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Journal of Controlled Release 97 (2004) 485–492

journal of controlled release

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Ion-exchange fibers and drugs: a novel device for the screening of iontophoretic systems

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Received 17 February 2004; accepted 1 April 2004

Abstract

The objective of this study was to theoretically model and experimentally measure the extent of drug release from ion-exchange fibers. The release was measured as a function of current density and NaCl concentration using a novel iontophoretic cell. The fibers tested contained weak carboxylate (–COOH) ion-exchange groups. The cationic model drugs tacrine and metoprolol were chosen on the basis of previous research, where tacrine had the lowest release rate and metoprolol the highest release rate. An in-house designed three compartment test cell was developed to test the suitability of drugs for iontophoretic drug delivery. In this cell, the anode and the drug containing ion-exchange fiber compartments were separated with a Nafion® ion-selective membrane, while the fiber and the return electrode compartments were separated with a porous membrane. Tacrine proved to be a good drug candidate for this system as the release of the tacrine from the device was controllable with salt concentration and current density. Metoprolol release from the device was, however, not controllable.

Keywords: Iontophoresis; Controlled release; Drug delivery; Ion-exchange fiber; Modelling

1. Introduction

Several types of permeation cells have been used to screen the feasibility of drug molecules during iontophoretic transport. A typical experimental arrangement is the horizontal side-by-side diffusion cell, where a sample of skin is sandwiched between two half cells. The drug solution under examination and an electrode are placed facing the *stratum corneum* side of the skin forming one half of the cell, which acts as the drug reservoir. The other half of the cell contains an electrode in a conducting solution, known as the return chamber [1,2]. A buffer solution can be added to the return chamber to simulate physiological conditions. A four-electrode system has been used in order to measure the potential drop across the skin [3] and to maintain the potential drop across the skin [4].

Bellantone et al. [5] produced a cell design, where the two electrodes are placed above the skin simulat-

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doi:10.1016/j.jconrel.2004.04.004

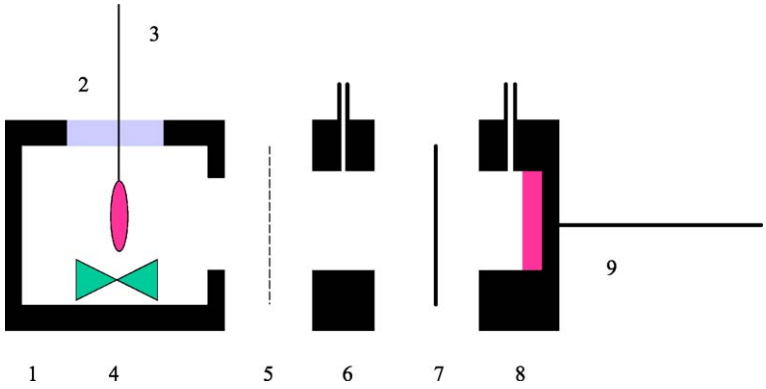

Fig. 1. In vitro iontophoretic cell. (1) The return compartment, (2) lid, (3) Ag/AgCl electrode, (4) magnetic stirrer, (5) porous membrane, (6) donor compartment including the ion-exchange material, (7) Nafion® membrane, (8) electrode compartment, (9) Ag/AgCl electrode.

ing in vivo conditions. A large skin membrane was used to overlap the edges of the diffusion cell and the electrode was attached to the *stratum corneum* side of the skin, the second electrode was placed in the drug reservoir. Glikfeld et al. [6] modified the vertical Franz diffusion cell, where the half cells are on top of each other and the skin sample is placed horizontally between them. On the upper half of the cell, a glass wall separates the two electrode compartments; the current thus flows from the drug reservoir across the skin into the receptor chamber and then back to the return chamber on the skin surface. Although both cell designs have yielded reliable data, the advantage of the cell with electrodes on the same side of the skin is, in addition to the close resemblance to the in vivo situation, that it offers the possibility to study lateral transport and examine iontophoresis for subcutaneous and non-invasive sampling [7].

Junginger's group used a three-chamber continuous flow-through transport cell in the in vitro modelling of apomorphine. This construction had two continuously stirred outer chambers which contained electrodes. Between these two chambers was an acceptor chamber separated from the outer chambers by *stratum corneum* and a supporting dialysis membrane, this chamber had a continuous flow of buffer solution. The advantage of a flow-through cell is the possibility to automate the set-up, which allows rapid collection of data. The disadvantage is that experimental variables (volume, sampling interval and flow rate) can have an effect on the value of the apparent flux, which may deviate from the intrinsic flux through the skin [8].

