



Iontophoretic transdermal drug delivery system using a conducting polymeric membrane

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ABSTRACT

This work investigated the application of a porous polyaniline (PANI) membrane as a conducting polymeric membrane as well as an electrode in an iontophoretic transdermal drug delivery (TDD) system. Model drugs studied were: caffeine (MW: 194.2), lidocaine HCl (MW: 270.8) and doxycycline HCl (MW: 480.1). The PANi membrane was first tested as a simple membrane between the donor and receptor solutions; it provided satisfactory permeation profiles; the observed flux values were well described by a simplified mass transport model. A mouse skin was then mounted beneath the PANi film; such a composite system also presented satisfactory permeation profiles. Iontophoretic TDD experiments were next performed using both Ag|AgCl electrodes and PANi|AgCl electrodes for comparison; a PANi anode replaced the Ag anode in the last set. For doxycycline HCl, the flux and the 24-h accumulation from the PANi|AgCl set were $94.4 \pm 81.2 \mu\text{g}/\text{cm}^2 \text{ h}$ and $2760 \pm 3980 \mu\text{g}/\text{cm}^2$, respectively; those from the Ag|AgCl set were zero. For lidocaine HCl, the flux and 10-h accumulation from the PANi|AgCl set were, respectively, $43 \pm 15 \mu\text{g}/\text{cm}^2 \text{ h}$ and $392 \pm 130 \mu\text{g}/\text{cm}^2$; the corresponding values from the Ag|AgCl set were $48 \pm 20 \mu\text{g}/\text{cm}^2 \text{ h}$ and $348 \pm 78 \mu\text{g}/\text{cm}^2$. Porous polyaniline membrane appears to be capable of replacing the Ag part of Ag|AgCl electrode system; further such a membrane can exercise additional control over agent transport rate. Aqueous-organic partitioning system through the porous membrane of PANi was tested with this novel technique as well. Because of the rather low porosity of the synthesized PANi film, such a system did not yield a high permeation rate.

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1. Introduction

As a non-invasive transdermal drug delivery (TDD) method [1], iontophoresis applies electrical current to deliver solubilized drugs through the skin to either the underlying tissue (local area) or capillaries and then to the whole circulating system (systemically) without any pain due to mechanical penetration such as injection. A voltage applied between two electrodes immersed in a drug solution causes the drug (in the form of charged ions) to be moved from the donor part into the skin. The positively charged electrode, i.e., the anode, attracts the negatively charged drug ions; the negatively charged electrode, i.e., the cathode, attracts the positively charged ions. Usually Ag|AgCl electrodes are used [2].

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As long as the current density is less than $0.5 \text{ mA}/\text{cm}^2$ [1–4], there is no disruption of the skin in iontophoresis. Further, drugs can be delivered locally or systemically without potential systemic side effects. As the current controls the drug delivery, it can also control the timing of delivery in an exact fashion. Since the current applied is quite low, there is no reason to worry about infection and tissue trauma. Iontophoresis has some disadvantages. Only water-soluble drugs of molecular weight (MW) under 10,000 (“10,000 Dalton Rule”) are amenable to delivery [3]. Some patients experience redness, burning, and/or itching at the drug administration site. Another concern is the size of the power supply which ideally should be as small and lightweight as possible. Iontophoresis is still very promising for TDD. The first pre-filled iontophoretic TDD patch for local anesthesia has been approved by FDA [4].

Delivery of drugs through a microporous polymeric membrane via aqueous-organic partitioning has been already investigated [5–8]. Compared to other controlled release technologies, preparation of such an aqueous-organic partition-based system is convenient and does not require dispersion of the drug into a polymer and the attendant processing steps. Such systems have also been studied *in vitro* using doxycycline hydrochloride (HCl), a larger

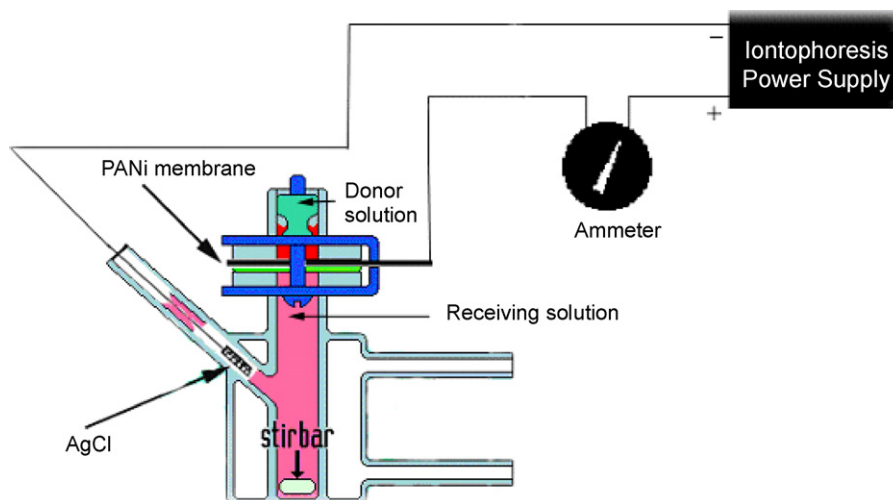


Fig. 1. The iontophoretic setup using PANi film as an electrode, the anode (modified from drawings from <http://www.permeagear.com/o-ring.htm>, last accessed on July 3, 2005).

(MW: 480.1), polar antibiotic as a model drug with and without a mouse skin. In the presence of linoleic acid as an enhancer, the permeation rates of this agent were found to be significant; a simplified mathematical model was developed to successfully describe the experimental data [9].

Topical/dermal route for doxycycline delivery has been extensively studied by a British group [10,11] to avoid known side effects of oral delivery. Heesch [12] reports no harmful effects of doxycycline use in skin treatment. The prophylactic oral dose of doxycycline is about 700 mg/weekly [13]. If 50% of it is bioavailable after the first-pass effect, around 50 mg should be transferred through skin in 24 h. Although the above TDD system using a porous polyvinylidene fluoride (PVDF) membrane [9] can introduce the total amount required in 24 h using appropriate patch dimensions, much faster delivery may be required for other drugs, e.g., lidocaine hydrochloride. Therefore, a first objective of this study was to investigate iontophoresis as a means of facilitation to achieve fast delivery of such drugs and increase the accumulation using the traditional Ag|AgCl electrode system.

In conventional iontophoresis with Ag|AgCl electrodes, the Ag electrode is the anode; the AgCl electrode acts as the cathode. The Ag electrode is easily oxidized and is therefore known to be unstable; the Ag|AgCl system is also quite costly. The Ag anode can be reused only by an intense cleaning process both before and after usage to prevent oxidation and damage ([14]). To overcome such limitations, a novel conducting polymeric membrane made of polyaniline (PANi) has been investigated here as an electrode replacing the Ag electrode in iontophoresis. As in the case of an Ag anode, the electrochemical reaction at the PANi anode with an AgCl cathode is:



Such a system will replace the easily oxidized unstable Ag part of the traditional Ag|AgCl electrodes; at the same time a patch based on such a new system is reusable unlike the Ag|AgCl electrode since drug agents can be refilled in the reservoir. This system is likely to be considerably cheaper than that based on Ag|AgCl electrodes.

As a conducting polymer, PANi has been extensively investigated [15–18] to explore its unique properties. In the area of controlled release, its possibility to transform itself from almost an insulator to a high conductor in different pH environments has been the focus. In other words, it may be a very good candidate membrane to carry out ion exchange, which matches the requirement of the

iontophoretic technique. Although many investigators have concentrated on the permeability of PANi membranes for gases, water and small carboxylic acids [16], little is available on iontophoretic TDD study, especially for large MW molecules such as lidocaine HCl, doxycycline HCl.

In the patent literature on TDD, there exist claims for its use as an electrode to bind agent ions (develop a reservoir) before administration and then release them when an electrical pulse or a DC voltage is applied [19–21]. A conductive membrane polymerized from materials such as polyaniline and other polymers from polypyrrole family was proposed to split the donor chamber into two to prevent unnecessary competition of ion migration [22–24]. The PANi material was also claimed to be useful as an anode in several patents [25–27]. However, none of them disclosed a doped³ PANi membrane functioning simultaneously as an anode and a control membrane for iontophoretic drug delivery system separating the donor reservoir from the receptor as shown in Fig. 1. This is a second objective of this study. The proposed configuration of the two electrodes vis à vis the skin is however traditionally employed in iontophoresis as opposed to the electrode-network transdermal delivery system proposed by Fischer et al. [28].

