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ABSTRACT

TRANSDERMAL AND TRANSBUCCAL DELIVERY OF LIDOCAINE AND NICOTINE: COMBINED EFFECTS OF IONTOPHORESIS AND CHEMICAL ENHANCERS

by

Ran Wei

This study focused on the effects of iontophoresis and chemical enhancers on drug release. The transport of Lidocaine HCl (LHCl) and Nicotine Hydrogen Tartrate (NHT) through the skin and mucosa was evaluated for potential clinical applications. These two potential delivery routes have the advantage of avoiding first-pass effect. Samples were pretreated with enhancer solutions for one hour before the experiments. Passive or 0.3 mA iontophoresis-assisted drug diffusion was conducted for 8 hours to monitor the cumulative amount of drug released. Graphical methods and mathematical optimization techniques were implemented to analyze the data. The effects of chemical enhancers on the delivery rate depend largely on the drug used while iontophoresis mainly increases the steady-state flux. Parametric analyses show that a balance between high flux and fast release should be considered when conducting formulation and optimization studies.

Keywords: Iontophoresis; Enhancer; Transdermal; Transbuccal

**TRANSDERMAL AND TRANSBUCCAL DELIVERY OF LIDOCAINE
AND NICOTINE: COMBINED EFFECTS OF IONTOPHORESIS
AND CHEMICAL ENHANCERS**

**by
Ran Wei**

**A Thesis
Submitted to the Faculty of
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in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Pharmaceutical Engineering**

**Otto H. York Department of
Chemical, Biological and Pharmaceutical Engineering**

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APPROVAL PAGE

**TRANSDERMAL AND TRANSBUCCAL DELIVERY OF LIDOCAINE
AND NICOTINE: COMBINED EFFECTS OF IONTOPHORESIS
AND CHEMICAL ENHANCERS**

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Dedicated to my family

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CHAPTER 1

INTRODUCTION

1.1 Transdermal and Transbuccal Delivery

Transdermal drug delivery employs intact skin as the site for drug administration [1]. The skin, which was once regarded as an impermeable membrane, has a unique way of absorbing small organic molecules. The superficial layer of the epidermis, or stratum corneum (SC), plays a critical factor in drug delivery. Most molecules penetrate through the skin via intercellular spaces among the corneocytes of the SC. These regions are filled with lamellar lipid structures derived from cellular granules of the viable layers of the epidermis. Advantages, such as no first-pass metabolism in the liver, extended release and better patient compliance, make the skin an attractive transport route. Approximately 40% of drug products under clinical evaluation are prepared in transdermal form [1, 2].

Due to the rich supply of blood and the mild pH conditions, the oral mucosa represents a potential site for drug delivery and absorption. Another advantage lies in the avoidance of the first-pass elimination in the gastrointestinal (GI) tract [3]. There has been some interest in the delivery of lidocaine and nicotine via the oral mucosa. This option would require the study of potential enhancers because of the low permeability of the buccal membrane which limits drug bioavailability [4].

1.2 Chemical and Physical Enhancement

Chemical enhancement methods may help with the transport of molecules through the SC and mucosal membranes without damaging neighboring cells. Iontophoresis, which causes the migration of ionic molecules in membranes by the application of an electric field, has also been studied [5] and resulted in the FDA-approved patch, Lidosite® (Vyteris Inc., Fairlawn, NJ) [1, 6]. In some investigations, the combination of both enhancement approaches was evaluated [7] without focusing on a mathematical analysis of the delivery mechanism. This work centers on the implementation of numerical tools to assess the effects of these methods on the steady-state flux and the time to reach a desired delivery rate.

1.3 Factors Influencing Chemically- or Physically-Aided Drug Transport

Both environmental factors and drug molecule properties control the transport rate. Chiang et al. (1991) investigated the percutaneous absorption of the acidic drug indomethacin and reported an increase in drug penetration when transport occurred at low pH. However, since the drug exhibited poor solubility under such conditions, a higher pH value was required to promote adequate drug release from the device [8]. Factors dominating the iontophoretic delivery processes include electric field intensity (or, current density), pH and the physicochemical properties of a drug molecule. To be delivered under the influence of an electrical field, the drug molecule should be ionic and in high concentration compared with competing ions (such as co-ions and counter-ions from the buffer and endogenous environment) [9]. A suitable pH helps keep most drug

molecules in ionized forms [10]. Moreover, a high current density (within the range of human tolerance) or a high level of electronic field can be applied for similar results, although saturation effects may become a concern [11].

1.4 Drug Selection

Transdermal and transbuccal pathways for lidocaine and nicotine were considered in this work. Lidocaine HCl (LHCl) is a local anesthetic [12, 13] administered intravenously or via hypodermic injections [14]. Some researchers have started to study less invasive drug delivery technologies [15, 16] such as transdermal and oral transbuccal patches. Perry et al. [17] reported the application of transmucosal delivery of lidocaine in tooth scaling and root planting, thereby replacing injections with local anesthetics.

Nicotine has been used to assist people endeavoring to quit smoking without experiencing withdrawal symptoms. It is available in different dosage forms ranging from nasal sprays [18] to transdermal formulations [19]. While transdermal nicotine hydrogen tartrate (NRT) preparations did not lead to high nicotine levels in the blood [20], oral transmucosal products yielded satisfactory results. Four forms are commercially available: chewing gums (e.g. Nicorette[®]), lozenges (e.g. Commit[™]), sublingual tablets (e.g. Stoppers[®]) and oral inhalers (e.g. Nicotrol[®]) [21]. Relevant investigations were conducted to evaluate the effects of those dosage forms. For instance, Muramoto et al. (2003) reported a suppression of withdrawal symptoms following the administration of oral transmucosal nicotine lozenges [22].

1.5 Novelty of the Research

The novelty of this research resides in the application of computational tools to discover the contributions of chemical enhancers and iontophoresis to the performance of drug-delivery systems. The way in which both methods can work in tandem will also be investigated. For passive diffusion, governed by Fick's law, the steady-state flux is a function of the partition coefficient (or surface concentration), the diffusion coefficient and the membrane thickness. The diffusion coefficient and membrane thickness fix the effective time constant. However, when a current is applied to the membrane, a new parameter is introduced into the model. As a result, there is a need to derive new mathematical expressions to properly analyze the roles of the electric field [23-25]. Both iontophoresis and chemicals may influence transport through the membranes.

CHAPTER 2
QUANTIFICATION OF THE EFFECTS OF IONTOPHORESIS
AND CHEMICAL ENHANCERS ON TRANSDERMAL
AND TRANSBUCCAL DELIVERY

When designing controlled-release systems for lidocaine and nicotine preparations, it is imperative to estimate the onset of action of the drug to ensure that the device is suitable for clinical applications. This metric is usually given by the lag time (t_{lag}) [3], which may be a poor predictor of the time to reach a steady-state value in some cases [23]. Collins recommended an effective relaxation time constant (t_{eff}), instead, for diffusive processes [26]:

$$t_{eff} = \frac{\lim_{s \rightarrow 0} \left(\frac{\psi_{ss}}{s^2} + \frac{d\bar{\psi}(s)}{ds} \right)}{\lim_{s \rightarrow 0} \left(\frac{\psi_{ss}}{s} - \bar{\psi}(s) \right)} \quad (2.1)$$

where $\bar{\psi}$ is the Laplace transform of ψ ; ψ_{ss} is the equilibrium value of the function. The final expression for t_{eff} depends on the mechanisms involved. This work considers t_{eff} as the primary indicator of the response time.

2.1 Passive and Chemically-Enhanced Transport

A model based on Fick's second law of diffusion is applied:

$$\frac{\partial C}{\partial t} = Da \frac{\partial^2 C}{\partial x^2} \quad (2.2)$$

where C is the concentration at a depth x within the membrane, Da is the diffusion coefficient of the drug in the membrane and t represents the time.

