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Controlled transdermal iontophoresis by ion-exchange fiber

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Abstract

The objective of this study was to assess the transdermal delivery of drugs using iontophoresis with cation- and anion-exchange fibers as controlled drug delivery vehicles. Complexation of charged model drugs with the ion-exchange fibers was studied as a method to achieve controlled transdermal drug delivery. Drug release from the cation-exchange fiber into a physiological saline was dependent on the lipophilicity of the drug. The release rates of lipophilic tacrine and propranolol were significantly slower than that of hydrophilic nadolol. Permeation of tacrine across the skin was directly related to the iontophoretic current density and drug concentration used. Anion-exchange fiber was tested with anionic sodium salicylate. The iontophoretic flux enhancement of sodium salicylate from the fiber was substantial. As the drug has to be released from the ion-exchange fiber before permeating across the skin, a clear reduction in the drug fluxes from the cationic and anionic fibers were observed compared to the respective fluxes of the drugs in solution. Overall, the ion-exchange fibers act as a drug reservoir, controlling the release and iontophoretic transdermal delivery of the drug.

Keywords: Transdermal; Iontophoresis; Ion-exchange fiber; Tacrine

1. Introduction

During oral administration, some drugs undergo first-pass metabolism in the intestinal tract or in the liver. Subsequently, the drugs may lose their activity [1] or give rise to liver toxic metabolites [2]. Transdermal drug delivery offers many important advantages over oral drug delivery [2]. A common aim in the development of new transdermal devices is controlled delivery of drugs, so that the rate of drug input into the blood stream is predictable and reproducible. The transdermal therapeutic systems act as drug reservoirs and control the penetration rate of the drug into the blood circulation. When the device controls the transdermal drug flux instead of the skin, delivery of the drug is more reproducible leading to smaller inter- and intrasubject variations. Obviously, release of the drug from the device can

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be controlled more exactly than permeability of drugs in the skin [3]. The permeability of the skin changes with age and anatomical site [4], therefore inter- and intrasubject variations in humans are high. Problem of variable in vivo delivery is common in both the passive and iontophoretic drug delivery, and this restricts the use of transdermal therapeutic systems [3,5].

One possibility to form a drug reservoir is binding of the drug with ion-exchange mechanism. Charged drugs are bound into the ion-exchange groups of the fiber until they are released by mobile ions. The complexation of the drugs with ion-exchange resins is a promising means to achieve controlled drug release [6,7], to enhance drug stability [7,8], and drug delivery [9]. Conaghey et al. [6,7] used a hydrogel containing ion-exchange resins to deliver nicotine across the skin, but the binding of nicotine to the ion-exchange resins rendered them unsuitable for use as passive transdermal devices. In contrast, iontophoretic current was observed to enhance the rates of nicotine delivery from ion-exchange resins. In general, the external conditions, pH, ionic strength, and temperature affect the drug release from ion-exchange resins [10–12].

The most commonly used methods to control iontophoretic drug delivery across the skin are current density and donor drug concentration, both of which are directly related to the drug flux [5]. Despite the relative slow down in maximal drug delivery, additional and more precise control of transdermal iontophoresis is expected to be achieved by ion-exchange approach [6,7], with possible reduction of the high biological variability in drug permeation across the skin. Stability of the drug in aqueous anode or cathode compartments of iontophoretic devices during storage is a practical concern. Binding of charged molecules into the ion-exchange material has been presented as a method to stabilize active molecules until they are released by mobile ions (e.g. Na^+ or Cl^-) introduced into the system at the time of application [8–10]. Furthermore, poorly water-soluble compounds may be incorporated into the aqueous formulation by partitioning to the more hydrophobic polyethylene backbone of the fiber.

The specific objective of this work was to study the properties of the ion-exchange fibers in the transdermal drug delivery. In particular, we investigated drug incorporation to the ion-exchange fibers, drug release from the fibers with and without iontophoresis and flux of the drugs through the human stratum corneum in vitro. Iontophoretic drug delivery from solution formulations and from the ion-exchange fiber were compared. Several model cationic (tacrine, propranolol and nadolol) and anionic (sodium salicylate) drugs were used. Reduction of variation in the in vitro permeation experiments was especially attempted by ion-exhange approach. Mathematical modeling and its mechanistical interpretation was used to compare drug release and skin permeation of both solution and ion-exchange fiber formulations.

2. Materials and methods

2.1. Chemicals

Tacrine (–HCl), nadolol, propranolol (–HCl), and HEPES were obtained from Sigma (St. Louis, MO, USA). Salicylic acid (sodium salt) was from Aldrich-Chemie (Steinheim, Germany). Physicochemical properties of the model drugs are presented in Table 1. All other chemicals were at least analytical grade and they were used without further purification. Deionized water with a resistance of $\geq$18 MΩ/cm

Table 1
Physico-chemical properties of the drugs studied [21][a]

Drug	MW (g/mol)	pK_a	log P	
Tacrine	198.0	9.8±0.2[b]	3.3	Anti-cholinergic
Propranolol	259.1	9.23	3.2	β-Blocker
Nadolol	309.4	9.39	0.9	β-Blocker
Sodium salicylate	160.1	3.0	1.5	Keratolytic

[a] MW, molecular weight; pK_a, dissociation constant; P octanol/water partition coefficient.
[b] Our determination.

was used to prepare all solutions. The pH was set to 7.4 through the addition of either HCl or NaOH. The ion-exchange fibers Smopex®-102 (–COOH groups) and Smopex®-108 ($-NH_2$ groups) were obtained from SmopTech Co. (Turku, Finland). Maximal ion-exchange capacity of the 102-fiber was 8.0 mmol/g and of the 108-fiber 3.4 mmol/g.