The PANi membrane can control the drug permeation rate via its pore size and porosity and therefore provide different permeation resistances; adjusting the voltage could lead to different current densities for iontophoresis. Since different sizes of molecules from small (<200 Da) to large (several thousand and larger) could go through such a membrane, one can deliver several agents at different rates in one system. Uncharged molecule transport will be controlled by its role as a simple porous membrane.

Porous PANi membranes were therefore prepared and used in a specific iontophoretic TDD system (Fig. 1) to study the permeation of the following agents: caffeine, lidocaine hydrochloride and doxycycline hydrochloride. The basis for selection of these agents is as follows. Caffeine was representative of a nonionic drug whose transport may be controlled by the porous membrane. The present work will also explore whether iontophoresis affects its transport.

Doxycycline HCl transport enhancement by iontophoresis is of considerable interest in view of earlier difficulty in delivering it [9]. Lidocaine HCl is currently being delivered by iontophoresis;

³ An insulating polymeric film of polyaniline can become a conducting one by treatment (doping) with HCl resulting in electron removal from the backbone.

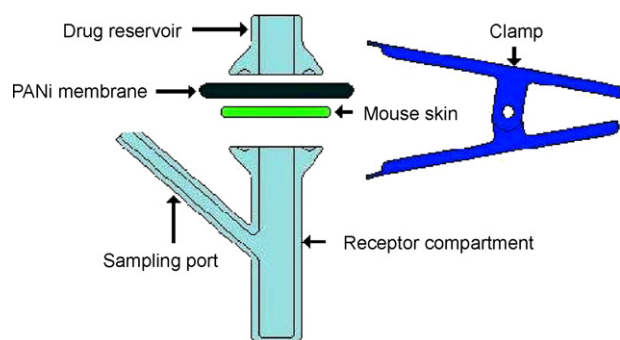


Fig. 2. Drug reservoir with PANi and skin membranes (modified from drawings from <http://www.permegear.com/o-ring.htm>, last accessed on July 3, 2005).

therefore its delivery in the proposed configuration would be useful to gain a perspective on the new configuration. Fig. 2 illustrates the details of the drug reservoir with the PANi and the mouse skin membranes. It is known that mouse skin is more permeable than human skin [29,30]; our earlier studies [9] indicate that the rate of doxycycline HCl delivery achieved with mouse skin was significantly higher than that through a cadaver skin. In this work, the results obtained using this model membrane electrode have also been compared with those from regular Ag/AgCl electrodes; theoretical justification of the observed differences will also be provided. Finally, controlled release of the agents via aqueous-organic partitioning between the reservoir and the aqueous liquid in the membrane pores investigated earlier [9] was also tested to illustrate the utility of the new configuration of this study.

2. Experiments

2.1. Materials

2.1.1. Chemicals

Polyaniline (emeraldine base, MW ca. 65,000), lidocaine hydrochloride (HCl) (MW: 270.8) were purchased from Aldrich, Milwaukee, WI. Potassium phosphate monobasic anhydrous and linoleic acid were obtained from Sigma, St. Louis, MO. Silver wire (99.9%, 0.5 mm), silver chloride (99.9%), hydrochloric acid solution (1 M), *N*-methylpyrrolidinone (NMP), glycerol, light mineral oil, ethanol, methanol (HPLC-grade), acetonitrile (HPLC-grade), and doxycycline hydrochloride (HCl) (Bioreagent grade) (MW: 480.1), caffeine (MW: 194.2) were purchased from Fisher Scientific, Fair Lawn, NJ. Phosphate buffered saline (PBS) was supplied by Fluka, Milwaukee, WI. All chemicals, except noted otherwise, were reagent grades.

2.1.2. Membranes

Polyaniline membrane was cast from a concentrated solution of polyaniline (emeraldine base) (PANi) in NMP obtained by evaporation (described later).

Skin membranes: Male hairless mice, strain SKH1, 8 weeks old, were supplied by Charles River Laboratories (Wilmington, MA). Mice were euthanized by carbon dioxide asphyxiation. Their skins were excised and kept at -30°C until used.

2.2. Experimental setup

Direct current (DC) was generated by the stimulus isolator (World Precision Instrument, Inc., Sarasota, FL). Standard Franz diffusion cell (PermeGear, Inc., Bethlehem, PA) with a diffusional area of 0.64 cm^2 and a receptor compartment volume of 5.1 ml were used in all experiments.

2.3. Experimental procedure

2.3.1. Drug solution

Solutions of caffeine and doxycycline HCl in water were prepared by dissolving about 200 mg of each agent into 10 ml water, while about 400 mg of lidocaine HCl was dissolved into 10 ml water. The solubility of doxycycline HCl in water is 50 mg/ml [31]. The concentrations used were much less than saturation value. A solution of about 200 mg doxycycline HCl dissolved into 15 ml of ethanol–water mixture (EtOH:H₂O = 2:1, v/v) with 5% (v/v) linoleic acid was also prepared. For the aqueous-organic partitioning system, an amount of 500 mg of doxycycline HCl was added into 50 ml light mineral oil to make a suspension [9]. No drug/agent was introduced into the PANi membrane or its solution in NMP. Specific concentration for each application is listed in each table.

2.3.2. Membrane preparation and its properties

An amount of 1.5 g of polyaniline was dissolved into 100 ml NMP and stirred for 1 h [32]. A regular gauze pad was used to filter the resulting dark blue solution. The clear filtrate solution was then transferred to a Rotavapor[®] RE 111 (Flawil, Switzerland) to evaporate the solvent at 50°C [32] for about 70 min to yield about 20 ml of a sticky solution. The PANi film was cast from such a solution on a glass plate by rolling a glass rod in order to maintain the uniformity of the thickness of the film. The thickness of the film was determined by an electrical caliber. Each piece of membrane was measured at different locations and at least 3 pieces of membranes were measured to get an average value. Doping such a film was achieved by keeping the film in a solution of 1N HCl for 24 h [32], then washing it by DI water and drying it.

The porosity of the membrane, ε_m , was obtained by measuring the weights of membrane wetted with glycerol and dry membrane. After the films were immersed into glycerol for certain time, KimWipes was used to gently wipe off the glycerol on the surfaces of both sides. The porosity was calculated by converting the difference into the void volume by taking the density of glycerol into account and then dividing by the dry volume of the film. The equation for the calculation of membrane porosity (ε_m) is:

$$\varepsilon_m = \frac{(W_{\text{wet}} - W_{\text{dry}}) / \rho_{\text{glycerol}}}{V} \quad (2)$$

where, W_{wet} and W_{dry} are the weights of wet and dry membrane, respectively. Here ρ_{glycerol} (1.475 g/ml) and V are the density of glycerol and the volume of the membrane, respectively.

The calculation of the value of the membrane parameter (ε_m / τ_m), where τ_m is membrane tortuosity, was carried out by measuring the flux data from three diffusion experiments of caffeine with three concentrations while all other conditions were kept the same (see Appendix A).

In the case of skin membranes, the plastic bags containing the mouse skins were first taken out of the freezer and put into a beaker filled with room temperature water until they were defrosted. The skin samples were then removed from the plastic bags and cleaned of adhering fat deposits. They were then cut into small pieces of appropriate size and carefully mounted on top of the diffusion cells and left to equilibrate for 1 h.

2.3.3. In vitro drug-permeation studies

The PANi membranes were cut to the dimensions of the Franz diffusion cells. In the case of iontophoresis-facilitated delivery, such films were applied in a large enough size to have their edges extruding out (as shown in Fig. 1) so that the film could be connected to the DC power source. The details of the preparation of Ag/AgCl electrodes, the setup of Franz diffusion cells, and sampling have been provided elsewhere [3,9]. Specifically, silver wire (0.5 mm) was cut

to make Ag anodes, while another cut silver wire was oxidized with an AgCl layer coated on the surface used as AgCl cathode. All results are based on an average from measurements in three Franz cells.

