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Dissertation for the degree of Doctor of Science in Technology to be presented with due permission of the Department of Chemical Technology for public examination and debate in Auditorium KE 2 (Komppa Auditorium) at Helsinki University of Technology (Espoo, Finland) on the 9th of October, 2004, at 12 noon.

Abstract

Transdermal iontophoresis is a method where the movement of ionic drugs (and sometimes also neutral drug molecules) across skin is enhanced using an externally applied potential difference. Iontophoretic devices contain three distinct components; 1) the drug reservoir which contains one electrode, the polarity chosen depends on the charge of the drug, 2) the return electrode and 3) the electronic controller. In this study ion-exchange fibers were investigated as a drug reservoir material for iontophoretic device.

The parameters affecting the drug release from the ion-exchange fibers without applied current were studied experimentally and theoretically modeled using five model drugs and four different ion-exchange fibers. It was found that lipophilic drugs were retained more strongly and for longer in the fibers than hydrophilic drugs. The hydrophilic drugs were also released more readily from fibers containing strong ion-exchange groups, whereas the lipophilic drugs attached more strongly to strong ion-exchange groups and released more easily from the weak ion-exchange groups. The salt concentration and the choice of the salt also had an effect; when using equimolar amounts of sodium chloride at lower salt concentrations, more drug was released. Incorporation of calcium chloride in the bathing solution increased considerably both the drug release rate and the total amount of drug released when compared to sodium chloride alone.

The drug release from the fibers were studied *in vitro* and *in vivo* using iontophoresis. Due to significantly different release properties, tacrine and metoprolol were chosen for screening of their suitability for this kind of iontophoretic system, using an in-house designed *in vitro* cell. It was found that the rate of tacrine release from the device could be controlled by adjusting the salt concentration and the current density used but the rate of metoprolol release could not be controlled this way. A semi-quantitative and pragmatic interpretation of the results also showed that it should be possible to manufacture a transdermal iontophoretic patch to delivery tacrine. It was also determined *in vivo* that clinically relevant plasma concentrations of tacrine could be achieved in a human volunteer using an in-house designed and manufactured iontophoretic transdermal drug delivery patch.

Preface

This work was carried out at the Laboratory of Physical Chemistry and Electrochemistry, Helsinki University of Technology between April 1998 and February 2004, in collaboration with the Pharmaceutical Technology Division of Helsinki University.

My instructor Prof. Kyösti Kontturi is gratefully acknowledged for giving me the opportunity to work on this interesting subject. I wish to express my gratitude to colleagues at the Pharmaceutical Technology Division Tarja Kankkunen Ph.D. and Prof. Jouni Hirvonen. I am grateful to co-authors Lasse Murtomäki D.Sc. (Tech.) and Prof. Jose A. Manzanares for their expertise in modelling. I wish to thank Lasse Murtomäki also for his valuable comments on this thesis. I express my gratitude to Prof. Arto Urtti who arranged time to supervise my minor subject studies of pharmaceutical technology. Many thanks to Prof. Kristiina Järvinen for her advice concerning this thesis.

My warmest thanks to my ex- and present officemates Eeva, Annika and Kirsi who had to cope with me (and the mess I made in my part of the office) during these years. I also thank all the personnel of the Laboratory of Physical Chemistry.

I also wish to thank Kenneth Ekman and Mats Sundell from Smoptech Co. for their interest in this project and providing fibers for the experimental work and Michael Barker Ph.D. for language revisions. TEKES is acknowledged for financial support.

Espoo, April 13th 2004

Marja Vuorio

Contents

List of publications

I. Tarja Jaskari, Marja Vuorio, Kyösti Kontturi, Arto Urtti, Jose A. Manzanares and Jouni Hirvonen: Controlled transdermal iontophoresis by ion-exchange fiber, *J. Controlled Release* **67** (2000) 179-190.

II. Tarja Jaskari, Marja Vuorio, Kyösti Kontturi, Jose A. Manzanares and Jouni Hirvonen: Ion-exchange fibers and drugs: an equilibrium study, *J. Controlled Release* **70** (2001) 219-229.

III. Tarja Jaskari, Raimo Sulkava, Marja Vuorio, Kyösti Kontturi and Jouni Hirvonen: Transdermal iontophoresis of tacrine, *Pharm. Res.* **19** (2002) 705-708.

IV. Marja Vuorio, Jose A. Manzanares, Lasse Murtomäki, Jouni Hirvonen, Tarja Kankkunen and Kyösti Kontturi: Ion-exchange fibers and drugs: a transient study, *J. Controlled Release* **91** (2003) 439-448.

V. Marja Vuorio, Lasse Murtomäki, Kyösti Kontturi and Jouni Hirvonen: Ion-exchange fibers and drugs: a novel device for the screening of iontophoretic systems, **97** (2004) *J. Controlled Release* 485-492.

Statement of the author's role in the listed publications

In publications I and II Marja Vuorio did part of the experimental work. She took active part in interpreting the results and writing the papers. In publication III the iontophoretic device used in the in vivo experiments was designed and tested by Vuorio prior to the clinical tests. In publications IV and V Marja Vuorio did all of the measurements, she also did most of the analysis and wrote the papers.

Espoo 5th April 2004

Kyösti Kontturi
Professor

1. Introduction

The benefits of using transdermal drug delivery include improved systemic bioavailability resulting from bypassing the first pass metabolism. Variables due to oral administration, such as pH, the presence of food or enzymes and transit times can all be eliminated. Transdermal drug delivery also allows fast interruption of the treatment in the case of adversed effects.

In the development of new transdermal drug delivery devices the aim is to obtain controlled, predictable and reproducible release of drugs into the blood stream of the patient. The transdermal device acts as a drug reservoir and controls the rate of drug transfer. When the transdermal drug flux is controlled by the device instead of the skin, delivery of the drug is more reproducible leading to smaller inter- and intrasubject variations, since the drug release from the device can be controlled more accurately than the permeability of the skin.[1]

One potential drug reservoir is to bind the drug within an ion-exchange system. Charged drugs remain bound to the ion-exchange groups of the ion-exchange matrix until released by mobile ions, e.g. sodium, Na^+. The release rate of the drug can be controlled with the current, the mobile ion concentration and pH.[2-4] The complexation of the drugs with ion-exchange resins has shown promise for achieving controlled drug release,[5,6] drug delivery[7] and also to enhance drug stability during storage.[6,8]

This project has studied the properties of ion-exchange fibers as a drug reservoir for iontophoretic transdermal drug delivery using several model drugs. An iontophoretic patch was developed in order to conduct a clinical study on tacrine, a reversible cholinesterase inhibitor used for treating patients with Alzheimer's disease, to determine whether therapeutically relevant plasma concentrations could be achieved in healthy human volunteers.

2. Background

2.1 An overview of iontophoresis

Iontophoresis is a method where the movement of ions across a membrane is enhanced using an externally applied potential difference. When the membrane under consideration is skin, the method is called transdermal iontophoresis.

The principal barrier to the transport of molecules into and across the skin is the *stratum corneum* (SC), this is the uppermost layer of the epidermis with a thickness of between 10 and 100 μm. The SC consists of several layers of corneocytes (anucleate keratin filled cells) inlaid in a lipid matrix, a continuous medium through the SC, arranged mainly in bilayers.[9,10] The intercellular lipids consist of approximately equal quantities of ceramides, cholesterol and free fatty acids.[11]

Percutaneous absorption may take place simultaneously by any combination of the three main pathways;[11-14]

- The intercellular (paracellular) pathway between the corneocytes along the lamellar lipids.
- The intracellular (transcellular) pathway through the cells.
- The appendageal (shunt) pathway via hair follicles, sweat ducts and secretary glands.

Ions prefer the route of the least electrical resistance, in the SC this is believed to be via the pores. Some investigations indicate that these pores are sweat glands,[15,16] others that transport occurs through both sweat glands and hair follicles. [17-19]

The physico-chemical properties of the molecule have an effect on the contribution of the follicular and non-follicular routes of penetration. Hydrophilic molecules tend to localize in the hair follicles, whereas lipophilic molecules are mostly distributed in the lipid intercellular regions of the *stratum corneum* and the lipid membranes of the epidermal keratinocytes.[20]

Since passive transdermal permeation of the majority of drugs needs enhancement to achieve clinically relevant plasma concentrations, both chemical and physical enhancement methods have been developed. Iontophoresis is one of the physical methods.

In transdermal iontophoresis, cationic or neutral therapeutic agents are placed under an anode, or anionic therapeutic agents under a cathode. When a low voltage and

low current density is applied, according to simple electrorepulsion, ions are repelled into and through the skin. Cationic drugs are driven into and through the skin by the anode (active electrode), which also exctracts anions from the tissue underneath the skin into the anode. At the cathode (return electrode) anionic buffer ions are driven into the skin and cations from the tissue are extracted into the cathode. See figure 1.

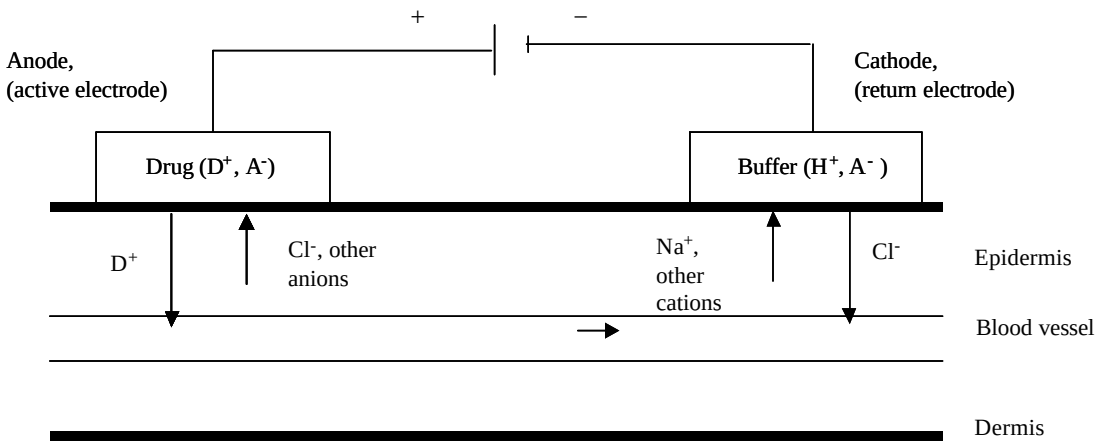


Figure 1. Schematic representation of the iontophoretic drug delivery. (Modified from ref. 21)

It is also possible to include an additional charged drug in the return electrode to be delivered simultaneously or to use a mixture of drugs in the active electrode to enhance the desired effect or to increase skin permeation, depending on which drugs/molecules are used.[22-24]

More formally, transdermal iontophoresis should be called electrically assisted transdermal delivery. There are three major enhancing mechanisms for drug flux through the skin, of which iontophoresis (also known as electrorepulsion, or electromigration, or the Nernst-Planck effect) is just one. The other mechanisms are: electroosmotic flow[25-29] and current induced increase in skin permeation, also known as damage effect.[30]

Electroosmotic flow is a flux of bulk fluid induced by a voltage difference across a charged membrane; it is always in the same direction as the flow of counter ions. Since human skin is negatively charged under physiological conditions, the counter ions are cations and the electroosmotic flow is thus from anode to cathode. Therefore the cathodic

delivery of anions is hindered and the anodic delivery of cations is assisted by electroosmosis.

The improved movement of neutral molecules under iontophoresis is based on electroosmosis. Ions are influenced by all of the above mechanisms so that electroosmosis has a positive contribution to the transport of cations and a negative contribution to the transport of anions under normal physiological conditions. The impact of electroosmosis on ion transfer increases with the size of the ion.[31] The contribution of electroosmosis can be so significant that the delivery of large anions from the anodic compartment can be more efficient than delivery from the cathode, this is called "wrong–way iontophoresis".[27]

The electrorepulsion effect gives the largest enhancement to the flux of small lipophilic cations.[32] When the concentration of the ionic drug is very high, so that the drug carries most of the current, electroosmotic flow has a very small effect on the drug flux.[25]

Transdermal iontophoresis has been used for both local and systemic drug delivery. Applications include local delivery of anesthetics (e.g. lidocaine),[33] steroids and retinoids to treat acne scarring,[34] for the relief of palmar and plantar hyperhidrosis[35] and the administration of pilocarpine in the diagnosis of cystic fibrosis.[36-38] Other applications of transdermal iontophoresis include the administration of anti-inflammatory drugs e.g. ketoprofen,[39] into subcutaneous tissues and joints. Iontophoretic delivery of several systemic drugs are still under investigation these include the analgesic fentanyl,[40] a reversible cholinesterase inhibitor tacrine[III] and several formulations of insulin.[41-46]

The symmetrical nature of iontophoresis, where ions are driven both into and out of the body, has been utilized for extracting information from the body without the need for blood sampling. A reverse iontophoresis device has already been introduced for glucose monitoring in patients with diabetes.[47-50] Reverse iontophoresis has also been tested for monitoring caffeine and theophylline in premature neonates.[51] Another possible use for reverse iontophoresis is in detecting phenylalanine for the diagnosis of phenylketonuria, a potentially fatal metabolic disease in infants.[52,53]

2.2 Iontophoretic devices

2.2.1 *In vitro* devices

Several types of permeation cell have been used to study the feasibility of drug molecules for iontophoretic transport. One experimental arrangement is the side-by-side diffusion cell, where a skin sample is sandwiched between two half cells. The drug under examination in solution and the electrode are placed facing the SC side of the skin in one half of the cell, which acts as the drug reservoir, whereas, the other half of the cell acts as the return reservoir containing an electrode in a conducting solution.[26,54] Sometimes a buffer solution is added to compartments in order to simulate physiological conditions. A four electrode system has been used in order to measure the potential drop across the skin,[55] Masada *et al.* developed this idea further to maintain the potential drop across the skin.[56]

Bellantone *et al.* produced a cell design where the two electrodes are placed above the skin simulating the *in vivo* conditions.[57] A large skin membrane is used to overlap the edges of the diffusion cell and the electrode is attached to the SC side of the skin and the second electrode is placed in the drug reservoir.