2.2. Preparation of human skin

The membrane tissue was human cadaver skin from Kuopio University Hospital. Each skin sample was heated for 2 min in 60°C water [13], and the epidermis was separated using surgeon's knife. The samples were dried at room temperature and cut into 3×3 cm pieces, which were kept in a freezer until used.

2.3. Iontophoretic apparatus

Silver–silver chloride electrodes [14] were used in all iontophoretic experiments. Ag/AgCl electrodes were preferred to platinum electrodes to avoid changes in pH due to electrolysis of water. During the experiments the electrodes were separated from the donor and receptor chambers by salt bridges, which consisted of 1 M NaCl gelled with 3% agarose inside plastic tubing (diameter 4 mm, length ≈15 cm). Salt bridges prevented direct contact and possible reactions of the drugs with the Ag/AgCl electrodes. The electrolyte that surrounded the electrodes was HEPES (25 mM) buffered saline (0.15 M) at pH 7.4. A constant current (6181C DC current source, Hewlett-Packard, USA) of 0.1, 0.25, and 0.5 mA/cm^2 was applied for 12 h, and for the next 12 h, the passive flux was monitored. The current/voltage was monitored throughout each experiment (F2378A multimeter, Hewlett-Packard, USA).

2.4. Preparation of the drug containing ion-exchange fiber discs

To study drug binding and release, circular discs (diameter 15 mm) were cut from the cation- (Smopex®-102) and anion- (Smopex®-108) exchange fibers. Polyethylene backbone of the fiber was grafted by radiation with polyacrylic acid (Smopex®-102) or polyamine (Smopex®-108), thus, the cation-exchange groups were carboxylic and the anion-exchange took place by primary amines, respectively. To increase ion-exchange capacity, the cation-exchange fiber discs were treated with 1 M nitric acid solution until all sodium had been exchanged (3 h). Thereafter, to remove the excess acid, the fiber discs were washed with purified water until the pH was about 4.5. The discs were immersed overnight in a 5% (m/v=50 mg/ml) tacrine (–HCl), propranolol (–HCl) or nadolol solution (25 ml). The squeezed discs were then washed repeatedly with a total of 150 ml of purified water and dried at room temperature. The weight of the discs was ≈40 mg and thickness of the discs was 3 mm. The amount of adsorbed drug in the fiber discs was determined by HPLC from the collected washing solutions. Anion-exchange fiber (Smopex®-108) was also cut into circular discs, treated with 1 M NaOH solution and washed with purified water until the pH was 8.5. To load the drug to the discs, a 5% (m/v) sodium salicylate solution was used. As before, the discs were then washed and dried, and the absorbed drug contents were determined by HPLC.

2.5. Drug release from the ion-exchange fiber

Drug release from the cation-exchange fiber discs was tested in Franz diffusion cells (Crown Glass Co., Somerville, NJ) at 25°C. The fiber discs were placed in the diffusion cells so that one side of the ion-exchange fiber was exposed to the dissolution medium (3.0 ml HEPES-buffered saline, pH 7.4). The surface area of the fiber discs exposed to the buffer was 0.64 cm^2. Samples were collected at fixed intervals for 24 h (1, 5, 10, 15, 20, 25, 30 and 45 min, 1, 2, 4, 6, 8, 12 and 24 h) and the drug concentrations in the samples were determined by HPLC.

Drug release with iontophoretic current from the cation-exchange fiber discs was tested in vitro in Side-by-Side®-diffusion cells (Crown Glass Co. Inc., Somerville, NJ). In these experiments the samples (50 μl) were collected also from the donor compartment at 1, 2, 4, 6, 8, 12 (current off), and 24 h.

2.6. Drug permeation across human skin in vitro

Permeation studies were performed in Side-by-

Side®-diffusion cells (Crown Glass Co. Inc., Somerville, NJ) at room temperature. The human stratum corneum was clamped between the two identical halves of the diffusion cell. The area of exposed skin was 0.64 cm^2. HEPES-buffered, physiological NaCl was placed in the receiver compartments of the diffusion cells. Drug-containing ion-exchange fiber discs or the drugs in 5% solution (150 mg/3 ml) were placed in the donor compartment in the same buffer. Positively charged drugs were iontophoresed from the anodic compartment; the negatively charged drug was delivered from the cathode. Samples (250 μl) were collected from the receiver compartment and replaced by fresh buffer at 1, 2, 4, 6, 8, 12 (current off), and 24 h.