2.3.4. HPLC analysis

For caffeine and lidocaine HCl, analysis was performed using an Agilent 1100 HPLC with a reverse-phase C₁₈ column (Microsorb-MV™, 15 cm, 5 μm, Agilent Technologies) at a flow rate of 1 ml/min. Caffeine was detected at 270 nm with a mobile phase composed of acetonitrile:methanol:water (10:20:70) and an injection volume of 20 μl. Lidocaine HCl was detected at 220 nm with a mobile phase composed of acetonitrile: 0.05 M monobasic potassium phosphate (45:55, pH 3.0) and an injection volume of 40 μl. The HPLC method for doxycycline HCl has been described elsewhere [9].

2.3.5. SEM imaging

The membrane structure was characterized using a scanning electron microscope (SEM) (LEO 1530 VP FE-SEM, Carl Zeiss, New York, USA).

2.4. Data processing

The permeation parameters of the agents were calculated by plotting the cumulative corrected amounts (μg/cm²) of the agent permeated through the skin versus time (h). The slope of the linear portion of the graph provided the average flux value (*J*) at steady state (μg/cm² h). The quantities *Q*₈, *Q*₁₀ and *Q*₂₄ are the accumulations, respectively, for 8, 10 and 24 h in the receptor chamber.

Permeability (*P*) was calculated by

$$P = \frac{\Delta C_{\text{receptor}}}{\Delta t \times A_{\text{receptor}}} \times \frac{V_{\text{receptor}}}{C_{\text{donor}}} \quad (\text{cm/h}) \quad (3)$$

Here Δ*C*_{receptor} (μg/ml): the difference of agent concentration in the receptor part in the given time Δ*t* (h); *C*_{donor} (μg/ml): agent concentration in the donor part; *A* (cm²): the area of receptor, *V*_{receptor} (ml): receptor volume. Statistical analysis was performed using one-way analysis of variance (one-way ANOVA).

3. Results and discussion

The results of characterization of PANi film needed for characterizing the membrane transport of various agents through the PANi films are presented first. The permeation profiles through a PANi membrane of three solutes, e.g., caffeine, lidocaine HCl and doxycycline HCl are then illustrated without any iontophoresis. Next the permeation rates are determined from Fick's law of diffusion and compared with the experimental data. The data obtained when a mouse skin is added to the PANi film are analyzed subsequently. This has been followed by iontophoretic study of the composite of a PANi film and a mouse skin using two different kinds of electrodes, one based on a conventional Ag|AgCl electrodes and the other based on PANi|AgCl electrodes. An aqueous-organic partitioning system with doxycycline HCl as the agent present in light mineral oil as a solution-suspension was also studied at the end and the observed rates were compared with those through a porous PVDF membrane obtained earlier [9].

3.1. Properties of PANi films

The porosity of PANi films was found to be 0.67 ± 0.08% based on measurements from three films. The magnitude of the porosity is quite low. The SEM pictures of their undoped form (Fig. 3) tend to support this observation. Introduction of low levels of pore forming agents in the casting solution would have led to a higher porosity. It is known from standard techniques employed to make porous

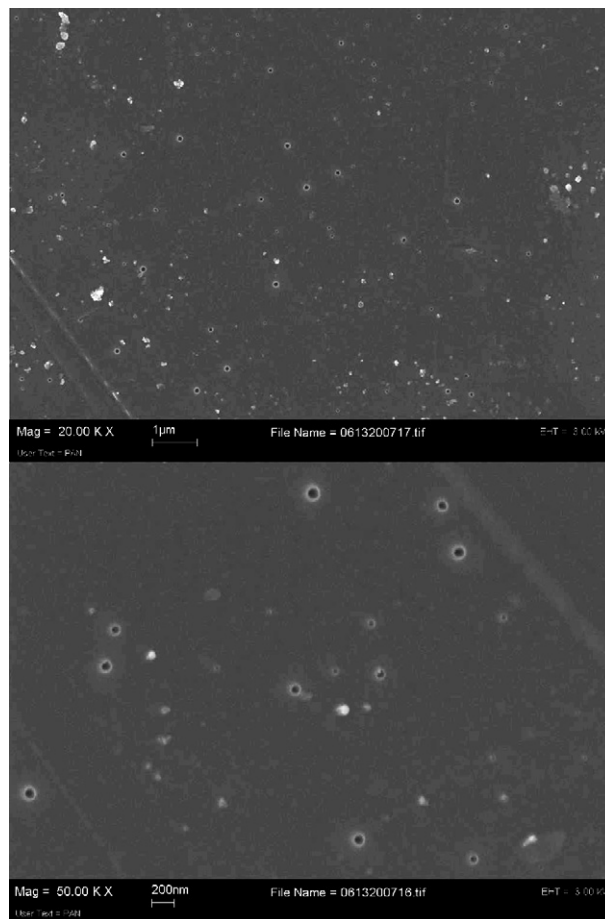


Fig. 3. SEM pictures of undoped PANi films.

membranes by phase inversion techniques that the surface porosity of ultrafiltration membranes are in the range of 0.5–2% [33]. Thus, the low porosity of the PANi membrane is not unusual. The value of the membrane parameter (ϵ_m/τ_m) including membrane porosity and tortuosity was found to be $9\text{E}-4 \pm 7\text{E}-5$ from an average of nine films (see Appendix A). The thickness of the PANi films was found to be 0.018 ± 0.002 mm.

3.2. Permeation profiles from PANi membranes

The permeation rates of three agents through the PANi membrane as obtained in the Franz cell are presented in Table 1. This table illustrates the permeation data for three different agents in terms of their permeability, flux and 24-h accumulation values. Obviously, doxycycline HCl, with the highest MW, had the lowest flux, permeability and accumulation. Between caffeine and lidocaine HCl, although their diffusion coefficients are quite close, the higher concentration of lidocaine HCl in the aqueous donor solution (by a factor of two) played a critical role in providing almost two-fold higher flux and six-fold higher drug accumulation compared to those for caffeine. The following calculations provide a possible explanation of the data.

Conventionally, the value of the flux of the permeating species may be obtained by simple diffusion through the water-filled membrane pores [34–37]:

$$J = D_{\text{eff}} \frac{\Delta C}{l} = \frac{D_{\text{eff}}}{l} (C_{1D} - C_{1R}) \quad (4)$$

Table 1
Permeation data of three agents released through PANi membrane and comparison of predicted flux data with experimental values

Agent and its concentration	Permeability (cm/h)	Flux ($\mu\text{g}/\text{cm}^2 \text{ h}$)	$D_{\text{water-agent}}$ (cm^2/s)	Model prediction of flux ($\mu\text{g}/\text{cm}^2 \text{ h}$)	Q_{24}^a ($\mu\text{g}/\text{cm}^2$)
Caffeine, 20.4 mg/ml	$1.2\text{E}-2 \pm 9.0\text{E}-3$	240 ± 177	$7.08\text{E}-6$	260	573 ± 246
Lidocaine HCl, 40.2 mg/ml	$1.1\text{E}-2 \pm 3.5\text{E}-3$	461 ± 147	$7.91\text{E}-6$	573	3330 ± 1760
Doxycycline HCl, 20.4 mg/ml	$3.5\text{E}-3 \pm 7.0\text{E}-4$	72 ± 14	$6.59\text{E}-6$	198	307 ± 97

^a 24 h accumulation in the receptor part.

in which, D_{eff} is the effective diffusion coefficient in the membrane, ΔC is the concentration difference in the pore liquid of the two external solution–pore liquid interfaces on two sides of the membrane: C_{1D} is the concentration in the pore liquid of the donor side and C_{1R} is that in the receptor side; l is the membrane thickness. The last formula is utilized in the following calculation with $C_{1R} \cong 0$, effectively zero concentration in the receiver vessel having an aqueous phase (since it was much less than those in the donor side and was always well mixed); for the donor chamber, $C_{1D} \cong C$, which is the agent concentration in the donor solution. The partition coefficient K of the agent between the reservoir liquid (aqueous solution) and membrane pore liquid (aqueous solution) is assumed to be 1.

