Pharm Res (2012) 29:961–971
DOI 10.1007/s11095-011-0636-x

RESEARCH PAPER

Effects of Iontophoresis and Chemical Enhancers on the Transport of Lidocaine and Nicotine Across the Oral Mucosa

Ran Wei • Laurent Simon • Longsheng Hu • Bozena Michniak-Kohn

Received: 7 September 2011 / Accepted: 21 November 2011 / Published online: 2 December 2011

ABSTRACT

Purpose To analyze the effects of chemical enhancers and iontophoresis on the buccal transmucosal delivery of lidocaine and nicotine.

Methods Porcine oral mucosal samples were pretreated with chemical enhancers before conducting 8-hr Franz diffusion-cell experiments. In studies addressing the influence of iontophoresis on molecular transport, the current density was set at 0.3 mA/cm^2. Data were analyzed using graphical and non-linear regression optimization techniques.

Results Both permeation enhancement techniques promote drug transport. In the absence of electricity, the flux increased as high as 4- and 200-fold, relative to a control, in the case of lidocaine hydrochloride (LHCl) and nicotine hydrogen tartrate (NHT) gel formulations, respectively. The combination of iontophoresis and chemical enhancers produced an even higher flux compared to the original passive diffusion process: up to 8-fold for LHCl and 450-fold for NHT. Mostly, the current helped to decrease the response time. However, a balance should be maintained between reaching a high delivery rate and reducing the time it takes to attain a desired flux value. In addition, the influence of chemical enhancers was drug-specific.

Conclusions The estimation of model parameters allows for a systematic approach to the design of chemical and physical penetration enhancers for transmucosal drug delivery.

KEY WORDS chemical enhancer · iontophoresis · oral mucosa

R. Wei · L. Simon (✉)
Otto H. York Dept. of Chemical, Biological & Pharmaceutical Engineering
New Jersey Institute of Technology
Newark, New Jersey 07102, USA
e-mail: laurent.simon@njit.edu

L. Hu · B. Michniak-Kohn
Ernest Mario School of Pharmacy
Rutgers—The State University of New Jersey
Piscataway, New Jersey 08854, USA

INTRODUCTION

This contribution focuses on the controlled delivery of two drugs: lidocaine and nicotine. Lidocaine is administered widely as a local anesthetic for both surgical (1) and anti-arrhythmic treatments (2). Traditional delivery methods of the drug include intravenous or hypodermic injections (3). However, because of growing concerns related to patient compliance and active life styles during medication, less intrusive, less painful and more localized methods of delivery, with long duration, are needed (4). One alternative is the use of a transdermal lidocaine dosage form in solution. EMLA® cream and Lidoderm®, manufactured by AstraZeneca and Endo Laboratories, respectively, are commercially available lidocaine products.

Nicotine replacement therapy has been proven successful in reducing withdrawal symptoms and promoting smoking cessation. Currently, most nicotine dosage forms employ transdermal systems to keep a sustained plasma level of nicotine. The technology is based on the drug's favorable solubility in both aqueous and lipid environments (5).

In addition to the skin, the oral mucosa also provides a site for drug absorption. Its rich blood supply and mild pH environment make the buccal mucosa a good candidate for drug uptake because first-pass effects and pre-systemic elimination in the gastrointestinal (GI) tract are avoided (6). Besides, the administration of oral transmucosal drugs is painless and only a relatively short time is needed for the drug to take effect. For lidocaine, Perry *et al.* reported clinical applications in small and local surgical analgesia in dentistry (7), whereas the nicotine lozenge has been employed in transmucosal delivery to overcome withdrawal symptoms (8). Considering these advantages, it is no surprise that researchers have been studying transbuccal dosage forms of both lidocaine and nicotine preparations. However, limitations, such as a low permeability of the buccal membrane, greatly reduce the flux of drug into the oral capillaries, resulting in low bioavailability (9). En-

hancement methods are being studied to increase the penetration of molecules through the buccal epithelium, a main barrier to drug transport. Chemicals are used to decrease the barrier resistance of the stratum corneum (SC) without causing damage to viable cells. The mechanisms involve disruption of the lipid structure, which may improve the partitioning of drugs into the SC, lower its interaction with intercellular proteins and improve the diffusion of the drug molecules across the membrane.

Physical enhancers are also being studied as possible strategies. Among these methods, iontophoresis is growing in popularity. This technique involves external electrodes that force the drug in a direction dictated by the established electric field and the charge carried on the drug. Such a technique would increase penetration through the skin or mucosa. Because of this approach, a lidocaine hydrochloride iontophoretic transdermal patch (Lidosite® Vyteris Inc.) was developed and recently gained FDA approval (10,11). Other investigations have focused on the combined effects of these two methods on the delivery rate. With nicotine transdermal delivery, a synergistic enhancement was detected (12). Brand *et al.* reported their findings in obtaining pulsatile nicotine delivery via iontophoresis in order to better suppress withdrawal (13). Jacobsen showed it was possible to increase the buccal delivery of *atenolol·HCl* by applying iontophoresis in a 3-chamber *in vitro* cell (14). The enhancement ratio reached 112 when a 90:10 cycle was used across porcine buccal mucosa. Permeation of naltrexone (NLX) through reconstituted human oral epithelium was improved in the presence of an electric field (15). This observation was made whether the drug was dissolved in natural or artificial human saliva. The enhancement, due to iontophoresis, was proportional to the current intensity when NLX was allowed to diffuse across an 800 μm-thick porcine buccal mucosa (16).

However, current experimental approaches do not provide information on the drug solubility in the membrane, the diffusional properties and the convective transport. This knowledge is useful for the development of new chemical enhancers and the use of iontophoresis for specific applications. For example, while the steady-state flux depends, among other factors, on the partition and diffusion coefficients and the current density, the time to reach the steady-state flux is not influenced by equilibrium thermodynamic properties, such as the partition coefficient. In addition to the membrane thickness, only parameters that influence the mobility of molecules through the matrix play a significant role in the process. The novelty of this work is the implementation of mathematical tools to explore the effects of enhancers on the oral transmucosal delivery rate of lidocaine and nicotine. To our knowledge, no published report has applied numerical tools to decipher the roles of excipients in altering the solubility and diffusion of either medicament in the oral mucosa. The application of an electric potential across the membrane complicates the situation considerably. This article is arranged as follows. A mathematical section that outlines a method to isolate and quantify the influences of distinct enhancer properties on the flux is presented. Experimental protocols and findings are described in the following sections: "Materials and Methods", "Results" and "Discussion".