2.7. Analysis of the drugs

Drug concentrations were analyzed by high-performance liquid chromatography (HPLC) (Beckman System Gold, Beckman Instruments Inc., San Ramon, CA, USA). The column was Supelcosil LC-18-DB (150×4.6 mm; 5 μm, Supelco USA), and in each case the flow-rate was 1.0 ml/min. For tacrine, the mobile phase included 22% acetonitrile, 1% triethylamine, and 77% deionized water at pH 6.5. The detection wavelength was 240 nm. For propranolol analysis the mobile phase was 35% acetonitrile and 65% acetate buffer at pH 4.0; the detection wavelength was 289 nm. Nadolol was analyzed with 25% acetonitrile, 1% heptane sulphonic acid, and 74% acetate buffer at pH 4.0; the detection wavelength was 223 nm. In the case of anionic sodium salicylate, the mobile phase included 40% methanol and 60% potassium phosphate buffer at pH 7.0; the detection wavelength was 298 nm. Sensitivity of the analyses were 0.05 μg/ml. Relative standard deviations 100% of propranolol, nadolol and tacrine were 1.16, 2.55, and 2.80, respectively.

2.8. Data analysis

The amount of drug that penetrated through the human stratum corneum during a given time interval was calculated from the concentrations measured in the receptor compartment, which were corrected for sampling dilution and volume. Drug fluxes (μg/cm^2/h) were calculated by linear regression of the permeation curves. All experiments were performed at least five times.

3. Results and discussion

3.1. Drug release from the cation-exchange fibers

The fiber discs containing cationic drugs were placed in the Franz cell and the passive drug release into HEPES-buffered physiological saline was followed (Fig. 1 and Table 2). The release rate observed was larger for nadolol (hydrophilic) than for tacrine and propranolol (both lipophilic), which shows the dependence of the release rate on the lipophilicity of the drug.

The release process can be understood as follows. During their preparation, the fiber discs in hydrogen form are immersed in a solution of the cationic drug and chloride ion. The fiber tends to equilibrate with this bathing solution and then exchanges hydrogen ions, that compensate the negative fixed charge groups within the fiber, and cationic drug. If the concentration of the cationic drug in the solution is sufficient and if enough time is allowed for this ion-exchange process, the fiber turns completely to drug form. If not, which is usually the case, the fiber contains both cationic drug and hydrogen ions.

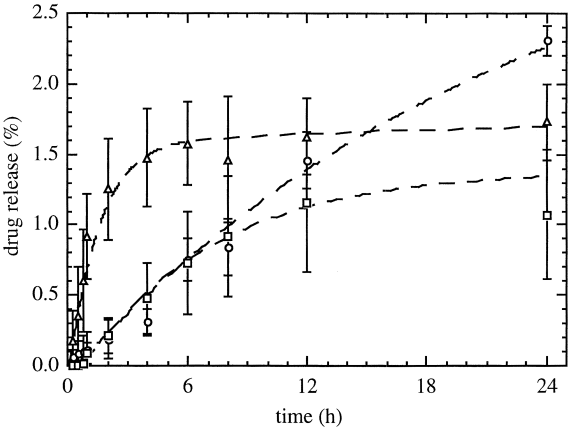

Fig. 1. Passive release of the positively charged drugs from the cation-exchange fiber Smopex®-102 into HEPES-buffered physiological saline: tacrine (○), propranolol (□) and nadolol (△). Average±standard deviation ($n=4$).

Table 2
Drug content and release rate of the cationic drugs from the ion-exchange fiber discs Smopex®-102[a]

Drug	Content (mmol/g)	Content (mg)	Release rate (μmol/cm²/h)
Tacrine	0.84	7.6	0.060
Propranolol	2.1	24.0	0.138
Nadolol	1.5	17.9	0.84

[a] The release rate was determined from the initial slope of the curves shown in Fig. 1.

Moreover, chloride ions, although electrostatically prevented by Donnan exclusion, are always present in the fiber phase in a concentration such that the local electroneutrality condition is satisfied. When these discs are placed in the Franz cell, they tend to equilibrate with the new bathing solution (HEPES buffered saline). The ion-exchange process must take place under open circuit condition, and this implies that the fluxes of the different species involved must be coupled through diffusion potential gradients in such a way that the net faradaic current is zero. However, when the diffusion coefficient of one ionic species (the cationic drug in the present case) is much smaller than the others, the transport of this species is mostly diffusional and the migrational contribution to its flux is negligible.