The effective diffusion coefficient of the agent through water in the porous membrane may be defined as [38]

$$D_{\text{eff}} = \frac{D_{\text{water}} \varepsilon_m}{\tau_m} \quad (5)$$

Wilke–Chang equation [39] was used to estimate the free diffusion coefficient in solution, D_{water} , of different agents. The implications of ionization on the partitioning behavior were also considered in the model calculations [9]. As for doxycycline HCl, since the donor solution concentration was higher than 0.01 M, its dimerized form was included in the calculation of its model flux value as well [31]. Therefore, the flux in the model calculations has contributions from three components: flux of the base (J_{Doxyc}), flux of the ionized base (J_{DoxycH^+}) and flux of the dimer (J_{dimer}). As for lidocaine HCl, however, such data for its dimerization are not available in literature; therefore, a general calculation was carried out in the manner illustrated in reference [9]. Results of model flux values (J) obtained when all experimental parameters were introduced into Eq. (4), are also shown in Table 1, which includes the corresponding experimentally observed values. Detailed calculation methodologies and results are provided in Appendix B.

The experimentally obtained flux values shown in Table 1 appear to be not far from those calculated from the model equations especially for caffeine and lidocaine HCl. If existence of dimerization of lidocaine HCl were considered, the model value would probably have been closer to the experimental one. All differences are likely to be due to the variations from film to film cut from different parts of a larger piece of film. From these results, it is clear that such a porous polymeric conducting membrane is unlikely to be a major obstacle for these agents to pass through. Therefore, a mouse skin was used next for tests with a PANi membrane placed on top of it.

3.3. Permeation profiles from a composite of PANi and mouse skin membranes

The permeation flux values of three agents through a composite membrane consisting of a PANi membrane with a mouse skin next to it were 7.6 ± 0.6 , 20.4 ± 1.0 , $0 \mu\text{g}/\text{cm}^2 \text{ h}$ for caffeine, lidocaine HCl and doxycycline HCl, respectively. It appears that doxycycline HCl, the largest molecule, had apparently no permeation at all. When compared with the data from the earlier investigation [9], it is not surprising; without an appropriate enhancer in the donor solution, it is very difficult for doxycycline HCl to go through

the mouse skin. Here there was no enhancer for doxycycline HCl present in the donor solution. (In so far as caffeine and lidocaine HCl are concerned, the magnitude of the higher concentration of lidocaine HCl solution is believed to be responsible for its higher flux.) Iontophoresis was therefore employed next as an enhancement.

As pointed out in our previous work [9], mouse skin was used in this study since it was an initial feasibility investigation. It is known to the authors, however, that data from mouse skin provide higher permeability values than would be observed in human cadaver skin [29,30].

3.4. Iontophoretic permeation profiles from PANi membranes

For caffeine and lidocaine HCl, the current density used was $0.2 \text{ mA}/\text{cm}^2$ because of their relatively small MWs; for doxycycline HCl, $0.3 \text{ mA}/\text{cm}^2$ was chosen because its MW is 480.1. To study the iontophoretic property of the PANi membranes, standard Ag|AgCl electrode was used. The values of the permeation flux rates of the three agents were 305 ± 79 , 411 ± 144 , $793 \pm 111 \mu\text{g}/\text{cm}^2 \text{ h}$ for caffeine, lidocaine HCl and doxycycline HCl, respectively. As for caffeine, a neutral molecule, there was only about 30% increase in its flux (vis à vis Table 1); we do not know whether it is due to electroosmosis [40–42] or not. For doxycycline HCl, the flux increased more than ten times (compared to that in Table 1), which indicated potentially a promising release behavior if applied on top of a mouse skin. A skin patch would be expected to deliver about 0.8 mg of doxycycline HCl in, say, 1 h through a contact area of 1 cm^2 . Here is an example where the porous PANi membrane exercises control on transport of uncharged species whereas a charged species flux is controlled by iontophoresis. If we need to deliver an ionic as well as a nonionic drug, at radically different rates, such a configuration will be useful. For lidocaine HCl, however, we observe that there is a small decrease in the flux.

According to Faraday's law, the iontophoretic flux of an ion can be expressed as [14,43]

$$J_i = \frac{t_i i}{F Z_i} \quad (6)$$

in which, i , F , t_i , and Z_i are, respectively, the applied current density, Faraday's constant, the transport number of ionic species i and the electrochemical valence of the ion i under consideration. To simplify the calculation of t_i , when the donor part contains only the agent solution without any other ion, the major competing ion with the agent ion is Cl^- , whose t_{Cl^-} may be assumed to be 0.86 [44]. The transport number for the agent ion is then most likely to be 0.14. As for lidocaine HCl, similarly, its cation transport number can be tentatively assumed as 0.19 [45]. For the values of the current density applied, and the electrochemical valence for the agent ion, the calculated flux results for lidocaine HCl and doxycycline HCl are shown in Table 2; they have also been compared with the experimentally observed values. For both lidocaine HCl and doxycycline HCl, the experimental values are quite close to the calculated values. The deviation may be partly explained by the existence of passive permeation taking place simultaneously.

Table 2
Comparison of model predictions with experimental iontophoretic flux data

Agent ion and donor concentration	Current density (mA/cm ²)	Valence Z _i	Model prediction of flux ^a (μg/cm ² h)	Experimental flux (μg/cm ² h)
Lidocaine HCl ion 40.2 mg/ml	0.2	1	383	411 ± 144
Doxycycline HCl ion 20.4 mg/ml	0.3	1	752	793 ± 111

^a Calculated from Eq. (6).

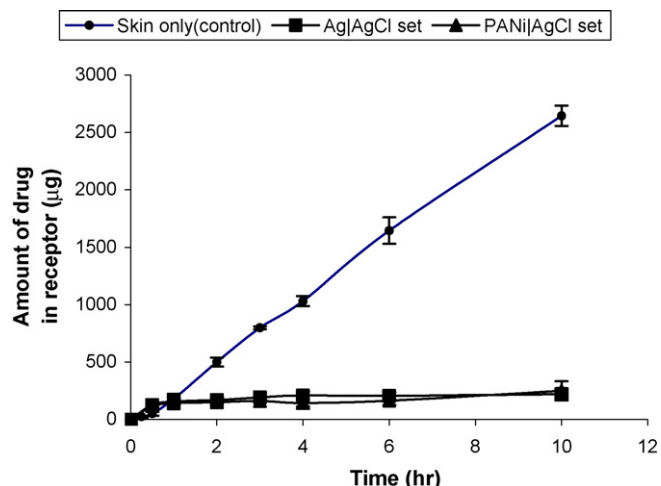


Fig. 4. Iontophoretic permeation profiles of lidocaine HCl through mouse skin with and without PANi membrane ($i = 0.2$ mA/cm²).

3.5. Iontophoretic permeation profiles from both PANi and mouse skin membranes

Three sets of iontophoretic experiments were carried out. In the first set, as a control test, traditional Ag|AgCl electrodes were used for the mouse skin only without the PANi membrane. In the other two sets, with the PANi membrane and the mouse skin together, either PANi|AgCl configuration or the Ag|AgCl configuration as electrodes was tested.

3.5.1. Lidocaine HCl

The results of the three sets of experiments are presented in Fig. 4. Table 3 illustrates the permeation data for the different experimental configurations. The results of the two different sets of electrodes were similar, which indicates that the conducting PANi membrane could be a good replacement for the Ag electrode. In addition, if its properties such as porosity is increased (correspondingly tortuosity is likely to be reduced), it is possible for a given applied voltage to enhance the flux and accumulation of drug permeated, i.e., an additional method to control of transdermal drug delivery.

Table 3
Iontophoretic permeation data of lidocaine HCl released through mouse skin with and without a PANi membrane ($i = 0.2$ mA/cm²), donor concentration: 40.22 mg/ml

Set	Permeability (cm/h)	Flux (μg/cm ² h)	Q ₁₀ ^a (μg/cm ²)
Skin only Ag AgCl electrodes	1.1E–2 ± 2.6E–4	433 ± 10	4160 ± 138
PANi + skin Ag AgCl electrodes	1.0E–3 ± 4.2E–4	48 ± 20	348 ± 78
PANi + skin PANi AgCl electrodes	1.0E–3 ± 3.5E–4	43 ± 15	392 ± 130

^a 10 h accumulation in the receptor part.