To model and test iontophoretic drug release and transdermal drug permeability, we constructed and patented a novel test cell system, a schematic representation of which is shown in Fig. 1 [9,10]. In this test system, both *stratum corneum* and porous membranes can be used, depending upon whether transdermal iontophoresis or just drug release from the patch formulation is under study. The patch type structure of the test cell makes it practical for testing different matrix-types as well as salt solution/gel type transdermal formulations. In this study, the new cell was used for testing ion-exchange fiber material as a matrix to control the release parameters of the cationic model drugs tacrine and metoprolol.

2. Experimental methods

2.1. Materials

The ion-exchange fiber material employed was the staple form of Smopex®-102 a poly(ethylene-*g*-acrylic acid) fiber (Smoptech, Turku, Finland) [11–14]. The fiber contained carboxylate ion-exchange groups. The cationic model drugs were tacrine (-HCl) and metoprolol (-tartrate) (both from Sigma, St. Louis, USA). The salt solution was prepared from NaCl (P.A. grade, Merck, Germany). Deionized Milli-Q® water (Millipore, Molsheim, France) with a resistivity ≥ 18 MΩ cm^{-1} was used to prepare all the solutions.

2.2. Iontophoretic apparatus and the test cell

A potentiostat type DT 2101 (HI-TEK, England) and 549 potentiostat–galvanostat (Amel, Italy) were used as constant current sources. The current was monitored using an MX-545 multimeter (Metrix Electronics, UK) and the voltage recorded using a chart recorder SE 120 (BBC Goertz Metrawatt, Austria). Ag/AgCl electrodes were used in all the experiments.

A schematic representation of the cell used is presented in Fig 1. The return compartment (4) was separated from the fiber compartment (6) by the membrane under investigation (5), here it was an hydrophilic Ultracel Amicon PLAC regenerated cellulose ultrafiltration membrane with a nominal molecular weight limit (NMWL) of 1000 (Millipore, USA). Any other membrane (including human or animal *stratum corneum*), could also be used in this cell system. The membranes were pre-treated in the test cells prior to use in a 0.15 M NaCl electrolyte, by applying a current density of 10 mA/cm^2 for 15 min. The fiber sample, onto which the model drug was loaded, was placed in the fiber compartment of the test system (Fig. 1). The salt concentration in the anode compartment (8) needed to be high enough to allow an 8-h experiment with a desired current density. Therefore, the anode compartment had to be separated from the fiber compartment by a reinforced Nafion® 90209 ion-selective membrane (7), (ElectroCell, Sweden). This membrane was soaked for at least 24 h in a 1.5 M NaCl solution before use. NaCl solution was injected into the drug containing fiber compartment (V=4 cm^3, c=0.15, 0.30 or 0.50 M) and into the delivering electrode (anode) compartment (V=3 cm^3, c=1.5 M NaCl); 30 cm^3 of the same salt solution as in the fiber compartment (c=0.15, 0.30 or 0.50 M) was added to the cathode (receiver) compartment.

2.3. Drug release from the ion-exchange fiber

Loading of the model drugs, tacrine and metoprolol, into the ion-exchange materials was performed by the method described previously [11–14], i.e. by immersing the fiber samples in a 1 w-% drug solution for 24 h. The ion-exchange capacity of the fiber reported by the manufacturer was 9.7 mmol/g. The tacrine concentration in the fiber was 2.8 mmol/g and metoprolol concentration was 1.7 mmol/g. The amount of the drug containing ion-exchange material to be used in the experiments was calculated and weighed so that each sample contained 60 mg of the drug. This was equivalent to 0.30 mmol of tacrine and 0.22 mmol of metoprolol.

A constant direct current of 0.05, 0.10, 0.25 and 0.50 mA/cm^2 was applied for each salt concentration (0.15, 0.30, 0.50 M) for 8 h and for the remaining 16 h the passive flux was monitored. Samples (500 μl) were collected from the cathode chamber after 45 min, 1 h 30 min, 2 h 15 min, 3, 4, 5, 6, 7, 8 and 24 h) and replaced each time by fresh salt solution. Passive diffusion experiments were performed the same way as the iontophoretic experiment, but no current was applied, samples were taken after 2, 4, 8 and 24 h.