The release of the cationic drug from the fiber can then be modeled as one-dimensional diffusion process, with the fiber located in region $-\delta_D < x < 0$ and the receiving compartment as region $0 < x < \delta_R$. Due to the stirring of the receiving compartment, a diffusion boundary layer of thickness δ_{BL} can be assumed adjacent to the fiber, while the bulk of the compartment $\delta_{BL} < x < \delta_R$ has a uniform concentration $c_R(t)$ of drug. The local concentration of drug in the donor compartment (fiber) is denoted by $c_D(x, t)$ and that in the receiving diffusion boundary layer is denoted by $c_{BL}(x, t)$. The uniform drug concentration $c_R(t)$ in the bulk of the receiving compartment $\delta_{BL} < x < \delta_R$ is $c_R(t) = c_{BL}(\delta_{BL}, t)$. The diffusion coefficient of the drug in the donor and receiving compartments is denoted by D_D and D_{BL}, respectively. These coefficients are effective values that take into account the interaction between the drug and the ion-exchange fiber. The second Fick's law takes then the form:

$$\frac{\partial c_D}{\partial t} = D_D \frac{\partial^2 c_D}{\partial x^2}, \quad -\delta_D < x < 0 \tag{1}$$

$$\frac{\partial c_{BL}}{\partial t} = D_{BL} \frac{\partial^2 c_{BL}}{\partial x^2}, \quad 0_D < x < \delta_{BL} \tag{2}$$

and the initial and boundary conditions are

$$c_D(x, 0) = c_0 \tag{3}$$

$$c_{BL}(x, 0) = 0 \tag{4}$$

$$\left(\frac{\partial c_D}{\partial x}\right)_{x=-\delta_D} = 0 \tag{5}$$

$$\left(\frac{\partial c_{BL}}{\partial x}\right)_{x=\delta_{BL}} = -\frac{V_R}{AD_{BL}} \frac{dc_R}{dt} \tag{6}$$

$$D_D\left(\frac{\partial c_D}{\partial x}\right)_{x=0} = D_{BL}\left(\frac{\partial c_{BL}}{\partial x}\right)_{x=0} \tag{7}$$

$$c_D(0, t) = Kc_{BL}(0, t) \tag{8}$$

where A is the exposed area of the fiber, V_R the volume of the receiving compartment and K is the partition coefficient of the drug which is defined as the drug concentration in the fiber divided by that in the bathing solution. This coefficient have both chemical and electrical contributions. The electrical contribution is such that K tends to be greater than one, because the cationic drug is electrostatically attracted by the negative fixed charges in the fiber. Moreover, since there are no significant differences in concentration (fixed charge concentration and ionic concentration within and outside the fiber), the electrostatic contribution to K is similar for all the drugs considered. The chemical contribution, however, depends on the nature of the drug and can be very different from one drug to another, being greater than one for the lipophilic drugs and lower than one for the hydrophilic ones.

Fig. 2 shows the results of the numerical solution of the above equations for the values $\delta_D = 3.0$ mm, $\delta_{BL} = 0.01$ mm, $V_R/A = 50.0$ mm, and different values

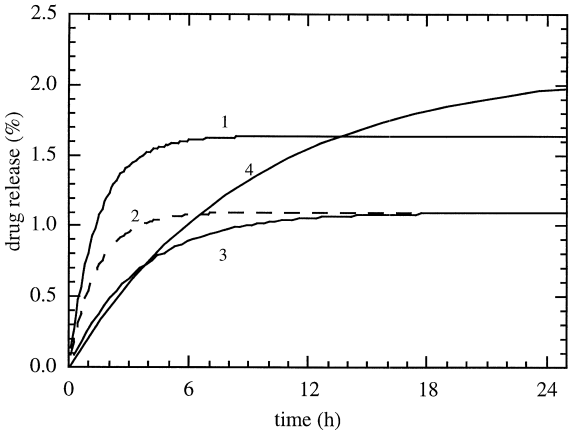

Fig. 2. Simulation of the passive release experiment from the cation-exchange fiber. The values of the partition coefficient K and the diffusion coefficients $D_D = D_{BL}$ used are: $K = 1000$, $D_D = D_{BL} = 10^{-6}$ cm^2/s (curve 1); $K = 1500$, $D_D = D_{BL} = 10^{-6}$ cm^2/s (curve 2); $K = 1500$, $D_D = D_{BL} = 4 \times 10^{-7}$ cm^2/s (curve 3); $K = 750$, $D_D = D_{BL} = 1.5 \times 10^{-7}$ cm^2/s (curve 4).

of K and $D_D = D_{BL}$. Curves 1 and 2 show that an decrease in the partition coefficient yields larger values of the initial release rate as well as of the drug release at long times. Curves 2 and 3 show that an increase in the diffusion coefficient yields larger values of the initial release rate but, obviously, it does not affect the equilibrium state (drug release at long times). Since very large values of the partition coefficient are required to make the release rates in Fig. 2 of the same order as those in Fig. 1, it is concluded that the drugs interact strongly with the hydrophobic fibers. Furthermore, since the drug release under equilibrium conditions (attained at very long times) is dictated only by the partition coefficient K, it is concluded from Fig. 1 that the K values of the drugs are in the order $K_{tacrine} < K_{nadolol} < K_{propranolol}$. This is a somewhat surprising observation because the octanol/water partition coefficient P of tacrine and propranolol are very similar and significantly larger than that of nadolol, $P_{nadolol} < P_{propranolol} \approx P_{tacrine}$ (see Table 1). However, the interaction of the cationic drugs with octanol is likely to be different to that with the grafted polyethylene fibers and therefore only a moderate correlation between P and K should be expected.