3.5.2. Doxycycline HCl

It should be noted that for the sets of PANi membrane and mouse skin together, no release of doxycycline HCl was achieved in the absence of a chemical enhancer added to the aqueous donor agent solution (as observed in reference [9] for conventional porous uncharged polymeric membranes). Therefore, instead of using a simple aqueous solution, 5% linoleic acid was added to the doxycycline HCl solution consisting of ethanol and water (EtOH:water = 2:1, v/v). The reason for using ethanol was to increase the solubility of linoleic acid in the water.

Conventionally ethanol is used as a chemical enhancer in many TDD applications [46,47]. However, our earlier investigation [9] of TDD of doxycycline HCl indicated that ethanol as well as many other common chemical enhancers, such as azone, cineole, etc. were not able to enhance the transport of the large polar molecule, doxycycline HCl. However, linoleic acid at 5–10% level was quite successful in enhancing the transport of doxycycline HCl substantially. Thus, here both chemical enhancement and physical enhancement are active in pushing doxycycline HCl through the mouse skin.

The results of three sets of experiments are presented in Fig. 5. Table 4 illustrates the permeation data for doxycycline HCl under different conditions.

Unlike the data obtained with lidocaine HCl, no release of doxycycline HCl was observed from the Ag|AgCl electrode set. By the end of the experiment, a white gel-like layer of AgCl was observed on the surface of the PANi film facing the Ag electrode (Fig. 6). It is possible that the deposited matter blocked the pathway for doxycycline HCl through the membrane first, and hence no drug was detected passing through the skin. Compared with the lidocaine HCl, it is believed that with the increased ethanol in the agent solution needed to solubilize linoleic acid, we also created conditions for increased dissolution of AgCl [48,49]. However, as shown in the SEM picture (Fig. 6), such an increased solubility of AgCl as a complex led to its precipitation on the PANi membrane surface. Since the solubility of AgCl in the lidocaine case was much smaller in the absence

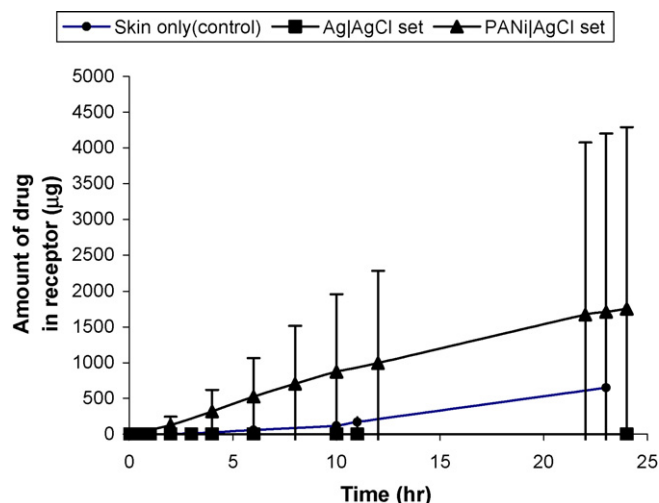


Fig. 5. Iontophoretic permeation profiles of doxycycline HCl through mouse skin with and without a PANi membrane ($i = 0.3$ mA/cm²).

Table 4
Iontophoretic permeation data of doxycycline HCl released through mouse skin with and without a PANi membrane ($i = 0.3 \text{ mA/cm}^2$)

Set donor concentration	Permeability (cm/h)	Flux ($\mu\text{g/cm}^2 \text{ h}$)	Q_{24} ($\mu\text{g/cm}^2$)
Skin only Ag AgCl electrodes 12.67 mg/ml ^a	$3.8\text{E}-3 \pm 6.7\text{E}-4$	48.5 ± 8.5	1020 ± 642
PANi + skin Ag AgCl electrodes 16.82 mg/ml ^b	0	0	0
PANi + skin PANi AgCl electrodes 16.82 mg/ml ^b	$5.6\text{E}-3 \pm 4.8\text{E}-3$	94.4 ± 81.2	2760 ± 3980

^a Aqueous solution without ethanol or linoleic acid.

^b 2:1 EtOH:H₂O solution with 5% linoleic acid.

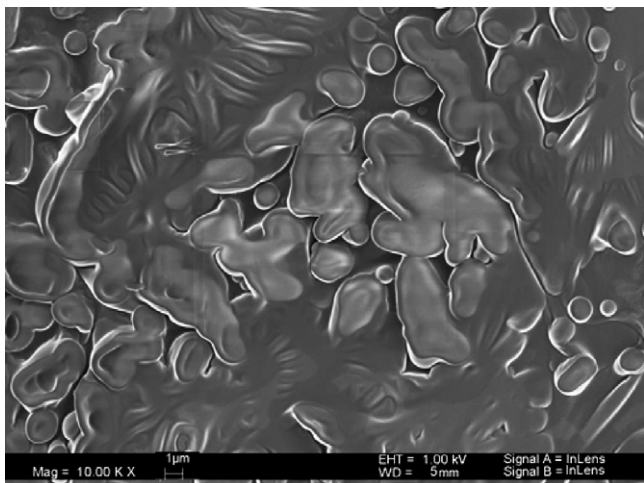


Fig. 6. SEM picture of doped PANi film used in the Ag|AgCl set for doxycycline HCl diffusion showing a white precipitation layer blocking the pathway for doxycycline HCl through the membrane.



Fig. 8. SEM picture of doped PANi film used in the PANi|AgCl set for doxycycline HCl diffusion showing no white-gel-like precipitation layer to block the pathway of doxycycline HCl transportation.

of alcohol, small individual particles were observed on the PANi film facing the Ag electrode (Fig. 7). For the PANi|AgCl electrodes set, however, since Ag was not used as electrode, no AgCl blocked the permeation (Fig. 8) and the results were even better than those of skin only set due to the enhancements of both iontophoresis and linoleic acid. The high values of deviations could be from the non-homogeneous porous structure of the mounted membranes, which is more important for larger molecules like doxycycline HCl than smaller ones like lidocaine HCl.

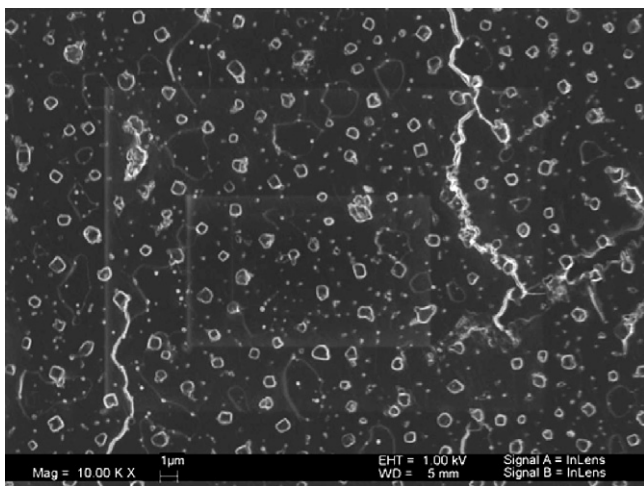


Fig. 7. SEM picture of doped PANi film used in the Ag|AgCl set for lidocaine HCl diffusion showing very small individual particles on the PANi surface without the presence of ethanol.

3.6. Aqueous-organic partitioning system

For the permeation study of PANi membrane based on aqueous-organic partitioning system, doxycycline HCl suspension in light mineral oil was used as the donor solution so that its permeation results could be compared with those from a hydrophilized polyvinylidene fluoride (PVDF) membrane in a general way. Table 5 illustrates the permeation data of doxycycline HCl through a PANi membrane based on aqueous-organic partitioning system with those through a hydrophilized PVDF membrane [9] for comparison.

