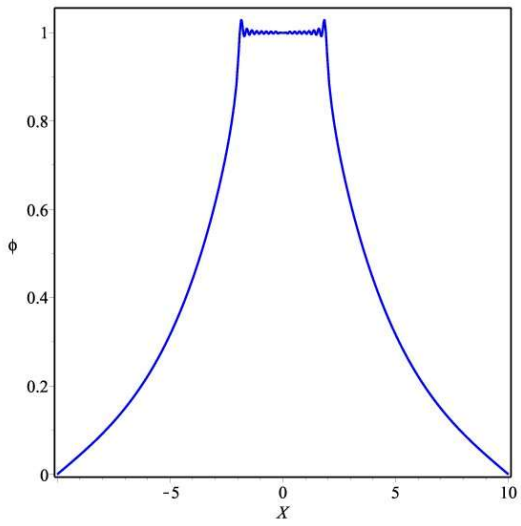

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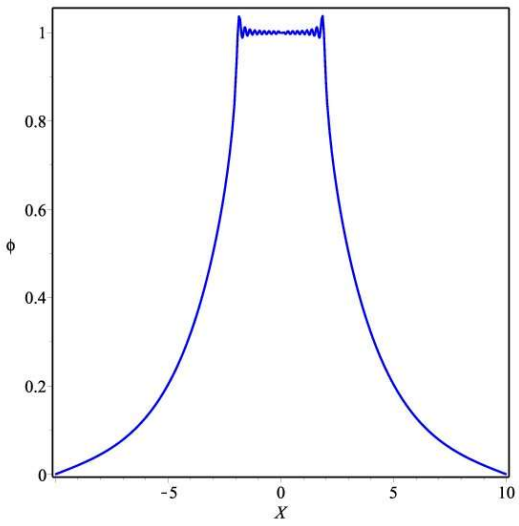

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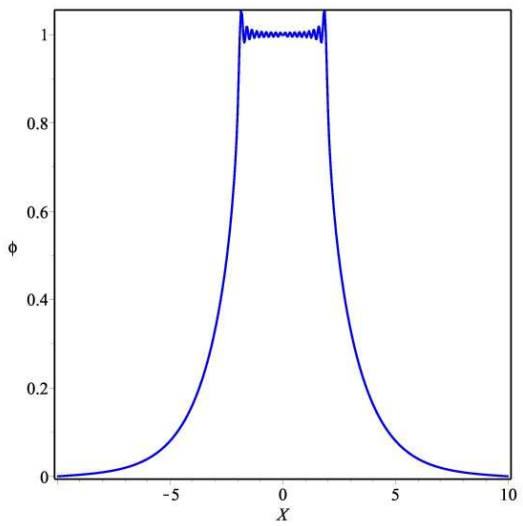

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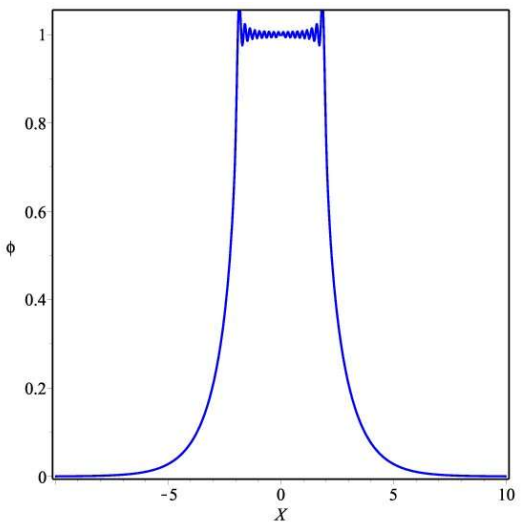
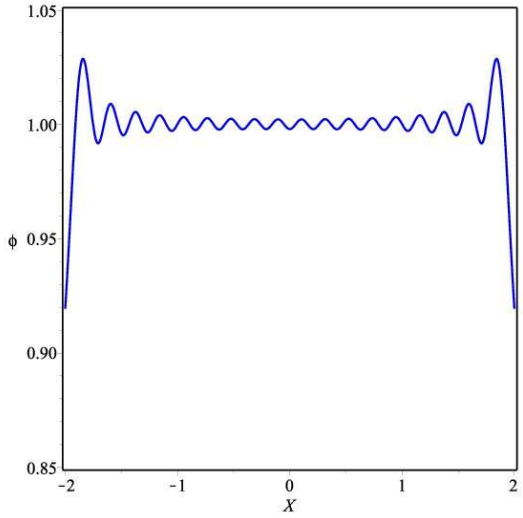


(d)

Figure 3. Distribution of mass concentration at the skin surface, N=100 and L=0.1 m for (a) Da=0.1, (b) Da=0.2, (c) Da=0.5, and (d) Da=1.



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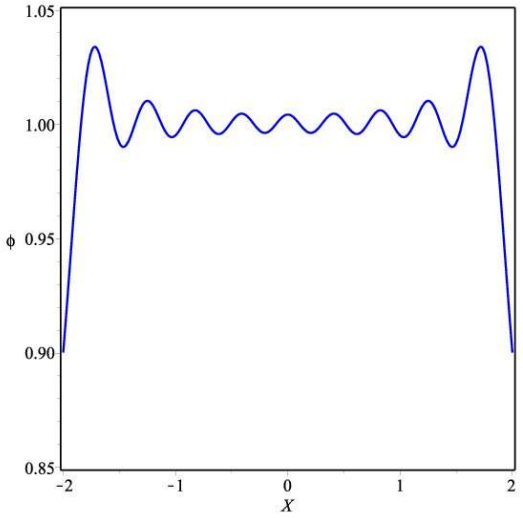