Glikfeld *et al.* modified the Franz diffusion cell, where the half cells are on top of each other and the skin placed horizontally between them.[58] Furthermore, in the upper half of the cell, a glass wall separates the two electrode compartments, the current thus flows from the active electrode compartment across the skin into the receptor compartment and then back to the upper cell half but now to the return compartment.

Although both cell designs have offered reliable data, the advantage of the cell with electrodes on the same side of the SC is that it offers the possibility to study lateral transport and examine iontophoresis for subcutaneous and non-invasive sampling.[59]

Junginger used a three-chamber continuous flow-through transport cell in his *in-vitro* modelling of apomorphine.[60] This construction had two continuously stirred outer chambers which contained electrodes. Between these two chambers lay the acceptor chamber separated from the outer chambers by the SC and the supporting dialysis membrane, this chamber had a continuous flow of buffer solution. The advantage of the flow-through cell was the possibility to automate the set-up, which allows fast collection of data. The disadvantage was that experimental variables (volume, sampling interval and

flow-rate) had an effect on the value of the apparent flux which may deviate from the intrinsic flux through the skin.

In the present studies an in-house designed test cell has been used, a schematic representation of which is shown in figure 2.[61] In this test system both SC and porous membranes can be used depending upon whether transdermal iontophoresis or just drug release from the patch formula is studied. The patch type structure of the cell makes it practical for testing different kinds of matrix as well as drug and salt solution combinations. In this work the cell was used for testing ion-exchange fibers as a matrix for ionic drugs.

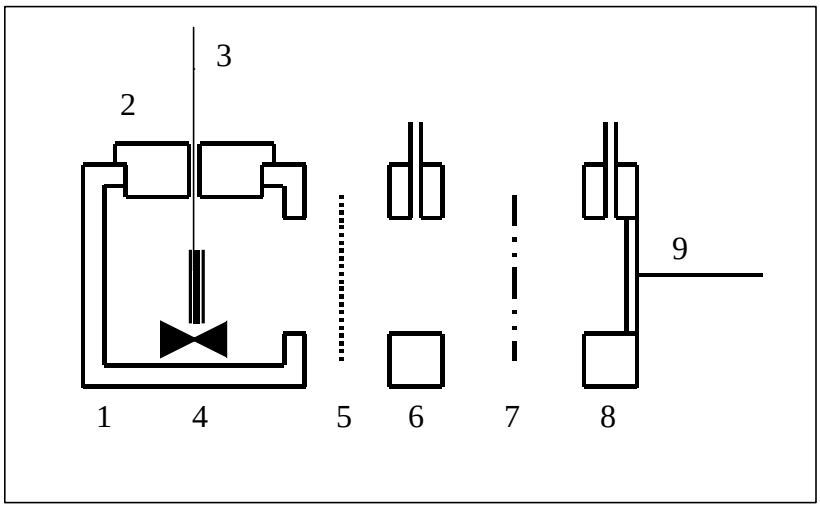


Figure 2. *In vitro* iontophoretic cell. 1) return chamber 2) lid 3) Ag/AgCl electrode 4) magnetic stirrer 5) stratum corneum or porous membrane 6) donor chamber 7) Nafion® membrane 8) salt solution chamber 9) Ag/AgCl electrode.

2.2.2 *In vivo* devices

Iontophoretic devices contain three distinct components; the drug reservoir, the return reservoir and the electronic controller.

One way to classify iontophoretic controllers is by the drug delivery mode used. Direct current (DC) mode systems are useful for acute conditions, as they give a constant intensity of direct current, resulting in continuous drug delivery. Pulsed direct current mode systems are applicable for chronic conditions reducing the risk of skin irritation. Some iontophoretic devices under different manufacturing stages are listed in table 1.

Table 1. Iontophoretic products listed by manufacturer.

Manufacturer	Commercial Name / System	Production status	Disease / treatment	Power supply	Current mode	Ref.
ALZA	E-Trans® patch	Awaiting FDA approval	Fentanyl dosing	Battery	Programmable	31, 62
Becton Dickinson Co.	Reusable power supply controllers	Under development				31
Cygnus Inc.	GlucoWatch®	On the market	Glucose monitoring system based on reverse iontophoresis	Battery		31, 63
Dermion Inc.	Wearable iontophoretic patches	Under development				31
Empi	Dupel® deviceDupel® B.L.U.E. electrodes	On the market		Battery	Two channel DC	64
General Medical Co.	Drionic® device	On the market	Hyperhidrosis treatment	Battery		65
Hidrex GmbH	1. Hidrex GS 2. Hidrex PS	On the market	Hyperhidrosis treatment	Battery or mains	1. DC 2. Pulsed DC	66
IOMED Inc.	- Phoresor® II (PM 850 & 900) - Iogel® electrodes - Trans-Q® electrodes, - Numby stuff® iontocaine electrodes	On the market		Battery	DC	67
Janssen Pharmaceutica	Delivery system for fentanyl	Phase III clinical trials	Acute pain management			31
Life-Tech Inc.	- Microphor® Model 6121 - Iontophor® Model 6111PM/DX - Meditrode® electrodes	On the market		Battery	Two channel DC	68
Optis	Eyegate II , ocular applicator and device	About to be commercialized		Battery	Programmable	69, 70
R.A. Fischer Co.	MD-1a Galvanic Unit	On the market	Hyperhidrosis treatment	Mains	DC	71
Vyteris Inc.	Pre-filled lidocaine patch & preprogrammed microcomputer	To be released 2004	Dermal anesthesia	Battery		72, 73
Wescor	Macroduct® Sweat collection system Model 3700	On the market	Diagnosis of cystic fibrosis	Battery		74

Most commercial products use Ag/AgCl electrodes, the drug reservoir is usually aqueous and the filling material is often made of a biocompatible gel which matches the shape of the skin surface. In general, electrode gel materials can be divided into two types; the wet type, which has been used in most commercial systems and solid dry gels.[31]

Wet type electrodes are often karaya gum based,[31, 75] but the major problem with these electrodes is poor durability, which can lead in the worst case to exposure of the skin to the bare electrode. Also, they are quite expensive to manufacture and have tendency to irritate the skin. Dry hydrogels are simple and economic to manufacture and have firm electrical contacts, but are less conductive than the gels.[76] Several filling materials under research including natural polymers and synthetic polymers are listed in table 2.

The return reservoir contains saline solution to complete the electronic circuit. Additionally it is possible to include a charged drug in the return reservoir to be delivered simultaneously. Otherwise the electrode material is similar to the drug reservoir materials described above.

A couple of novel systems have been reported: One uses a buffering system and bilayer design in which the electrode comprises of a mixture of electroconductive material, where the polymer functions as an electrode as well as a matrix to immobilize the competitive ions.[77] In another novel work, Haga *et al.*[78] utilized microfabrication technology; they developed photo-etched devices with efficient current distribution for transdermal iontophoretic drug delivery.

Even though iontophoretic systems usually have a patch type formulation, this is not the only way to solve the problem. A pencil shaped system for topical delivery has been used to deliver antihistamines.[79] In this application the drug is delivered in the style of an injection, the end with the anode gel carrier system is placed onto the skin and the circuit is completed by the patient's finger at the cathode. However, for continuous drug delivery this is perhaps not the most practical solution.

Table 2. Materials tested for the drug reservoirs (or as a component of the reservoir material).

Material tested	Drug	Type	Author	References
Agar based hydrogels containing ion-exchange resins	Nicotine	Wet	Conaghey *et al*	5, 6
Chitosan	SNA (a)	Wet	Fang *et al.*	87
Gelatin containing microemulsion based organogels	Sodium salicylate	Wet	Kantaria *et al.*	80
Carboxymethyl cellulose sodium (CMC)	Enoxacin	Wet	Fang *et al.*	93
Hydroxyethyl methacrylate hydrogel	Gentamicin	Wet	Frucht-Pery *et al.*	81
Hydroxypropylcellulose (HPC)	SNA (a)		Fang *et al.*	87
Hydroxypropyl methyl cellulose (HPMC)	SNP (b), Diclofenac sodium, SNA, Enoxacin	Wet	Fang *et al.*	82, 83, 84, 93
Hydrophilic microporous membrane	GHRP (c)	Wet	Ellens *et al.*	61
Hydrophilic polyacrylate	SNA	Wet	Fang *et al.*	87
Ion-exchange fibers	Tacrine, Metoprolol	Wet	Jaskari *et al.* Vuorio *et al.* Murtomäki *et al.*	I, III V 85
Karayagum/ glycerin / acrylamide	Metoprolol	Wet	Okabe *et al.*	86
Methyl cellulose	SNP, SNA	Wet	Fang *et al.*	84, 87
Pectin	SNA	Wet	Fang *et al.*	87
Poloxamer 407	Insulin, Arginine vasopressin	Wet	Panchagnula *et al.*	88, 89
Polyacrylamide (PAA) hydrogel	Insulin, Arginine vasopressin, Calcitonin	Wet	Banga *et al.*	90
Polymer electrolytes (Polyethyleneoxide)	Lidocaine(-HCl), Lithium Chloride	Dry	Sahota *et al.*	91, 92
Polyvinylalcohol (PVA)	Enoxacin	Wet	Fang *et al.*	93
Polyvinylpyrrolidine (PVP) hydrogels	Enoxacin, SNA, Diclofenac sodium	Wet	Fang *et al.*	83, 87, 93

(a) Sodium nonivamide acetate
(b) Sodium nonivamide propionate
(c) Growth hormone-releasing peptide (L-histidyl-D- tryptophyl-L-alanyl-L-tryptophyl-D-phenylalanyl-L-lysinamide)

3. Materials under research

3.1 Ion-exchange fibers

All the fibers under investigation were manufactured by SmopTech Co. (Turku, Finland). Three different cation- and one anion- exchanger groups were used, these were radiation grafted onto the polyethylene backbone of the fibers. More detailed information about the fibers is presented in table 3.

Table 3. Ion-exchange fibers under investigation.

Fiber	Publication	Ion-exchange groups	Fiber material	Ion-exchange capacity (mmol g^{-1})
Smopex® -101	I, II, IV	$-SO_3H$	Poly(ethylene-*g*-styrene sulfonic acid)	3.2
Smopex® -102	I -V	-COOH	Poly(ethylene-*g*-acrylic acid)	8.0-9.7
Smopex® -107	I, II	1:1 $-SO_3H$ and -COOH	Poly(ethylene-*g*-acrylicacid-*co*-vinyl sulphonic acid)	8.0
Smopex® -108	I	$-NH_2$	Amidoxime	3.4

The fibers were either woven into a cloth-like structure (I, II, III) or short strips of 4 mm length (IV) or 2.3 mm length (V). Also, two commercial ion-exchange matrices containing carboxylate ion-exchange groups were tested in paper IV; Diaion WK100 ion-exchange resin and Amberlite IRC-86 gel (both from Supelco, Bellefonte, PA, USA).

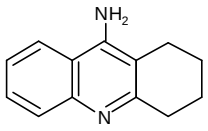
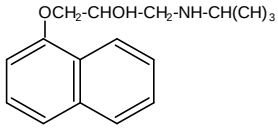
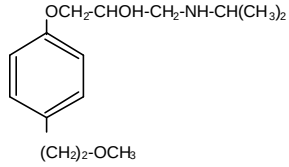
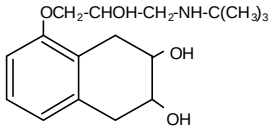
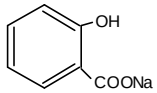
3.2 Model drugs

Tacrine (-HCl), propranolol (-HCl), metoprolol (-tartrate) and nadolol were obtained from Sigma (St. Louis, USA), sodium salicylate was from Aldrich-Chemie (Steinheim, Germany). In table 4, the physicochemical properties and molecular structures of the drugs studied are presented.

