Numerical Simulation of Transdermal Iontophoretic Drug Delivery System.

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Abstract. Transdermal Iontophoretic Drug Delivery System (TIDDS) is a non-invasive method of systemic drug delivery that involves applying a drug formulation to the skin. The drug penetrates through the stratum corneum, epidermis and dermis layers. Once the drug reaches the dermal layer, it is available for systemic absorption via dermal microcirculation. However, clinical testing of new drug developed for the iontophoretic system is a long and complex process. Recently, most of those major pharmaceutical companies have attempted to consider computer-based bio-simulation strategies as a means of generating the data necessary to help make a better decision. In this work, we used computational modelling to investigate the TIDDS behaviour. Our interest is to study the efficacy of drug diffusion through transdermal delivery, including the thermal effect on the skin. We found that drug will be delivered more efficiently if the electrical potential and the position of electrodes are optimum. We analysed the drug diffusion time of the system using 1,3 and 5 mA DC source. In addition, we also modify the electrode distance from 10 mm to 30 mm long and analysed the effect of delivery time and the effect to the skin thermal. We conclude that, a high electrical current, as instance, a 5 mA DC, delivered the drug faster into the skin but increased the skin temperature because of skin joule heating effect. However, a 30 mm electrodes distance setting decreased the skin temperature significantly than the 10 mm distance with more than 9.7 °C under 5 mA DC and 60 minutes of operation. TIDDS enhanced drug delivery compared to oral consumption and might be suitable used for localizing treatments such as chronic disease. This work provides great potential and is useful to efficiently design of iontophoretic drug delivery system including new drugs delivery applications.

1. Introduction

The concept of Transdermal Iontophoretic Drug Delivery System (TIDDS) of medications is not new. The use of transdermal delivery of homemade medicinal preparations dates to the early 20\textsuperscript{th} century [1]. TIDDS is a non-invasive method of systemic drug delivery that involves applying a drug formulation to the intact and healthy skin. The drug penetrates the stratum corneum, epidermis and deeper dermis, without accumulating in the dermal layer. Once the drug ions reaches the dermal layer, it becomes applicable for systemic absorption via the dermal microcirculation.

While transdermal drug delivery has made significant contributions to medical practice, its full potential as an alternative to oral administration and hypodermic injections has yet been realized. The first generation of TIDDS have maintained a steady increase in clinical use for the delivery of small, lipophilic, low-dose drugs without the use of a patch system. The second-generation of drug delivery...
systems incorporate passive techniques such as chemical enhancers for instances urea, terpenes, sulphoxides, and pyrrolidone, and others. Passive methods typically include for modifying the stratum corneum structure which influence the drug-vehicle interactions and formulation optimization [2]. While the third-generation TIDDS was developed to improve and enhance the efficiency of drug delivery. It is based on active or energy-driven techniques such as thermal ablation, electrical, mechanical, acoustic, and light. Additionally, the third generation of TIDDS is occasionally based on a combination of several techniques. Active methods employ external energy to act as a propellant for drug transport across the skin or disrupt the stratum corneum physically [3].

Iontophoresis is a technique that is widely studied and used in clinical applications. While considerable attention has been paid to this technique in recent years, the efficacy of the drug transported via this delivery system is not well investigated. For instance, only drugs with a low molecular weight and a high penetration property are suitable for use [4][5]. Additionally, a variety of factors such as skin conditions, electrode dimensions, and current amplitude, contribute to the efficacy of the drug being transferred [6].

We utilized computational modelling to investigate the behaviour of an iontophoresis drug delivery system in this work. Our objective is to investigate the efficacy of drug diffusion via the transdermal delivery. We show that if the current and position of the electrodes are optimised, drugs are delivered more efficiently. However, the iontophoresis process has a significant effect on the skin temperature, which may cause mild irritation or maybe skin burns. Despite the limitations of the iontophoresis technique for drug delivery, this method is low-cost, self-handling and has a great potential for non-invasive localize treatment.

2. Mathematical Model Related to the Iontophoretic Drug Delivery System

The Nernst–Planck equation is used to model transdermal iontophoresis. This equation defines species flux through homogeneous media. Typically, the flux produce by an electrochemical potential gradient is decoupled into a diffusion term representing activity or concentration gradient-driven flow and an electromigration term representing the force of the electric field on charged molecules. The representation of the Nernst–Planck flux shows below

\[ J_i = -D_i \frac{dC_i}{dx} - \frac{\varepsilon F C_i}{RT} \frac{d\Phi}{dx} \]  \hspace{1cm} (1)

where \( J_i \) is the flux across the membrane of species \( i \), \( D_i \) is the diffusion coefficient, \( C_i \) is the concentration of species \( i \), \( Z_i \) charge on species \( i \), \( F \) is the Faraday constant, \( R \) is the gas constant, \( T \) is absolute temperature (K), \( X \) is distance, and \( \Phi \) is the electric potential.