For this system, there is no drug in the membrane at the beginning of each experiment:

$$C(x, 0) = 0 \quad (2.3)$$

The boundary conditions are:

$$C(0, t) = C_s; C(h, t) = 0 \quad (2.4)$$

where C_s is the concentration at the vehicle-membrane boundary. At the position h (membrane thickness), a sink condition is maintained and the flux is written as:

$$J = \frac{\partial Q}{\partial t} \quad (2.5)$$

where Q is the cumulative amount of the drug released into the receiver compartment.

The solution for the system defined by Equation (2.1–2.4) is:

$$Q = hC_s \left[\frac{tDa}{h^2} - \frac{1}{6} - \frac{2}{\pi^2} \left(\sum_{n=1}^{\infty} \frac{(-1)^n \exp\left[-n^2 \pi^2 \frac{tDa}{h^2}\right]}{n^2} \right) \right] \quad (2.6)$$

After applying a long-time approximation, Equation (2.6) becomes:

$$Q_{ss} = hC_s \left(\frac{tDa}{h^2} - \frac{1}{6} \right) \quad (2.7)$$

with the time derivatives given by:

$$\frac{\partial Q_{ss}}{\partial t} = \frac{DaC_s}{h} \quad (2.8)$$

According to Equation (2.5), the steady-state flux is:

$$J_{ss} = \frac{DaC_s}{h} \quad (2.9)$$

The effective time, available from an analytical solution, and the lag time are [24]:

$$t_{eff} = \frac{7h^2}{60Da} \quad (2.10)$$

and

$$t_{lag} = \frac{h^2}{6Da} \quad (2.11)$$

respectively.

2.2 Iontophoresis System

The classic Fick's second law expression for the iontophoretic systems is:

$$\frac{\partial C}{\partial t} = Da \frac{\partial^2 C}{\partial x^2} - \frac{\gamma D}{h} \frac{\partial C}{\partial x} \quad (2.12)$$

where γ is a dimensionless number that stands for the influence of current. The convective flow of ionic drug transport across the membrane is neglected. The cumulative amount of drug released is [23, 24]:

$$Q = \frac{DaC_s}{h} \frac{\gamma}{1-e^{-\gamma}} \left\{ t + \frac{2h^2}{Da} \frac{\sinh\left(\frac{\gamma}{2}\right)}{\frac{\gamma}{2}} \sum_{n=1}^{\infty} \frac{n^2 \pi^2 (-1)^n}{\left(\frac{\gamma^2}{4} + n^2 \pi^2\right)^2} \left[1 - \exp\left(-\frac{\left(\frac{\gamma^2}{4} + n^2 \pi^2\right)^2 t Da}{2}\right) \right] \right\} \quad (2.13)$$

The steady-state conditions are:

$$Q_{ss} = \frac{DaC_s}{h} \frac{\gamma}{1-e^{-\gamma}} \left[t + \frac{2h^2}{D} \frac{\sinh\left(\frac{\gamma}{2}\right) - \frac{\gamma}{2} \cosh\left(\frac{\gamma}{2}\right)}{2\gamma \sinh^2\left(\frac{\gamma}{2}\right)} \right] \quad (2.14)$$

and

$$J_{ss} = \frac{DaC_s}{h} \frac{\gamma}{1-e^{-\gamma}} \quad (2.15)$$

The determination of the effective time and lag time yields [23]:

$$t_{eff} = \frac{h^2 \operatorname{csc} h^2 \left(\frac{\gamma}{2} \right) (3\gamma^2 - 2 \sinh(\gamma)\gamma + (\gamma^2 - 4) \cosh(\gamma) + 4)}{4Da\gamma^2 \left(\gamma \coth \left(\frac{\gamma}{2} \right) - 2 \right)} \quad (2.16)$$

$$t_{lag} = -\frac{h^2}{Da} \frac{2 \sinh \left(\frac{\gamma}{2} \right) - \gamma \cosh \left(\frac{\gamma}{2} \right)}{\gamma^2 \sinh \left(\frac{\gamma}{2} \right)} \quad (2.17)$$

Equation (2.6–2.17) will be used to study the effects of chemical enhancers and the electric field on the drug release.

CHAPTER 3

EXPERIMENT

3.1 Source of Experimental Data

The original data were supplied by Dr. Bozena B. Michniak-Kohn and Dr. Longsheng Hu. The enhancing roles of several chemicals were examined in this work.

Azone (1-dodecylazacycloheptan-2-one or laurocapram) was the first artificially designed skin penetration enhancer. The compound is compatible with most organic solvents including propylene glycol (PG). Its effectiveness lies in the ability to partition into the bilayer lipids and to interfere with the stacking arrangement, thus raising the diffusion of various drugs including antiviral agents, antibiotics and steroids [1].

Dodecyl-2-(*N,N*-dimethyl amino) (DDAIP) and dodecyl-2-(*N,N*-dimethyl amino) propionate hydrochloride (DDAIP HCl) are long chained alcohols. DDAIP is not water-soluble, but dissolves in water-alcohol mixtures and most organic solvents; DDAIP HCl is soluble in water. The enhancement mechanism of both molecules involves interactions with SC keratin, resulting in the increase in hydration efficiency and thereby skin penetration. The effect of DDAIP in promoting drug permeability is comparable to that of azone [27].

Br-iminosulfurane was also examined in this study. Due to the interaction between its aromatic ring structure and the skin's lipid plane, the small br-iminosulfurane molecule is able to affect drug diffusion by attaching to the SC. In addition, the presence of the solvent may induce further enhancement [28].

Propylene glycol (PG) was used as the enhancer vehicle. The combined effects of chemical enhancers and iontophoresis were also studied. Previous work by Nolan et al. (2007) showed that the treatments could have a synergistic effect on the permeation of salbutamol [7].

3.2 Methodology

The experimental protocols are provided in Hu's work [9]. A Franz diffusion cell system (PermeGear, Inc., Hellertown, PA, USA), with a donor cell and a receiver compartment, was used as the *in-vitro* model. The donor cell contained the prepared drug solution and the receiver cell was filled with a phosphate buffer saline (PBS) solution at physiological pH. The tissue samples used in the study originated from the skin and cheek mucosa of a pig. Before each experiment, the membranes were placed in PBS at physiological pH for one hour. They were then inserted between two chambers with the exterior side of tissue facing the donor side. The drug solution was added into the donor compartment at the beginning of each experiment. Three hundred micro liter samples were collected from the receptor cell at specific times. For the enhancer pretreatments, 30 μL chemical enhancer solutions were added to the upper surface of the tissue. The system remained quiescent for one hour. During the iontophoretic delivery experiments, an Ag-AgCl electrode was employed to keep a controlled current density of 0.47 mA/cm^2 (for the 0.64 cm^2 effective diffusion area) between the two sides of the membrane for 8 hours. The experiment was conducted at $37 \text{ }^\circ\text{C}$ using the protocol in [9].

3.3 Modeling Work

The model parameters were calculated using a technique similar to the one adopted in [25] and Equation (2.6), (2.7), (2.13) and (2.14). In the absence of an electric field, the lag time method, based on Equation (2.7), was implemented. Data, at the beginning of the experiment, were removed until a linear trend (i.e., steady-state diffusion) was observed. Extrapolation would give the x-intercept (lag time) and the slope of the line (steady-state flux). With these two terms known, the values of the diffusion coefficient and surface concentration can be estimated using Equation (2.8) and (2.11). For iontophoresis, it was assumed that the diffusion coefficient did not change from the value obtained for passive diffusion. The lag time was plotted and the root γ estimated. The concentration C_s was calculated from the slope of Q . Equation (2.6) and (2.14) were applied with a nonlinear regression routine, in MATLAB (Natick, MA), to refine the results from the graphical methods:

$$\min_{\{Da, Cs, \gamma\}} \sum_{i=1}^{\infty} [Q_i(Da, Cs, \gamma) - Q_{i,e}]^2 \quad (3.1)$$

and

$$\min_{\{Da, Cs\}} \sum_{i=1}^{\infty} [Q_i(Da, Cs) - Q_{i,e}]^2 \quad (3.2)$$

CHAPTER 4

RESULTS AND DISCUSSION

The case studies investigated differ by the transport mechanism (passive or iontophoretic delivery), the nature of the drug and the type of chemical pretreatment. Appropriate equations were chosen to analyze the release kinetics and help decipher the specific roles of chemical enhancers and iontophoresis in the transdermal or transmucosal delivery. The methodology will help identify systems that meet the objectives of high flux and quick drug delivery.