Model drugs were chosen on the grounds of their physicochemical properties, such as lipophilicity; the higher the logP value the greater the lipophilicity. All of the drugs chosen had shown some potential for iontophoretic transdermal delivery.[80, 86, 94, 95]

Tacrine was chosen for the *in vivo* test. It was hoped that using iontophoresis would minimize the difficulties associated with oral administration, such as low bioavailability, short elimination half-life,[96] hepatotoxicity and peripheral cholinergic side effects.[94] Additionally, it has been suggested that constant levels of tacrine in the brain may maximize the effect on memory enhancement and iontophoretic delivery may give more constant plasma concentration for prolonged time.[94]

Table 4. Physico-chemical properties of the drugs under investigation. [97, I]

Drug	Structure	Molecular weight (g mol^{-1})	Dissociation constant (pK_a)	octanol/water partition coefficient (logP)	Classification
Tacrine		198.27	9.8±0.2 (a)	3.30 (b)	Anti-cholinergic
Propranolol		259.35	9.45	3.56 b, 2.75 (c)	ß-blocker
Metoprolol		267.37	9.70	1.88 (b), 1.20 (c)	ß-blocker
Nadolol		309.41	9.39	0.71 (b) , 0.23 (c)	ß-blocker
Sodium salicylate		160.1	3.0	1.5	Keratolytic

a) Our determination (I)
b) Determined experimentally [96]
c) Calculated using CLOGP version 3.54. [96]

4. Results and Discussion

4.1 An equilibrium study (II)

The cationic model drugs in this study were tacrine (-HCl), propranolol (-HCl) and nadolol, the cation-exchange fibers studied were Smopex® -101, -102 and -107. All of the fibers were in woven form.

The fibers were activated by soaking in 0.1 M NaCl or a 1:1 mixture of 0.1 M NaCl and 0.1 M NaOH solutions prior to use and then washed with MilliQ water (Millipore, France). The fibers were immersed in a 1 w-% drug solution for 24 hours so that drug solution was changed three times during the procedure (at the beginning of the

immersion, after 3h and after 6h) and finally the fibers were washed with pure water to remove any excess unbound drug.

Drug release from the fibers was tested by placing the fibers in the electrolyte solution (0.0015, 0.015, 0.15 or 1.5 M NaCl and in the case of tacrine also 0.015 M 1:9, 1:1 or 9:1 $CaCl_2$ / NaCl solutions). The volume of the electrolyte solution was chosen so that each solution contained an equimolar amount of the salt as there was drug in the fiber. The electrolyte solutions were changed five times during a week (at 1, 2, 3, 4 and 7 days). After every change of the electrolyte solution the fibers were washed with MilliQ water and the drug concentration was determined by HPLC from the combined solutions of electrolyte and washing water.

4.1.1 Drug partition equilibrium

The cationic drug (D^+) is released from the fiber by an ion-exchange mechanism, where sodium ions from the solution phase replace the drug ion in the fiber as follows.

$$D^+_{(fiber)} + Na^+_{(aq)} \leftrightarrow D^+_{(aq)} + Na^+_{(fiber)}$$

The distribution of the drug between the fiber and the solution phases in the equilibrium arises from electrostatic and hydrophobic interactions, the former of which is measured by the electrical partition coefficient ($K_{e,d}$) [98, 99]

$$K_{e,d} = exp\left(\frac{-z_d F \phi_D}{RT}\right) \quad (1)$$

where z_d represents the charge number, F is Faraday constant, R is the gas constant and T is the thermodynamic temperature. $\phi_D \equiv \bar{\phi} - \phi$ is the Donnan potential, which is defined by the ion-exchange capacity of the fiber and the concentration and character of the external solution, the overbar denotes the fiber phase. In this case, where a cationic drug is in a cation exchanger $z_d > 0$ and $\phi_D < 0$ resulting $K_{e,d}>1$.

The chemical partition coefficient ($K_{c,d}$), defined in Eq. (2), measures the specific interactions of the drug with the fiber *i.e.* the tendency of the drug to get into the hydrophobic fiber,[100]

$$K_{c,d} = \exp \frac{\left(m_d^0 - \overline{m}_d^0 \right)}{RT} \qquad (2)$$

where μ_d^0 is the standard chemical potential of the drug species. The decrease in free energy due to interactions between the drug and the fiber grows with the hydrophobicity of the drug, yielding a greater value of $K_{c,d}$ (>1). In the case that the drug is hydrophilic $K_{c,d}$ can be <1, since the water content of the fiber also has an effect on the value of $K_{c,d}$.

Combining these two coefficients results in the molar concentration ratio of the drug.[99, 101]

$$\frac{\overline{c}_d}{c_d} = K_{p,d} = K_{e,d} K_{c,d} \qquad (3)$$

This equation presents the Donnan equilibrium *i.e.* the electrochemical potential of the drug in the fiber phase and the external phase take the same value under equilibrium conditions. Since the drug concentration is comparatively low in both phases activity coefficients are not included in Eq. (3).

Table 5 represents the released amount of the drug from different fibers as a function of NaCl concentration. For the release rate of drugs from the fibers the lipophilicity scale tacrine $\approx$ propranolol > nadolol was valid for all fibers, the rate of drug release decreased with increasing lipophilicity.

For the 101 fiber, the release rate of hydrophilic nadolol was over ten times higher than the release rate of lipophilic tacrine, whilst in the case of 102 fibers the difference in rates was only about factor of two. These results suggest that the specific interactions of the lipophilic drugs are stronger with sulphonic acid fibers than with the carboxylic acid fibers and vice versa for the hydrophilic drugs. This was also noted when the fibers were loaded with the drugs; propranolol and tacrine adsorbed more to the 101 fiber than to the 102 fiber and again the opposite effect was observed for the nadolol. The same effect *i.e.* the drug is released faster from the carboxylic acid groups than from the sulphonic acid groups has also been observed in the case of resins.[102]

Table 5. The effect of the salt concentration and the fiber to total released amount of the drug (%) during one week test. Average ± standard deviation (N=3).

Drug	[NaCl] / (moldm^{-3})	Smopex®-101	Smopex®-102	Smopex®-107
Tacrine	0.0015	3.8 ± 1.0	8.7 ± 0.3	13.8 ± 1.2
	0.015	4.4 ± 1.2	9.4 ± 2.1	14.0 ± 1.9
	0.15	3.2 ± 0.3	7.5 ± 0.7	10.6 ± 0.7
	1.5	1.8 ± 0.4	10.2 ± 2.0	10.0 ± 3.4
Propranolol	0.0015	7.9 ± 0.1	13.8 ± 0.7	12.6 ± 1.2
	0.015	5.4 ± 0.4	10.6 ± 0.3	8.1 ± 1.2
	0.15	4.8 ± 0.6	9.4 ± 0.5	9.4 ± 0.6
	1.5	3.3 ± 0.3	5.5 ± 0.6	7.5 ± 1.0
Nadolol	0.0015	59.9 ± 5.3	16.5 ± 0.9	46.4 ± 2.0
	0.015	51.4 ± 2.2	12.7 ± 0.4	27.9 ± 2.8
	0.15	44.4 ± 3.7	11.3 ± 0.5	24.2 ± 1.1
	1.5	43.0 ± 3.8	6.6 ± 0.7	22.7 ± 1.7

The effect of drug concentration in the fibers to the release rate was also detected (in 102 fiber), when the drug content in the fibers increased it naturally lead to a greater amount of the drug released, but the fraction of the drug being released remained about the same. The same effect has also been detected in ion-exchange resins.[6]

4.1.2 The effect of ionic strength

The volume V of the electrolyte solution was inversely proportional to its concentration, so that the number of moles of electrolyte cations used was the same in each experiment.

$$n_+^0 = c_+^0 V \qquad (4)$$

The limited amount of electrolyte in the partitioning equilibria gave the result that the drug release was influenced by both the electrostatic and volume effects.

The molar concentration ratio of the electrolyte ions was mainly influenced by electrostatic interactions and so the partition coefficient for the electrolyte ions is simply

$$\frac{\bar{c}_i}{c_i} = K_{e,i} = K_e^{z_i} \tag{5}$$

where K_e = exp(Fϕ_D/RT) and z_i is the charge number of species i.[99, 101] Given that the drug solution is completely dissociated, the Donnan potential, ϕ_D, is defined by the electroneutrality conditions in the fiber and external solutions.[98] Using the electroneutrality conditions in the fiber and external solution and eqs. (3) and (5) lead to the relationship

$$K_e = \frac{-c_m + \left[c_m^2 + 4(c_+ + c_d)(c_+ + c_d K_{c,d})\right]^{1/2}}{2(c_+ + c_d)} \tag{6}$$

where $c_m = |z_d / z_m| \bar{c}_d^0$ is the concentration of ion-exchange groups bound to the fiber and z_m is the charge number of the groups.

It is important to note that concentrations c_d and c_+ depend on K_e since the limited amount of the drug and external electrolyte ions requires that the following conditions are satisfied.

$$n_d^0 = c_d V + \bar{c}_d \bar{V} \tag{7a}$$

$$n_+^0 = c_+ V + \bar{c}_+ \bar{V} \tag{7b}$$

Also note from Eq.(6) that ϕ_D = (RT/F)lnK_e may become positive (i.e. K_e > 1) when $K_{c,d}$ >>1. That is, the fiber might act as an anion-exchanger due to strong chemical interactions with the drug.

The experimental results showed that the effect of electrolyte concentration on the drug release rate was more profound on nadolol and propranolol, the drug release rate increased with decreasing concentration and increasing volume (Table 5). In the case of tacrine the trend was not as clear, possibly due to stronger specific interactions, which resulted in a low drug release rate. These results can be explained by considering Eq. (4) and the change in electrolyte volume with the concentration. The volume was one thousand times greater for the most dilute concentration compared to the most concentrated solution, which is bound to have an effect on the drug release as described in eqs. (7a) and (7b). First, the increasing electrolyte concentration decreases the Donnan

potential, (*i.e.* the electrostatic affinity between the drug and the fiber) leading to an increase in drug release. Second, a smaller external solution volume requires a very small amount of released drug to reach the equilibrium drug concentration in the external solution. From these experiments we can conclude that the latter of these competing effects is dominant.

The increase in drug release rate with increasing electrolyte concentration would be detected if the volume of the external solution were kept constant. This had been observed earlier with ion-exchange resins.[5, 103]

The release of tacrine was also studied with mixed solutions of NaCl and $CaCl_2$ at fixed total concentrations to see if divalent Ca^{2+} ions had any effect on release rate. It was discovered that even 10 % $CaCl_2$ had a considerable effect on the tacrine release rate, see Table 6. The release was enhanced from all the fibers, to a lesser extent for the 101 (from ~4% to up to ~16 %) and substantially from 102 (from ~10% to up to ~100%) and 107 (from ~15 % to up to ~100 %). Calcium ions are known to bind strongly with carboxylic groups at the pH used in these experiments, which explains the increased release rates from the fibers.[104]

Table 6. Effect of Ca^{2+} fraction in the NaCl/CaCl electrolyte solution to tacrine release from the fibers. Average ± standard deviation (N=3).

Ca^{2+} -%	**Smopex®-101**	**Smopex®-102**	**Smopex®-107**
10	13.6 ± 3.6	90.5 ± 14.4	91.8 ± 12.9
50	13.7 ± 0.4	99.2 ± 3.6	95.7 ± 16.8
90	15.9 ± 2.2	71.6 ± 23.8	102.8 ± 12.7

The calcium chloride fraction also seemed to have an effect on the drug release rate; although the distribution of the results is rather large. Simply increasing the calcium chloride fraction decreases the Donnan potential, which lead to an increase in the drug amount of released. In the case of the 101 and 107 fibers the increase is due to the reduction of the effective charge of the fiber resulting from the formation of $-[COOCa]^+$ groups which leads to a reverse of the effective charge of the fiber when the fraction of $CaCl_2$ is 90 %. For lower fractions of $CaCl_2$ the effective fixed charge does not reverse in sign but is so small that the fiber acts as an anion exchanger (i.e. K_e<1). In the case of the

102 fibers the trend of drug release increasing with the fraction of $CaCl_2$ is reversed between 50 and 90 %. This is due to the increase of chloride ions with increasing fraction of $CaCl_2$, which is equivalent to the increasing concentration of the electrolyte solution, thus it makes the Donnan potential closer to 1 which means a lower amount of drug released in the case where the fibers act as an anion exchanger.

4.2 A transient study (IV)

In this study the cationic model drugs were tacrine (-HCl), propranolol (-HCl), metoprolol (-tartrate) and nadolol, the ion-exchange fibers under investigation were Smopex® -101, -102 either in the woven form or 4 mm long staples. Also, commercially available ion-exchange resin (Diaion WK100) and gel (Amberlite IRC-86) containing carboxylate ion-exchange groups were tested.