In relation to the diffusion coefficients used in Fig. 2, it is noticeable that curve 4, which could be compared to that of tacrine in Fig. 1, corresponds to the lowest value of the diffusion coefficient, while tacrine has the smallest molecular weight. It must be stressed, however, that these are effective values that take into account molecular interactions and not only the molecular size.

3.2. Drug permeation from 5% (m/v) solution across human skin in vitro

Transdermal permeation data of the model drugs across the human skin at pH 7.4 is presented in Table 3 both under passive and iontophoretic conditions ($I = 0.5$ mA/cm^2). The lag-time for permeation was about 24 h in the case of passive flux and 0.5 h in the case of iontophoretic flux (data not shown). Since all drugs were delivered from a 5% solution, the differences observed in the passive flux values are obviously related to the nature of the drug. The hydrophilic drug nadolol exhibits the lowest flux, thus showing that it hardly enters the skin. The hydrophobic drugs (tacrine, propranolol and salicylate) permeate at a much faster rate than nadolol, but the differences observed do not correlate well with the octanol/water partition coefficient (see Table 1).

Increase of transdermal permeation during iontophoresis was observed for all drugs. The enhancement factor varied from 70 to 1200, corresponding the larger enhancement to the more hydrophilic nadolol, which has been reported earlier [15]. The

Table 3
Passive and iontophoretic fluxes (μg/cm^2/h) across human skin in vitro from a 5% (m/v) solution[a]

Drug	Passive flux	Iontophoretic flux	Enhancement factor
Tacrine	3.00±0.7	220±50	70
Propranolol	0.26±0.07	43±7	170
Nadolol	0.04±0.05	49±7	1200
Sodium salicylate	0.34±0.07	45±6	130

[a] Direct current iontophoresis (0.5 mA/cm^2) was on for 12 h. Average±standard deviation ($n = 4$–7).

lowest enhancement factor corresponded to tacrine, which exhibited the largest passive flux. This fact might indicate some kind of limitation of the permeation rate as discussed also in next section.

Fig. 3 shows the variation of the permeation rate of tacrine with the iontophoretic current density, from 0 (passive) to 0.5 mA/cm^2, which is considered the upper limit for safe iontophoresis [16]. The iontophoretic permeation rate remained constant until the current was switched off, and its value was directly related to the iontophoretic current density I used which is in accordance with several literature reports [7,17–19]. After current termination the transdermal permeation rate of tacrine returned rapidly to the passive level, which indicates that iontophoretic flux enhancement does not lead to permanent changes in the skin permeability.

The permeation experiments, either passive or iontophoretic, involve ternary electrodiffusion processes which can be described approximately by the Nernst–Planck equations under quasi-steady state conditions. Considering a single transport region $0<x<\delta$ (composed of skin and diffusion boundary layers) where the concentration and electric potential changes take place, the effective permeability of species i is given by $P_i = D_i/\delta$, where the effective diffusion coefficient D_i incorporate the effects of skin porosity and partitioning between the skin and the bathing solution. Without loss of generality, the following expressions are presented for the case of a cationic drug. The species are denoted by subscripts $i=+$ (sodium ion), $i=-$ (chloride ion), and $i=d$ (cationic drug). The transport equations are then:

$$-\frac{J_i}{D_i} = \frac{\mathrm{d}c_i}{\mathrm{d}x} + z_i c_i \frac{F}{RT}\frac{\mathrm{d}\phi}{\mathrm{d}x}, \quad i = +, -, d \tag{9}$$

where J_i, c_i and z_i are the molar flux density, molar concentration and charge number of species i, ϕ is the electric potential, F is the Faraday constant, R the gas constant, and T the absolute temperature. The flux density J_i is assumed to be independent of position because of the quasi-steady state approximation. The local electroneutrality assumption relates the local concentration values:

$$c_- = c_+ + c_d \tag{10}$$

and the boundary conditions for concentration are

$$c_d(0) = c_{d,0}, \quad c_d(\delta) = 0 \tag{11}$$

$$c_+(0) = c_{+,0}, \quad c_+(\delta) = c_{+,0} \tag{12}$$

$$c_-(0) = c_{d,0} + c_{+,0}, \quad c_-(\delta) = c_{+,0} \tag{13}$$

The electric potential drop within the diffusion region, $\Delta\phi = \phi(\delta) - \phi(0)$, can be obtained as:

$$\Delta\phi = \frac{RT}{F}\Gamma \ln\frac{c_-(\delta)}{c_-(0)} \tag{14}$$

where

$$\Gamma = \frac{J_+/D_+ - J_-/D_- + J_d D_d}{J_+/D_+ + J_-/D_- - J_d D_d} \tag{15}$$