Analysis of Transmucosal Absorption of Drugs Using Iontophoresis

Clinically effective oral mucosal delivery systems for lidocaine and nicotine should cause a rapid onset of action, i.e., a very short response time for the steady-state flux. The speed of drug release is traditionally measured using the time lag (t_{lag}) (11). However, it has been proven that a criterion that only depends on t_{lag} may not accurately reflect how long it takes to attain an equilibrium delivery rate (17). For diffusive processes, Collins proposes a single relaxation time constant (t_{eff}), instead, to describe the time required for a certain relaxation process to complete. For drug delivery, this parameter is given as (18)

$$t_{eff} = \frac{\lim\limits_{s\to 0}\left(\frac{\Psi_{ss}}{s^2} + \frac{d\overline{\Psi}(s)}{ds}\right)}{\lim\limits_{s\to 0}\left(\frac{\Psi_{ss}}{s} - \overline{\Psi}(s)\right)} \tag{1}$$

where $\overline{\Psi}$ is the Laplace transform of Ψ; Ψ_{ss} is the steady-state value of Ψ. The form of Eq. 1 is preferred over the expression in the time domain:

$$t_{eff} = \int_0^\infty t\Omega(t)dt \tag{2}$$

where

$$\Omega(t) = \frac{(\psi_{ss} - \psi(t))}{\int_0^\infty (\psi_{ss} - \psi(t))dt} \tag{3}$$

because a complete solution is not necessary. In this contribution, t_{eff} is used to measure the speed of the response for passive or current-assisted processes; t_{lag} is given for comparison.

Passive and Chemically Enhanced Transport Across the Mucosa

Fick's second law of diffusion is applied in the cases of passive as well as chemically-enhanced transport across the mucosa:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{4}$$

where C is the concentration at a position x within the membrane, D is the diffusion coefficient and t is the time. The initial condition is

$$C(x > 0, 0) = 0 \tag{5}$$

and the boundary conditions are given by

$$C(0, t > 0) = C_s; \;\; C(h, t > 0) = 0 \tag{6}$$

where C_s is the surface concentration at the mucosa-vehicle interface, with h as the thickness of membrane. At h, the flux is given as

$$J = -D\frac{\partial C}{\partial x}\bigg|_{x=h} = \frac{dQ}{dt} \tag{7}$$

where Q is the cumulative amount of drug released and is obtained after solving the system defined by Eqs. 4–7 (19):

$$Q = hC_s\left[\frac{tD}{h^2} - \frac{1}{6} - \frac{2}{\pi^2}\left(\sum_{n=1}^{\infty}\frac{(-1)^n \exp\left[-n^2\pi^2\frac{tD}{h^2}\right]}{n^2}\right)\right] \tag{8}$$

The steady-state flux, Q_{ss} and t_{lag} are

$$J_{ss} = \frac{DC_s}{h}, \tag{9}$$

$$Q_{ss} = hC_s\left(\frac{tD}{h^2} - \frac{1}{6}\right) \tag{10}$$

and

$$t_{lag} = \frac{h^2}{6D} \tag{11}$$

The effective time constant was derived in (17) after applying Eq. 1:

$$t_{eff} = \frac{7h^2}{60D} \tag{12}$$

At $4t_{eff}$ (called response time thereafter), the flux has reached 98% of the steady-state value.

Iontophoresis Transport Across the Mucosa

Considering negligible convective flow in transbuccal preparations, a new term is introduced into the Fick's second law expression:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} - \frac{\gamma D}{h}\frac{\partial C}{\partial x} \tag{13}$$

where γ is a dimensionless number which represents the influence of the current. With the same initial and boundary conditions as those used for passive transport, a closed-form expression for Q is (20)

$$Q = \frac{DC_s}{h}\frac{\gamma}{1-e^{-\gamma}} \times \left\{t + \frac{2h^2}{D}\frac{\sinh\left(\frac{\gamma}{2}\right)}{\frac{\gamma}{2}}\sum_{n=1}^{\infty}\frac{n^2\pi^2(-1)^n}{\left(\frac{\gamma^2}{4}+n^2\pi^2\right)^2}\left[1 - \exp\left(-\frac{\left(\frac{\gamma^2}{4}+n^2\pi^2\right)Dt}{h^2}\right)\right]\right\} \tag{14}$$

The following expressions were obtained (17,20):

$$J_{ss} = \frac{DC_s}{h}\frac{\gamma}{1-e^{-\gamma}}, \tag{15}$$

$$Q_{ss} = \frac{DC_s}{h}\frac{\gamma}{1-e^{-\gamma}}\left[t + \frac{h^2}{D}\frac{2\sinh\left(\frac{\gamma}{2}\right) - \gamma\cosh\left(\frac{\gamma}{2}\right)}{\gamma^2\sinh\left(\frac{\gamma}{2}\right)}\right], \tag{16}$$

$$t_{lag} = -\frac{h^2}{D}\frac{2\sinh\left(\frac{\gamma}{2}\right) - \gamma\cosh\left(\frac{\gamma}{2}\right)}{\gamma^2\sinh\left(\frac{\gamma}{2}\right)} \tag{17}$$

and

$$t_{eff} = \frac{h^2\,\mathrm{csch}^2\left(\frac{\gamma}{2}\right)\left(3\gamma^2 - 2\sinh(\gamma)\gamma + (\gamma^2-4)\cosh(\gamma) + 4\right)}{4D\gamma^2\left(\gamma\coth\left(\frac{\gamma}{2}\right) - 2\right)} \tag{18}$$

It can be concluded from Eqs. 9, 12, 15 and 18 that drug solubility in the oral mucosa (i.e., C_s) directly affects the delivery rate. However, this property does not influence the time it takes to reach a particular J_{ss} value (i.e., $4t_{eff}$). As a result, mathematical tools, that help detect respective changes in the partition and diffusion coefficients from drug-release experiments, become essential. This initiative may accelerate the selection of chemical penetration enhancers for the controlled delivery of lidocaine and nicotine through the mucosa. Synergistic effects are expected when electric current is applied to the membrane.