The ion-exchange material loaded with the drug was placed in the flow-cell. NaCl solution (0.15 M) was pumped through the cell at varying flow rates (0.1 - 5.0 cm^3min^{-1}). The resulting mixture of salt and drug was gathered using a fraction collector. Drug concentrations from the mixture were analysed by HPLC.

4.2.1 Kinetics of ion-exchange

The ion-exchange mechanism in the case where a cationic drug (D^+) is in the fiber and Na^+ in the solution has three steps: (1) Na^+ ions diffuse to the solid surface through the solution, (2) the Na^+ ions diffuse inside the solid phase, (3) the chemical exchange reaction between the Na^+ and D^+ occurs in the ion-exchange groups. Finally, the D^+ diffuses back into the solution through the same steps. The slowest step of these three is called the rate determining step (RDS). Depending upon which of steps 1, 2 or 3 is the RDS the reaction is called accordingly “liquid film diffusion controlled”, “particle diffusion controlled” or “chemical reaction controlled”.

The equilibrium constant K for the ion-exchange reaction where the cationic drug is replaced in the fiber phase by sodium ion is defined by Eq. (8)

$$K = \frac{P_{\mathrm{Na}}^0}{P_{\mathrm{d}}^0} = \frac{c_{\mathrm{d}}\bar{c}_{\mathrm{Na}}}{\bar{c}_{\mathrm{d}}c_{\mathrm{Na}}} \tag{8}$$

where P^0 is the partition coefficient between the water and the fiber phase.

The ion-exchange reaction is fast compared to the rate of diffusion and the Donnan equilibrium is assumed to be valid on the fiber,[98] hence the kinetic problem is reduced to a transport problem. The Nernst-Planck equation is used in a unidimensional form to describe the molar flux density J_i of the ionic species i

$$-j_i = \frac{\mathrm{d}c_i}{\mathrm{d}x} + z_i c_i \frac{F}{RT}\frac{\mathrm{d}f}{\mathrm{d}x} - \frac{uc_i}{D_i} \qquad (9)$$

where $j_i = J_i/D_i$, D_i is the diffusion coefficient of i, x is the perpendicular distance from the fiber surface and u is the convective velocity of the solution.

The solution of the equations in the diffusion boundary layer must satisfy the electroneutrality condition $c_2 = c_1 + c_3$, where the subscripts 1, 2 and 3 denote Na^+, Cl^- and the ionic form of the drug respectively. To reduce the number of fitting parameters several approximations are introduced. First, the diffusion coefficients D_i are given by values $D_1 = D_2 = 2D_3 = D$. Second the Goldman constant electric field assumption is presented, the electric field in dimensionless form is marked by E, where $E = -(\mathrm{F}d/\mathrm{R}T)\mathrm{d}\phi/\mathrm{d}x$ and d is the diffusion boundary layer thickness. E must be evaluated from the open circuit condition $I = \mathrm{F}(\Sigma J_i) = 0$. Also, the Peclet number $Pe \equiv \frac{u\delta}{D} = \frac{\dot{V}\delta}{D\bar{A}}$ is introduced and this conceals all the simplifying assumptions made ($\bar{A}$ is the effective surface area and $\dot{V}$ is the volume flow). The Cl^- ions are assumed to be completely excluded from the ion-exchange fiber, hence $P_2^0 = 0$ and $J_2 = 0$. Now, when $x = 0$ and $i = 2$, at the fiber solution interface, Eq. 9 gives

$$c_2^{\mathrm{b}} = c_2^{\mathrm{s}} e^{Pe-E} \qquad (10)$$

where superscripts b and s denote the bulk aqueous phase and the interface, respectively and $c_2^{\mathrm{s}} = c_2(0)$ and $c_2^{\mathrm{b}} = c_2(\delta)$.

To solve the flux equations for each component it was assumed that the flux density J_i is independent of position within each time interval Δt (a quasi-stationary state assumption). Now the transport equations for Na^+ and D^+ can be solved similarly, solved for the flux densities they give

$$j_1 = \frac{Pe+E}{\delta}\frac{c_1^{b} - c_1^{s} e^{Pe+E}}{1-e^{Pe+E}} \tag{11a}$$

$$j_3 = \frac{2Pe+E}{\delta}\frac{c_3^{b} - c_3^{s} e^{2Pe+E}}{1-e^{2Pe+E}} \tag{11 b}$$

$I = \Sigma_i z_i D_i j_i = 0$ and the value of E can now be obtained from the numerical solution of

$$2(Pe+E)\frac{c_1^{b} - c_1^{s} e^{Pe+E}}{1-e^{Pe+E}} + (2Pe+E)\frac{c_3^{b} - c_3^{s} e^{2Pe+E}}{1-e^{2Pe+E}} = 0 \tag{12}$$

Dimensionless variables are now introduced for convenience, $y_k = c_k / c^0$, where c^0 is the concentration of the feed solution. Also, the concentration of ionic species in the membrane is represented as dimensionless variables $\bar{y}_i = \bar{c}_i / \bar{c}$. First, $\bar{y}_3 = 1 - \bar{y}_1 = 1$, $y_3^{b} = 0$ and $y_1^{b} = y_2^{b} = 1$. Also, when we assume that the kinetics of ion-exchange are very fast, the D^+ bound to the fiber is immediately replaced by Na^+, hence first $y_1^{s} = 0$ (diffusion is too slow to compensate for the amount of Na^+ exchanged into the fiber). Electroneutrality must also be satisfied at the interface so Eq. (10) implies that first

$$y_3^{s} = y_2^{s} = e^{Pe-E} \tag{13}$$

where E is obtained from the solution of Eq. (12) at $t = 0$

$$\frac{2(Pe+E)}{1-e^{Pe+E}} = \frac{(2Pe+E)e^{Pe+2E}}{1-e^{2Pe+E}} \tag{14}$$

After the initial stage, the Donnan equilibrium defines the relationship between the surface concentrations, Eq. (8) can be rewritten as

$$K = \frac{y_1^{s}\bar{y}_3}{y_3^{s}\bar{y}_1} = \frac{y_1^{s}\bar{y}_3}{y_3^{s}(1-\bar{y}_3)} \tag{15}$$

The electroneutrality condition $y_1^{s} = y_2^{s} - y_3^{s}$ can now be used and Eq. (15) is now written as

$$y_3^{s} = \frac{y_2^{s}\bar{y}_3}{(1-\bar{y}_3)K + \bar{y}_3} \tag{16}$$

Mass balances for the drug and Na^+ ions, i = 1 and 3, inside the membrane need to be considered to evaluate the time dependence of concentrations

$$-\frac{\mathrm{d}\bar{n}_\mathrm{i}}{\mathrm{d}t} = J_\mathrm{i}\bar{A} \tag{17}$$

where $\bar{n}_\mathrm{i} = \bar{V}\bar{c}_\mathrm{i}$ now the time scale is changed to the amount of the salt introduced to the cell, to compare different convection rates $\dot{V}$

$$\mathrm{d}n_\mathrm{salt} = \dot{V}c^0\mathrm{d}t \tag{18}$$

Eq. (17) is then rewritten for the cations

$$-\frac{\mathrm{d}\bar{y}_1}{\mathrm{d}n_\mathrm{salt}} = \frac{j_1\delta}{Pe\bar{n}_0} \tag{19 a}$$

$$-\frac{\mathrm{d}\bar{y}_3}{\mathrm{d}n_\mathrm{salt}} = \frac{j_3\delta}{2Pe\bar{n}_0} \tag{19 b}$$

and outside the membrane

$$\frac{\mathrm{d}y_1^\mathrm{b}}{\mathrm{d}n_\mathrm{salt}} = \frac{j_1\delta}{Pe\,n_0} + \frac{1-y_1^\mathrm{b}}{n_0} \tag{20 a}$$

$$\frac{\mathrm{d}y_3^\mathrm{b}}{\mathrm{d}n_\mathrm{salt}} = \frac{j_3\delta}{2Pe\,n_0} - \frac{y_3^\mathrm{b}}{n_0} \tag{20 b}$$

The following iterative procedure is employed

Step 1: *E* is calculated from Eq. (14)

Step 2: Insert the initial values of all the quantities as old values to obtain the new ones by means of the following expressions (taking salt increments Δn_salt):

$$\bar{y}_{3,\mathrm{new}} = \bar{y}_{3,\mathrm{old}} - \frac{1}{2\bar{n}_0}\left[\left(2+\frac{E}{Pe}\right)\frac{y_3^\mathrm{b}-y_3^\mathrm{s}e^{2Pe+E}}{1-e^{2Pe+E}}\right]_\mathrm{old}\Delta n_\mathrm{salt}$$

$$y_{3,\mathrm{new}}^\mathrm{b} = y_{3,\mathrm{old}}^\mathrm{b} + \frac{1}{2n_0}\left[\left(2+\frac{E}{Pe}\right)\frac{y_3^\mathrm{b}-y_3^\mathrm{s}e^{2Pe+E}}{1-e^{2Pe+E}} - y_3^\mathrm{b}\right]_\mathrm{old}\Delta n_\mathrm{salt}$$

$$y_{1,\mathrm{new}}^\mathrm{b} = y_{1,\mathrm{old}}^\mathrm{b} + \frac{1}{n_0}\left[\left(1+\frac{E}{Pe}\right)\frac{y_1^\mathrm{b}-y_1^\mathrm{s}e^{Pe+E}}{1-e^{Pe+E}} + 1 - y_1^\mathrm{b}\right]_\mathrm{old}\Delta n_\mathrm{salt}$$

$$y^{b}_{2,new} = y^{b}_{1,new} + y^{b}_{3,new}$$

$$y^{s}_{2,new} = y^{b}_{2,new} e^{E-Pe}$$

$$y^{s}_{3,new} = \frac{y^{s}_{2,new} \bar{y}_{3,new}}{(1-\bar{y}_{3,new})K + \bar{y}_{3,new}}$$

$$y^{s}_{1,new} = y^{s}_{2,new} - y^{s}_{3,new}$$

Step 3: Solve Eq. (12) numerically using the new values of the concentrations obtained in step 2 to obtain the new value of *E*.

Step 4: Go to step 2 for the next salt increment inserting all these calculated values as old values. n_0 and $\bar{n}_0$ are always taken as 1.

In all cases the Peclet number was the main fitting parameter, whereas the partition coefficient *K* was not allowed to change for a given pair of drug species and ion-exchange material. From the results (figure 2) it was clear that the release rate of tacrine was much higher from the staple fiber than from the cloth and even greater than from the gel or the resin. This trend was the same for all the model drugs.

As the flow of electrolyte solution was increased, the drug release rate and extent usually increased accordingly. Only tacrine showed different behaviour, since when the flow rate was changed from 1.0 cm^3min^{-1} to 5.0 cm^3min^{-1} the release rate of tacrine did not increase. An explanation for this was that possible ion-exchange kinetics started to affect the release of tacrine.

The release rates of tacrine from the fibers, as noted earlier (II), and from the other ion-exchange matrices were slower than the release rates of the rest of the model drugs with the same flow rate. This was due to the strong interaction between tacrine and the ion-exchange materials. The difference in the structure of tacrine and the other model drugs is that tacrine does not contain any bulky or flexible substituents. The calculuated van der Waals volumes for nadolol, propranolol and tacrine were, 275, 245 and 160 $Å^3$ respectively.[105] Comparing these values may help to visualise the bulkiness of substituents.