Note that D_i can be replaced by P_i in Eq. (15). The chloride flux density is obtained by introducing the expression for the electric potential gradient, $\mathrm{d}\phi/\mathrm{d}x = (RT/F)\,\Gamma(\mathrm{d}\ln c_-/\mathrm{d}x)$, into its flux equation and further integration, thus yielding:

$$J_- = P_-(\Gamma - 1)[c_-(\delta) - c_-(0)] \tag{16}$$

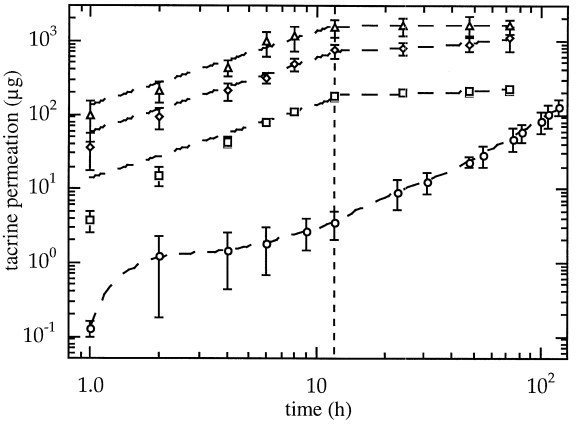

Fig. 3. Effect of iontophoretic current density on the permeation of tacrine from a 5% solution across the human skin in vitro. Current density was 0 (○), 0.10 (□), 0.25 (◇), and 0.50 mA/cm^2 (△). The current was on for 12 h, whereafter passive drug permeation was followed up to 72 h. The dashed lines have unit slope in this log-log plot when the iontophoretic current is different from zero, while in the passive permeation studies the dashed lines are only indicative of the experimental trends. Average±standard deviation (n=4–6).

The ratio of sodium to drug flux density:

$$\frac{J_+}{J_d} = \frac{P_+}{P_d} \frac{c_+(\delta)\, e^{F\Delta\phi/RT} - c_+(0)}{c_d(\delta)\, e^{F\Delta\phi/RT} - c_d(0)} \quad (17)$$

is determined by multiplying their flux equations by $e^{F\phi/RT}$ and further integration. Finally, the current density equation:

$$I = F(J_+ + J_d - J_-) \quad (18)$$

closes this equation system and allows for its iterative solution.

The theoretical results obtained from the above equations are compared to the experimental results in Table 4. In the theoretical simulations, the ratio of permeabilities between sodium and chloride has been set equal to 2/3, thus being equal to the ratio of their infinite dilution diffusion coefficients in aqueous solution. The permeabilities of the chloride ion and the cationic drug have been used as fitting parameters (though no rigorous fitting procedure has been applied), resulting in the values $P_- = 1.5\times10^{-7}$ cm/s and $P_d = 1.8\times10^{-8}$ cm/s. This last value could have been roughly estimated from the experimental passive flux as the ratio between flux density and concentration, which yields the value 1.7×10^{-8} cm/s (the difference in the factor is due to the small diffusion potential that exists under passive conditions). Table 4 shows that a good agreement between the experimental and theoretical flux densities is obtained with reasonable values of the permeability coefficients, which implies that the above theoretical modeling can be used for the description of the permeation process across the human skin in vitro.

3.3. Drug permeation from ion-exchange fibers across human skin in vitro

If one wants to achieve steady-state flux of drug(s) across the skin, concentrations of the drug and mobile ions in the bathing solution of the donor compartment need to be constant. In that case direct current results in constant drug flux across the skin. The validity of this assumption was confirmed, e.g. by taking samples in both the donor and receiver compartments of the diffusion cell. Tacrine concentration in the donor chamber and the flux across the skin during iontophoretic delivery increased for 3–4 h (see Fig. 4). After that, tacrine concentration in the donor chamber and the flux across the skin remained constant. This indicates that at steady-state the amount of tacrine released from the fiber equals the permeation of the drug across the skin as long as the current is turned on.

Table 5 shows the iontophoretic fluxes ($I = 0.5$ mA/cm^2) across human skin in vitro when the drugs were delivered from ion-exchange fibers. The fluxes are smaller than those presented in Table 3 due to the lower concentration of drug in the donor solution. Note that not only the drug content in the fiber is much smaller (see Table 5) than the drug content in the 5% solution (150 mg), but also the drug has to be released from the fiber before permeation and time required for the fiber to equilibrate with the solution in the donor compartment is larger than the duration of the iontophoretic experiments, except for nadolol (see Fig. 1). Thus, the actual drug concentration in the donor solution is smaller than what could be deduced from the drug content values in fiber. Nevertheless, the values of drug content in fiber can

Table 4
Passive and iontophoretic flux density of tacrine from a 5% solution across the human skin in vitro as determined from the experimental data in Fig. 3 (by using the data corresponding to longer times in the case of passive flux and the 12-h period in the case of iontophoretic flux) and from the theoretical approach [Eqs. (14)–(18)] with $P_- = 1.5\times10^{-7}$ cm/s, $P_+/P_- = 2/3$, and $P_d = 1.8\times10^{-8}$ cm/s

