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Controlled transport of timolol maleate through artificial membranes under passive and iontophoretic conditions

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Abstract

The passive and iontophoretic permeability of timolol maleate (TM) through porous and dense artificial membranes was investigated in order to select the most optimal membrane for a transdermal drug delivery system. For the meso-porous membranes (pore diameter 2–50 nm), the TM permeability for passive diffusion and iontophoresis was practically the same. For the micro-porous membranes (pore diameter<2 nm), a significant transport contribution of iontophoresis was observed, which was more pronounced when higher current densities were applied. The electrical resistance of all the porous membranes was lower than the electrical resistance of human skin. For dense membranes, passive and iontophoretic TM permeability was significantly lower than for porous membranes and in most cases their electrical resistance was comparable or even higher than the resistance of human skin. For most of the membranes studied the average adsorption of TM at 37 °C was low (0.02–0.33 mg/cm^2) and independent of the TM concentration. For the meso-porous mixed cellulose acetate–cellulose nitrate membrane the TM adsorption was significantly higher and increased with the TM concentration. Based on our results, the optimum membrane for an iontophoretic transdermal TM delivery system is the LFC 1 micro-porous membrane because it mainly controls the TM delivery (TM iontophoretic permeability: 0.86×10^{-6} cm/s), has very low electrical resistance (0.9–1.5 kΩ cm^2) and the TM adsorption to it is low (0.15 mg/cm^2). The therapeutic plasma TM concentration is achievable by application of this membrane in realistic sizes (5–64 cm^2) and by application of current densities between 0.13 and 0.5 mA/cm^2.

Keywords: Iontophoresis; Timolol maleate; Artificial membranes; Transdermal delivery

1. Introduction

The skin is the largest organ of the human body, with a surface area of about 2 m^2. Historically, the skin was viewed as an impermeable barrier as its primary purpose is protection against entry of foreign agents into the body. However, in recent years, it has been increasingly recognized that intact skin can be considered as a port for topical or continuous systematic administration of drugs [1a]. Skin can be

Abbreviations: A, membrane area; $C_{acceptor}$, acceptor concentration; C_{donor}, donor concentration; C_{ss}, steady state concentration in the plasma; F, acceptor flow rate; J_{app}, apparent flux; J_{ss}, steady state flux; $(J_{ss})_{total}$, steady state flux through membrane+skin; h, membrane thickness; I, electrical current; $(K_P)_{memb}$, membrane permeability; $(K_P)_{skin}$, skin permeability; $(K_P)_{total}$, total permeability of the drug through the membrane and the skin

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used as a route of administration for systematic delivery of a drug via a transdermal patch. For drugs that have short half-lives, a transdermal route provides a continuous mode of administration, somewhat similar to that provided by an intravenous infusion. However, unlike an intravenous infusion, delivery is non-invasive and no hospitalization is required. Once absorbed, the hepatic circulation is bypassed, thus avoiding another major site of potential degradation [2].

Transdermal delivery of the drugs can be assisted by electrical energy. The physical force can be the application of either direct constant current (iontophoresis) or pulsed current (electroporation) [1a,3]. Iontophoresis implies the use of small amounts of physiologically acceptable electric current to drive charged drug molecules into the body. By using an electrode of the same polarity as the charge of the drug, the drug is driven into the skin by electrostatic repulsion (Fig. 1) [1a]. In addition, bulk fluid flow or volume flow occurs in the same direction as the flow of the counter ions. This phenomenon, which accompanies iontophoresis, is called electro-osmosis. In this paper, under the term 'iontophoresis' both the phenomena of electrostatic repulsion and electro-osmosis are included. Because the amount of drug transported by iontophoresis is proportional to the current applied; it is possible to deliver the drug in a controlled manner using pre-programmed delivery rates [4,5].

A very important component of the drug delivery patch is the membrane. It is the part in direct contact with the skin and acts as the interface between the drug solution reservoir and the skin to give optimal control for the transdermal drug delivery (Fig. 1). The membrane should have the following requirements:

1. It should be made of biocompatible material to avoid skin irritation.
2. It should control the drug delivery (the permeability of the drug through the membrane should be lower than through the skin). In this case the transdermal bioavailability of the drug becomes independent of any possible intra- and/or inter-patient variability in skin permeability.
3. It should have very low electrical resistance so the overall resistance of membrane+skin during iontophoresis does not become high. If the latter happens, the system's voltage drop becomes high, which is not favorable for iontophoretic delivery systems due to the depletion of the electrical power source.
4. The drug adsorption to it should be low.