This study also showed again that the release rates from the fiber were higher for the hydrophilic drugs than for the lipophilic drugs. It was also clear that all the model drugs had higher release rates from the fibers than from the resin or the gel and that the

difference in release rates between the fiber or the gel/resin was greater for more lipophilic drugs. The difference in release rates between the fiber and the resin or the gel can be explained by an increase in surface area of the ion-exchange matrix and/or a decrease in the diffusion layer thickness, which allows the rapid access of ions to the ion-exchange groups.[106, 107]

The small differences between the model and the experimental results can be explained by the nonspecific adsorption of chloride ions to the fiber or drug adsorption on the ion-exchange matrix or onto the side chains of the bound drugs.[6, 108]

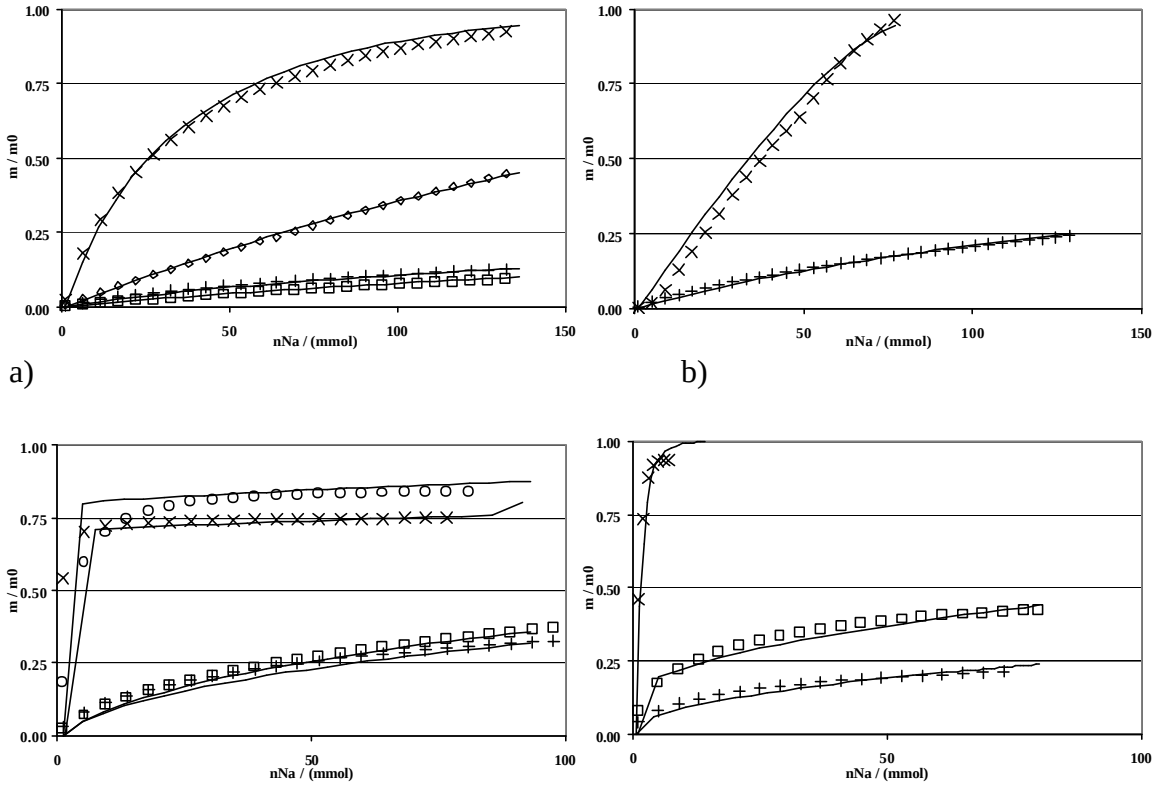


Figure 2. Experimental (○, ×, ◊, +, □□ stand for staple 101, staple 102, cloth 102, gel and resin, respectively) and theoretical (solid lines) fractions of drug released as a function of the amount of Na^+flowed through the cell at a flow rate of 5.0 cm^3min^{-1} for, a) tacrine b) propranolol c) metoprolol and d) nadolol. Parameters used in modeling can be found in paper IV.

4.3 An iontophoretic study

4.3.1 Iontophoresis *in vitro* (I, V)

4.3.1.1 Iontophoresis using a side-by-side cell (I)

The model drugs in this paper were tacrine (-HCl), nadolol, propranolol (-HCl) and sodium salicylate. The ion-exchange fibers were Smopex®-102 (-COOH) and -108 (-NH_2), in the woven form.

In this paper the transdermal delivery of model drugs was assessed using transdermal iontophoresis. Charged model drugs were complexed with anion and cation-exchange fibers as reservoirs for controlled drug delivery. Also, the iontophoretic drug delivery from the ion-exchange fiber were compared to the iontophoretic delivery from solution formulations.

A side-by-side cell (described in 2.2.1.) was used to test the release of the drugs from the ion-exchange fibers or from a 5 w-% drug solution across cadaver skin samples into a physiological saline solution. Drug concentrations were determined by HPLC.

In vitro drug permeation from a 5 w-% solution across human skin was investigated under both passive and iontophoretic (I = 0.5 $mAcm^{-2}$) conditions. The results are presented in table 7. The differences in the values of passive flux are evidently related to the chemical characteristics of the drug. The lipophilic drugs (tacrine, propranolol and salicylate) had considerably higher permeation rate than the more hydrophilic nadolol. Iontophoresis enhanced the transdermal permeation for all of the drugs but it was much larger for nadolol (enhancement factor $E_{i,e}$ = 1200) than for the lipophilic drugs, which has also been detected earlier.[95] Tacrine which had the highest passive permeation rate, also had the lowest enhancement factor.

The flux of tacrine through the skin from the solution was also studied as a function of the current density (I = 0, 0.10, 0.25 and 0.5 $mAcm^{-2}$). In all cases the iontophoretic permeation rate remained constant until the current was switched off, after which the permeation rate returned to the passive level. The value of the permeation rate was directly proportional to the iontophoretic current density used, in accordance with earlier studies.[6, 109-111]

The release rate from the fiber was dependent on the lipophilicity of the drug. The release rates of the lipophilic drugs tacrine and propranalol were significantly lower than

that of the more hydrophilic nadolol. Anion-exchange fiber 108 was tested using anionic sodium salicylate. The iontophoretic flux enhancement of salicylate ions across the skin due to the fibers was substantial. (See table 7.)

Since the drug content in the fiber experiment was lower than that in the solution experiment (e.g. for the 5 w-% solution), and the drug had also to be released from the ion-exchange fibers before permeating across the skin, then the drug flux from the fibers was clearly lower than the flux of the drug in solution. (See table 7.)

Table 7. *In vitro* passive and iontophoretic fluxes ($\mu gcm^{-2}h^{-1}$) and enhancement factors across human skin from a 5 % (w-%) solution and from a cation-exchange fiber Smopex®-102 or anion-exchange fiber Smopex®-108. Direct current iontophoresis (0.5 $mAcm^{-2}$) for 12 hours. Average ± standard deviation (N=4-7.)

Drug	**Passive flux (solution)**	**Iontophoretic flux (solution)**	**Enhacement factor (solution)**	**Iontophoretic flux (fiber)**
Tacrine	3.00 ± 0.70	220 ± 50	70	4.1 ± 0.7
Propranolol	0.26 ± 0.07	43 ± 7	170	27.0 ± 6.0
Nadolol	0.04 ± 0.05	49 ± 7	1200	10.5 ± 1.3
Sodium salicylate	0.34 ± 0.07	45 ± 6	130	28.0 ± 5.0

The iontophoretic flux of tacrine across skin was also investigated as a function of the amount of drug in the fiber (in the range 7.6 to 104.0 mg of tacrine). It was observed that the flux increased with increasing concentration, however, the increase was non-linear at the end of the scale. One possible reason could be a limiting mechanism of the skin at higher drug concentrations.[6] Alternatively, the electrodiffusion process under consideration involves an electric field determined by differences in permeabilities of the three transferring species, as well as the current density. In paper I the iontophoretic flux of this system was modeled and the simulation showed a non-linear behaviour similar to that observed experimentally.

4.3.1.2. Iontophoresis using a in-house designed test cell (V)

The ion-exchange fiber material employed was Smopex®-102 in the staple form. The cationic model drugs were tacrine (-hydrochloride) and metoprolol (-tartrate).

Ag/AgCl electrodes were used in all experiments. Nafion® 90209, (ElectroCell AB, Sweden) soaked for at least 24 hours in a 1.5 M NaCl solution before use, was used in the test cell between the anode and the fiber compartment. Hydrophilic Ultracel Amicon PLAC (regenerated cellulose) NMWL (nominal molecular weight limit): 1000 ultrafiltration membranes (Millipore Co., U.S.A.) were placed between the fiber and the cathode compartment.

The amount of the drug containing ion-exchange material to be used in the experiments was calculated and weighed so that each sample contained the same mass of the drug (60 mg). Tacrine concentration in the fiber was 2.8 $mmolg^{-1}$ and metoprolol concentration was 1.7 $mmolg^{-1}$. The ion-exchange material under analysis was placed inside the cell (figure 1). The NaCl solution (V = 4 cm^3, 0.15, 0.30 or 0.50 M) was injected into the fiber compartment, 30 cm^3 of the same salt solution was added to the cathode (receiver) compartment and 3 cm^3 of 1.5 M NaCl was added into the anode compartment.

A constant direct current of 0.05, 0.10, 0.25 and 0.50 $mAcm^{-2}$ was applied for every salt concentration in room temperature for 8 h. Samples (500 µl) were collected from the cathode chamber in fixed intervals and replaced by fresh salt solution. The passive diffusion experiments were done 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.

It was shown that the release rate of tacrine was enhanced with increasing NaCl concentration and increasing current density until the limiting current value was reached. Also, the effect of the amount of drug loaded into the fibers versus the amount of drug released was investigated. It was clear that when a certain maximum drug concentration was used in the fibers, the amount of released reached a maximum, and with increasing amount of drug loaded the amount of drug released remained constant, which was also detected earlier.[I]

From the release profiles of tacrine it was observed that the release followed first order kinetics, which could be achieved from a source of constant concentration to a sink. Then the flux is given by

$$J = K_p c \; ; \; K_p \approx D_{eff} / h \tag{21}$$

where K_p is the permeability coefficient, 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^2s^{-1}.[112] The membrane thickness is of the order of 250 µm, making $K_p \approx 3\times10^{-4}$ cms^{-1}, but a conservative estimate $K_p = 10^{-4}$ $cm\,s^{-1}$ is used. The passive flux ($I = 0$) for [NaCl] = 0.15 M is 2.5 $\mu gcm^{-2}h^{-1}$ ($\approx$ 0.7 $ngcm^{-2}s^{-1}$), which means that the concentration of free tacrine in the fiber chamber is only in the order of 7 μgcm^{-3}. As the chamber volume is 4 cm^3, only ca. 30 ng of tacrine is present in the free volume of the fiber chamber, in contrast to the loading of the fiber, ca. 60 mg of tacrine. The equilibrium of tacrine between the aqueous phase and the fiber is strongly on the fiber side.

For the pure ion exchange mechanism the (formal) equilibrium constant K of the ion-exchange reaction (Ch 4.1.1.) would be

$$K = \frac{c_d(w)\bar{c}_{Na}}{\bar{c}_d c_{Na}(w)} = \frac{x^2}{\left(\bar{n}_d^0 - x\right)\left(n_{Na}^0 - x\right)} \approx \frac{x^2}{\bar{n}_d^0 n_{Na}^0} \tag{22}$$

where the overbar denotes the fiber and x is the amount of tacrine (in moles) released from the fiber; the latter approximation holds as $x \ll \bar{n}_d^0, \bar{n}_{Na}^0$, the initial amounts of tacrine and NaCl, respectively. Therefore, doubling the NaCl concentration would increase x and the flux by the factor of $\sqrt{2} \approx 1.4$. the ratios of the fluxes is 1 : 1.7 : 2.7, in contrast to the expected ratios 1 : 1.4 : 2.2 ($1 : \sqrt{2} : \sqrt{5}$) (results shown in paper V). Thus, 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 shown in paper IV.

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). Using the data from paper V t_{app} = 0.04 in all 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 relation

$$J = K_{\mathrm{p}} c \frac{n}{1 - e^{-n}} = K_{\mathrm{p}} c E_{\mathrm{i,e}} \quad ; \quad n = \frac{z\mathrm{F}\Delta f}{\mathrm{R}T} \tag{23}$$

where $E_{\mathrm{i,e}}$ is the iontophoretic enhancement factor. The potential drop, $\Delta\phi$, can be obtained from the ratio of the passive and iontophoretic fluxes.

Considering, for example, the case where I = 0.25 mAcm^{-2} , [NaCl] = 0.15 M, and $\Delta\phi$ = 143 mV, then the potential drop is purely ohmic:

$$\Delta f = \frac{IL}{k} \tag{24}$$

In Eq. (24), 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^{-1}. Hence, $L = \kappa\Delta\phi / I \approx 8.5$ cm, so it can be deduced that potential drop does not occur solely across the membrane, but across the length between the electrodes. This result is, however, expected, because the membrane is so porous and thin that its resistance does not contribute to the total cell resistance significantly.

$\Delta\phi$ increases as the current density increases, agreeing with Eq. (24). More problematic is that $\Delta\phi$ increases also with the increasing NaCl concentration, although the conductivity increases as well, thus conflicting with Eq. (24). A possible explanation is that as the electric field is operative also within the stack of fibers, it affects the partition equilibrium between the fiber and its bathing solution. The potential drop was 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, then $\Delta\phi$ was overestimated.

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

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \frac{JA}{V} - kc \quad \Leftrightarrow \quad \frac{\mathrm{d}n}{\mathrm{d}t} = JA - kVc = JA - CL\,c \tag{25}$$

In Eq. (25), 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

$$A = \frac{CLc}{J} \qquad (26)$$

The clearance of tacrine is 150 dm^3h^{-1} and the therapeutic level is 5-30 μgdm^{-3}.[113] Taking, for example J = 25 $\mu gcm^{-2}h^{-1}$ then the required area of the device A = 30-180 cm^2 which can be uptained by using circular patches with a diameter in the range 6-15 cm.

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.[II, IV] Only when using the most dilute salt concentration was there some discernable difference between passive diffusion and iontophoretic transport. When using higher salt concentrations the diffusion of metoprolol was so high that it was impossible to control the release rate by varying the current density.

Iontophoresis of tacrine in a solution did not show any maximum limiting current values in our earlier studies.[I] 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, but tests of adsorption showed that the tacrine concentration in the cathode compartment decreased with time and the decrease in concentration was further increased with current density.