4.1 Transdermal Delivery

4.1.1 Case study 1: Chemically-Enhanced Diffusion

Figure 4.1 shows the data for the diffusion of LHCl across the skin (thickness: $550 \pm 50 \mu\text{m}$) using PG as the vehicle. The procedure was described in Section 3.2. The predictions agree very well with the laboratory data (Figure 4.1). The calculated parameter values are listed in Table 4.1. As stated previously, the effective time constant is a measure of the time it takes the flux to reach an equilibrium value. Based on the definition in [29, 30], the response time can be viewed as the time elapsed before J reaches 98% of J_{ss} , or about 4 times the time needed to attain 63.2% of the J_{ss} , ($4t_{\text{eff}}$). In the following discussions, the parameter $4t_{\text{eff}}$ denotes the response time constant unless specified otherwise.

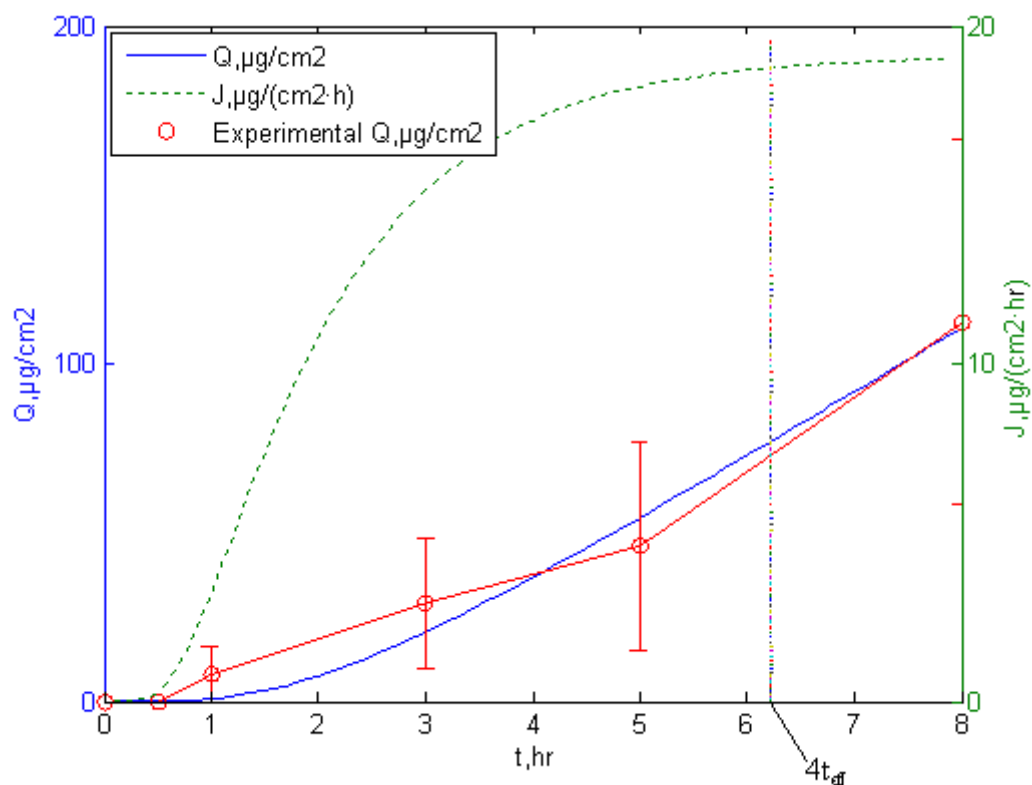


Figure 4.1 Predicted vs. experimental cumulative amount of LHCl (Q) pretreated in a PG vehicle and the time flux profile (J). The response time used was $4 t_{\text{eff}}$. The transdermal system was pretreated with 5% DDAIP in PG.

Table 4.1 The Model Parameters of DDAIP Enhanced LHCl Transdermal Delivery System

| | |
|--|-----------------------|
| Thickness of mucosa, h (μm) | 550 ± 50 |
| Diffusion coefficient, D_a (cm^2/hr) | 0.00025 ± 0.00010 |
| Surface concentration, C_s ($\mu\text{g}/\text{cm}^3$) | 4028.94 ± 2344.21 |
| Effective time, t_{eff} (hr) | 1.42 ± 0.64 |
| Lag time, t_{lag} (hr) | 2.02 ± 0.91 |
| Flux, J ($\mu\text{g}/\text{cm}^2\text{hr}$) | 18.24 ± 13.10 |

4.1.2 Case Study 2: Iontophoretic-Chemical Enhancement

These data were generated from $0.47\text{mA}/\text{cm}^2$ current-assisted LHCl diffusion across a dermal membrane pretreated with 5% DDAIP in PG. In this case, Equation (2.12-2.13) determined the cumulative amount of drug released. Figure 4.2 shows a good agreement between predicted and experimental data. The calculated parameter values are listed in Table 4.2.

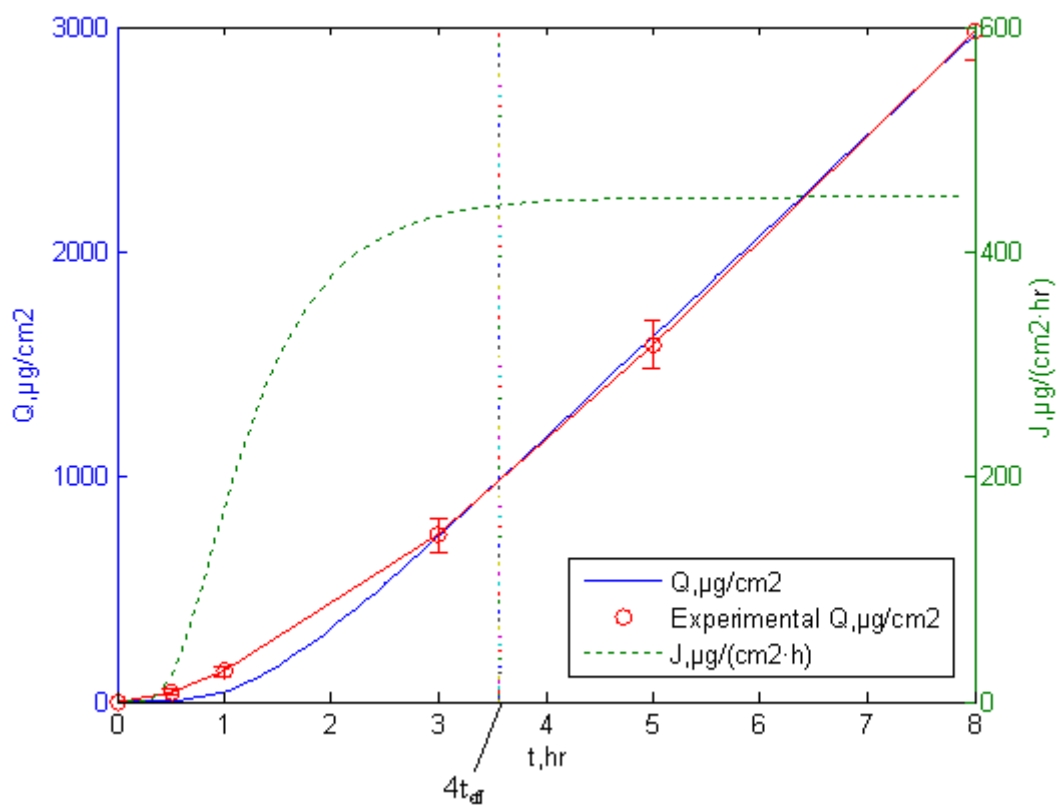


Figure 4.2 Predicted vs. experimental cumulative amount of LHCl (Q) and the time flux profile (J). The response time used was $4t_{\text{eff}}$. The transdermal system was pretreated with 5% DDAIP in PG before applying 0.3 mA of current.