In the transdermal drug delivery by a patch, the

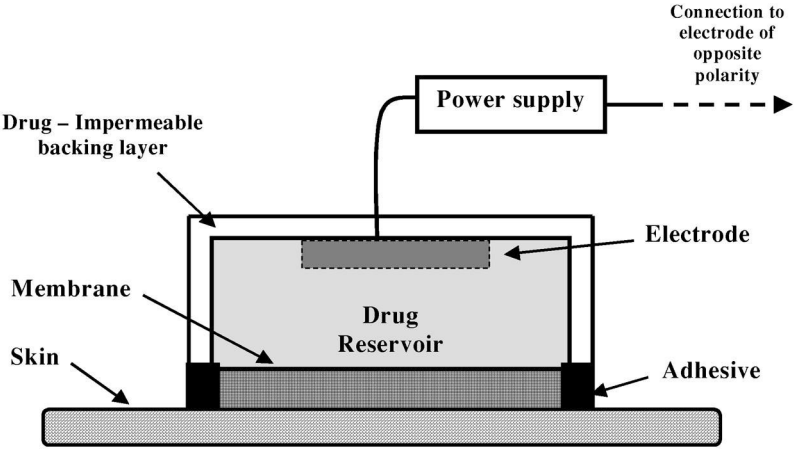

Fig. 1. Schematic illustration of a transdermal drug delivery patch in contact with skin. For iontophoretic delivery, an electrode of the same polarity as the charge of the drug is placed in the drug reservoir. The electrical circuit is completed by the application of a second electrode of the opposite polarity at a different skin site.

total permeability $(K_P)_{total}$ of the drug through the membrane+skin is given by [6]:

$$\frac{1}{(K_P)_{total}} = \frac{1}{(K_P)_{memb}} + \frac{1}{(K_P)_{skin}} \quad (1)$$

where $(K_P)_{memb}$, $(K_P)_{skin}$ represents the permeability of the drug through the membrane and the skin, respectively. Depending on the ratios of $(K_P)_{memb}$ and $(K_P)_{skin}$ the TM delivery may be primarily skin-rate controlled or primarily membrane-rate controlled. When the ratio $(K_P)_{memb}/(K_P)_{skin}$ is less than 0.2, the delivery is considered to be membrane controlled. When the ratio $(K_P)_{memb}/(K_P)_{skin}$ is larger than 5, it is considered to be skin-rate controlled. If the ratio $(K_P)_{memb}/(K_P)_{skin}$ is in between 0.2 and 5, the systematic dosage received is controlled by both the skin and the membrane [7].

In the present work, the passive and iontophoretic delivery of timolol maleate (TM) through artificial membranes is studied. TM is a nonselective beta-adrenergic blocking agent that is used in the management of hypertension, angina pectoris, myocardial infarction and glaucoma. It undergoes extensive first-pass hepatic metabolism and its elimination half-life is 2–2.6 h [8]. Transdermal delivery of TM would avoid hepatic first pass metabolism after oral administration.

For the investigation of the TM delivery through the membranes, several biocompatible materials were selected and artificial membranes of these materials (porous and dense) were either purchased or prepared. The aim of this work is, based on the above-mentioned membrane requirements, to select the optimum one for the TM transdermal delivery system.

2. Experimental

2.1. Materials

Timolol maleate salt (MW=432.5) was obtained from Sigma. Several porous [meso-porous (pore diameter 2–50 nm), micro-porous (pore diameter<2 nm)] and dense membranes were either purchased or prepared [see Table 1; in this table, Molecular Weight Cut Off (MWCO) of the membrane: solutes having this molecular weight are 90% rejected by the membrane].

The FKB and CM2 are dense cation-exchange membranes and contain negatively charged groups fixed to the polymer matrix. When they are placed in an electrolyte solution, the cations, i.e. the positively charged ions in the solution are able to penetrate through the swollen membrane due to the negatively charged fixed groups on the matrix. In contrast, the anions are more or less excluded [9a]. The silicone rubber (SR) membranes were prepared from a two-component rubber (RTV 615, supplied by General Electric, composed of viscous liquid RTV 615A and cross linker RTV 615B in a ratio 10:1) by casting the above solution on a Teflon plate followed by cross linking at 70 °C for 18 h. Silicone rubber membranes have been frequently used in drug controlled delivery systems [10].