Comparing the release rate values of metoprolol to the release rate of tacrine at the same salt concentration and current density, shows that the release rates of metoprolol were an order of magnitude higher 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[IV] and that the release of tacrine from several types of ion-exchange fiber is slower compared to other drugs.[I, II] Also, it was established that tacrine was adsorbed on the electrode surfaces, which was not detected in the case of metoprolol.

4.3.2 Iontophoresis *in vivo* (III)

Here iontophoresis was used *in vivo* on ten healthy adult volunteers to investigate whether therapeutically relevant concentrations of tacrine could be achieved in the blood stream. The clinically relevant steady state level of tacrine after oral intake is 5-30 ng per

cm^3 of blood plasma.[113] In-house made ion-exchange fiber (woven form) electrodes and commercial Iogel®-electrodes were used, in both experiments a battery (9V) operated constant current source Phoresor® II Auto was used. The structure of the ion-exchange fiber electrodes is presented in figure 3.

Tacrine formulations were applied to the forearms of ten healthy adult subjects with three hours of current delivery (0.4 $mAcm^{-2}$), after which passive tacrine flux followed for one hour. The position of the electrodes was changed three times during the experiment. Blood samples were withdrawn after 30, 60, 90, 120, 150, 180 and 240 min. Plasma concentrations of the drug were determined by HPLC.

The alanine aminotransferase (ALT) level of the volunteers was determined before and after the experiments. The value had to be = 50 Ul^{-1} before acceptance for the test. After the experiment the ALT levels of the volunteers was found to be below the limit mentioned above.

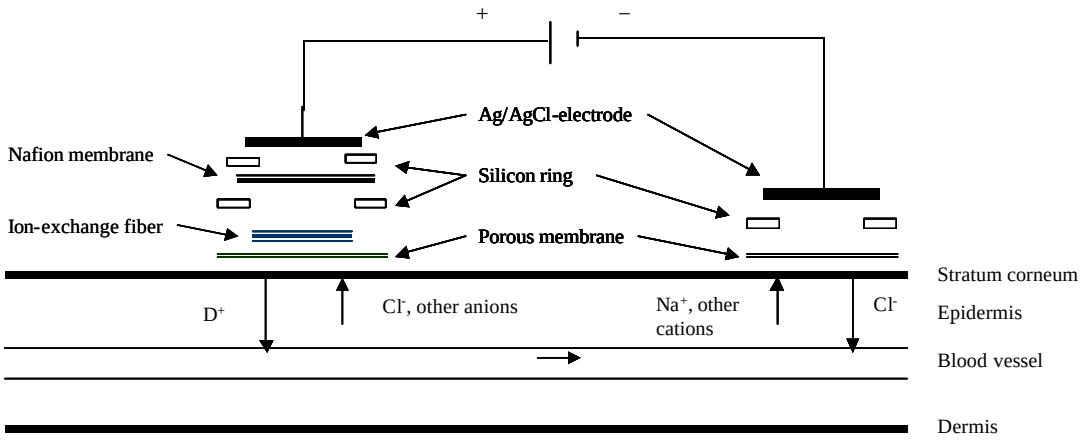


Figure 3. Schematic representation of the in-house designed ion-exchange fiber electrodes (modified from III).

The iontophoretic delivery of tacrine resulted in therapeutically significant plasma concentrations in all of the experiments using both the gel and ion-exchange devices. The average tacrine *in vivo* plasma concentrations were 21.3 $ngcm^{-3}$ and 14.9 $ngcm^{-3}$, respectively (figure 4). Constant plasma concentrations of tacrine were achieved within 30 min with both patch formulations. The passive permeation period of one hour did not have a great effect on the plasma concentrations, but only a small decrease was detected.

This is possibly due to the lipophilicity of tacrine which allows it to bind into the lipophilic skin structures and then release slowly to systemic circulation.

As one of the problems with gel type transdermal iontophoresis is the inter- and intrasubject variability, it was hoped that ion-exchange fibers would show less variable results. However, in the case of tacrine, even though the standard deviations during the test II (fiber) were slightly smaller than during test I (gel), the difference was not statistically significant.

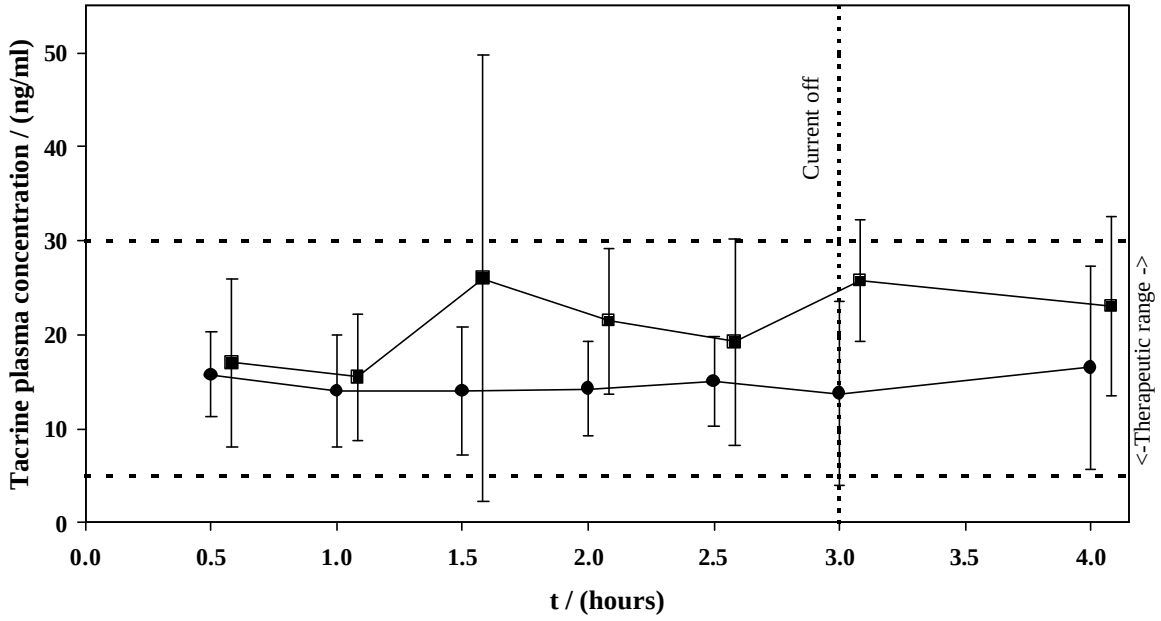


Figure 4. Plasma concentrations (average ± SD) of tacrine as a function of time. Test I, Iogel- electrodes (N=10) (■■) and test II, ion-exchange fiber electrodes (N=9) (●). To distinguish the test I and II, the curve of the former has been transformed forward by 5 min. Dashed horizontal lines express the upper and lower limits of the therapeutic range. [Modified from III]

Adverse skin reactions, either due to iontophoresis or to the drug, were monitored. Transient skin irritation reactions which occurred included pinching or prickling sensations, erythema, drying of the skin and coldness of the skin and fingertips. Skin irritation reactions correlated directly with the current density and the duration of the current application, however, none of the adverse effects were regarded as serious. The possible irritating effect of the tacrine (without application of current) and iontophoresis

(0.1 - 0.4 $mAcm^{-2}$, without tacrine) was also tested on five volunteers. No additional erythema on the skin was attributed to the use of tacrine in these short experiments. All of the side effects caused by the iontophoresis were similar to those reputed elsewhere.[40, 114, 115]

After this short term test all the values of ALT on test subjects were under the normal range. Naturally, to determine the possible effects of long-term delivery of tacrine on the liver function more trials are needed. However, the liver toxicity of tacrine is expected to be lower transdermally than by oral administration due to the decreased first-pass metabolism.

4.3.3 *In vivo* / *in vitro* correlation of tacrine permeation from the test formulations (III)

The *in vitro* experiments were performed using Franz type diffusion cells (the bottom half, the upper half was replaced with a patch formulation). The excised human *epidermis* was placed between the patch formulation and the receiver compartment, which was filled with HEPES buffered physiological NaCl. 200 µl samples were collected from the receiver compartment and replaced by fresh buffer at 30, 60, 90, 120, 150, 180 (current off) and 240 min. The surface area of the skin was 2.41 cm^2. The current source was Phoresor® II Auto, the same equipment that was used in the *in vivo* experiments. The patch formulation acted as the anode and a Ag/AgCl electrode was placed in the receiver compartment as the cathode.

The *in vitro* steady state fluxes of tacrine J_{SS}, $\mu g min^{-1} cm^{-2}$ were calculated from the linear part of the permeation curves by linear regression. The predicted *in vivo* plasma levels were calculated using Eq. (27)[1]

$$c_{SS} = \frac{J_{SS} A}{CL} \tag{27}$$

where c_{SS} ($ngcm^{-3}$) is steady state plasma concentration, A is the area for drug absorption and CL (dm^3h^{-1}) is the pharmacokinetic clearance of the drug from the body, for tacrine CL is 150 dm^3h^{-1}.[113] The area of the devices was related to 10 cm^2.

From table 8 it can be seen that the correlation between the *in vitro* and *in vivo* data was very good for the gel formulation. However, in the case of the ion-exchange

fiber formulation the *in vitro* data predicted a significantly smaller flux than the measured *in vivo* drug delivery.

Table 8. Steady state concentrations (c_{SS}/ ngcm^{-3}) of tacrine in human plasma based on *in vitro* (calculated) and *in vivo* experiments. The iontophoretic current density was 0.4 mAcm^{-2} for 3 h.

Formulation	*In vitro* c_{SS} / ng cm^{-3}	*In vivo* c_{SS} / ng cm^{-3}
Test I Iogel® formulation	22.4 ± 5.3	21.3 ± 5.9
Test II Ion-exchange fiber formulation	0.43 ± 0.19	14.9 ± 2.6

The correlation between the *in vitro* and *in vivo* seems to be dependant on the experimental conditions, the individual skin source and the drug in question, since the results from several research groups vary significantly. [23, 83, 114, 116-118] Phipps and Gyory,[116] for instance observed that the *in vivo* concentration was generally higher than the *in vitro* concentration, whereas Van der Geest *et al.*[114] obtained the opposite result. Therefore, further studies are needed to solve the reasons for the poor correlation between *in vivo* and *in vitro* experiments.

5. Conclusions

Studies with ion-exchange fibers showed that they are promising materials for transdermal iontophoretic drug delivery systems. According to these studies, when the lipophilicity of the drug is known, the most suitable ion-exchange fiber can be estimated.

From the *in vitro* tests it can be seen that tacrine release can be controlled by the device and that tacrine is a suitable candidate for this kind of iontophoretic transdermal drug delivery system. Metoprolol, however, needs a system where the release rate from the device is lower. This can be achieved for instance by using more dilute salt concentration or using different ion-exchange matrix. The test cell designed for screening suitable systems for transdermal iontophoresis although applicable needs further refining, *e.g.* the Ag/AgCl electrode in the sample compartment should be covered to prevent possible drug adsorption.

The transdermal iontophoretic patch system used in the clinical trial was at an early stage of development, however, still proved to be functional. Thus, transdermal iontophoresis can be utilized to deliver clinically relevant plasma concentrations of

tacrine at the expense of minor irritation of the skin. Also, since the drug plasma concentrations in the blood were higher than the therapeutic concentration, it is possible to use a lower or an intermittent current density and still reach a clinically relevant concentration and reduce the adverse effects of iontophoresis.

The final construction of the iontophoretic patch and the optimization of materials, such as membranes and electrode materials, are still under consideration. Especially, the use of porous cation-exchange membranes instead of PLAC could increase the control over the amount of drug released by the current density and salt concentration.