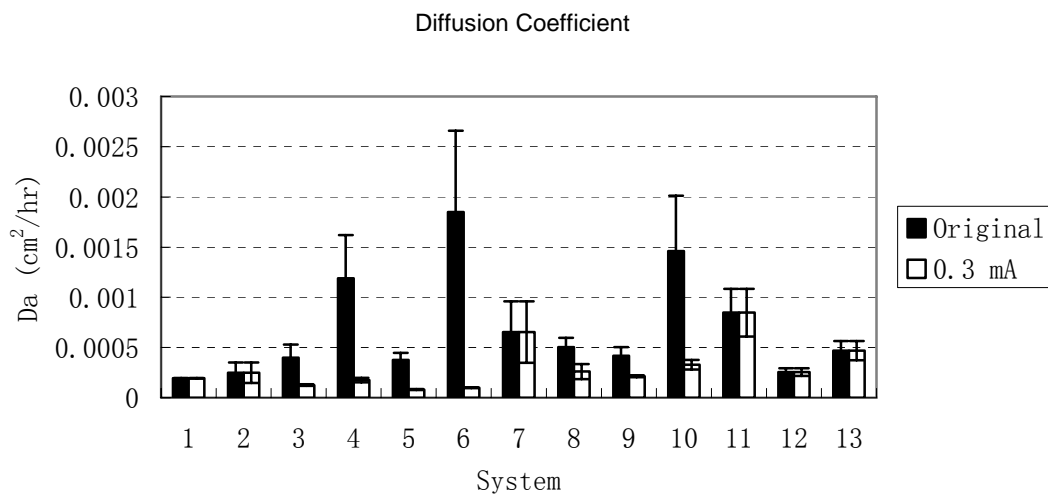
Table 4.2 The Model Parameters of a 0.3mA Iontophoretic Lidocaine Delivery System Pretreated with DDAIP

| | |
|--|------------------------|
| Thickness of mucosa, h (μm) | 550 ± 50 |
| Diffusion coefficient, D_a (cm^2/hr) | 0.00025 ± 0.00010 |
| Surface concentration, C_s ($\mu\text{g}/\text{cm}^3$) | 25496.30 ± 7619.05 |
| Dimensionless number, γ | 4.75 ± 1.36 |
| Effective time, t_{eff} (hr) | 1.00 ± 0.47 |
| Lag time, t_{lag} (hr) | 0.62 ± 0.26 |
| Flux, J ($\mu\text{g}/\text{cm}^2\text{hr}$) | 553.15 ± 230.02 |

The examples, given above, show that the mathematical models in Section 3.3 are well suited to explain passive and iontophoretic transports. Table 4.3 lists the systems investigated and the results are depicted in Figures 4.3-4.6.

Table 4.3 List of Enhanced Transdermal Delivery Systems Studied

| No. | System |
|-----|---|
| 1 | Transdermal LHCl passive for 8 hrs |
| 2 | LHCl Transdermal - PG pretreatment for 1.0 hr |
| 3 | LHCl Transdermal - 2.5% Azone in PG pretreatment for 1.0 hr |
| 4 | LHCl Transdermal - 5% Br-iminosulfurane in PG pretreatment for 1.0 hr |
| 5 | LHCl Transdermal - 5% DDAIP HCl in PG pretreatment for 1.0 hr |
| 6 | LHCl Transdermal - 5% DDAIP HCl in water pretreatment for 1.0 hr |
| 7 | Transdermal - Nicotine Hydrogen Tartrate (NHT) control |
| 8 | Transdermal - NHT PG pretreatment for 1 hr |
| 9 | Transdermal - NHT 2.5% Azone in PG pretreatment for 1 hr |
| 10 | Transdermal - NHT 5% Br-iminosulfurane in PG pretreatment for 1 hr |
| 11 | Transdermal – NHT 5% DDAIP in PG pretreatment for 1 hr |
| 12 | Transdermal – NHT 5% DDAIP HCl in PG pretreatment for 1 hr |
| 13 | Transdermal – NHT 5% DDAIP HCl in water pretreatment for 1 hr |

**Figure 4.3** Drug diffusion coefficients for the enhanced transdermal delivery systems.

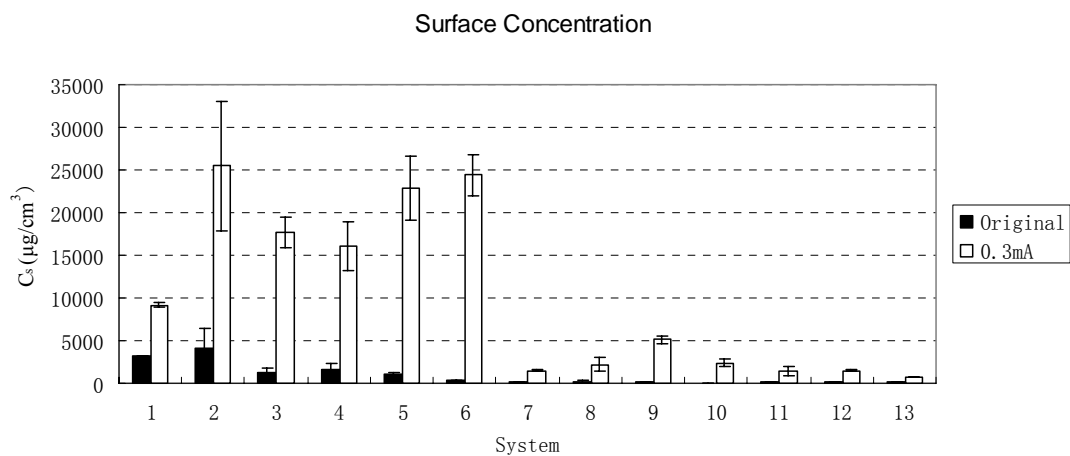


Figure 4.4 Surface concentrations for the enhanced transdermal delivery systems.

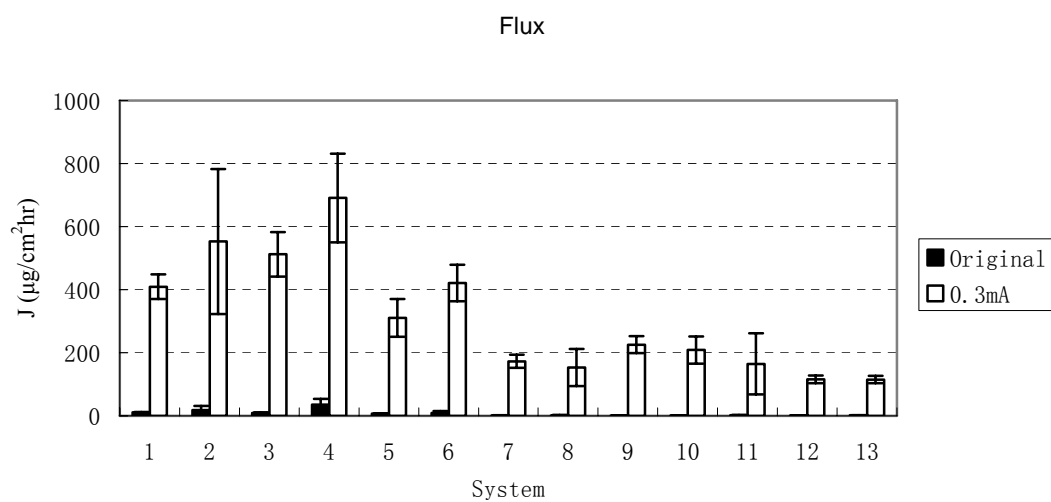


Figure 4.5 Fluxes for the enhanced transdermal delivery systems.