2.2. Diffusion cell

The type of diffusion cell used in this work was developed and introduced by van der Geest et al. [11] (Fig. 2). It is a three-chamber compartment continuous flow through transport cell. The two outer chambers have a volume of 2 ml. They contain two vertical openings on the topside for the electrodes (one for the driving and one for the reference electrode) and a downward protruding volume close to the diffusion surface for stirring. The acceptor volume is 0.54 ml and the exposed area for transport is 0.64 cm^2. Circulating water at 37 °C controls the temperature of the acceptor chamber. The temperature in the donor chamber reaches 32 °C. A Perspex clamp holds cells and membranes together. A 1-mm silver plate electrode and a silver/silver chloride electrode were used as driving electrodes in the anodal and cathodal compartment, respectively (silver plate and dipped silver/silver chloride 99.99% obtained from Aldrich). Silver/silver chloride electrodes were also used as reference electrodes (Fig. 2).

TM was dissolved in phosphate buffered saline (PBS) 0.153 M solution at pH 7.4 [PBS: NaCl (8 g/l), KCl (0.19 g/l), KH_2PO_4 (0.2 g/l), $Na_2HPO_4.12H_2O$ (2.86 g/l) in Ultrapure Milli-Q= deionised water]. Under these conditions, TM exists as predominantly positively charged ions (98.5%). In

Table 1
Membrane materials and their characteristics

Membrane	Material/ manufacturer	MWCO[a] (kDa)	Thickness h (μm)	pH range[a]	Temperature range (°C)[a]
Meso-porous					
Mill F-0.025 μm	Mixed CA, CN/Millipore	(Pore 0.025 μm)	94	2–8	0–75
CT-10 kDa	CT/Sartorius	10	100	4–8	0–50
CT-20 kDa	CT/Sartorius	20	119	4–8	0–50
Dialysis-5 kDa	NC/Diachema	5	55	3–10	0–60
PES-30 kDa	PES/Sartorius	30	116	1–14	0–50
PSf-100 kDa	PSf/Sartorius	100	100	1–14	0–50
CA-10 kDa	CA/Amika	10	93	2–8	0–50
CA-25 kDa	CA/Amika	25	89	2–8	0–50
CA-50 kDa	CA/Amika	50	86	2–8	0–50
CA-100 kDa	CA/Amika	100	99	2–8	0–50
Micro-porous					
LFC 1	AP/Hydronautics	Unknown	140	3–10	0–45
UTC 70	AP/Toray	Unknown	186	3–10	0–45
NF 45	AP/Film-Tec	Unknown	142	3–10	0–45
NF-PES-10	PES/Nadir Filtration	Unknown	290	1–14	0–75
NF-CA-30	CA/Nadir Filtration	Unknown	232	2–8	0–50
Dense					
Cotran™ 9702	PEVAc (9% VAc)/3M	–	59	2–8	–
Cotran™ 9728	PEVAc (19%VAc)/3M	–	59	2–8	–
SR	PDMS/self made	–	150	–	(−60)–200
CM2	Neosepta®/Tokuyama	–	150	1–14	–
FKB	–/Fuma-tech	–	150	1–14	–

AP, aromatic polyamide; CA, cellulose acetate; CN, cellulose nitrate; CT, cellulose triacetate; PEVAc, polyethylene vinyl acetate; NC, neutral cellulose; PES, polyethersulfone; SR, silicone rubber; PDMS, poly dimethyl siloxane; PSf, polysulfone.
[a] Given by the manufacturer.

all cases, unless stated otherwise, the concentration of TM applied to the donor chamber was 25 mg/ml.

Most of the porous commercial membranes contain glycerin and/or other preservatives that have to be removed prior to the transport experiments. Therefore, the membranes were washed for at least 24 h in Ultrapure Milli-Q water at room temperature and then soaked in a PBS solution for at least another 24 h. For the dense membranes the same washing and hydration procedure was followed for consistency. The porous membranes have an asymmetric structure. They consist of an active selective layer and a porous 'support' [9b]. In all the experiments the active selective layer was always facing the TM donor solution.