Parameter Estimation

With passive diffusion, the lag-time method was applied to estimate C_s and D (19). After estimating D from Eq. 11, C_s was computed by measuring the slope and using Eq. 9. The parameters of the iontophoresis-based model (C_s, D and γ) were first calculated by following the graphical method outlined in (21). The procedure consists of assuming that the current does not change the diffusion coefficient obtained from passive release experiments. Plots, produced from the line represented by Eq. 16, yields approximate C_s and γ values. These estimations were later refined by fitting the cumulative release data to Eq. 14 using tools available in MATLAB (Natick, MA). In the studies reported in (21), the improvement created by the extra regression step was not significant. Poor agreements noted between predicted and experimental release data would suggest that the effective diffusion coefficient changed after applying the current. The computer code would then be adjusted to compute all three parameters: C_s, D and γ.

Table I Chemical Permeation Enhancers and Treatment Protocols

Label	System
p1	Transbuccal LHCl - control
p2	Transbuccal LHCl - 2.5% Azone in PG pretreatment for 1.0 h
p3	Transbuccal LHCl - 5% Br-iminosulfurane in PG pretreatment for 1.0 h
p4	Transbuccal LHCl - 5% DDAIP HCl in PG pretreatment for 1.0 h
p5	Transbuccal LHCL - PG pretreatment for 1.0 h
p6	Transbuccal NHT - control
p7	Transbuccal NHT - 2.5% Azone in PG pretreatment for 1 h
p8	Transbuccal NHT - 5% Br-iminosulfurane in PG pretreatment for 1 h
p9	Transbuccal NHT - 5% DDAIP HCl in PG pretreatment for 1 h
p10	Transbuccal NHT - PG pretreatment for 1 h

MATERIALS AND METHODS

Materials

Four enhancers were used in the study. Azone (1-dodecylazacycloheptan-2-one), also known as laurocapram, is a colorless and odorless liquid which melts at −7°C (10). This compound is greatly compatible with virtually any organic solvent including propylene glycol (PG). After partitioning into the bilayer lipid, azone works by disturbing the packing arrangement, which increases the diffusion of a wide variety of drugs comprising steroids, antibiotics and antiviral agents (10).

Dodecyl-2-(*N*,*N*-dimethyl amino) propionate (DDAIP) and its salt form dodecyl-2-(*N*,*N*- dimethylamino) propionate hydrochloride (DDAIP HCl) are long chained alcohols. The former is not soluble in water, but soluble in most of the organic solvents and in water and alcohol

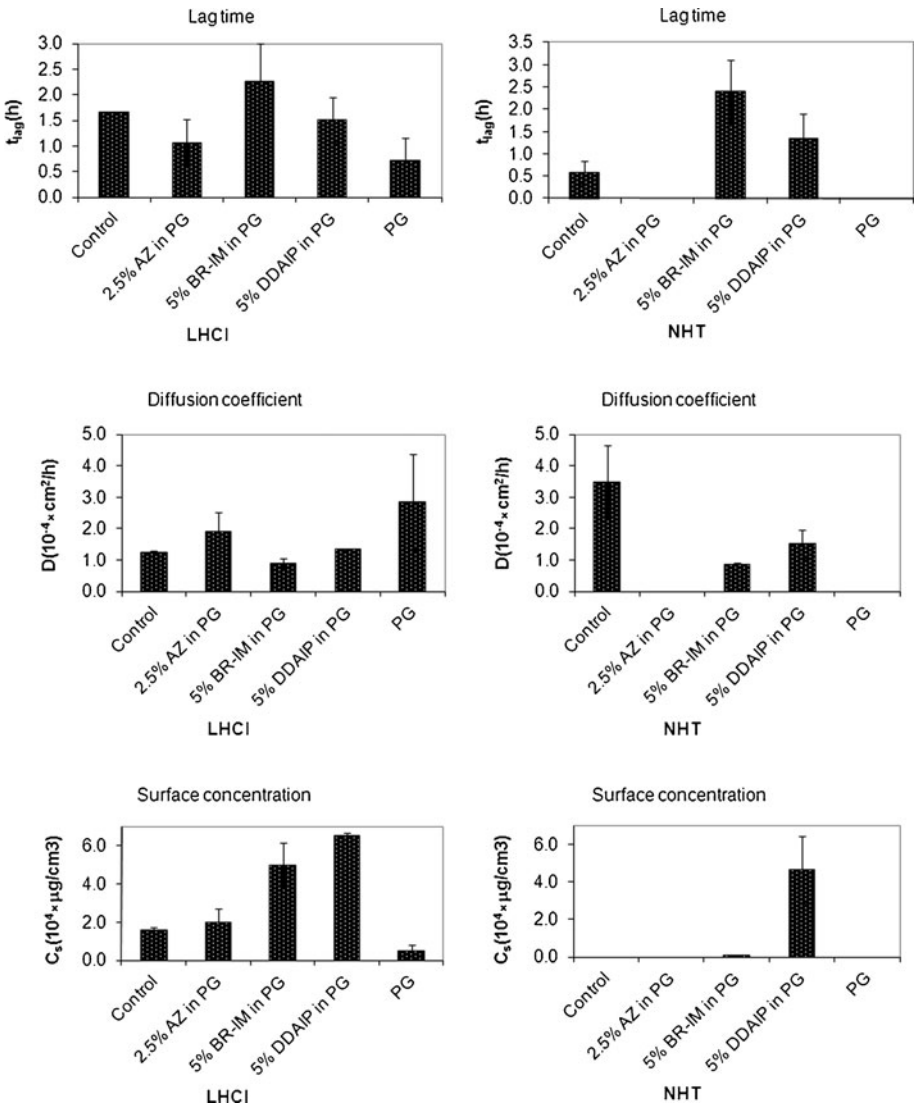

Fig. 1 Model parameters in passive transmucosal drug delivery with chemical enhancers: Lag time (t_{lag}), diffusivity (D) and surface concentration (C_s).

mixtures. The latter is water soluble. Both chemicals promote skin penetration by interacting with the stratum corneum keratin structure, causing an increase in the hydration of the SC. Studies revealed that DDAIP increases the permeability of skins at least as well as Azone (22). Br-iminosulfurane is a small and polar molecule, which may work by disrupting the integrity of the SC lipid matrix. This compound plays a role in increasing drug partitioning in the SC in addition to interacting with proteins (23).