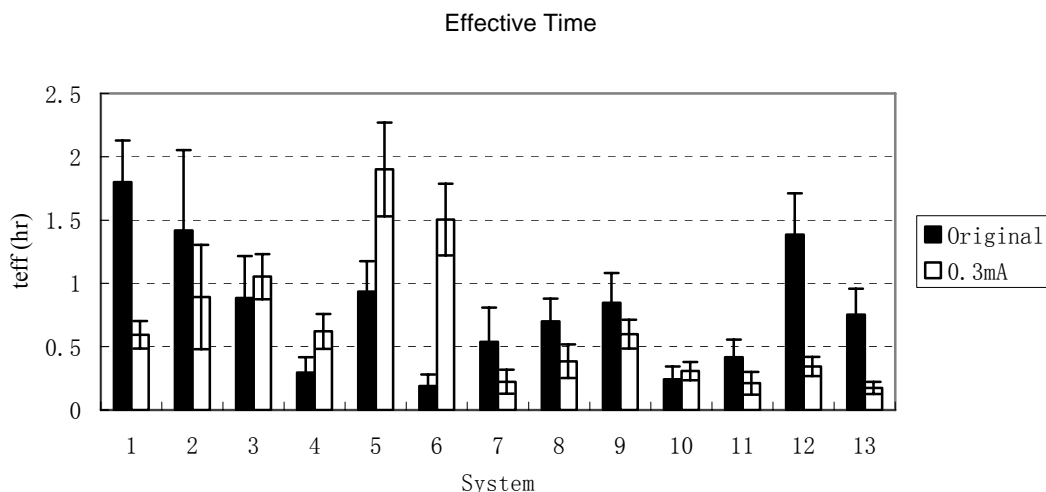


Figure 4.6 Effective time constants for the enhanced transdermal delivery systems.

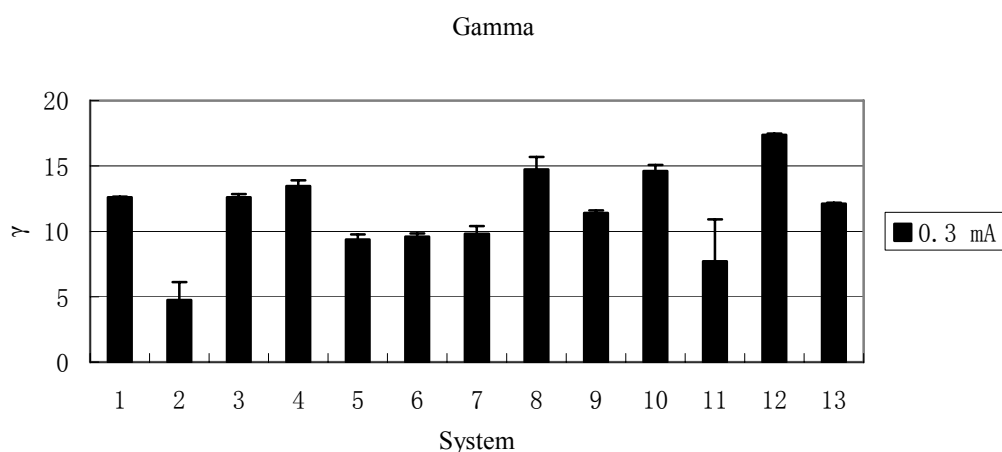


Figure 4.7 Gamma values for the iontophoretic transdermal delivery systems.

4.1.3 Discussion

4.1.3.1 Passive and Chemically-Enhanced Delivery. For passive and chemically-enhanced deliveries, the diffusion coefficient (D_a) and surface concentration (C_s) were the key model parameters. Based on Figure 4.3 and 4.4, not all chemical enhancers would bring an increase in D_a and C_s . For example, in system 13 (5% DDAIP HCl in water), the pretreatment led to a decrease in the diffusion coefficient ($0.00047 \pm 0.00010 \text{ cm}^2/\text{hr}$).

Figure 4.5 and 4.6 show the effects of pretreatments on the flux and the effective time constants, respectively. For example, in the delivery of LHCl, the highest flux level was detected when the membrane was pretreated with 5% br-imosulfurane in PG for 1.0 hr ($35.28 \pm 18.94 \mu\text{g}/\text{cm}^2\text{hr}$). However, the shortest response time corresponded to 5% DDAIP HCl in water ($0.76 \pm 0.36 \text{ hr}$, $4t_{\text{eff}}$). The enhancement effects were also drug-specific. For the NHT transport, the highest flux and shortest response time were obtained when the skin was pretreated with 5% DDAIP in PG and 5% br-imosulfurane, respectively.

The figures also revealed the roles played by Da and Cs in the diffusion process. Equation 2.10 demonstrates that Da is the main factor influencing t_{eff} . The system with the highest Da should produce the shortest response time. Both Da and Cs are important in determining the delivery rate. For example, in NHT delivery, system 10 (5% br-imosulfurane) has the highest Da level and the shortest response time, whereas system 13 has the largest Cs value. System 11 (5% DDAIP in PG) yields the largest flux with moderate Da and Cs values.

4.1.3.2 Iontophoresis-chemical Enhancement. The introduction of parameter γ , in Equation 2.11, reflects the difference between passive and iontophoretic transport. The definition expression for γ is:

$$\gamma = zF\Delta\Psi / RT \quad (4.1)$$

where z is defined as the charge on the drug molecule; F is the Faraday constant; $\Delta\Psi$ represents the voltage drop across the membrane (proportional to the resistance of membrane under the same current condition); R is the ideal gas constant and T is the

absolute temperature. The value of γ varies with the chemical enhancer used (Figure 4.7). These results also show that the membrane resistance has been modified, indicating an alteration in the physiological properties of the membrane. A sharp increase in the C_s can be seen in Figure 4.4 following the application of an electric current. As expected, no significant changes were detected in Da , except for systems 4, 6 and 10, where a decrease was recorded.

The flux and effective time are used to evaluate the effectiveness of the delivery systems. According to Figure 4.5, the flux, resulting from the iontophoretic-chemical enhancement, increases compared to the original passive or chemically-enhanced system. For the same drug, the flux variations were of the same order of magnitude regardless of the enhancers applied. As for the response time constant, the enhancement is less significant than the flux. With enhancers, such as 5% br-iminosulfurane in PG pretreatment (system 4), 5% DDAIP HCl in PG pretreatment (system 5) and 5% DDAIP HCl in water pretreatment (system 6), the iontophoresis would delay drug delivery, which can be regarded as a further proof of a change in the membrane structure.

To obtain a high LHCl blood drug concentration for cure, any pretreatment except 5% DDAIP HCl in PG (system 5) is acceptable, since the enhancers play no significant role in increasing the transport rate compared with the control (Figure 4.5). However, if a quick response is needed, system 5 or 1 can be selected. For NHT delivery, all of the pretreatments, except 12 (NHT 5% DDAIP HCl in PG) and 13, can be applied to reach a large flux. Enhancer 11 or the enhancer-free control can be chosen if a fast transport rate is required.