2.3. Procedure for passive diffusion and iontophoresis

Membrane pieces were introduced between the cell chambers (Fig. 2) and the cell acceptor chamber was equilibrated for 30 min with PBS at a flow rate of 6.5 ml/h using a peristaltic pump (Watson-Marlow 205U/CA). The TM donor solution was applied in the anodal chamber and PBS solution was applied in the cathodal chamber. During the experiment the outer chambers were stirred continuously at 375 rpm.

In the iontophoretic experiments, the driving electrodes were connected to a power supply (LAB/SL 120/Al/mod, ET System Electronic GmbH, Germany). The resistance of each cell was monitored independently by digital multi-meters (Dynatek 9001a) connected to the reference electrodes. Current density up to 0.5 mA/cm^2 was mainly applied, which has been reported as the maximum acceptable for the iontophoretic transdermal delivery producing minimal skin damage and irritation [11,12]. Nevertheless, for testing purposes, iontophoretic experiments were also carried out with the application of current densities up to 5.5 mA/cm^2. Further increase

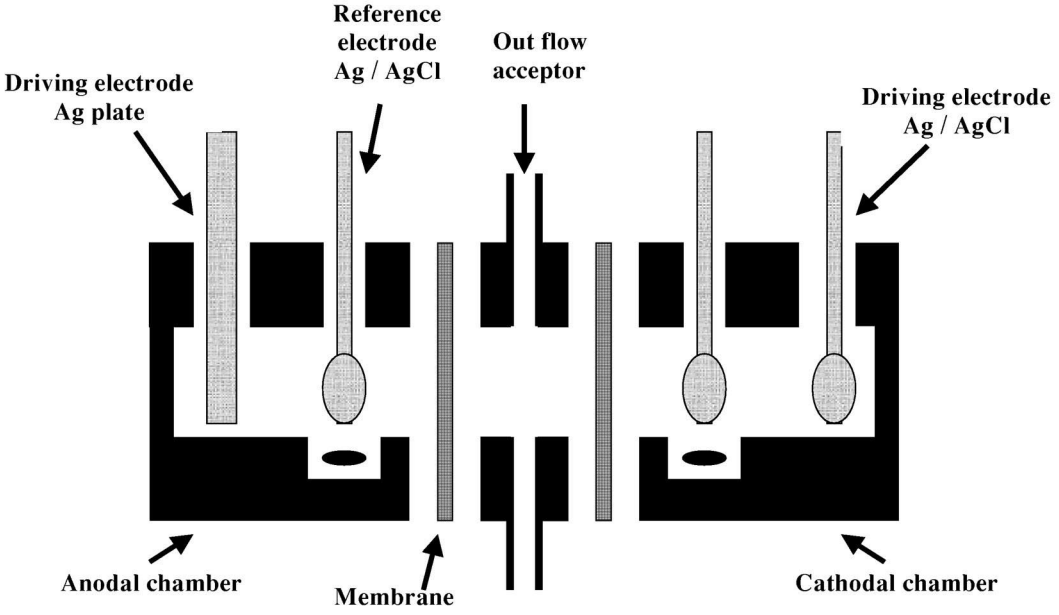

Fig. 2. Schematic drawing of the three-chamber continuous flow through transport cell.

in the applied current density proved impossible; the integrity of the silver/silver chloride electrodes was lost, pH shifting was observed and therefore some sensitive membrane materials were damaged.

All the experiments were carried out for at least 8 h. The flow through acceptor solution was being collected every hour and the concentration of TM was determined by UV and/or HPLC depending on the concentration range. UV spectroscopy was used for all the meso-porous membranes (UV–Vis spectrophotometer, Philips PU 8720 at 294 nm, detection limit 2.5 μg). HPLC was used for the micro-porous and the dense membranes because of the low TM concentration {HPLC with UV detector at 294 nm. Column: Supercosil LC 18-DB 15 cm×4.6 cm; 5 μm (Waters); retention time ~2.9 min. Mobile phase: acetonitrile/buffer at pH 4.0 (25:75, v/v). Mobile phase buffer: 2.02 g triethyl amine; 10.0 g acetic acid; 1 l of Millipore water, adjusted to pH 4 with 5 N NaOH. The flow rate was 1 ml/min and chromatography was carried out at room temperature, detection limit 0.05 μg [13]}.

All the experiments were performed at least in triplicate for each membrane material. During all the experiments, the pH and the temperature of the donor and acceptor chambers were carefully monitored.