Drug concentrations were analyzed by HPLC (Waters, USA) using a chromatographic method similar to that reported earlier. The metoprolol mobile phase included 25% acetonitrile (Rathburn Chemicals, Scotland), 1% triethylamine (Fluka, Germany) and deionized water buffered to pH 3.5 using phosphoric acid (Riedel-de Haen, Germany) [14]. The mobile phase used for tacrine analysis was the same as earlier [11]. The column was a Waters Nova-Pak C18 (150 × 3.9 mm, 4 μm, Waters). The analytical wavelength used for tacrine and metoprolol was 254 nm. The flow rate was 1.0 ml/min for both drugs.

2.4. Additional tests

The drug permeability of the Nafion® 90209 membrane was tested in a diffusion cell. A 1% mass to volume drug solution was placed on the cathode side of the membrane and a 1.5 M NaCl solution on the other side, as used in the anode chamber of the test cell. The temperature was 37 °C and solution samples were drawn after 2, 4, 8 and 24 h. It was established that tacrine did not diffuse through the membrane, but metoprolol did.

The stability of the Ag/AgCl electrodes was tested in the cell, where 30 ml of 0.1% drug solution in 0.15 M NaCl was added in the receiver compartment, a current of 0.5 mA/cm^2 was applied for 8 h, during which 500 μl samples were taken hourly and 500 μl of