In equation (1), the overall flow is composed of two components: one related to concentration and another to the voltage across the membrane. When a drug is not charged (\( Z_i = 0 \)) or when the voltage is zero (\( d\Phi/dx = 0 \)), the Nernst–Planck equation reduces to which is just the Fick’s first law of diffusion, as the Nernst-Planck equation simplifies. A concentration gradient across a membrane result in passive diffusion. Substances flow down a concentration gradient or from a concentration gradient to a concentration gradient.

\[ J_{ip} = -D_i \frac{dC_i}{dx} \]  \hspace{1cm} (2)

Additionally, if the concentrations on both sides of the membrane are equal (\( dC/dx = 0 \)), the Nernst–Planck equation is simplified to include only the electrical driving component (electro-transport).

\[ J_{ie} = - \frac{\varepsilon F C_i}{RT} \frac{d\Phi}{dx} \]  \hspace{1cm} (3)

Electro-transport occurs when a potential or voltage is delivered across a membrane, as presented by equation (3). Convective flux is the third mechanism of transfer that may occur during iontophoretic administration. The terms electroosmosis or iontohydrokinesis which refer to convective flux.
Convective flux occurs when drug ions are dragged or pulled along when water transport occurs. Thus, the Nernst–Planck equation can be modified to include all three components of iontophoretic delivery, which are passive diffusion, electron transport and convective flux by:

\[
J_{it} = J_{ip} + J_{ie} + J_{ic} = J_i = -D_i \frac{dc_i}{dx} - \frac{D_i z_i F c_i}{RT} \frac{d\Phi}{dx} + C_i v
\]  

(4)

where \(J_{ip}\) is the passive delivery of each species (the \(ith\) species); \(J_{ie}\) is the electrotransport (active delivery) of each species; \(J_{ic}\) is the convective flux of each species; \(v\) is the solvent velocity.

Thus, equation (4) forms the physical basis for iontophoretic transport.

On the other hand, we used the Nernst-Einstein equation to determine ionic conductivity and transference numbers from the ion’s diffusion coefficients. The diffusion coefficient and electric mobility are proportionality constants between flux and the concentration and potential gradients, respectively. The migration of drug in electrical field is defined using this Nernst-Einstein relation

\[
U_m = \frac{z_i D_i F}{RT}
\]  

(5)

where \(U_m\) is the electrical mobility.

3. Numerical Simulation Model

The numerical analysis and development of the two-dimensional (2D) skin model were performed using COMSOL Multiphysics 5.6 (COMSOL Inc., USA). The stratum corneum, epidermis, dermis and subcutaneous tissue or fat, are the four layers of the skin model (Figure 1(a)). The electrodes are attached to the skin model, with the terminal electrode containing the target medication (Figure 1(b)). The skin model's boundary conditions as shown in Table 1, as well as the drug and electrical properties, are derived from a several literatures [7][8]. Additionally, we established assumptions for the electrical and thermal properties of the drug, including the density, charge, and other related parameters.

**Figure 1.** Iontophoresis transdermal drug delivery model. (a) Skin layers including stratum corneum, epidermis, dermis, and subcutaneous tissue. (b) Terminal and ground electrodes. (c) Drug formulation mixed with conductive hydrogel. (d) electrodes distance. (e) 2D model
### Table 1. Model parameter