The apparent flux of TM through the membrane, J_{app}, is obtained using the basic equation [11]:

$$J_{app} = \frac{FC_{acceptor}}{A} \quad (2)$$

where $C_{acceptor}$ is the TM acceptor concentration (in mg/cm^3), A is the available membrane area for diffusion (in cm^2) and F is the acceptor flow rate (in cm^3/h). The flux reaches steady state after a certain time. This steady state flux (J_{ss}) is obtained from the linear part of the cumulative flux. The J_{ss} (in mg cm^{-2} h^{-1}) is expressed as:

$$J_{ss} = (K_P)_{memb} C_{donor} \quad (3)$$

where C_{donor} is the concentration of TM in the donor chamber.

2.4. Adsorption of TM to the membrane materials

During the permeation experiments, part of the TM is adsorbed on the membrane material. High adsorption of the drug to the membrane, besides the loss of valuable drug molecule, probably causes fouling of the material, which influences the membrane's permeability [9c].

For the selection of the proper membrane material

for the TM delivery system, the measurement of the adsorption of TM on the membranes was performed as follows: The membrane samples were dipped in a TM solution at 37 °C for at least 3 days. The membranes were then removed from the solution and the concentration of the TM adsorbed to the membrane was calculated from the difference between the concentration of the TM solution before and after membrane dipping. Alternatively, the membranes after their removal from the drug solution were dipped in pure buffer solution. TM adsorbed to the membrane is then desorbed out and into the buffer solution where it is detected by UV and/or HPLC. The results of both techniques were in very good agreement.

3. Results and discussion

3.1. Permeability of TM through the membranes

The results of the passive (current density: $I/A=0$) and iontophoretic ($I/A=0.5$ mA/cm^2) transport of TM through the membrane materials are presented in Table 2. The average permeability of TM through the membrane materials was in the range of $(0.02–90.7)\times10^{-6}$ cm/s. The lowest permeability was measured (as was expected) in the case of the dense membranes and the highest in the case of the CT-20 kDa meso-porous membranes.

3.1.1. Meso-porous membranes

The permeability of TM through the meso-porous membranes with or without current application was practically the same (Table 2). For these membranes, the contribution of passive diffusion greatly outweighed the contribution of electrical current thereby making the TM transport with and without applied current indistinguishable. For some membranes the standard deviation of TM permeability was higher than in others. This is probably due to variation in membrane porosity when different (small) samples are used.

In the series of CA membranes (MWCO range:

Table 2
Permeability of TM through membranes during passive diffusion and iontophoresis ($I/A=0.5$ mA/cm^2)

Membrane	$(K_p)_{memb}\times10^6$ (cm/s)		Electrical resistance (kΩ cm^2)
	Passive diffusion	Iontophoresis	
Meso-porous			
Mill F-0.025 μm	83.8±9.2	85.4±10.5	0.12–0.16
CT-10 kDa	61.3±3.6	64.3±0.8	0.12–0.18
CT-20 kDa	90.5±9.0	90.7±10.5	0.16–0.32
CA-10 kDa	19.6±4.4	20.9±1.3	0.16–0.24
CA-25 kDa	42.2±3.9	47.4±10.0	0.22–0.24
CA-50 kDa	62.6±7.9	78.1±14.3	0.18–0.24
CA-100 kDa	75.9±13.7	85.8±7.4	0.14–0.20
Dialysis-5 kDa	51.8±2.8	52.8±5.1	0.16–0.26
PES-30 kDa	42.9±7.1	41.0±8.6	0.16–0.23
PSf-100 kDa	52.8±4.1	51.6±3.3	0.30–0.32
Micro-porous			
NF-CA-30	14.3±3.6	18.2±4.3	0.16–0.26
NF-PES-10	5.2±0.5	6.7±0.8	0.38–0.42
NF 45	0.79±0.13	1.80±0.25	0.72–0.88
UTC 70	0.33±0.08	1.13±0.08	1.02–3.08
LFC1	0.26±0.03	0.86±0.05	0.90–1.54
Dense			
Cotran™ 9702	0.02±0.01	0.02±0.01	256.5
Cotran™ 9728	0.04±0.01	0.08±0.06	32.5–240
CM2	0.02±0.01	0.02±0.01	0.14–0.22
FKB	0.03±0.01	0.03±0.01	42.2–56.8
SR	Not measurable	Not measurable	