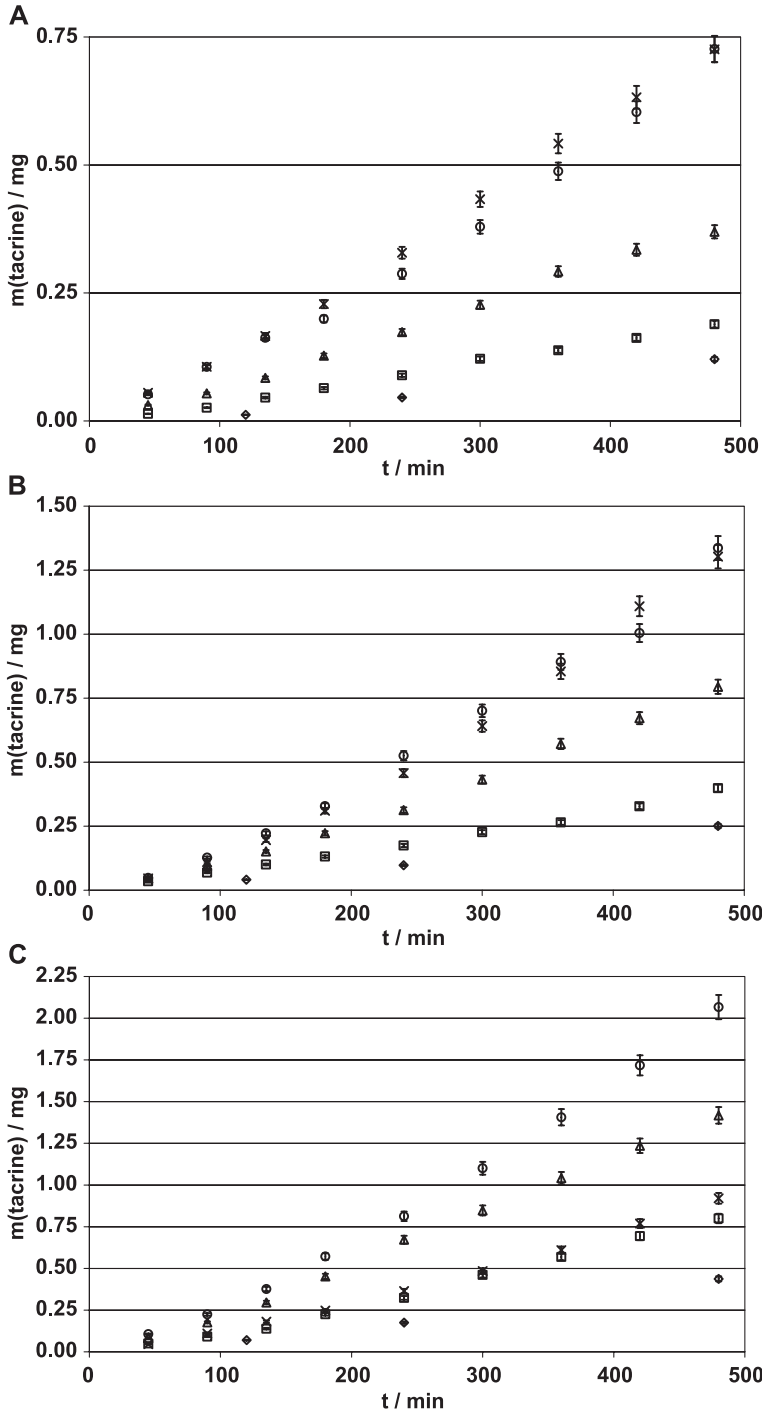

Fig. 2. (a–c) The experimental curves for tacrine release with constant salt concentration, but at different current densities, (a) [NaCl] = 0.15 M, (b) [NaCl] = 0.3 M and (c) [NaCl] = 0.5 M. ◇, □, Δ, × and ○ denote passive diffusion, 0.05, 0.10, 0.25 and 0.50 mA/cm^2 respectively.

fresh solution was added to replace the volume removed during sampling. This was followed by a passive diffusion test period for a further 16 h and at the end ($t = 24$ h) a final sample was taken. It was established that the metoprolol concentration in the chamber did not vary during the measurements by more than the analytical error ($\pm 2.5\%$), indicating that neither drug adsorption on the electrode nor drug decomposition occurred in the cell system. Tacrine concentration, however, decreased by up to 20%, indicating either drug decomposition or drug adsorption on the electrode.

3. Results and discussion

3.1. Tacrine

Fig. 2a–c shows the experimental curves for tacrine release with constant salt concentration at different current densities and Table 1 shows the corresponding release rates. It is clear that the release rate of tacrine was enhanced with an increasing NaCl concentration and with an increasing current density until a limiting current value was reached. Table 2 shows the effect of the amount of drug loaded into the fiber on the extent of drug release. When using a fiber sample with 60 mg of tacrine, the drug release reached a maximum after which the rate of tacrine release remained constant. The tacrine concentration in the fiber was 2.8 mmol/g, in tests where the tacrine amount was increased, it was done simply by adding more fiber.

The first observation that can be made from the release profiles of tacrine is that they followed first order kinetics, which can be achieved from a source of constant concentration to a sink. Hence, the flux is given simply by

$$J = K_p c; K_p \approx \frac{D_{eff}}{h} \quad (1)$$

where K_p is the permeability coefficient and D_{eff} is the effective diffusion coefficient of the drug, including porosity and tortuosity factors in the membrane and h is the membrane thickness. Since the membrane is rather porous, D_{eff} is of the same order of magnitude as the diffusion coefficient of tacrine in water, ca. 7×10^{-6} cm^2/s [15]. The membrane thickness is of the order of 250 μm, resulting in a $K_p \approx 3 \times 10^{-4}$ cm/s, but let us take a conservative estimate $K_p = 10^{-4}$ cm/s. In Table 1, it can be seen that the passive permeability ($I = 0$) for tacrine at NaCl concentration of 0.15 M was 2.5 μg/(h cm^2) (≈ 0.7 ng/(s cm^2)), which means that the concentration of free tacrine in the fiber chamber is in the order of 7 μg/cm^3. As the chamber volume is 4 cm^3, only ca. 30 μg of tacrine is present in the free volume of the fiber chamber, in contrast to the drug loading in the fiber of ca. 60 mg of tacrine. The same can be naturally seen from Fig. 2, as less than 0.2 mg, ca. 0.3%, of the drug was released at the end of the experiment. Hence, the equilibrium of tacrine between the aqueous phase and the fiber resides strongly on the fiber phase.

Considering a pure ion-exchange mechanism

$$D^+(\text{fiber}) + Na^+(w) \leftrightarrow D^+(w) + Na^+(\text{fiber}) \quad (2)$$

the (formal) equilibrium constant K of the reaction (2) would be

$$K = \frac{c_{D(w)}\bar{c}_{Na}}{\bar{c}_D c_{Na(w)}} = \frac{x^2}{(\bar{n}_D^0 - x)(n_{Na}^0 - x)} \approx \frac{x^2}{\bar{n}_D^0 n_{Na}^0} \quad (3)$$

where the overbar denotes the fiber phase, and x is the amount of tacrine (in moles) released from the fiber;

Table 1
Effect of salt concentration and current density on the release rate of tacrine (μg/(h cm^2)) ± the calculated error due to sampling and analysis, from the Smopex-102 ® ion-exchange fiber