Compared to permeation data from the PVDF membrane system, all flux values obtained here are much smaller. It is believed that the rather small porosity (for PANi, about 1%; for PVDF, 70%) is the primary reason for this low delivery rate. Therefore, it would be essential to increase the PANi membrane porosity to further improve delivery from both aqueous solution system and aqueous-organic partitioning system. However, PANi membrane is anyway not a good candidate for non-iontophoresis systems [9]. On the other hand, it has been clearly shown here that it is quite good for iontophoretic TDD.

Table 5
Permeation data of doxycycline HCl through PANi membrane based on aqueous-organic partitioning system with those through PVDF system

Membrane system and donor concentration	Permeability (cm/h)	Flux ($\mu\text{g/cm}^2 \text{ h}$)	Q ($\mu\text{g/cm}^2$)
PANi 9.98 mg/ml ^a	0.003 ± 0.002	31 ± 18	6 h: 80 ± 46
PVDF 9.98 mg/ml ^a	0.03 ± 0.01	146 ± 27	24 h: 1440 ± 240

^a Doxycycline HCl in light mineral oil.

4. Conclusions

Iontophoretic TDD was studied using porous membranes of polyaniline, a conducting polymer. Three model agents of different molecular weights, caffeine, lidocaine HCl and doxycycline HCl, were studied. The transport rate of each agent through such a porous conducting membrane was predicted well using simplified mass transport models in the absence of any applied voltage. Satisfactory permeation profiles were achieved not only from the *in vitro* membrane test but also from *in vitro* iontophoretic TDD system using mouse skin. The permeation rates for the *in vitro* membrane test without mouse skin in the iontophoresis mode were predicted well. Iontophoresis with PANi/AgCl electrodes presented satisfactory permeation data indicating a potential for practical use. As a dosage of 100 mg/day is required for prophylaxis, our data obtained using mouse skin suggests that a small patch of 5-cm diameter will work. In practice, a larger diameter will be required for the human skin. For aqueous-organic partitioning systems, due to the rather low porosity of PANi membrane, the permeation rates were much lower than those from their hydrophilized PVDF counterpart membranes. In conclusion, the PANi membrane offers interesting potential uses in iontophoretic TDD delivery systems and is worthy of further investigations.

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Appendix A. Calculation of the membrane parameter (ε_m/τ_m) of PANi films

Combining Eqs. (4) and (5), the equation of flux (J) is changed to:

$$J = \frac{D_{\text{water}} \cdot \varepsilon_m}{\tau_m \cdot l} (C_{1D} - C_{1R}) \quad (\text{A.1})$$

Therefore, the membrane parameter (ε_m/τ_m) can be expressed as:

$$\frac{\varepsilon_m}{\tau_m} = J \cdot \frac{l}{D_{\text{water}}} \cdot \frac{1}{C_{1D} - C_{1R}} \quad (\text{A.2})$$

Next, three caffeine solutions of different concentrations were prepared: 5, 10, 20.4 mg/ml. From each solution in donor part, a flux value was obtained and used in Eq. (A.2) to calculate the membrane's (ε_m/τ_m); the averaged value, 0.0009, was used in later calculations.

In addition to the thickness (l) as a known value, the diffusion coefficient of caffeine in free solution ($D_{\text{Caf,water}}$) was obtained from the Wilke and Chang Equation [39]:

$$D_{\text{Caf,water}} = 7.4 \times 10^{-8} \frac{(\phi M_{\text{Water}})^{0.5} T}{\eta_{\text{Water}} V_{\text{Caffeine}}^{0.6}} \quad (\text{A.3})$$

in which M_{Water} , η_{Water} , V_{Caffeine} , ϕ and T are the molecular weight, viscosity of water (cP), molar volume of caffeine (cm^3/gmol), association factor of solvent and temperature (K), respectively. The association factor of water and molar volume are equal to 2.6, 159.3 cm^3/gmol , respectively, and the value of $D_{\text{Caf,water}}$ is $7.08 \times 10^{-6} \text{ cm}^2/\text{s}$.

Table A.1 lists the membrane parameter (ε_m/τ_m) calculated from different flux levels for different donor concentrations; the averaged value was used in the following calculations.

Table A.1

The value of PANi membrane parameter (ε_m/τ_m) calculated from data of different fluxes for caffeine^a

Concentration of caffeine (mg/ml)	Flux ($\mu\text{g}/\text{cm}^2 \text{ h}$)	ε_m/τ_m	Avg. ε_m/τ_m
5	66.6	0.00094	9E-4 ± 7E-5
10	136.2	0.00096	
20.4	239.5	0.00083	

^a Using Eq. (A.2).

Appendix B. Calculation of model flux for Table 1

B.1. Model flux of caffeine

Since caffeine is a neutral molecule which does not produce any charged ions in solution, its flux is determined simply by using its concentration values in Eq. (4), where the donor solution concentration of caffeine is 20,400 $\mu\text{g}/\text{ml}$,

$$J = \frac{D_{\text{eff}}}{l} (C_{1D} - C_{1R}) = \frac{7.08 \times 10^{-6}}{0.0018} \times 0.0009 \times (20,400 - 0) \times 3600 = 260.0 \mu\text{g}/\text{cm}^2 \text{ h}$$

B.2. Model flux of doxycycline HCl

Reference [9] describes generally how to calculate the model flux value of an ionizable salt agent (such a method is applicable to water/ethanol solution, see Ref. [50]). Since the concentration of doxycycline HCl was quite high (0.0425 M), the role of its dimerization has to be considered in the flux calculation [31].

There are four species of doxycycline agent in the aqueous phase; the formula of each and the symbol for its concentration are indicated in separate brackets: the original base doxycycline (Doxy) (C_{Doxy}), doxycycline H^+ (DoxyH^+) (C_{DoxyH^+}), doxycycline dimer (DoxyH^+)₂ (C_{di}) or (Doxy)₂ H^+ (C_{di}) [31].

First, the total concentration C_T of doxycycline in all forms was related to the total concentration (C_m) of Doxy (C_{Doxy}) and DoxyH⁺ (C_{DoxyH^+}) as the monomer forms of doxycycline by the following equation from Reference [31]:

$$C_T = C_m + 2K_d C_m^2 \quad (\text{B.1})$$

where K_d is the dimerization constant and equal to 24 [31], while

$$C_T = C_m + C_{\text{di}} = 20,400 \mu\text{g}/\text{ml} = 0.0425 \text{ mol}/\text{l} \quad (\text{B.2})$$

where C_{di} is the concentration of doxycycline dimer.

By solving Eq. (B.1) for this value of C_T ,

$$C_m = C_{\text{Doxy}} + C_{\text{DoxyH}^+} = 0.0211 \text{ M} \quad (\text{B.3})$$

$$C_{\text{di}} = 0.0214 \text{ M} = 10,274 \mu\text{g}/\text{ml} \quad (\text{B.4})$$

From Eq. (B.3), the concentration values of each monomer form of doxycycline were obtained by the solution of a quadratic equation obtained from Eq. (B.5) [9]:

$$K_1 = 10^{-3.3} = \frac{C_{\text{Doxy}} \cdot C_{\text{H}^+}}{C_{\text{DoxyH}^+}} \quad (\text{B.5})$$

By solving Eq. (B.5) together with Eq. (B.3), $C_{\text{Doxy}} = 3.01 \times 10^{-3} \text{ M} = 1445 \mu\text{g}/\text{ml}$, and $C_{\text{DoxyH}^+} = 0.0181 \text{ M} = 8685 \mu\text{g}/\text{ml}$.

Using Wilke–Chang estimation method [39], the diffusion coefficients of monomers and dimers of doxycycline HCl in free solution

are (see [9] for $D_{\text{DoxyH}^+, \text{water}}$ and the same method for that of dimers):

$$\begin{cases} D_{\text{Doxy, water}} = 3.93 \times 10^{-6} \text{ cm}^2/\text{s} \\ D_{\text{DoxyH}^+, \text{water}} = 6.59 \times 10^{-6} \text{ cm}^2/\text{s} \\ D_{(\text{DoxyH}^+)_2, \text{water}} = D_{(\text{Doxy})_2\text{H}^+, \text{water}} = 4.58 \times 10^{-6} \text{ cm}^2/\text{s} \end{cases} \quad (\text{B.6})$$

Therefore, the total flux of doxycycline HCl had three components: J_{Doxy} , J_{DoxyH^+} and J_{dimer} :

$$\begin{aligned} J &= J_{\text{Doxy}} + J_{\text{DoxyH}^+} + J_{\text{dimer}} = (3.93 \times 10^{-6} \times 1445 + 6.59 \times 10^{-6} \\ &\quad \times 8685 + 4.58 \times 10^{-6} \times 10,274) \times 0.50 \times 3600 \\ &= 197.9 \mu\text{g}/\text{cm}^2 \text{ h} \end{aligned} \quad (\text{B.7})$$

where $(\varepsilon_m/\tau_m) \cdot (1/l) = 0.50 \text{ cm}^{-1}$.