Propylene glycol (PG) served as the vehicle in these studies. Data were also collected to assess the combined effects of iontophoresis and the chemical enhancers on the delivery rate. Previous work by Nolan *et al.* showed synergy in salbutamol diffusion when fatty acid was combined with iontophoresis (12). In this work, a 0.3 mA/cm^2 current was applied. Lidocaine hydrochloride (LHCl) and nicotine hydrogen tartrate (NHT) gel formulations were prepared (24,25).

Methodology

Franz diffusion cells (PermeGear, Inc., Hellertown, PA, USA) consisting of a donor and a chamber receptor were assembled. The former was filled with the prepared drug solution, whereas the latter contained 5.1 mL of phosphate buffer saline (PBS) solution adjusted to physiological pH 7.4. The prepared buccal mucosae were prepared from a pig cheek area through surgically removing its underlying connective tissue. Before use, the oral tissues were first soaked in PBS (pH = 7.5) for 1.0-hour and then clamped between the two chambers. The side of connective tissues was attached to the donor compartment with a diffusion area of 0.64 cm^2. Initially, the drug formulation was pipetted into the donor compartment. At the following time points: 0.0, 0.5, 1.0, 3.0, 5.0, 8.0 h, 300 μl samples were collected from the receptor compartments filled with PBS. An equal volume of PBS (pH = 7.5) was immediately introduced into the chamber. In studies focusing on the effects of enhancer pretreatment, 30 μl of chemical enhancer solutions were added onto the surface of the buccal tissue from the donor compartment. One hour was allowed for the solution to permeate through the membrane before introducing the drug. To examine the influence of iontophoresis, the anodal electrode (Ag) was inserted into the gel formulation in the donor cell at a distance of two mm above the tissue membrane (24,25). The cathode electrode (AgCl) was placed in the receptor compartment. The Ag and AgCl electrodes were then connected to the positive and negative terminators of an Iomed Phoresor II Auto (model PM 850) to form an electric circuit. Eight hours of 0.3 mA were used for each iontophoretic treatment (24,25).

RESULTS

Chemically Enhanced Diffusion

The systems included in the study are listed in Table I. Model parameters estimated from the passive diffusion

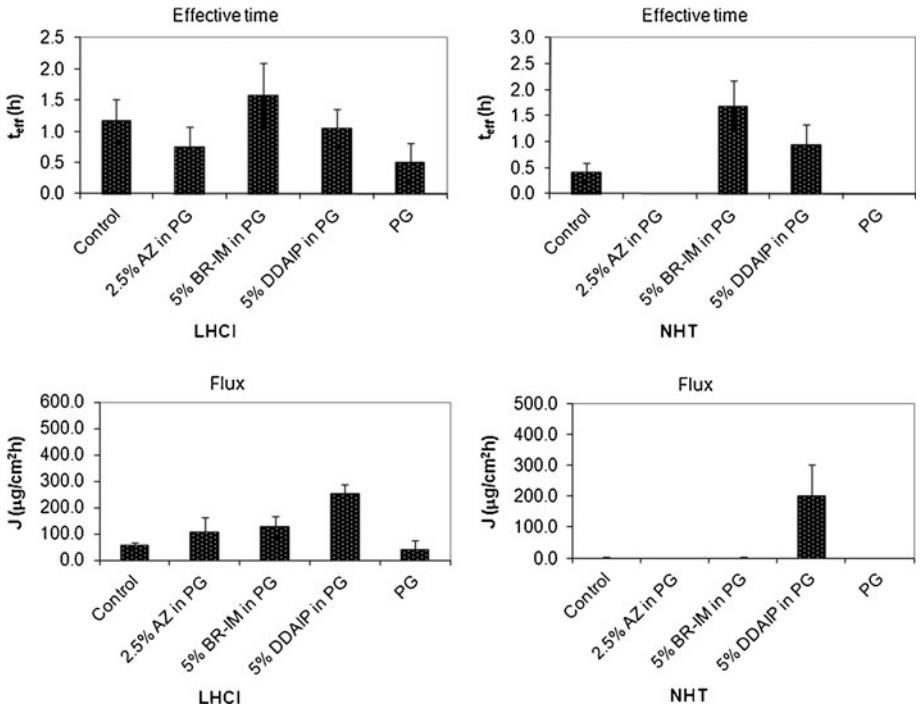

Fig. 2 Effective time constant (t_{eff}), and flux (J) in passive drug transmucosal delivery with chemical enhancers.

experiments and the methods outlined in Parameter Estimation are given in Figs. 1 and 2. The thickness of the mucosa membrane was 350±50 μm. The experiments were conducted at 37°C to mimic the body temperature.

Figure 3a represents a contour plot of the ultimate flux in terms of K and the diffusion coefficient D. The flux J_{ss} is constant along a contour line and is shown by a rectangle with the flux value expressed in μg/cm^2.h. Points found in the upper right corner of Fig. 3a would result in a high delivery rate and a fast response time (see Fig. 3b). The data from Table I are shown as circles. As portrayed in Fig. 3, point p4 corresponds to the highest flux. However, the