I (mA/cm^2)	0.15 M NaCl	0.30 M NaCl	0.50 M NaCl
0.00 (Passive diffusion)	2.5 ± 0.1	5.1 ± 0.1	8.5 ± 0.2
0.05	3.4 ± 0.1	6.7 ± 0.3	15.3 ± 0.6
0.10	6.8 ± 0.3	15.3 ± 0.6	27.2 ± 1.0
0.25	13.6 ± 0.5	25.5 ± 0.9	17.0 ± 0.6
0.50	12.7 ± 0.5	24.6 ± 0.9	38.2 ± 1.5

Table 2
Effect of drug amount on the release rate of tacrine (μg/(h cm^2)) ± the calculated error due to sampling and analysis ± the calculated error due to sampling and analysis. $I = 0.1$ mA/cm^2, [NaCl] = 0.3 M

Amount of tacrine (mg)	Release rate (μg/(h cm^2))
30	3.4 ± 0.1
60	15.3 ± 0.6
120	13.6 ± 0.6

the latter approximation holds as $x \ll \bar{n}_D^0, n_{Na}^0$, the initial amounts of tacrine and NaCl, respectively. Therefore, doubling the NaCl concentration would increase x and, consequently, the flux by the factor of $\sqrt{2} \approx 1.4$. In Table 1, however, the ratios of the fluxes are 1:1.7:2.7, in contrast to the expected ratios 1:1.4:2.2 ($1:\sqrt{2}:\sqrt{5}$). Therefore, it is clear that the ion-exchange mechanism is not solely responsible for the release of tacrine, but nonspecific adsorption also takes place on the fiber, as previously shown [14]. It would be possible to model the adsorption equilibrium assuming, for example, the Langmuir isotherm for the nonspecific adsorption, but here we are content to give a semi-quantitative and pragmatic interpretation of the results.

The first way to analyze the data is to compare the flux of tacrine with the electric current density via its apparent transport number $t_{app} = FJ/I$. This transport number is called apparent, as the flux J also includes the contribution of diffusion. Using the data in Table 1, $t_{app} = 0.04$ in all the cases, which means that tacrine is a trace ion in the transport process, i.e. its contribution to the total conductivity of the membrane is insignificant. In such a case, the Goldmann constant field approximation applies and the flux can be estimated by the well-known relation

$$J = K_p c \frac{v}{1 - e^{-v}} = K_p c E; \quad v = \frac{zF\Delta\phi}{RT} \tag{4}$$

where E is the iontophoretic enhancement factor. The potential drop, $\Delta\phi$, can be obtained from the ratio of the passive and iontophoretic fluxes of tacrine given in Table 1.

The results in Table 3 reveal interesting features of the measurements. Let us consider, for example, the case that $I = 0.25$ mA/cm^2 and [NaCl] = 0.15 M, where $\Delta\phi = 143$ mV. The potential drop is purely ohmic:

$$\Delta\phi = \frac{IL}{\kappa} \tag{5}$$

In Eq. (5), L is the length over which the potential drop is effective and κ is the conductivity of the system within L. The conductivity of 0.15 M NaCl solution is ca. 15 mS/cm [16]. Hence, $L = \Delta\phi\kappa/I \approx 8.5$ cm, so it can be deduced that the potential drop does not prevail solely across the membrane, but across the entire length between the electrodes. This result is expected, due to the thin and porous membrane, the resistance of which does not significantly contribute to the total cell resistance.

Table 3
Iontophoretic enhancement factors of tacrine release and the corresponding potential drops, according to the Goldmann constant field assumption

I (mA/cm^2)	0.15 M NaCl		0.30 M NaCl		0.50 M NaCl	
	E	$\Delta\phi$ (mV)	E	$\Delta\phi$ (mV)	E	$\Delta\phi$ (mV)
0.05	1.36	17	1.62	27	2.20	48
0.10	2.72	64	3.57	89	3.97	100
0.25	5.50	143	5.95	152	2.50	57
0.50	5.20	133	5.48	140	5.59	143

As can be seen in Table 3, the values of $\Delta\phi$ increase as a function of current density, agreeing with Eq. (5). More problematic is that the values of $\Delta\phi$ also increase with the increasing NaCl concentration, although the conductivity increases as well, which conflicts with Eq. (5). A possible explanation is that as the electric field operates also within the stack of fibers, which has an effect on the partition equilibrium between the fiber and its bathing solution. The potential drop has been calculated assuming implicitly that the concentration of the donor solution remains constant, but if the electric field enhances the release of tacrine from the fiber, the values of $\Delta\phi$ will be overestimated. Modelling of such a phenomenon would be rather demanding and prone to a number of freely adjustable parameters, such as potential-dependent adsorption equilibrium constants, the values of which would be unknown.