4.2 Transbuccal Delivery

The transbuccal delivery data were analyzed using the methodology implemented in the transdermal studies. A $350 (\pm 50)$ μm thick swine cheek mucosa sample was used. Two representative case studies are given below to compare the experimental data with the predictions from the models when chemical and iontophoretic - chemical enhancements were applied.

4.2.1 Case study 1: Passive and Chemical Enhancement

Figure 4.8 illustrate how well the theoretical models predict the experimental data. The data given in Figure 4.8 were obtained from the delivery of LHCl across a transbuccal mucosa pretreated by 5% DDAIP with PG as the vehicle. A good agreement was observed between the two data sets (Figure 4.9). The computed parameters are listed in Table 4.4. The response time constant ($4t_{\text{eff}}$) is also shown in the graph.

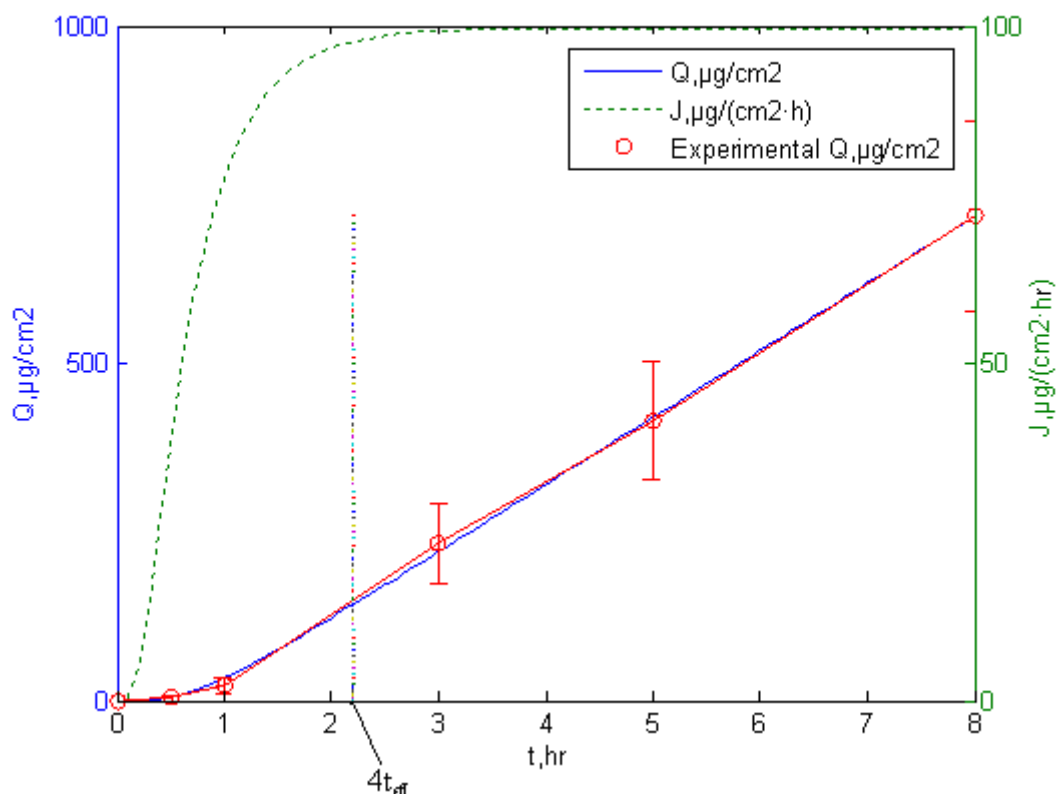


Figure 4.8 Predicted vs. experimental cumulative amount of LHCl (Q) and the time flux profile (J). The response time used was $4 t_{\text{eff}}$. The transdermal system was pretreated with 5% DDAIP in PG.

Table 4.4 The Parameters of LHCl Transbuccal Delivery System Enhanced by DDAIP in PG

| | |
|--|------------------------|
| Thickness of mucosa, h (μm) | 350 ± 50 |
| Diffusion coefficient, D_a (cm^2/hr) | 0.00026 ± 0.00003 |
| Surface concentration, C_s ($\mu\text{g}/\text{cm}^3$) | 13392.99 ± 1971.30 |
| Effective time, t_{eff} (hr) | 0.55 ± 0.17 |
| Lag time, t_{lag} (hr) | 0.79 ± 0.25 |
| Flux, J ($\mu\text{g}/\text{cm}^2\text{hr}$) | 99.37 ± 24.04 |

The enhanced transdermucosal systems studied are listed in Table 4.5.

Table 4.5 List of Enhanced Transbuccal Delivery Systems Studied

| No. | System |
|-----|---|
| 1 | LHCl Transbuccal – Control (passive) |
| 2 | LHCl Transbuccal – PG Pretreated 1.0 hr |
| 3 | LHCl Transbuccal - 2.5% Azone in PG Pretreated 1.0 hr |
| 4 | LHCl Transbuccal – 5% Br-iminosulfurane in PG Pretreated 1.0 hr |
| 5 | LHCl Transbuccal – 5% DDAIP in PG Pretreated 1.0 hr |
| 6 | LHCl Transbuccal – 5% DDAIP HCl in PG Pretreatment 1.0 hr |
| 7 | LHCl Transbuccal - 5% DDAIP HCl in water Pretreatment 1.0 hr |
| 8 | NHT Transbuccal - Control (passive) |
| 9 | NHT Transbuccal –5% Br-iminosulfurane in PG pretreatment for 1 hr |
| 10 | NHT Transbuccal –5% DDAIP in PG pretreatment for 1 hr |
| 11 | NHT Transbuccal – 5% DDAIP HCl in PG pretreatment for 1 hr |
| 12 | NHT Transbuccal – 5% DDAIP HCl in water pretreatment for 1 hr |

4.2.2 Case Study 2: Iontophoretic and Chemical Enhancement

For the study of the combined effect of iontophoresis and chemical enhancers, a direct current with an intensity of $0.47\text{mA}/\text{cm}^2$ was applied to the mucosa sample. The systems in Table 4.5 were investigated. The experimental procedures were described in Section 3.2. Figure 4.7 shows the performance of the model in predicting the cumulative amount of drug released. A detailed list of the parameters is included in Table 4.6.