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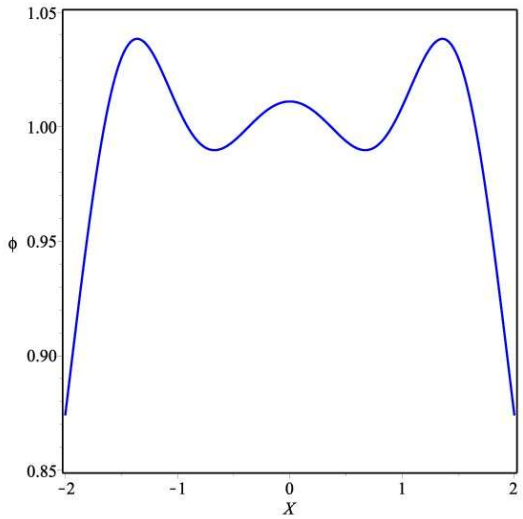

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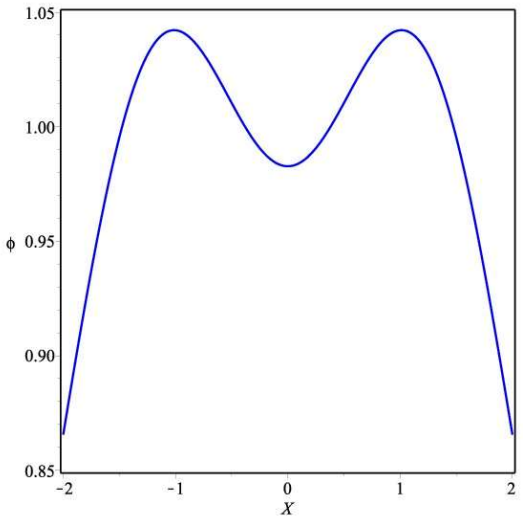
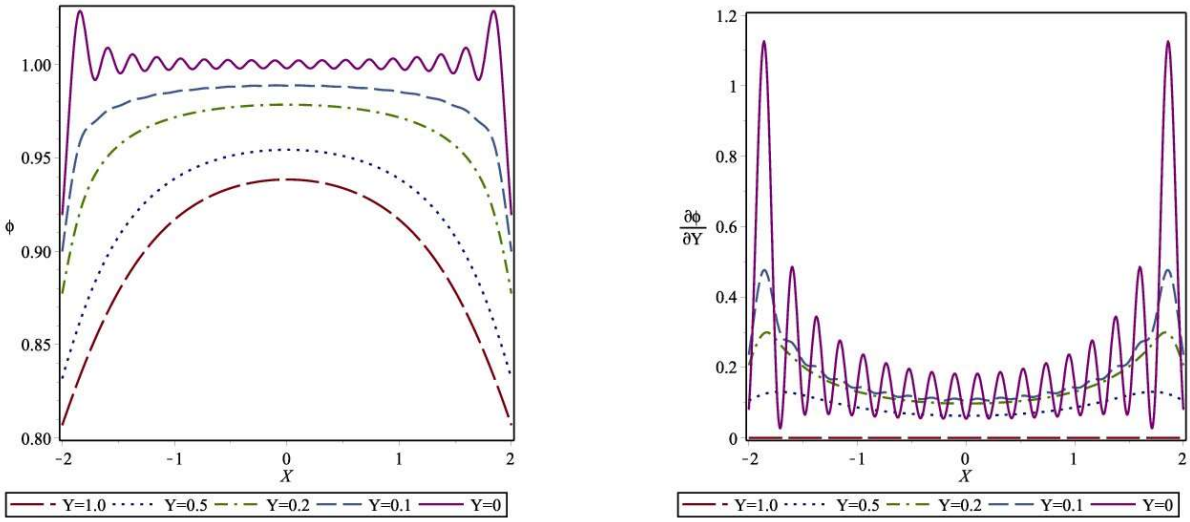


(d)

Figure 4. Distribution of mass concentration over the contact area, N=100 and Da=0.1 for (a) L=0.1 m, (b) L=0.2 m, (c) L=0.5 m, and (d) L=1 m.



(a) (b)

Figure 5. Distribution of (a) mass concentration and (b) mass diffusion flux in the skin thickness for N=100, Da=0.1, and L=0.1 m.

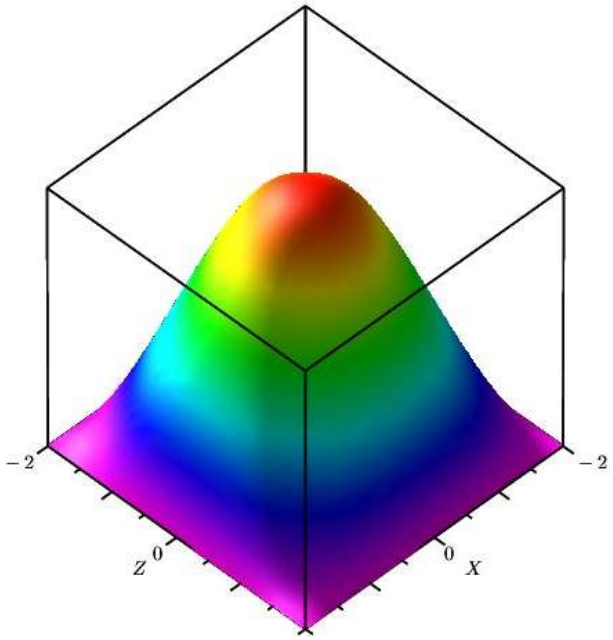


Figure 6. Three dimensional schematic of the mass concentration contour at Y=1.

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