List of abbreviations

ALT	alanine aminotransferase
CMC	carboxymethyl cellulose sodium
DC	direct current
GHRP	growth hormone-releasing peptide (L-histidyl-D- tryptophyl -L-alanyl-L-tryptophyl-D-phenylalanyl-L-lysinamide)
HEPES	N-2-hydroxyethylpiperazine-N-2-ethanesulphonic acid
HPC	hydroxypropylcellulose
HPLC	high performance liquid chromatography
HPMC	hydroxypropyl methyl cellulose
NMWL	nominal molecular weight limit
PAA	polyacrylamide
PLAC	Millipore ultrafiltration membrane
PVA	polyvinyl alcohol
PVP	polyvinylpyrrolidine
RDS	rate determining step
SC	s*tratum corneum*
Smopex®-101	poly(ethylene-*g*-styrene sulfonic acid) fiber
Smopex®-102	poly(ethylene-*g*-acrylic acid) fiber
Smopex®-107	poly(ethylene-*g*-acrylicacid-*co*-vinyl sulphonic acid) fiber
Smopex®-108	amidoxime functional fiber
SNA	sodium nonivamide acetate
SNP	sodium nonivamide propionate

List of symbols

A	area for drug absorption
$\overline{A}$	effective surface area
c	concentration
CL	clearance
D_{eff}	effective diffusion coefficient
D_{i}	diffusion coefficient of *i*
E	electric field
$E_{\text{i,e}}$	iontophoretic enhancement factor
F	Faraday constant
h	membrane thickness
I	current density
J	molar flux density
k	first order metabolic rate constant
K_c	chemical partition coefficient
K_{e}	electrical partition coefficient
K_p	permeability coefficient
L	length over which the potential drop is effective
N	number of experiments

P	partition coefficient
Pe	Peclet number
R	gas constant
T	thermodynamic temperature
t_{app}	apparent transport number
u	convective velocity of the solution
V	volume
$\dot{V}$	volume flow
x	perpendicular distance from the fiber surface
z_i	charge number of species i
d	diffusion boundary layer thickness
κ	conductivity
μ^0	standard chemical potential
ϕ_D	Donnan potential
$\Delta\phi$	potential drop

Superscripts:

b	bulk aqueous phase
s	interface
overbar	fiber phase
0	initial stage

Subscripts:

d	drug
+	cation
-	anion
m	ion-exchange groups bound to the fiber
SS	steady state

References

[1] Guy, R.H., Hadgraft, J., Rate control in transdermal drug delivery, *Int. J. Pharm.* **82** (1992) R1-R6.

[2] Åkerman, S., Svarfvar, B., Kontturi, K., Näsman, J., Urtti, A., Paronen, P., Järvinen, K., Influence of ionic strength on drug adsorption onto and release from a poly(acrylic acid) grafted poly(vinylidene fluoride) membrane, *Int. J. Pharm.* **178** (1999) 67-75.

[3] Åkerman, S., Viinikka, P., Svarfvar, B., Järvinen, K., Kontturi, K., Näsman, J., Urtti, A., Paronen, P., Transport of drugs across porous ion-exchange membranes, *J. Controlled Release* **50** (1998) 153-166.

[4] Järvinen, K., Åkerman, S., Svarfvar, B., Tarvainen, T., Viinikka, P., Paronen, P., Drug release from pH and ionic strength responsive poly(acrylic acid) grafted poly(vinylidene fluoride) membrane bags in vitro, *Pharm. Res.* **15** (1998) 802-805.

[5] Conaghey, O.M., Corish, J., Corrigan, O.I., The release of nicotine from a hydrogel containing ion-exchange resins, *Int. J. Pharm.* **170** (1998) 215-224.

[6] Conaghey, O.M., Corish, J., Corrigan, O.I., Iontophoretically assisted in vitro membrane transport of nicotine from a hydrogel containing ion-exchange resins, *Int. J. Pharm.* **170** (1998) 225-237.

[7] Irwin, W.J., Machale, R., Watts, P.J., Drug delivery by ion-exchange. VII. Release of acidic drugs from anionic exchange resinate complexes, *Drug Dev. Ind. Pharm.* **6** (1990) 883-898.

[8] Jani, R., Gan, O., Ali, Y., Rodstrom, R., Hancock, S., Ion exchange resins for ophthalmic delivery, *J. Ocul. Pharm.* **1** (1992) 57-67.

[9] Bouwstra, J.A., de Vries, M.A., Gooris, G.S., Bras, W., Brussee, J., Ponec, M., Thermodynamic and structural aspects of the skin barrier, *J. Controlled Release* **15** (1991) 209-220.

[10] Elias, P.M., Epidermal barrier function: intercellular lamellar lipid structures, origin, composition and metabolism, *J. Controlled Release* **15** (1991) 199-208.

[11] Schnetz, E., Fartasch, M., Microdialysis for the evaluation of penetration through the human skin barrier - a promising tool for future research, *Eur. J. Pharm. Sci.* **12** (1991) 165-174.

[12] Singh, J., Bhatia, K.S., Topical iontophoretic drug delivery: Pathways, principles, factors and skin irritation, *Med. Res. Rev.* **16** (1996) 285-296.

[13] Cullander, C., What are the pathways of iontophoretic current flow through mammalian skin?, *Adv. Drug. Del. Rev.* **9** (1992) 119-135.

[14] Riviere, J.E., Heit, M.C., Electrically-assisted transdermal drug delivery, *Pharm. Res.* **14** (1997) 687-697.

[15] Abramson, H.A., Gorin, H.H., Skin reactions. IX The electrophoretic demonstration of the patent pores of the living human skin; its relation to the charge of the skin, *J. Phys. Chem.* **44** (1940) 1094-1102.

[16] Grimnes, S., Pathways of ionic flow through human skin in vivo, *Acta Derm. Venereol.* **64** (1984) 93-98.

[17] Burnette, R.R., Marrero, D., Comparison between the iontophoretic and passive transport of thyrotropin releasing hormone across excised nude mouse skin, *J. Pharm. Sci.* **75** (1986) 738-743.

[18] Del Terzo, S., Bhel, C.R., Nash, R.A., Iontophoretic transport of a homologous series of ionized and nonionized model compounds: Influence of Hydrophobicity and mechanistic interpretation, *Pharm. Res.* **6** (1989) 85-90.
[19] Burnette, R.R., Ongipipattanakul, B., Characterization of the pore transport properties and tissue alteration of excised human skin during iontophoresis, *J. Pharm. Sci.* **77** (1988) 132-137.
[20] Turner, N.G., Guy, R.H., Iontophoretic transport pathways: dependence on penetrant physicochemical properties, *J. Pharm. Sci.* **86** (1997) 1385-1389.
[21] Cullander, C., Guy, R.H., Transdermal delivery of peptides and proteins: Routes of delivery: Case studies, *Adv. Drug Del. Rev.* **8** (1992) 291-329.
[22] Deagle, W.R., Iontophoresis disc pain blocker, US patent No. US2003100884, acc. 29.5.2003.
[23] Riviere, J.E., Sage, B., Williams, P.L., Effects of vasoactive drugs on transdermal lidocaine iontophoresis, *J. Pharm. Sci.* **80** (1991) 615-650.
[24] Riviere, J.E., Monteiro-Riviere, N.A., Inman, A.O., Determination of lidocaine concentrations in skin after transdermal iontophoresis: Effects of vasoactive drugs, *Pharm. Res.* **9** (1992) 211-214.
[25] Pikal, M.J.,Transport mechanisms in iontophoresis. I. A theoretical model for the effect of electroosmotic flow on flux enhancement in transdermal iontophoresis, *Pharm. Res.* **7** (1990) 118-126.
[26] Pikal, M.J., Shah, S., Transport mechanism in iontophoresis. II. Electroosmotic flow and transference number measurement for hairless mouse skin. *Pharm. Res.* **7** (1990) 213-221.
[27] Pikal, M.J., The role of electroosmosic flow in transdermal iontophoresis, *Adv. Drug Del. Rev.* **46** (2001) 281-305.
[28] Uitto, O.D. White, H.S., Electroosmotic pore transport in human skin, *Pharm. Res.* **20** (2003) 646-652.
[29] Pikal, M.J., The role of electroosmotic flow in transdermal iontophoresis, *Adv. Drug Del. Rev.* **9** (1992) 201-237.
[30] Inada, H., Ghanem, A.-H., Higuchi, W.I., Studies on the effects of applied voltage and duration on human epidermal membrane alteration/recovery and the resultant effects upon iontophoresis, *Pharm. Res.* **11** (1994) 687-697.
[31] Panchagula, R., Pillai, O, Nair, V.B., Ramarao, P., Transdermal iontophoresis revisited, *Curr. Opin. Chem. Biol.* **4** (2000) 468-473.
[32] Marro, D., Kalia, Y.N., Delgado-Charro, M.B., Guy, R.H., Contributions of electromigration and electroosmosis to iontophoretic drug delivery, *Pharm. Res.* **18** (2001) 1701-1708.
[33] Maloney, J.M., Local anesthesia obtained via iontophoresis as an aid to shave biopsy, *Arch. Dermatol.* **128** (1992) 331-333.
[34] Schmidt, J.M., Binder, M., Maicheiner, W., Bielglmayer, C., New treatment of atrophic acne scars by iontophoresis with estriol and tretinoin, *Int. J. Dermatol.* **34** (1995) 53-57.
[35] Sloan, J.B., Soltani, K., Iontophoresis in dermatology, *J. Am. Acad. Dermatol.* **15** (1986) 671-684.

[36] Gibson, L.E., Cooke, R.E., A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis, *Pediatrics* **23** (1959) 545-549.
[37] Gibson, L.E., Iontophoretic sweat test for cyctic fibrosis: technical details, *Pediatrics* **39** (1967) 465.
[38] Webster, H.L., Barlow, W.K., New approach to cystic fibrosis diagnosis by use of an improved sweat-induction/collection system and osmometry, *Clin. Chem.* **27** (1981) 385-387.
[39] Panus, P.C., Campbell, J., Kulkarni, S.B., Herrick, R., Ravis, W.R., Banga, A.K., Transdermal iontophoretic delivery of ketoprofen through human cadaver skin and in humans, *J. Controlled Release* **44** (1997) 113-121.
[40] Ashburn, M.A., Streisand, J., Zhang, J., Love, G., Rowin, M., Niu, S., Kievit, J.K., Mertens, M.J., The iontophoresis of fentanyl citrate in humans, *Anesthesiology* **82** (1995) 1146-1153.
[41] Chien, Y.W., Siddiqui, O., Shi, W.M., Lelawongs, P., Liu, J.C., Direct current iontophoretic transdermal delivery of peptide and protein drugs, *J. Pharm. Sci.* **78** (1989) 376-383.
[42] Stephen, R.L., Petelenz, T.J., Jacobsen, S.C., Potential novel methods for insulin administration: I. Iontophoresis, *Biomed. Biochim. Acta* **43** (1984) 553-558.
[43] Pillai, O., Borkute, S.D., Sivaprasad, N., Panchagnula, R., Transdermal iontophoresis of insulin II. Physicochemical considerations, *Int. J. Pharm.* **254** (2003) 271-280.
[44] Pillai, O., Nair, V., Panchagnula, Transdermal iontophoresis of insulin IV. Influence of chemical enhancers, *Int. J. Pharm.* **269** (2004) 109-120.
[45] Pillai, O., Panchagnula, Transdermal iontophoresis of insulin V. Effect of terpenes, *J. Controlled Release* **88** (2003) 287-296.
[46] Rastogi, S.K., Singh, J., Transepidermal transport enhancement of insulin by lipid exctraction and iontophoresis, *Pharm. Res.*, **19** (2002) 427-433.
[47] Rao, G., Glikfeld, P., Guy, R.H., Reverse iontophoresis: Development of a noninvasive approach for glucose monitoring, *Pharm. Res.* **10** (1993) 1751-1755.
[48] Glikfeld, P., Hinz, R.S., Guy, R. H., Noninvasive sampling of biological fluids by iontophoresis, *Pharm. Res.* **6** (1989) 988-990.
[49] Rao, G., Guy, R.H., Glikfeld, P., LaCourse, W.R., Leung, L., Tamada, J., Potts, R.O., Azimi, N., Reverse iontophoresis: noninvasive glucose monitoring *in vivo* in humans, *Pharm. Res.* **12** (1995) 1869-1873.
[50] Tierney, M.J., Tamada, J.A., Potts, R.O., Jovanovic, L., Garg, S., Cygnus Research Team, Clinical evaluation of the GlucoWatch biographer: A continual, non-invasive glucose monitor for patients with diabetes, *Biosens. Bioelectron.* **16** (2001) 621-629.
[51] Sekkat, N., Naik, A., Kalia, Y.N., Glikfeld, P., Guy, R., Reverse iontophoretic monitoring in premature neonates: feasibility and potential, *J. Controlled Release* **81** (2002) 83-89.
[52] Merino, V., Lopez, A., Hochstrasser, D., Guy, R.H., Noninvasive sampling of phenylalanine by reverse iontophoresis, *J. Controlled Release* **61** (1999) 65-69.
[53] Degim, I.T., Ilbasmis, S., Dündaröz, R., An application of reverse iontophoresis for transporting urea through membranens-I: A non-invasive technique for measuring or monitoring blood urea level, *Proceedings of the 11th International Pharmaceutical*

Technology Symposium, Hacettepe University, Pharmacy Faculty, Department of Pharmaceutical Technology, Istanbul 2002,150-151.

[54] Siddiqui, O., Roberts, M.S., Polack, A.E., The effect of iontophoresis and vehicle pH on the *in vitro* permeation of lignocaine through human stratum corneum, *J. Pharm. Pharmacol.* 37 (1985) 732-735.

[55] Wearley, L., Liu, J.C., Chien, Y.W., Iontophoretic facilitated transdermal delivery of verapamil (I): In vitro evaluation and mechanistic studies, *J. Controlled Release* **8** (1989) 237-250.

[56] Masada, T., Higuchi, W.I., Srinivasan, V., Rohr, V., Fox, J., Behl, C., Pons, S., Examination of iontophoretic transport of ionic drugs across skin: Baseline sudies with the four electrode system, *Int. J. Pharm.* 49 (1989) 57-62.