| Model Parameter          | Unit   | Value  |
|--------------------------|--------|--------|
| **Corneum Stratum**      |        |        |
| Relative Permittivity    |        | 2.4    |
| Diffusion coefficient    | m^2/s  | 1e-11  |
| Density                  | kg/m^3 | 1000   |
| Thermal conductivity     | W/(m.K)| 0.213  |
| Heat capacity at constant pressure | J/(Kg.K) | 1880 |
| Electrical conductivity  | S/m    | 0.0005 |
| Thickness                | µm     | 5.00E+01 |
| **Epidermis**            |        |        |
| Relative Permittivity    |        | 1      |
| Diffusion coefficient    | m^2/s  | 1.00E-09 |
| Density                  | kg/m^3 | 1200   |
| Thermal conductivity     | W/(m.K)| 0.62   |
| Heat capacity at constant pressure | J/(Kg.K) | 4400 |
| Electrical conductivity  | S/m    | 0.026  |
| Thickness                | µm     | 1.50E+02 |
| **Dermis**               |        |        |
| Relative Permittivity    |        | 3.9    |
| Diffusion coefficient    | m^2/s  | 1.00E-08 |
| Density                  | kg/m^3 | 1100   |
| Thermal conductivity     | W/(m.K)| 0.5820 |
| Heat capacity at constant pressure | J/(Kg.K) | 4184 |
| Electrical conductivity  | S/m    | 0.227  |
| Thickness                | µm     | 2.00E+03 |
| **Subcutaneous tissue**  |        |        |
| Relative Permittivity    |        | 5.6    |
| Diffusion coefficient    | m^2/s  | 1.00E-08 |
| Density                  | kg/m^3 | 900    |
| Thermal conductivity     | W/(m.K)| 0.2930 |
| Heat capacity at constant pressure | J/(Kg.K) | 2600 |
| Electrical conductivity  | S/m    | 4.00E-02 |
| Thickness                | µm     | 2.50E+03 |
| **Electrode Distance**   |        |        |
| (Terminal-Ground)         |        |        |
| short distance model      | mm     | 10     |
| long distance model       | mm     | 30     |
| **Electrical**            |        |        |
| Current Source            | DC-A   | 1.00E-03 |
| **Temperature**           |        |        |
| Skin                      | °C     | 36.3   |
| Ambient                   | °C     | 27     |
4. Two-dimensional Model Analysis
We analysed several relationships relating to drug delivery via iontophoresis, including the transdermal drug delivery rate concentration, the electrical current intensity as a function of the time required to deliver the drug, the effect of the electrode distance on the diffusion rate, and the skin temperature. According to the equation (1), increasing the electrical current that used to force the drug through the skin reduces the time required for drug delivery. Additionally, the electrode dimension influences the electrical current density \( \text{A/m}^2 \), which affects the drug ion migration through the skin. On the other hand, iontophoresis transdermal drug delivery modifies the skin’s temperature due to the applied electrical current. As iontophoresis uses electrical fields, it causes a thermal effect on the skin tissues (Joule heating). Because the electric field and the resulting Joule heating are related, when calculating the true thermal effect, both thermal and electrical effects should be considered. The Pennes bioheat equation is a well-known equation for determining the heat flow in living tissues [9]. However, the Pennes’ model is not useful in this model as it is more suitable for deep tissues analysis which is focused on heat transfer between capillary blood and tissue. Additionally, we did not considered heat sources form blood perfusion and tissue metabolism. Thus, in this work, the joule heating analysis was preferred and carried out. Although joule heating approximates skin thermal analysis in this transdermal drug delivery model compared to the Pennes bioheat transfer equation, the analysis result could still be useful in determining skin thermal condition during the iontophoresis process.

Resistive heating in a time-dependent heat equation

\[ \rho C_p \frac{\partial T}{\partial t} + \nabla (-k \nabla T) = Q_e \]  

(6)
where \( \rho \) is the tissue density, \( C_p \) is the tissue specific heat capacity at constant stress, \( T \) is the absolute temperature, \( k \) is the tissue thermal conductivity and \( Q \) contains additional heat sources. The equation related to the current density can be defined as

\[ Q_e = J \cdot E \]  

(7)
where \( J \) is the current density and \( E \) is the electrical filed strength.

5. Result and Discussion
5.1. Transdermal drug delivery rate
The delivery rate (time of drugs released from the electrode) is determined from the time taken starting when the electrical current is applied until all the drug is delivered to the skin. As shows in Figure 2(c), during first 10 minutes of operation, the drug concentration in the skin delivered about 2 mmol/L at subcutaneous tissue. This condition increased over time, as instance, at minute 60, we could observe that the subcutaneous tissue been delivered to the maximum concentration value which is 5 mmol/L shows in Figure 2(e). In addition, due to the model simulation has limitation to the determined the amount of drug diffused by the skin, therefore, we still be able to see the movement of delivered drug ions towards ground terminal.