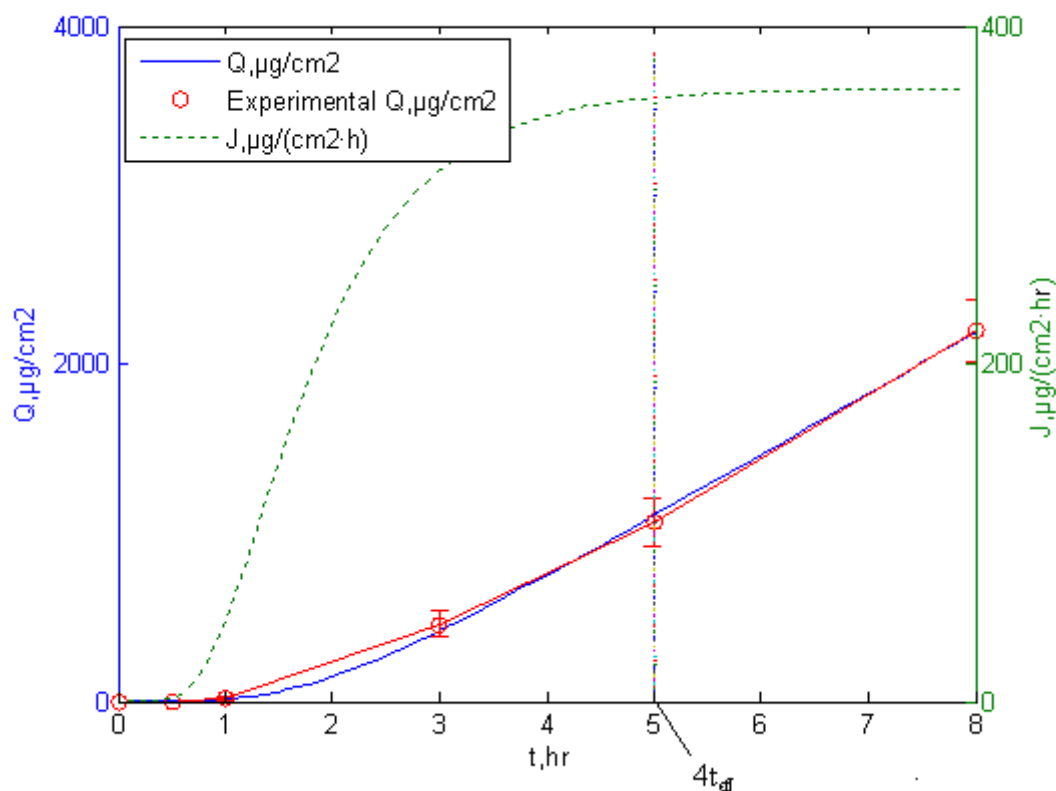


Figure 4.9 Predicted vs. experimental cumulative amount of LHCl (Q) and the flux time profile (J). The response time used was $4 t_{\text{eff}}$. The transdermal system was pretreated with 5% DDAIP in PG before applying 0.3 mA of current.

Table 4.6 Model Parameters of a 0.3mA Iontophoretic LHCl Delivery System Pretreated with Enhancer DDAIP in PG

| | |
|--|-------------------------|
| Thickness of mucosa, h (μm) | 350 ± 50 |
| Diffusion coefficient, D_a (cm^2/hr) | 0.000064 ± 0.000003 |
| Surface concentration, C_s ($\mu\text{g}/\text{cm}^3$) | 29070.09 ± 4361.61 |
| Dimensionless number, γ | 6.76 ± 0.53 |
| Effective time, t_{eff} (hr) | 1.24 ± 0.37 |
| Lag time, t_{lag} (hr) | 1.99 ± 0.14 |
| Flux, J ($\mu\text{g}/\text{cm}^2\text{hr}$) | 361.69 ± 80.10 |

The results show that the mathematical modeling methodology given in Section 3.2 is also suitable for the transbuccal delivery studies. The parameters for the remaining systems are given in Figures 4.9-4.11.

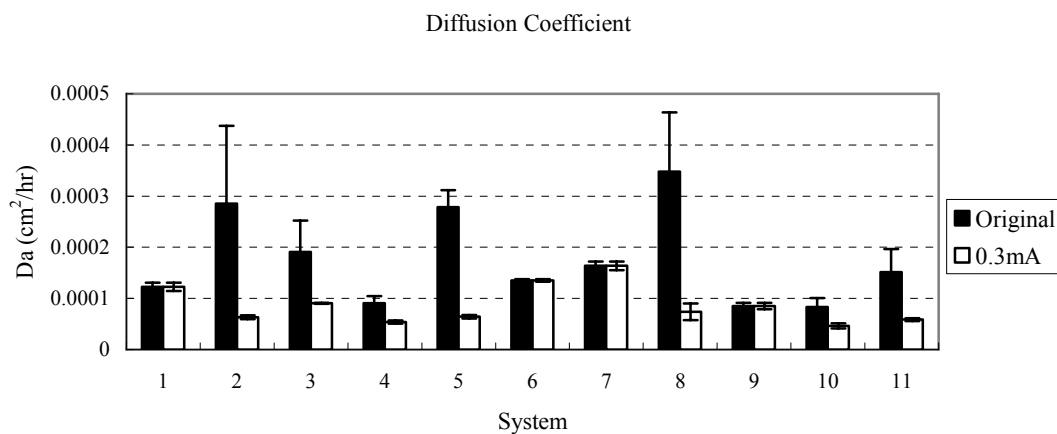


Figure 4.10 Drug diffusion coefficients for the enhanced transbuccal delivery systems.

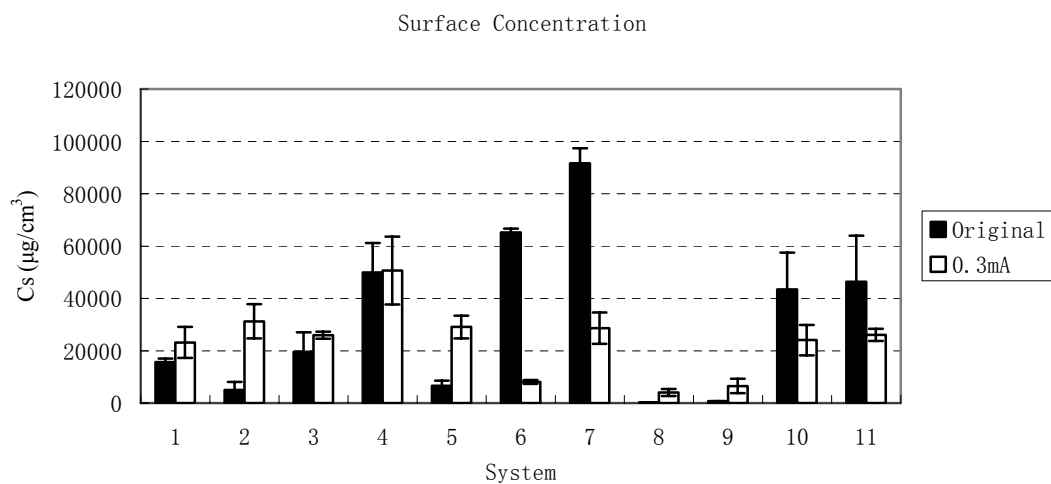


Figure 4.11 Surface concentrations for the enhanced transbuccal delivery systems.

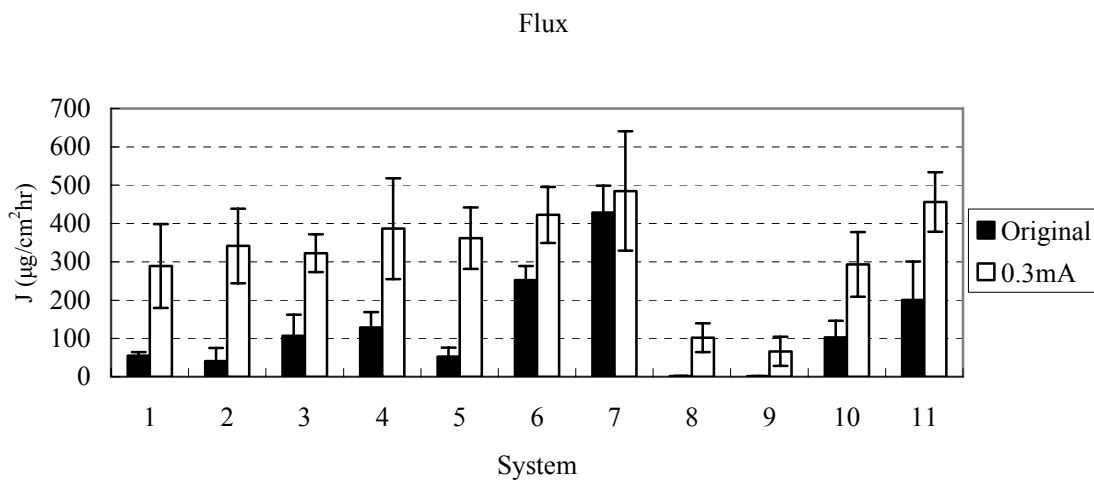


Figure 4.12 Fluxes of the enhanced transbuccal delivery systems.