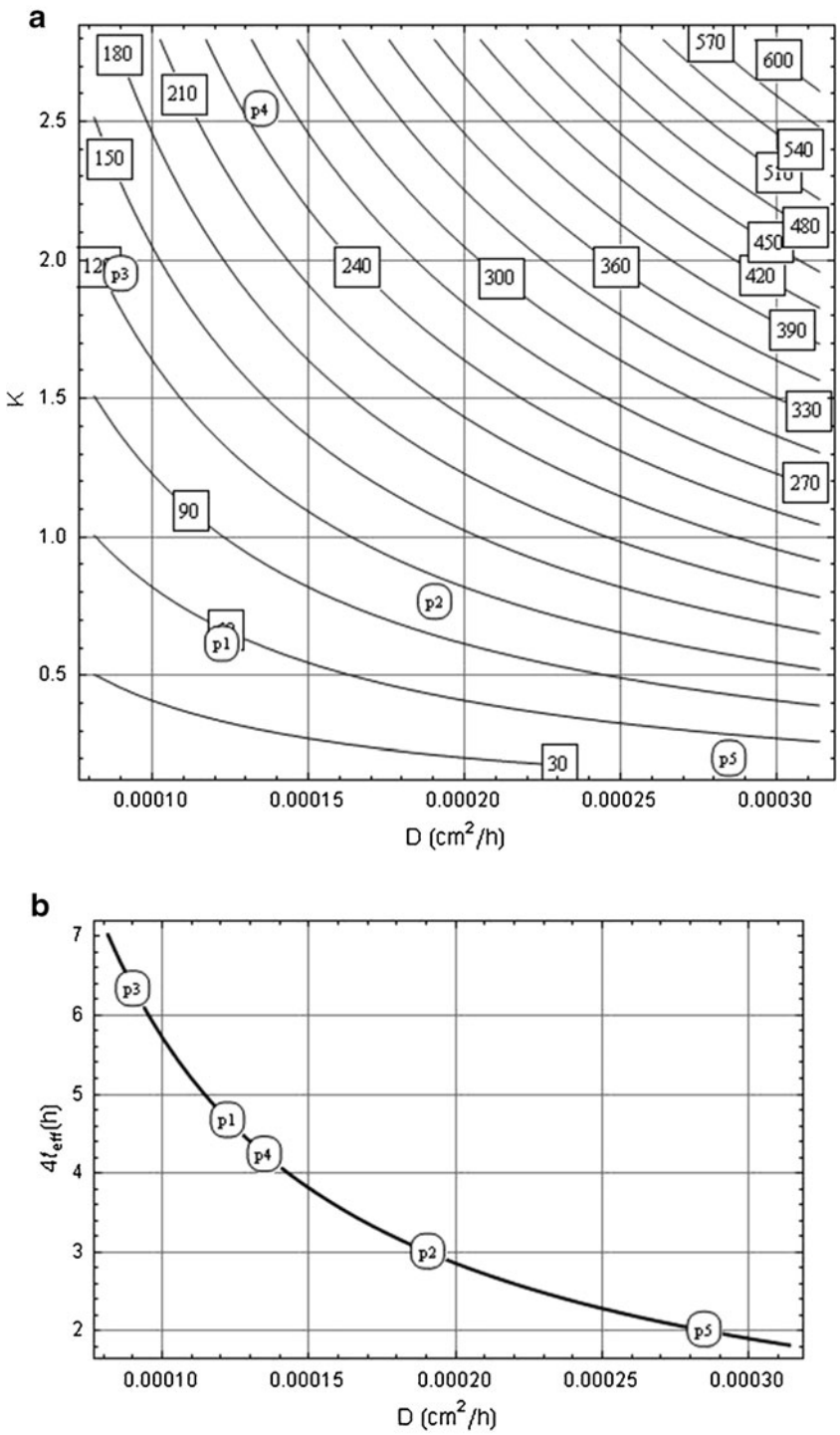

Fig. 3 (**a**) Contour plot of ultimate flux in terms of partition coefficient (K) and diffusion coefficient (D) for lidocaine transport (**b**) Plot of effective time (t_{eff}) *vs.* D for lidocaine.

response is not as fast as p5. Similar observations are made for NHT (Fig. 4) with point p9.

Iontophoretic and Chemical Enhancement

A constant direct current was maintained across the membrane using the same systems given in Table I. The parameter γ, introduced in the governing Eq. 13, is by $\gamma = zF\Delta\Psi/RT$ where $\Delta\Psi$ represents the electric potential across the membrane; R is the gas constant; T denotes the absolute temperature and F indicates the Faraday constant. At constant current density, the voltage drop $\Delta\Psi$ is proportional to the membrane resistance, which is a function of the membrane properties, including the porosity. As a result, γ is expected to vary with the chemical enhancer. The effects of the current on the lag time, diffusivity and