The current density which flows through the skin is highly reliable by the skin layer conductivity. The most higher current density area in the skin model was at the dermis layer, which has higher conductivity than the other skin layers (Table 1). Therefore, higher concentration of drug delivered at this dermis skin layer. Nevertheless, the concentration of drug in the skin is not dependent to the current density only, but other parameters including the density, diffusion coefficient and the expressions of electric ionic mobilities. Therefore, the concentration of subcutaneous tissue or fat also increased by ionic mobilities over the time (Figure 2).
5.2. **Effect on electrodes distance and current applied**

The second 2D skin model with a longer electrode distance (30 mm) explained in the previous topic shows that only a small change in the drug delivery rate and drug concentration in the skin. Comparing the simulation results for 10 mm and 30 mm distances as shown in Figure 3, the concentration drug in the skin is almost similar between the two distance. As instance, at minute 30 the result at reference arc length line at 4000 um (dermis layer) is about 3.6 mmol/L for the 10 mm electrodes distance, while for 30 mm electrodes distance shows about 3.9 mmol/L which the concentration difference is about only 0.3 mmol/L. This is because, when the electrodes are separated by a long distance, the voltage difference between them increases, due to an increase in ohmic resistance in skin electrical conductivity.

Although electrodes distance on the transdermal system has small changes to the concentration of drug in the skin, the current applied to drive the drug ions has a significant impact on the performance of iontophoretic system. Drug ions migrated faster as the current was increased. From equation (1), the migration of ions described in equation (4) is affected due to the electrical potential. The result shows 5 mA applied made the drug delivery rate faster compared to the 1 mA current (Figure 4). The reference arc length at the dermis layer shows that the concentration of drug moves (ions migration) faster towards the ground terminal. This caused the drug supplied at the terminal to drain faster over time under high electric potential.
Figure 3. Drug delivered to the skin. (a) 10 mm electrode distance. (b) 30 mm electrode distance. The model reference arc line length is defined from the electrode terminal to the bottom of subcutaneous tissue (Figure 1).

Figure 4. Comparison of drug concentration in skin. (a) 1 mA. (b) 5 mA (colour scale in concentration, mmol/L)

5.3. Thermal effect on the skin
In general, iontophoresis is a safe procedure. Nevertheless, the thermal effect from electrical potential increases local skin temperature, which could cause skin burns or irritation. However, if the electrical potential is small, the skin thermal effect could be reduced. As a result, 1 mA current shows that skin thermal increased gradually over time (Figure 4 (a)). Meanwhile, a higher current will cause a significant increase in skin thermal condition over time (Figure 4 (c)). Therefore, the available iontophoresis systems on the market prefer a low electrical potential which less than 10 mA preferred to reduce the thermal effect on the skin. However, reducing the electrical potential will result of increasing the drug delivery time and greatly affect the drug ions diffusion efficacy through the skin.
On the other hand, the thermal effect on the skin could be reduced by increasing the distance of electrodes. On the 30 mm electrodes distance setup, for instance, a 5 mA current is applied up to 60 minutes of iontophoresis process, the temperature of the skin is decreased significantly. As a result shows in Figure 5(c) and Figure 6, difference between 5 mA (at 72.4 °C) using 10 mm with 30 mm distances (at 63 °C is about 9.4 °C. Initially, the model skin temperature is set to be 36.4 °C and the external temperature (temperature outside skin surface) is at the standard room temperature (27 °C). At the centre of the electrodes, the temperature difference between 10 mm (Figure 5(c)) and 30 mm (Figure 6) distances difference is determined to be about 13.4 °C. It is caused by the skin thermal convection effect, efficiently cool the skin compared to shorter distance electrodes where the heat source (electrodes) is close together causing the convection to be less efficient.

![Figure 5](image1)

**Figure 5.** Skin thermal effects by the electric potential at 60 minutes of iontophoretic. (a) 1 mA, with maximum thermal of 37.75 °C, (b) 3 mA, with maximum thermal of more than 49.3 °C, (c) 5 mA, with more than 72.4 °C. (Colour scale in temperature, °C)

![Figure 6](image2)

**Figure 6.** Skin thermal effect on 30 mm electrode distance setup at 60 minutes of iontophoretic. (Colour scale in temperature, °C)

6. Conclusion

Iontophoresis enhanced drug delivery and diffusion through transdermal. The numerical transdermal drug delivery has been made to show the effects of transdermal iontophoresis drug delivery. Furthermore, numerical analysis enables more realistic models to be treated. In this work, we show that parameters such as delivery rate concentration, electrical potential, electrode distance and thermal effect by the electro-transport are and feasibility for a new drug for transdermal delivery applications. As an example, a low current potential such as less than 5 mA for iontophoretic system is preferred, however it is trade-off from efficient time taken for the delivery. On top of that, it is interesting to study the skin thermal effect which is useful for lower the risk of skin burns or irritation for long period iontophoretic process. As example, a pulse current has been identified to lower skin thermal effect, however, the
delivery rate consumes longer process time. On the other hand, this technique enhanced drug delivery compared to oral consumption and might be suitable for localize treatments of chronic diseases such as cancers or tumors.

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