A relevant question for the drug release profiles is whether the delivery system presented here can provide release rates high enough to achieve the therapeutic level. The mass balance can be written as follows:

$$\frac{dc}{dt} = \frac{JA}{V} - kc \Leftrightarrow \frac{dn}{dt} = JA - kVc = JA - CLc \tag{6}$$

In Eq. (6), c is the drug concentration in plasma, V the distribution volume, k the first order metabolic rate

constant and CL is the clearance. At steady state $dn/dt = 0$, and

$$A = \frac{CLc}{J} \quad (7)$$

The clearance of tacrine is 150 dm^3/h and the therapeutic level in plasma 5–30 μg/dm^3 [17]. Taking, for example $J = 25$ μg/(h cm^2) then the required area of the device $A = 30–180$ cm^2, which can be easily achieved by using circular patches with a diameter in the range of 6–15 cm.

Iontophoresis of tacrine in a solution did not show any maximum limiting current values [11]. Therefore, we also tested for possible electrode reactions or drug adsorption to the electrodes. Cyclic voltammetry did not show any evidence of drug decomposition on the electrodes (data not shown), but tests of adsorption showed that the tacrine concentration in the cathode compartment decreased with time and the concentration was further decreased with higher current densities (Table 4), suggesting that tacrine is adsorbed on to the Ag/AgCl electrode.

3.2. Metoprolol

Some iontophoretic applications may require a rapid but controlled release of the drug from the device. Metoprolol has significantly different release properties to tacrine and was chosen as a second example drug due to its rapid release from the Smopex-102 fiber [14]. Only with the most dilute (0.15 M) salt concentration and the lowest current densities was there some discernable difference between the passive diffusion and iontophoretic transport of metoprolol. When higher salt concentrations (0.3 or 0.5 M) were used, the diffusion of metoprolol was so high that it was impossible to control the release rate by varying the current density (data not shown).

Table 4
Maximum amount of adsorbed tacrine as a percentage of the original drug amount during the test

I (mA/cm^2)	Max ads. tacrine (%)
0.05	5
0.10	5
0.25	15
0.50	20

Table 5
Release rates of metoprolol (μg/(h cm^2)) ± the calculated error due to sampling and analysis, from the Smopex-102® fiber, [NaCl] = 0.15 M

I (mA/cm^2)	Release rate (μg/(h cm^2))
0.00 (Passive diffusion)	54.3 ± 4.1
0.05	63.6 ± 3.6
0.10	97.6 ± 5.1
0.25	101.8 ± 5.4

Comparing the release rate values of metoprolol (Table 5) to the release rate of tacrine (Table 1) at the same salt concentration and current density shows that the release rates of metoprolol were an order of magnitude greater than the corresponding release rates of tacrine. The differences between the release rates did, however, decrease when the current density was increased. Our earlier studies already established that metoprolol is released from the fibers substantially faster than tacrine [14] and that the release of tacrine from several types of ion-exchange fiber is slower compared to other drugs [11]. It was suggested that the differences in the release rates could be due to the lipophilicity of the drug; lipophilic drugs were more strongly bound to the fibers than hydrophilic drugs [11–13]. This appears to be the case in the present work, as the log$P$ for tacrine is 3.3 and for metoprolol 1.88 [18]. Additionally, it was established that tacrine adsorbed on to the electrode surfaces (Table 4), which was not detected in the case of metoprolol.

4. Conclusions

It is shown that the release of tacrine can be adjusted by the current density, fiber amount and salt concentration in the test system. Thus, tacrine is a suitable drug candidate to be delivered by this kind of iontophoretic transdermal drug delivery system. Metoprolol, however, requires a system, where the release from the ion-exchange matrix is slower. This can be achieved by using a more dilute salt concentration. Also, the use of a porous (weak) cation-exchange membrane, instead of the PLAC used here, could increase the control over the amount of drug

released together with the adjustment of the current density and salt concentration.

Acknowledgements

The authors acknowledge the support of Smoptech, Finland, for supplying the fibers for this study.

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