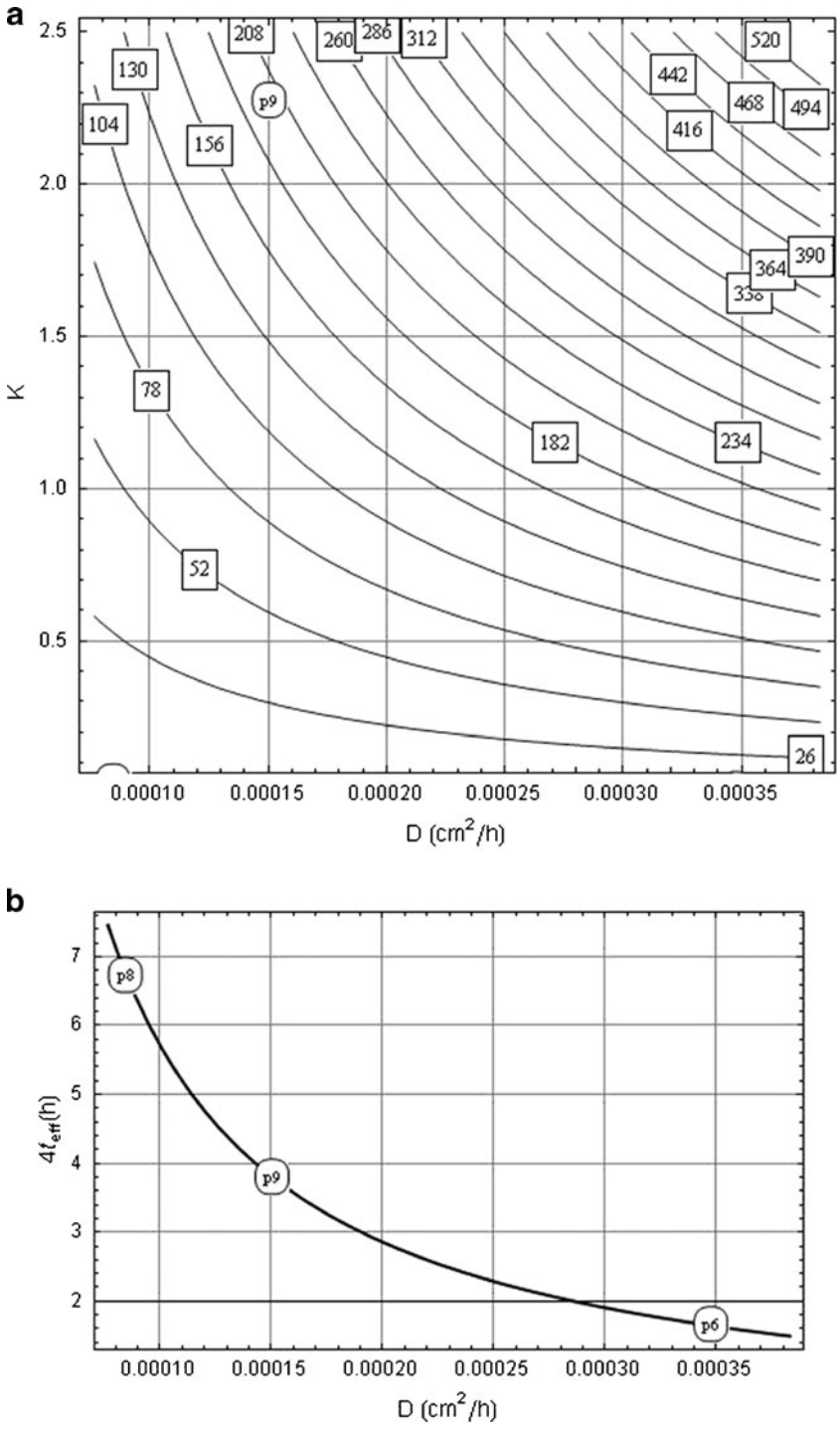

Fig. 4 (**a**) Contour plot of ultimate flux in terms of partition coefficient (*K*) and diffusion coefficient (*D*) for nicotine transport (**b**) Plot of effective time (t_{eff}) *vs. D* for nicotine.

surface concentration are shown in Fig. 5. The effective time constant and the steady-state flux are shown in Fig. 6.

DISCUSSION

Figures 1 and 2 show how the model parameters are affected by the type of chemical enhancers used for lidocaine hydrochloride and nicotine hydrogen tartrate. During the eight-hour experiments, the concentrations of NHT in p7 (see Table I: 2.5% azone in PG pretreatment for 1.0 h) and p10 (PG pretreatment for 1 h) did not reach detectable levels in the receiver compartment. The highest flux was obtained when the mucosa was pretreated with 5% DDAIP HCl in PG for both drugs: 251.9 ± 36.8 μg/cm^2.h for LHCl and 200.2 ± 100 μg/cm^2.h for NHT. A close look at Fig. 1 shows that these elevated values may be driven by an increased drug solubility C_s in the membrane and not by an enhancement in the effective diffusion coefficient.

Because the skin properties and lipid structures are expected to be affected by the pretreatment, physicochemical analyses using techniques, such as Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FT-IR) Spectroscopy, are important for completely elucidating the mechanisms of action of these enhancers.

Using the formula $C_s = KC_d$, which relates C_s to the donor concentration C_d, the partition coefficients K are 2.54 ± 0.06 and 2.27 ± 0.86 for LHCl and NHT, respectively. The conditions that led to flux improvement did not result in the shortest response time $4t_{eff}$, a situation that is depicted in Figs. 3 and 4. In these experiments, the effective time constant follows a pattern similar to the lag time, as predicted by Eqs. 11 and 12. This reduction has been reported in the literature. The lag time of triamcinolone

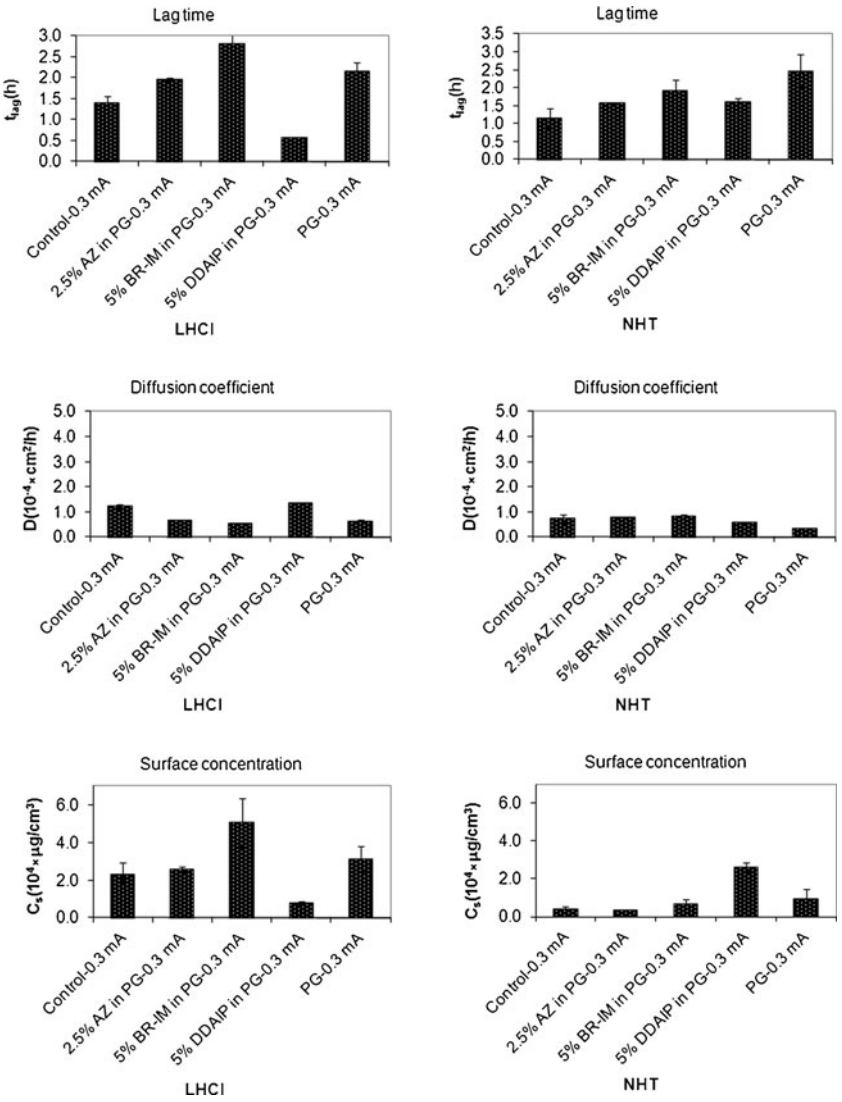

Fig. 5 Model parameters for iontophoresis and chemical enhancers: Lag time (t_{lag}), diffusivity (D) and surface concentration (C_s).

acetonide (TAC) was shortened when porcine buccal mucosa was pretreated with azone (26).