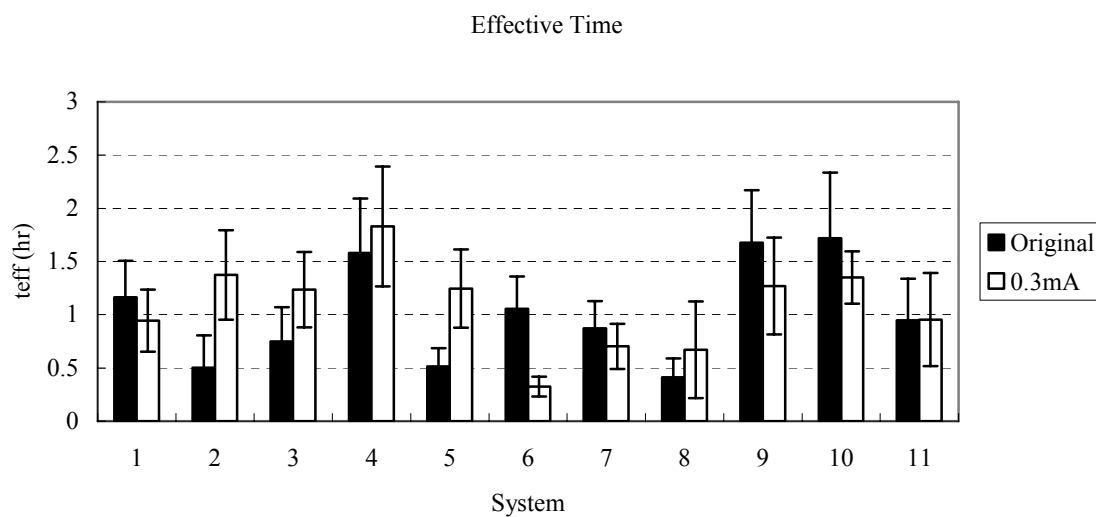


Figure 4.13 Effective time constants for the enhanced transbuccal delivery systems.

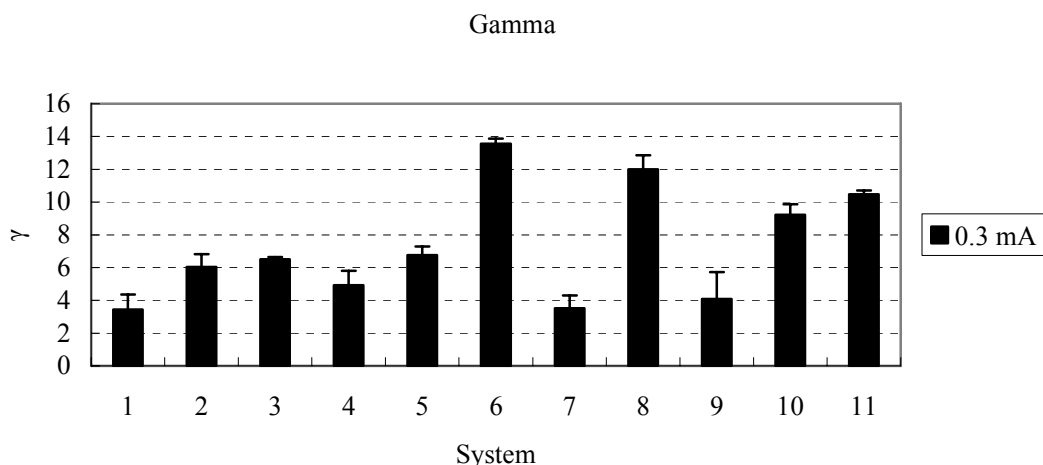


Figure 4.14 Gamma values for the iontophoretic transbuccal delivery systems.

4.2.3 Discussion

4.2.3.1 Passive and Chemically-Enhanced Delivery. As described in sub-section 4.1.3.1, for passive and chemically-enhanced oral transmucosal delivery, Da and C_s were the key factors that determine the rate and the level of drug delivery. From Figure 4.9, it can be observed that the effect of chemical enhancement differs significantly for the two drugs as indicated by the values of Da or C_s , which influences the delivery rates and response times.

The highest LHCl flux was obtained with the 5% DDAIP HCl in water pretreatment (system 7): $19357.64 \pm 369.90 \mu\text{g}/\text{cm}^2\text{hr}$. However, the shortest response time was recorded for the 5% DDAIP in PG pretreatment (system 5): $2.20 \pm 0.68 \text{ hr}$ ($4t_{\text{eff}}$). Similarly, there is no optimal NHT delivery that produces both a high steady-state flux and a fast delivery. The 5% DDAIP HCl in PG pretreatment (system 11) gave the highest flux, whereas the control group (system 8, no enhancers added) yields the shortest response time. The value of the effective time constant varies with Da .

Further analysis of Figures 4.10-4.12 suggests the relative contributions of Da and C_s in determining the flux value. Although both parameters influence the flux according to Equation 2.2, the data reveal that C_s is the main driving force in increasing the flux. The enhancers did not bring significant changes to Da (e.g. a one fold increase in system 5 compared with the control), but were able to increase C_s dramatically (Figure 4.11).

4.2.3.2 Iontophoretic-Chemical Enhancement. As described in sub-section 4.1.3.2, the variations in γ (Figure 4.13) are indicative of an alteration in the structure of the mucosa sample as a result of the chemical enhancers.

The application of current increased the flux significantly. However, iontophoresis did not play an important role in changing the effective time constant. A moderate decrease in t_{eff} was observed when delivering LHCl pretreated with 5% DDAIP HCl in PG (system 6). Similar observations were made for the release of NHT pretreated with 5% br-iminosulfurane in PG and 5 % DDAIP in PG (systems 9 and 10, respectively). However, in other cases, an increase in t_{eff} was noticed. If the flux was the only criterion for enhancer selection, the pretreatment with 5% DDAIP HCl in PG or 5% DDAIP HCl in water are viable selections as they both resulted in high LHCl delivery rates. However, based on the response time, the former system was a better selection (1.3 hr vs. 2.8hr, in terms of $4t_{\text{eff}}$). In the case of NHT transbuccal delivery, the synergistic effect between the current and chemical enhancer is apparent for the 5% DDAIP HCl in PG and 5% DDAIP HCl in water (system 11), although the latter exhibits a shorter response time (3.8hr vs. 2.9 hr, $4t_{\text{eff}}$).

CHAPTER 5

CONCLUSION

The discussions above suggest several important points. First, pretreatment with the same chemical enhancer may lead to different results depending on the nature of the membrane (e.g., skin and oral mucosa). For example, the 5% DDAIP HCl in water pretreatment results in a sharp increase in the diffusion coefficient for transermal LHCl delivery. However, when applied to LHCl oral transmucosal delivery, only a mild improvement was detected in the same parameter. Second, the influence of the enhancers also varies with the drug analyzed. In the presence of br-iminosulfurane in PG pretreatment, a synergistic effect between iontophoresis and chemical enhancers increases LHCl flux. The combination did not produce similar results in the case of NHT transport. Third, the relative contributions of iontophoresis and chemical enhancers change with the drug and the membrane. Iontophoresis plays a significant role in increasing the steady-state flux regardless of the pretreatment. The overall extent of increase seems to be higher for LHCl than NHT. On the other hand, chemical enhancers play an important role in determining the response time. In fact, only a few pretreatments were able to increase the flux and decrease the response time simultaneously. As seen from the figures, when designing a delivery system several factors, such as the drug (LHCl or NHT), the membrane (dermal or mucosa) and the enhancer (chemical enhancer or iontophoresis) need to be considered.

The approach proposed in this work provides a method to quantify the influences of iontophoretic and chemical enhancers on controlled delivery systems. In the

development of a suitable drug-release device, the notion of an “optimum design” should be linked to both the delivery rate (J_{ss}) and the time to reach J_{ss} : a high flux does not guarantee a quick response time. Even when a balance between the two design criteria is achieved, the desired clinical outcomes should determine the strategy adopted in the end.

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