[57] Bellantone, N.H., Rim, S., Francoeur, M.I., Rasadi, B., Enhanced percutaneous absorption via iontophoresis I. Evaluation of an in vitro system and transport of model compounds, *Int. J. Pharm.* **30** (1986) 63-72.

[58] Glikfeld, P., Cullander, C., Hintz, R.S., Guy, R.H., A new system for *in vitro* studies of iontophoresis, *Pharm. Res.* **5** (1988) 443-446.

[59] Green, P., Flanagan, M., Shroot., B., Guy., R.H., Iontophoretic drug delivery, in *Pharmaceutical Skin Penetration Enhancement*, Walters, K.A., Hadgraft, J. (Eds.) Marcel Dekker, New York 1993, 311-333.

[60] Junginger, H.E., Iontophoretic delivery of apomorphine: from in-vitro modelling to the Parkinson patient, *Adv. Drug Deliv. Rev.*, Suppl.1 (2002) S57-S75.

[61] Ekman, K., Jaskari, T., Hirvonen, J., Peltonen, R., Sundell, M., Vuorio, M., Kontturi, K., Apparatus for dosaging an active ingredient and for investigating the dosage, Pat. WO0066326 Acc.11.9.2000.

[62] Anon., Press Release, http://www.alza.com/alza/pr_1064504571, 18.02.2004.

[63] Anon., What is the GlucoWatch® Biographer?, http://www.glucowatch.com/uk/consumer/frame_set.htm, 18.02.2004.

[64] Anon., Our Products, http://www.empi.com/b/b4.htm, 18.02.2004.

[65] Anon., Hyperhidrosis or Sweating Stopped by Drionic®, http://www.drionic.com/, 18.02.2004.

[66] Anon., Therapy Devices, http://www.hidrex.de/english/seiten/frameset.htm, 18.02.2004.

[67] Anon., Products, http://www.iomed.com/products/index.htm, 18.02.2004.

[68] Anon., Pain Management Instruments, http://www.life-tech.com/pain/index.html, 18.02.2004.

[69] Anon., http://www.optisgroup.com/Technology_Eyegate.htm, 08.03.2004

[70] Halhal, M., Renard, G., Courtois, Y., BenEzra, D., Behar-Cohen, F., Iontophoresis: from the lab to the bed side, *Exp. Eye Res.* **78** (2004) 751-757.

[71] Anon., Products, http://www.rafischer.com/prod05.htm, 18.02.2004.

[72] Anon., B. Braun Medical Inc. And Vyteris Inc. Sign Marketing Agreement, http://www.vyteris.com/release10802.html, 18.02.2004.

[73] Kalia, Y.,N., Naik, A., Garrison, J., Guy, R.H., Iontophoretic drug delivery, *Adv. Drug Deliv. Rev.* **56** (2004) 619-658.

[74] Anon., Products, http://www.wescor.com/biomedical/html/products.html, 18.02.2004.

[75] Wouters, S.E., Dinh, S.M., Microelectrochemical systems for drug delivery, *Electrochim. Acta* **42** (1997) 3385-3390.
[76] Lai, P.M., Roberts, M.S., Iontophoresis. In *Dermal absorption and toxicity assessment*, Roberts, S., Walters, K.A., (Eds.), Marcel Dekker, New York 1998, 371-414.
[77] Ziping, L., Okabe, K., High efficiency electrode system for iontophoresis, *US Pat. 5766144*, Acc. 16.6.1998.
[78] Haga, M., Akatani, M., Kikuchi, J., Ueno, Y., Hayashi, M., Transdermal iontophoretic delivery of insulin using a photoetched microdevice, *J. Controlled Release* **43** (1997) 139-149.
[79] Gröning, R., Electrophoretically controlled dermal or transdermal application systems with electronic indicators, *Int. J. Pharm.* **36** (1987) 37-40.
[80] Kantaria, S., Rees, G.D., Lawrence, M.J., Gelatin-stabilised microemulsion-based organogels: rheology and application in iontophoretic transdermal drug delivery, *J. Controlled Release* **60** (1999) 355-365.
[81] Frucht-Pery, J., Mechoulam, H., Siganos, C.S., Ever-Hadani, P., Shapiro, M., Domb, A., Iontophoresis- gentamicin delivery into the rabbit cornea using a hydrogel delivery probe, *Exp. Eye Res.* **78** (2004) 745-749.
[82] Fang, J.Y., Huang, Y.B., Wu, P.C., Tsai, Y.H., Transdermal iontophoresis of sodium nonivamide acetate II: optimization and evaluation on solutions and gels, *Int. J. Pharm.* **145** (1996) 175-186.
[83] Fang, J.Y., Sung, K.C., Lin, H.H., Fang C.L., Transdermal iontophoretic delivery of diclofenac sodium from various polymer formulations: *in vitro* and *in vivo* studies, *Int. J. Pharm.* **178** (1999) 83-92.
[84] Fang, J.Y., Kuo, C.T., Huang, Y.B., Wu, P.C., Tsai, Y.H., Transdermal delivery of sodium nonivamide propionate by iontophoresis, *Biol. Pharm. Bull.* **21** (1998) 1117-1120.
[85] Murtomäki, L., Barker, M.H., Manzanares, J.A., Kontturi, K., Study of the membrane composition on ion transfer across a supported liquid membrane, *J. Electroanal. Chem.* **561** (2003) 95-103.
[86] Okabe, K., Yamaguchi, H., Kawai, Y., New iontophoretic transdermal administration of the beta blocker metoprolol, *J. Controlled Release* **4** (1986) 79-85.
[87] Fang, J.Y., Huang, Y.B., Lin, H.-H., Tsai, Y.H., Transdermal iontophoresis of sodium nonivamide acetate. IV. Effect of polymer formulations, *Int. J. Pharm.* **173** (1998) 127-140.
[88] Pillai, O., Panchagnula, R., Transdermal delivery of insulin from poloxamer gel: *ex vivo* and *in vivo* skin permeation studies in rat using iontophoresis and chemical enhancers, *J. Controlled Release* **89** (2003) 127-140.
[89] Nair, V., Panchagnula, R., Poloxamer gel as a vehicle for transdermal iontophoretic delivery of arginine vasopressin: evaluation of in vivo performance in rats, *Pharmacol.Res.* **47** (2003) 555-562.
[90] Banga, A.K., Chien, Y.W., Hydrogel based iontotherapeutic delivery devices for transdermal delivery of peptide/protein drugs, *Pharm. Res.* **10** (1993) 697-702.
[91] Sahota, T.S., Latham, R.J., Lindford, R.G., Taylor, P.M., Physical characterization of polymer electrolytes as novel iontophoretic drug delivery device, *Drug Dev. Ind. Pharm.* **25** (1999) 307-313.

[92] Sahota, T.S., Latham, R.J., Lindford, R.G., Taylor, P.M., In vitro iontophoretic release of lithium chloride and lidocaine hydrochloride from polymer electrolytes, *Drug Dev. Ind. Pharm.* **26** (2000) 1039-1044.

[93] Fang, J.Y., Hsu, L.R., Huang, Y.B., Tsai, Y.H., Evaluation of transdermal iontophoresis of enoxacin from polymer formulations: in vitro skin permeation and in vivo microdialysis using Wistar rat as animal model, *Int. J. Pharm.* **180** (1999) 137-149.

[94] Sathyan, G., Ritschel, W.A., Hussain, A.S., Transdermal delivery of tacrine: I. Identification of a suitable delivery vehicle, *Int. J. Pharm.*, **114** (1995) 75-83.

[95] Hirvonen, J., Guy, R.H., Iontophoretic delivery across the skin: electroosmosis and its modulation by drug substances, *Pharm. Res.* **14** (1997) 1258-1263.

[96] Telting-Diaz, M., Lunte, C.E., Distribution of tacrine across the blood-brain barrier in awake, freely moving rats using in vivo micridialysis sampling, *Pharm. Res.* **10** (1993) 44-48.

[97] Drayton, C.J., Cumulative subject index and drug compendium, in: Hansch, C., Sammes, P.G., Taylor, J.B. (Eds.), *Comprehensive Medicinal Chemistry*, Vol. 6, Pergamon press, Oxford, 1990.

[98] Helfferich, F., *Ion Exchange*, Dover, New York, 1995.

[99] Laksminarayanaiah, N., *Equations of Membrane Biophysics*, Academic Press, Orlando, FL, 1984, Sections 3.4, 3.6, 3.7.

[100] Lyklema, J., *Fundamentals of Colloid and Interface Science*, Vol.1, Academic Press, London, 1991, Section 2.20.

[101] Sørensen, T.S., Rivera, S.R., Electrochemical characterization of membranes and membrane surfaces by EMF measurements, in: Sørensen, T.S.(Ed.), *Surface chemistry and electrochemistry of membranes*, Marcel Dekker, New York, 1999, Chapter 10.

[102] Sprockel, O.L., Price, J.C., Evaluation of sustained release aqueous suspensions containing microencapsulated drug resin complexes, *Drug Dev. Ind. Pharm.* **15** (1989) 1275-1287.

[103] Irwin, W.J., Belaid, K.A., Alpar, H.O., Drug delivery by ion-exchange. Part III: interactions of ester pro-drugs of propranolol with cationic exchange resins, *Drug Dev. Ind. Pharm.* **13** (1987) 2047-2066.

[104] Charman, W.N., Christy, D.P., Geunin, E.P., Monkhouse, D.C., Interaction between calcium, a model divalent cation, and a range of poly(acrylic acid) resins as a function of solution pH, *Drug Dev. Ind. Pharm.* **17** (1991) 271-280.

[105] Vihola, H., Laukkanen, A., Hirvonen, J., Tenhu, H., Binding and release of drugs into and from thermosensitive poly(N-vinylcaprolactam) nanoparticles, *Eur. J. Pharm. Sci.* **16** (2002) 69-74.

[106] Chen, L., Yang, G., Zhang, J., A study of the exchange kinetics of ion-exchange fiber, *React. Funct. Polym.* **29** (1996) 139-144.

[107] Lin, W., Hsieh, Y.L., Kinetics of metal ion absorption on ion-exchange resins and chelating fibers, *Ind. Eng. Chem. Res.* **35** (1996) 3817-3821.

[108] Marchal-Heusser, L., Colling, N., Benoit, E., Maincent, P., Bessierre, J., Applicability of dielectric measurements to the adsorption of beta blockers onto a pharmaceutical grade ion-exchange resin, *Pharm. Res.* **17** (2000) 1144-1147.

[109]Srinivasan, V., Higuchi, W., Sims, S., Ghanem, A., Behl, C., Transdermal iontophoretic drug delivery: Mechanistic analysis and application to polypeptide delivery, *J. Pharm. Sci.* **78** (1989) 370-375.

[110] Delgado-Charro, B., Rodriguez-Bayon, A., Guy, R.H., Iontophoresis of nafarelin: effects of current density and concentration on electrotransport in vitro, *J. Controlled Release* **35** (1995) 35-40.

[111] Behl, C., Kumar, S., Malick, A., DelTerzo, S., Higuchi, W., Nash, R., Iontophoretic drug delivery: Effects of physicochemical factors on the skin uptake of nonpeptide drugs, *J. Pharm. Sci.* **5** (1989) 355-360.

[112] Mälkiä, A., Liljeroth, P., Kontturi, A.K., Kontturi, K., Electrochemistry at lipid monolayer-modified liquid-liquid interfaces as an improvement to drug partitioning studies, *J. Phys. Chem. B*, **105** (2001) 10884-10892.

[113] Wagstaff, A.J., McTavish, D., Tacrine: a review of its pharmakokinetic properties, and therapeutic efficacy in Alzheimer's disease, *Drugs Aging* **4** (1994) 510-540.

[114] Van der Geest, R., van Laar, T., Gubbens-Stibbe, J.M., Boddé, H.E., Danhof, M., Iontophoretic delivery of apomorphine II:, An in vivo study in patients with Parkinson's desease, *Pharm. Res.* **14** (1997) 1804-1810.

[115] Gupta, S.K., Bernstein, K.J., Noorduin, H., van Peer, A., Sathyan, G., Haak, R., Fentanyl delivery from an electrotransport system: Delivery is a function of total current, not duration of current, *J. Clin. Pharmacol.* **38** (1998) 951-958.

[116] Phipps, B.J., Gyory, R.J., Transdermal ion migration, *Adv. Drug Del. Rev.* **9** (1992) 137-176.

[117] Riviere, J.E., Sage, B.H., Monteiro-Riviere, N.A., Transdermal lidocaine iontophoresis in isolated perfused porcine skin, *J. Toxicol. Cut. Ocular. Toxicol.* **9** (1989/1990) 493-504.

[118] Green, P., Shroot, B., Bernerd, F., Pilgrim, W.R., Guy, R.H., In vitro and in vivo iontophoresis of a tripeptide across nude rat skin, *J. Controlled Release* **20** (1992) 209-217.