The application of an electric current increases the flux (Fig. 6). Similar results were obtained in (15) and (16). In (14), the increase in the iontophoretic delivery rate of atenolol·HCl was attributed to the current density and the on/off ratio. The enhancement shown in Fig. 6 is not triggered by a rise in the diffusion coefficient or a higher drug concentration at the membrane surface (Fig. 5), as reported in (27) and (28). The effective time constant did not change dramatically as a result of electro-migration for both drugs except in the case of p4 (LHCl and 5% DDAIP HCl in PG pretreatment for 1.0 h).

In order to administer a desired LHCl flux higher than 350 $\mu g/cm^2.h$, pretreatment p3 (5% Br-iminosulfurane in PG pretreatment for 1.0 h) or p4 can be used. Compared to the control, the pretreatments did not seem to play a significant role in increasing the LHCl delivery rate although γ values indicate a change in some properties of the mucosa when the chemical enhancers are applied (Fig. 6). Other researchers made analogous observations. Nicolazzo *et al.* noted that the effect of pretreatment with Sodium Dodecyl Sulfate (SDS) on drug permeation through the membrane was a function of the concentration of SDS and the physicochemical characteristics of the drug (26). A concentration of 0.05% (w/v) did not influence the flux of estradiol and was able to improve caffeine delivery rate by a factor of 1.5. When the response time is taken into consideration, p4 is a better option ($4t_{eff} \approx 1.3$ h) than p3 ($4t_{eff} \approx 7.3$ h). In the case of NHT, the synergistic effect of the current and the 5% DDAIP HCl in PG is apparent. Moreover, the relatively fast response time of 3.8 h provides an additional advantage for using this enhancer. Concentrations of NHT in p2 (i.e, 2.5% azone in PG pretreatment

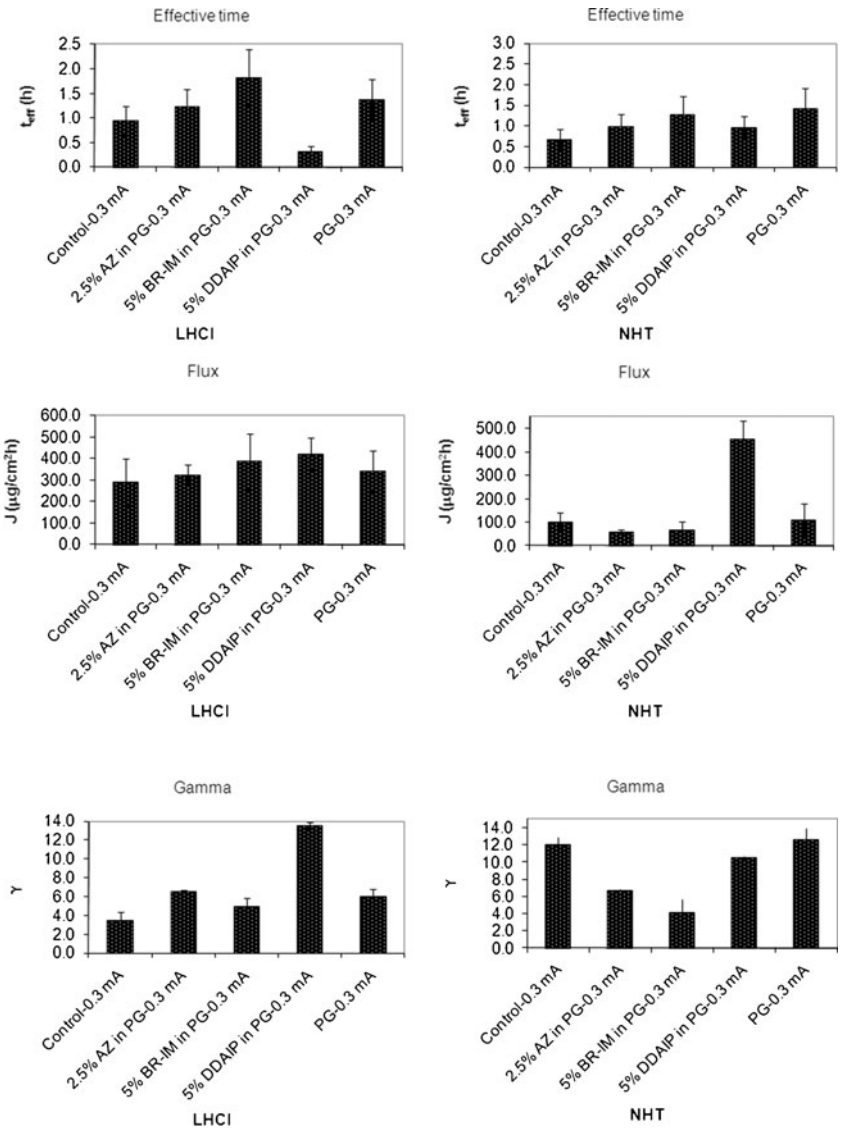

Fig. 6 Effective time constant (t_{eff}), and flux (J) for iontophoresis and chemical enhancers.

for 1.0 h) and p10 (PG pretreatment for 1 h) now attain important levels in the receiver chamber.

CONCLUSIONS

The investigation reveals that the effect of iontophoresis and the chemical enhancers studied depends on the drug used. For LHCl, the effects of enhancement are comparable to those of the control. The maximum fluxes obtained by pretreatment with the chemical enhancers, alone and combined with iontophoresis were 251.94 ± 36.82 μg/cm^2.h and 422.46 ± 73.05 μg/cm^2.h, respectively, compared with a control level of 54.77 ± 9.86 μg/cm^2 h. Similarly, the lowest response times ($4t_{eff}$) were 2.00 ± 1.21 h (chemical) and 1.32 ± 0.36 h (chemical and applied current) relative to 4.64 ± 1.36 h recorded for the standard. Chemical enhancers play a more significant role on the delivery rate in the case of NHT as evidenced by variations among the pretreatments. Because conditions for the highest flux do not automatically reduce the time it takes to reach a steady-state delivery rate, the medical needs of the end-user must be considered: fast-acting medication *versus* a high drug delivery rate. The parametric methods allow drug manufacturers to identify the mechanism by which the enhancers are affecting the flux.