Without consideration of the existence of dimer forms of doxycycline HCl, the predicted value of flux would be $232.0 \mu\text{g}/\text{cm}^2 \text{ h}$.

B.3. Model flux of lidocaine HCl

Similarly, the model flux of lidocaine HCl should have three parts also. But the formation of its dimers under high concentration as 0.1485 M is so far a hypothesis [51]; the following calculation is therefore based on the general method followed in Reference [9].

There are two species of lidocaine agent in the aqueous phase, the undissociated lidocaine (Lido) and lidocaine H^+ (LidoH^+). There are two unknowns here whose values are needed before the total agent flux can be calculated. First, the relative distribution between the two species has to be determined. Second, their diffusion coefficients also need to be known. The first dissociation equilibrium constant K_1 for lidocaine H^+ is $10^{-7.2}$ [52]:

$$K_1 = 10^{-7.2} = \frac{C_{\text{Lido}} \cdot C_{\text{H}^+}}{C_{\text{LidoH}^+}} \quad (\text{B.8})$$

For a total agent concentration of lidocaine HCl,

$$C_T = C_{\text{Lido}} + C_{\text{LidoH}^+} = 40,220 \mu\text{g}/\text{ml} = 0.1485 \text{ mol}/\text{l} \quad (\text{B.9})$$

the following values were obtained for the individual species by the solution of a quadratic equation obtained from Eq. (B.8): $C_{\text{Lido}} = 26 \mu\text{g}/\text{ml}$ and $C_{\text{LidoH}^+} = 40,194 \mu\text{g}/\text{ml}$. It was assumed that their concentration in the receptor was zero. Therefore, the total agent flux is:

$$J = \frac{D_{\text{Lido}}}{l} \cdot \left(\frac{\varepsilon_m}{\tau_m} \right) \cdot (C_{\text{Lido}} - 0) + \frac{D_{\text{LidoH}^+}}{l} \cdot \left(\frac{\varepsilon_m}{\tau_m} \right) \cdot (C_{\text{LidoH}^+} - 0) \quad (\text{B.10})$$

The diffusion coefficients of lidocaine in free solution ($D_{\text{Lido, water}}$) can be obtained from the Wilke–Chang Equation and is equal to $4.91 \times 10^{-6} \text{ cm}^2/\text{s}$. The diffusion coefficient of D_{LidoH^+} compound is to be obtained from considerations of diffusion potential-based diffusion coefficient $D_{\text{LidoH}^+\text{Cl}^-}$ obtained from the individual values of D_{LidoH^+} and D_{Cl^-} and their charges:

$$D_{\text{LidoH}^+\text{Cl}^-} = \frac{D_{\text{LidoH}^+} \cdot D_{\text{Cl}^-} \cdot (z_+ - z_-)}{z_+ \cdot D_{\text{LidoH}^+} - z_- \cdot D_{\text{Cl}^-}} \quad (\text{B.11})$$

D_{LidoH^+} for this calculation is assumed essentially equal to $4.91 \times 10^{-6} \text{ cm}^2/\text{s}$ corresponding to the undissociated D_{Lido} . Here $z_+ = +1$, $z_- = -1$ and $D_{\text{Cl}^-} = 2.03 \times 10^{-5} \text{ cm}^2/\text{s}$ [53], so that

$$\begin{aligned} D_{\text{LidoH}^+\text{Cl}^-} &= \frac{4.91 \times 10^{-6} \times 2.03 \times 10^{-5} [1 - (-1)]}{4.91 \times 10^{-6} - (-2.03 \times 10^{-5})} \\ &= 7.91 \times 10^{-6} \text{ cm}^2/\text{s} \end{aligned}$$

Therefore, the total flux of lidocaine HCl in both forms from Eq. (B.10) is:

$$\begin{aligned} J &= (4.91 \times 10^{-6} \times 26 + 7.91 \times 10^{-6} \times 40,194) \times 0.50 \times 3600 \\ &= 572.5 \mu\text{g}/\text{cm}^2 \text{ h} \end{aligned}$$

If dimerization existed and its effect were included in the calculation, the model flux would be lower as shown in the calculation for doxycycline HCl.

Nomenclature

<i>A</i>	diffusional area (cm^2)
<i>C</i>	agent concentration ($\mu\text{g}/\text{ml}$)
<i>D</i>	diffusivity of the agent (cm^2/s)
<i>D_{eff}</i>	effective diffusion coefficient of the agent in the pore (cm^2/s)
<i>D_{water}</i>	diffusion coefficient of the agent in free solution (cm^2/s)
<i>D_{H₂O}</i>	diffusion coefficient of the agent in free solution (cm^2/s)
<i>F</i>	Faraday's constant (C/mol)
<i>i</i>	current density (mA/cm^2)
<i>J</i>	permeate flux ($\mu\text{g}/\text{cm}^2 \text{ h}$)
<i>k</i>	mass transfer coefficient (cm/s)
<i>K</i>	distribution coefficient
<i>K₁</i>	first dissociation equilibrium constant
<i>K_d</i>	dissociation equilibrium constant of dimer
<i>l</i>	membrane thickness (mm)
<i>M</i>	molecular weight (Da)
<i>P</i>	permeability (cm/h)
<i>Q</i>	receptor accumulation after certain time ($\mu\text{g}/\text{cm}^2$)
<i>Sh</i>	Sherwood number (kd_i/D_0)
<i>t</i>	time (h)
<i>t_i</i>	transport number of ionic species <i>i</i>
<i>T</i>	temperature (K)
<i>W</i>	weight
<i>V</i>	volume
<i>V_{caffeine}</i>	the molar volume of caffeine
<i>z</i>	charge value
<i>Z_i</i>	electrochemical valence of the ion <i>i</i>

Greek letters

ε_m	membrane porosity
ϕ	association factor of solvent, dimensionless; for water: 2.6
η	viscosity (cP)
ρ	density
τ_m	membrane tortuosity
Δ	difference of the specific amount in the given time

Subscripts

di	dimer
<i>i</i>	species <i>i</i>
m	membrane
m	monomer as the subscript of <i>C</i>
T	total
1	first
1D	pore liquid of the donor side
1R	pore liquid of the receptor side