Current density (mA/cm^2)	Experimental flux (μg/cm^2/h)	Theoretical flux (μg/cm^2/h)	Experimental enhancement factor
0	3.0±0.7	4.1	1
0.10	25±4	45	8
0.25	100±40	107	30
0.50	220±50	211	70

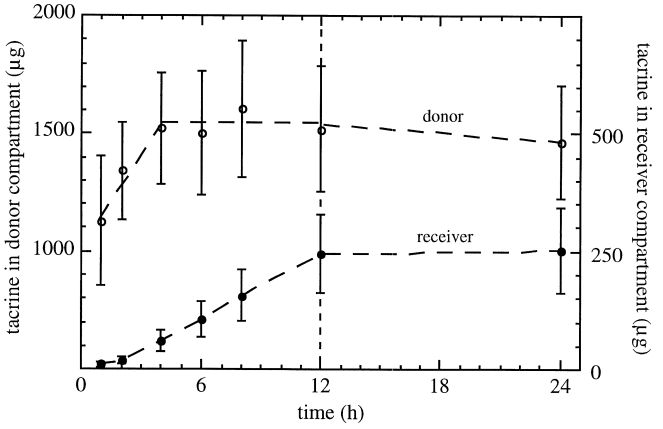

Fig. 4. Amount of tacrine in the donor (s) and the receiver compartment (d) during iontophoretic delivery across the human skin from Smopex®-102 ion-exchange fiber in vitro. Current density was 0.50 mA/cm^2. The current was on for 12 h, whereafter passive drug permeation was followed up to 24 h. Average standard deviations ($n=6$).

be used to make an interesting observation. The ratio of drug flux to drug concentration (in mg/cm^3) in the donor compartment represents a measurement of the skin permeability to the drug under iontophoretic conditions. The permeability values estimated from Table 3 (solution formulations) are 1.2×10^{-6} cm/s (tacrine), 2.4×10^{-7} cm/s (propranolol), 2.7×10^{-7} cm/s (nadolol), and 2.5×10^{-7} cm/s (sodium salicylate). Correspondingly, the values of ion-exchange formulations from Table 5 are 4.5×10^{-7} cm/s (tacrine), 9.4×10^{-7} cm/s (propranolol), 4.9×10^{-7} cm/s (nadolol), and 9.1×10^{-7} cm/s (sodium salicylate). These latter values are probably lower estimates due to the difference between released drug and total drug (released plus bound to fiber) in the donor compartment. The above values show that the effective skin permeability to the different drugs does not remain constant with the drug concentration, but contrarily decreases with increasing drug concentration in donor compartment.

The comparison between the passive permeation rates of tacrine across skin from the 5% solution and from the cation-exchange fiber is also interesting. The passive permeation rate from the solution is (3.0 ± 0.7) μg/cm^2/h (Table 3), while that from the cation-exchange fiber (7.6 mg in fiber) is 0.003 μg/cm^2/h. The factor 1000 between these two fluxes is explained by the different tacrine concentration in the two solutions. While the 5% solution contains 150 mg of tacrine, the fiber only releases ≈2% (see Fig. 1) of the 7.6 mg it contains, which amounts only to 0.15 mg.

Table 5
Drug content in Smopex®-102 (tacrine, propranolol and nadolol) or Smopex®-108 (sodium salicylate) and iontophoretic flux density (μg/cm^2/h) across human skin in vitro from the fiber discs[a]

Drug	Content (mmol/g)	Content (mg)	Iontophoretic flux
Tacrine	0.84	7.6	4.1±0.7
Propranolol	2.1	24.0	27±6
Nadolol	1.5	17.9	10.5±1.3
Sodium salicylate	1.4	25.7	28±5

[a] Direct current iontophoresis (0.5 mA/cm^2) was on for 12 h. Average±standard deviation ($n=4$–7).

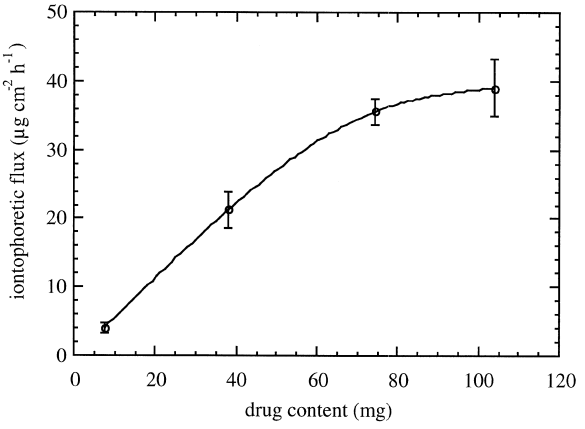

Fig. 5. Iontophoretic tacrine delivery rate across human skin in vitro as a function of the drug content in the Smopex-102® cation-exchange fiber. Average±standard deviation (n=4–6).