ACKNOWLEDGMENTS & DISCLOSURES

We thank NexMed (USA), Inc., San Diego, CA, USA for their generous gifts of the chemical enhancers DDAIP and DDAIP HCl. We also thank Iomed, Inc., Salt Lake City, UT for their donation of the Phoresor II Auto (model PM 850) devices to our laboratory. Peter J. Zhang from Ernest Mario School of Pharmacy, Rutgers-The State University of New Jersey, Piscataway, NJ is acknowledged for synthesizing the enhancer Br-iminosulfurane. New Jersey Center for Biomaterials, Rutgers-The State University of New Jersey, Piscataway, NJ, USA provided the azone for this study.

REFERENCES

1. Smith DW, Peterson MR, DeBerard SC. Regional anesthesia: nerve blocks ofthe extremities and face. Postgrad Med. 1999;106 (4):69–73. 77–78.
2. Pfeifer HJ, Greenblatt DJ, Koch-Weser J. Clinical use and toxicity of intravenous lidocaine: a report from the Boston Collaborative Drug Surveillance Program. Am Heart J. 1976;92(2):168–73.
3. Lee PJ, Ahmad N, Langer R, Mitragotri S, Prasad Shastri V. Evaluation of chemical enhancers in the transdermal delivery of lidocaine. Int J Pharm. 2006;308(1–2):33–9.
4. Varshosaz J, Karimzadeh S. Development of cross-linked chitosan films for oral mucosal delivery of lidocaine. Res Pharm Sci. 2007;2(1):43–52.
5. Gorsline J, Gupta SK, Dye D, Rolf CN. Steady-state pharmacokinetics and dose relationship of nicotine delivered from Nicoderm® (Nicotine Transdermal System). J Clin Pharmacol. 1993;33(2):161–8.
6. Sangeetha S, Venkatesh DN, Krishan PN, Saraswathi R. Mucosa as a route for systemic drug delivery. Res J Pharm Biol Chem Sci. 2010;1(3):178–87.
7. Perry DA, Gansky SA, Loomer PM. Effectiveness of a transmucosal lidocaine delivery system for local anaesthesia during scaling and root planning. J Clin Periodontol. 2005;32(6):590–4.
8. Muramoto ML, Ranger-Moore J, Leischow SJ. Efficacy of oral transmucosal nicotine lozenge for suppression of withdrawal symptoms in smoking abstinence. Nicotine Tob Res. 2003;5 (2):223–30.
9. Hassan N, Ahad A, Ali M, Ali J. Chemical permeation enhancers for transbuccal drug delivery. Expert Opin Drug Del. 2010;7 (1):97–112.
10. Pathan IB, Setty CM. Chemical penetration enhancers for transdermal drug delivery systems. Trop J Pharm Res. 2009;8 (2):173–9.
11. Dixit N, Bali V, Baboota S, Ahuja A, Ali J. Iontophoresis - an approach for controlled drug delivery: a review. Curr Drug Deliv. 2007;4(1):1–10.
12. Nolan LMA, Corish J, Corrigan OI, Fitzpatrick D. Combined effects of iontophoretic and chemical enhancement on drug delivery II. Transport across human and murine skin. Int J Pharm. 2007;341(1–2):114–24.
13. Brand RM, Guy RH. Iontophoresis of nicotine *in vitro*: pulsatile drug delivery across the skin? J Contr Release. 1995;33(2):285–92.
14. Jacobsen B. Buccal iontophoretic delivery of *atenolol·HCl* employing a new *in vitro* three-chamber permeation cell. J Contr Release. 2001;70(1–2):83–95.
15. Giannola LI, De Caro V, Giandalia G, Siragusa MG, Campisi G, Florena AM, Ciach T. Diffusion of naltrexone across reconstituted human oral epithelium and histomorphological features. Eur J Pharm Biopharm. 2007;65(2):238–46.
16. Giannola LI, De Caro V, Giandalia G, Siragusa MG, Tripodo C, Florena AM, Campisi G. Release of naltrexone on buccal mucosa: permeation studies, histological aspects and matrix system design. Eur J Pharm Biopharm. 2007;67(2):425–33.
17. Simon L. Timely drug delivery from controlled-release devices: dynamic analysis and novel design concepts. Math Biosci. 2009;217(2):151–8.
18. Collins R. The choice of an effective time constant for diffusive processes in finite systems. J Phys D Appl Phys. 1980;13 (11):1935–47.
19. Crank J. The mathematics of diffusion. 2nd ed. Oxford: Clarendon; 1975.
20. Keister JC, Kasting GB. Ionic mass transport through a homogeneous membrane in the presence of an electric field. J Membr Sci. 1986;29(2):155–67.
21. Simon L, Weltner A, Wang Y, Michniak B. A parametric study of iontophoretic transdermal drug delivery systems. J Membr Sci. 2006;278(1–2):124–32.
22. Büyüktimkin S, Büyüktimkin N, Rytting JH. Synthesis and enhancing effect of dodecyl 2-(N, N-dimethylamino) propionate (DDAIP) on the transepidermal delivery of indomethacin, clonidine, and hydrocortisone. Pharm Res. 1993;10(11):1632–7.
23. Song Y, Xiao C, Mendelsohn R, Zheng T, Strekowski L, Michniak B. Investigation of iminosulfuranes as novel transdermal penetration enhancers: enhancement activity and cytotoxicity. Pharm Res. 2005;22(11):1918–25.

24. Hu L. Transdermal and transbuccal drug delivery enhancement using iontophoresis and chemical enhancers. Ph.D. Dissertation, New Brunswick, New Jersey: Rutgers University; 2010.
25. Hu L, Silva SM, Damaj BB, Martin R, Michniak-Kohn BB. Transdermal and transbuccal drug delivery systems: Enhancement using iontophoretic and chemical approaches. Int J Pharm. 2011 Sep 22. [Epub ahead of print].
26. Nicolazzo JA, Reed BL, Finnin BC. Enhancing the buccal mucosal uptake and retention of triamcinolone acetonide. J Contr Release. 2005;105(3):240–8.
27. Tojo K. Mathematical models of transdermal and topical drug delivery. Fukuoka, Japan: Biocom Systems; 2003.
28. Wearly LL. Iontophoresis-facilitated transdermal delivery of verapamil. II. Factors affecting the reversibility of skin permeability. J Contr Release. 1989;9(3):231–42.