References

- [1] W.E. Rhodes III, Iontophoretic drug delivery: new advantages revitalize an established technology, *Drug Deliv. Technol.* 2 (2002) 34.
- [2] R. Panchagnula, O. Pillai, V.B. Nair, P. Ramarao, Transdermal iontophoresis revisited, *Curr. Opin. Chem. Biol.* 4 (2000) 468.
- [3] Y. Wang, Q. Fan, Y. Song, B. Michniak, Effects of fatty acids and iontophoresis on the delivery of midodrine hydrochloride and the structure of human skin, *Pharm. Res.* 20 (2003) 1612.
- [4] Y.N. Kalia, A. Naik, J. Garrison, R.H. Guy, Iontophoretic drug delivery, *Adv. Drug Deliv. Rev.* 56 (2004) 619.
- [5] S. Farrell, Ph.D. Thesis in Chemical Engineering, 1996, New Jersey Institute of Technology, Newark, NJ.
- [6] S. Farrell, K.K. Sirkar, A reservoir-type controlled release device using aqueous-organic partitioning and a porous membrane, *J. Membr. Sci.* 130 (1997) 265.
- [7] S. Farrell, K.K. Sirkar, A mathematical model of an aqueous-organic partition-based controlled release system using microporous membranes, *J. Controlled Release* 61 (1999) 345.
- [8] S. Farrell, K.K. Sirkar, Mathematical model of a hybrid dispersed network-membrane-based controlled release system, *J. Controlled Release* 70 (2001) 51.
- [9] Q. Fan, K.K. Sirkar, Y. Wang, B. Michniak, In vitro delivery of doxycycline hydrochloride based on a porous membrane-based aqueous-organic partitioning system, *J. Controlled Release* 98 (2004) 355.
- [10] T.P. Banning, C.M. Heard, Binding of doxycycline to keratin, melanin and human epidermal tissue, *Int. J. Pharm.* 235 (2002) 219.
- [11] N.C. Perkins, C.M. Heard, In vitro dermal and transdermal delivery of doxycycline from ethanol/migliol 840 vehicles, *Int. J. Pharm.* 190 (1999) 155.
- [12] G.V. Heesch, Skin treatment with a water soluble antibiotic dissolved in an electrolyzed water, U.S. Patent 6,544,502 (2003).
- [13] MMWR, Recommendations for the Prevention of Malaria Among Travelers, Morbidity and Mortality Weekly Report, 39, 1990, p. 1.
- [14] A.K. Banga, Electrically Assisted Transdermal and Topical Drug Delivery, Taylor & Francis Inc., London, UK, 1998 (Chapter 2).
- [15] P. Wang, K.L. Tan, E.T. Kang, K.G. Neoh, Preparation and characterization of semi-conductive poly(vinylidene fluoride)/polyaniline blends and membranes, *Appl. Surf. Sci.* 193 (2002) 36.
- [16] L. Wen, N.M. Kocherginsky, Doping-dependent ion selectivity of polyaniline membranes, *Synth. Met.* 106 (1999) 19.
- [17] G. Illing, K. Hellgardt, R.J. Wakeman, A. Jungbauer, Preparation and characterization of polyaniline based membrane for gas separation, *J. Membr. Sci.* 184 (2001) 69.
- [18] A. Mirmohseni, R. Solhjo, Preparation and characterization of aqueous polyaniline battery using a modified polyaniline electrodes, *Eur. Polym. J.* 39 (2003) 219.
- [19] J.R. Reynolds, H. Ly, J. Kinlen, Burst electrode, U.S. Patent 2002/0022826 A1 (2002).
- [20] R.P. Haak, F. Theeuwes, J.R. Gyory, Electrotransport transdermal system, U.S. Patent 4,927,408 (1990).
- [21] E.J. Parsi, Cell for electrically controlled transdermal drug delivery, U.S. Patent 4,731,049 (1988).
- [22] J.B. Phipps, Iontophoresis electrode, U.S. Patent 5,057,072 (1991).
- [23] J.B. Phipps, Iontophoresis electrode, U.S. Patent 5,084,008 (1992).
- [24] J.E. Sanderson, S.R. Deriel, Method and apparatus for iontophoretic drug delivery, U.S. Patent 4,722,726 (1988).
- [25] E.R. Scott, Electrotransport device electrode assembly having lower initial resistance, U.S. Patent 6,195,582 B1 (2001).
- [26] J. Siman, J. Dove, Medical devices having improved antimicrobial/antithrombogenic properties, U.S. Patent 6,273,875 B1 (2001).
- [27] D.F. Untereker, J.B. Phipps, G.A. Lattin, Iontophoretic drug delivery, U.S. Patent 5,135,477 (1992).
- [28] W. Fischer, R. Haas, C. Zimmermann, Transdermal delivery system (TDS) with electrode network, U.S. Patent 2004/0193089 A1 (2004).
- [29] B. Ghosh, L.H. Reddy, R.V. Kulkarni, J. Khanam, Comparison of skin permeability of drugs in mice and human cadaver skin, *Indian J. Exp. Biol.* 38 (2000) 42.
- [30] S.D. Roy, S.Y. Hou, S.L. Witham, G.L. Flynn, Transdermal delivery of narcotic analgesics: comparative metabolism and permeability of human cadaver skin and hairless mouse skin, *J. Pharm. Sci.* 83 (1994) 1723.
- [31] J.B. Bogardus, R.K. Blackwood Jr., Solubility of doxycycline in aqueous solution, *J. Pharm. Sci.* 68 (1979) 188.
- [32] A.G. MacDiarmid, E. Scherr, X. Tang, High molecular weight polyaniline films, U.S. Patent 5,484,884 (1996).
- [33] M. Cheryan, Ultrafiltration and Microfiltration Handbook, CRC Press, Boca Raton, FL, 1998.
- [34] S.B. Kessler, E. Klein, in: W.S. Winston Ho, K.K. Sirkar (Eds.), *Membrane Handbook*, Kluwer Academic, Boston, 2001 (Chapter 11).
- [35] F. Wöhnsland, B. Fallner, High-throughput permeability pH profile and high-throughput alkane/water log P with artificial membranes, *J. Med. Chem.* 44 (2001) 923.
- [36] M. Kansy, F. Senner, K. Gubernator, Physicochemical high throughput screening: parallel artificial membrane permeation assay in the description of passive absorption processes, *J. Med. Chem.* 41 (1998) 1007.
- [37] R. Ghosh, Novel membranes for simulating biological barrier transport, *J. Membr. Sci.* 192 (2001) 145.
- [38] R. Prasad, K.K. Sirkar, Dispersion-free solvent extraction with microporous hollow-fiber modules, *AIChE J.* 44 (1988) 177.
- [39] C.R. Wilke, P. Chang, Correlation of diffusion coefficients in dilute solutions, *AIChE J.* 1 (1955) 264.
- [40] M.J. Pikal, The role of electroosmotic flow in transdermal iontophoresis, *Adv. Drug Deliv. Rev.* 46 (2001) 281.
- [41] J.E. Riviere, M.C. Heit, Electrically-assisted transdermal drug delivery, *Pharm. Res.* 14 (1997) 687.
- [42] P. Singh, H.I. Maibach, Iontophoresis in drug delivery: basic principles and applications, *Crit. Rev. Ther. Drug Carr. Syst.* 11 (1994) 161.
- [43] J.B. Phipps, R.V. Padmanabhan, G.A. Lattin, Iontophoretic delivery of model inorganic and drug ions, *J. Pharm. Sci.* 78 (1989) 365.
- [44] D. Marro, Y.N. Kalia, M.B. Delgado-Charro, R.H. Guy, Optimizing iontophoretic drug delivery: identification and distribution of the charge-carrying species, *Pharm. Res.* 18 (2001) 1709.
- [45] K. Karami, H. Sjöberg, P. Beronius, Ionization conditions for iontophoretic drug delivery. Electrical conductance and aggregation of lidocaine hydrochloride in 1-octanol at 25 °C, *Int. J. Pharm.* 154 (1997) 79.
- [46] K.A. Walters, in: J. Hadgraft, R.H. Guy (Eds.), *Transdermal Drug Delivery, Developmental Issues and Research Initiatives*, Marcel Dekker, Inc., New York, 1989 (Chapter 10).
- [47] A.C. Williams, B.W. Barry, Penetration enhancers, *Adv. Drug Deliv. Rev.* 56 (2004) 603.
- [48] J. Kratochvil, B. Tezak, The influence of the composition and the properties of the solvent on complex formation between silver and chloride, bromide, iodide, and thiocyanate ions, *Recueil des Travaux Chimiques des Pays-Bas et de la Belgique* 75 (1956) 774.
- [49] K.P. Anderson, E.A. Butler, D.R. Anderson, E.M. Woolley, The solubility of silver chloride and the concentration of silver-containing species in ethanol–water mixtures, *J. Phys. Chem.* 71 (1967) 3566.
- [50] R.G. Bates, *Determination of pH: Theory and Practice*, John Wiley & Sons, New York, 1964.
- [51] P. Beronius, Personal communication, 09/13/2004.
- [52] H. Sjöberg, K. Karami, P. Beronius, L. Sundelöf, Ionization conditions for iontophoretic drug delivery. A revised pKa of lidocaine hydrochloride in aqueous solution at 25 °C established by precision conductometry, *Int. J. Pharm.* 141 (1996) 63.
- [53] J.S. Newman, *Electrochemical Systems*, Prentice-Hall, Englewood Cliffs, NJ, 1973.