In order to check the apparent limitation in the permeation rate, the iontophoretic permeation rate of tacrine across the skin was measured from fiber discs containing different amounts of drug, from 7.6 to 104 mg. The tacrine flux across skin was observed to increase with increasing concentration, and the variation was not linear in the whole range considered (Fig. 5). Since Eqs. (1)–(8) allow to state that the concentration in solution is proportional to the concentration within the fiber, this non-linearity cannot be due to the difference between the drug concentration in solution and the concentration in the fiber. It is then concluded that the permeation across skin shows a kind of limiting mechanism at higher concentrations. This supports the observations reported of a similar drop off in the delivery rates of nicotine at high concentrations from a hydrogel containing ion-exchange resins across the skin [7].

This observed non-linear dependence of the iontophoretic drug delivery with the drug concentration can also be explained on the basis of the theoretical modeling presented in Section 3.2. Although both migration due to an applied electric field and diffusion give a linear dependence of flux with concentration, the electrodiffusion process under consideration involves an electric field which is determined not only by the current density but also by the differences in permeabilities of the three transferring species. Fig. 6 shows theoretical simulations of passive and iontophoretic fluxes obtained from Eqs. (14)–(18). It is observed that, while the passive flux is nearly linear with concentration, the iontophoretic flux shows a non-linear behavior similar to that presented by the experimental data in Fig. 5. Note that these simulations can equally be used to interpret results of drug delivery from donor compartments with the drug contained in fiber discs.

Tacrine flux across the skin in vitro was very reproducible as indicated by the small experimental standard deviation values (6–17%, Fig. 5). In contrast, the standard deviation values for the iontophoretic tacrine fluxes from the solution in Fig. 3

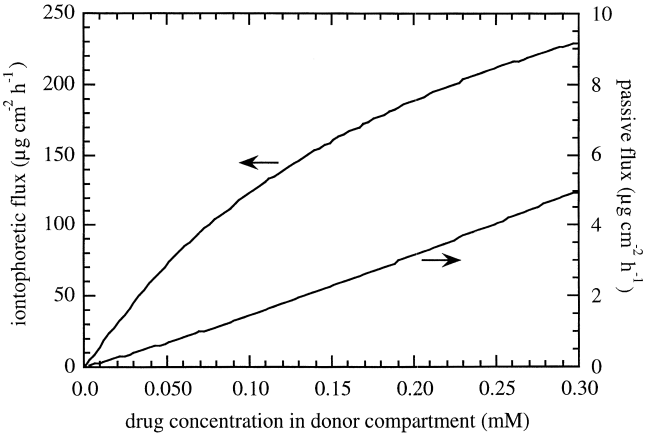

Fig. 6. Simulated passive and iontophoretic tacrine delivery rate across human skin in vitro as a function of the drug concentration in the donor compartment. The parameters used in the simulation are the same as in Fig. 3.

are rather big (14–37%, note the logarithmic scale). This may indicate a more precise control of tacrine delivery and reduced biological variation in the skin permeation by the use of ion-exchange fiber and, therefore, the blood concentrations might be predicted better.

During oral administration tacrine undergoes extensive first-pass metabolism and its dose-dependent hepatotoxicity and peripheral cholinergic side-effects have been observed. It has been postulated that maintenance of constant levels of tacrine in the brain may be required to maximize its effects on memory enhancement [2]. Transdermal delivery of tacrine may minimize above-mentioned problems. Steady-state plasma concentrations after transdermal drug permeation can be calculated using equation $c_{ss} = A \times J/CL$ [3], where A is the surface area for drug absorption (typically 25 cm^2), J is the steady-state flux density ($\mu g/cm^2/h$), and CL is the clearance from the body. For tacrine $CL = 150$ l/h and the target plasma levels after oral tacrine ingestion are 5–30 ng/ml [20]. Using these parameters, the passive tacrine permeation from 5% solution would result in plasma level of 0.50 ng/ml and the ion-exchange reservoir will attenuate that approximately three orders of magnitude. Thus, a need for permeation enhancement is obvious. Iontophoretic tacrine delivery from 5% solution should result in plasma levels of 4.3 ng/ml at 0.1 mA/cm^2 and 36 ng/ml at 0.5 mA/cm^2. Iontophoretic delivery from ion-exchange fiber (0.5 mA/cm^2) is expected to yield 7.3 ng/ml of tacrine in plasma at steady state. Overall, it seems that clinically relevant amounts of tacrine may be delivered transdermally by the ion-exchange fiber and iontophoresis.

4. Conclusion

Cation- and anion-exchange fibers have been shown to be promising drug reservoir materials for iontophoretic transdermal drug delivery. The ion-exchange fibers may be used to retard and control drug release from the system. The charged drugs can be bound into the ion-exchange groups of the fiber until their release by mobile ions, e.g. Na^+ or Cl^-. The release rate is related to the drug lipophilicity, although the octanol/water partition coefficient only provides a rough estimate for the behaviour of the drugs in this kind of grafted hydrophobic fibers.

The combination of iontophoresis and ion-exchange fibers may be used to control drug release and to increase drug permeation across the skin. Large biological variation of the skin may be reduced using ion-exchange fibers as compared to solution formulations of drugs. However, more work is needed to optimize and evaluate the suitability of these materials in controlled release drug delivery.

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