10–100 kDa) and CT membranes (MWCO: 10 and 20 kDa), the permeability of TM was increasing with the increase in the MWCO (i.e. pore size) as expected (Table 2). The results of the permeability of TM through membranes made of different polymeric material but of similar MWCO were not in agreement in most of the cases. The permeability of TM through PES-30 kDa and CA-25 kDa was similar but this was not the case for CA-10 kDa and CT-10 kDa or CA-25 kDa and CT-20 kDa membranes (Table 2). It is important to note that the MWCO of the membrane (and only that) does not give a 'full picture' of the membrane structure. The observed differences between the TM permeability through the different materials could also be due to differences in the properties of the respective membrane materials such as membrane thickness, pore radii, pore size distribution and pore density. The relative material hydrophobicity/hydrophilicity, the relative swelling of the membrane in the TM solution may also play an important role in the TM permeability. Moreover the MWCO values given by the respective manufacturers (Table 1) are not really comparable because they are obtained by different methods and under different conditions (flow rate, trans-membrane pressure, type of solute, solute concentration etc.).

The permeability of TM through the meso-porous membranes did not increase even with the application of higher currents. Typical results of the relation of the TM permeability with the applied current density through Mill F-0.025, Dialysis 5 kDa and CA-10 kDa membranes are presented in Fig. 3.

The electrical resistance of the meso-porous membranes during iontophoresis was in the range of 0.12–0.32 kΩ cm^2 (Table 2) and was significantly lower than the respective values of electrical resistance commonly measured during iontophoresis with human skin (16–50 kΩ cm^2) [1b].

Fatouros and Bouwstra (Leiden University, The Netherlands) studied the permeability of TM through human skin under the same conditions as this work. They reported $(K_P)_{skin} = 3.4 \times 10^{-6}$ cm/s at a current density of 0.5 mA/cm^2, (unpublished results, personal communication). The permeability of TM through meso-porous membranes is always much higher than through the skin. Therefore, meso-porous membranes are not suitable for a transdermal delivery patch where transport should be controlled by the membrane. In these systems, the skin controls the TM delivery $\{(K_P)_{memb}/(K_P)_{skin} > 5\}$.

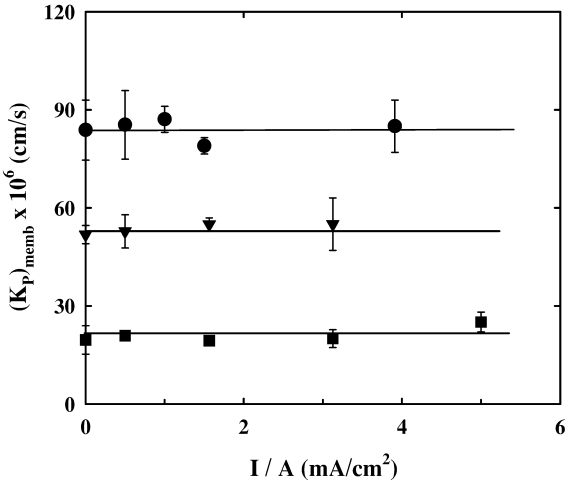

Fig. 3. Results of the relation of the membrane permeability with the applied electrical current density during transport of TM through: Mill F-0.025 (●), Dialysis-5 kDa (▼), CA-10 kDa (■) meso-porous membranes.

3.1.2. Micro-porous membranes

When micro-porous membranes were used, all except NF-CA-30 showed an increase in TM transport due to current application (Table 2). This increase was more pronounced when the applied current was higher. Typical results of the TM permeability through these membranes versus the applied current density are presented in Fig. 4. Their electrical resistances during iontophoresis were in the range of 0.16–3.08 kΩ cm^2 (Table 2) and always lower than the electrical resistance of human skin.

The permeability of TM through micro-porous membranes is mostly lower than through human skin. When a LFC 1 membrane is applied in an iontophoretic patch, it mainly controls the TM transport $\{(K_P)_{memb}/(K_P)_{skin} = 0.25\}$. Application of the other micro-porous membranes results in a system where both membrane and skin control $\{5.3 < (K_P)_{memb}/(K_P)_{skin} < 0.3\}$.

3.1.3. Dense membranes

When dense membranes were applied, the passive and iontophoretic TM permeability was significantly lower than when porous membranes were applied (Table 2). Polyethylene-co-vinyl acetate membranes

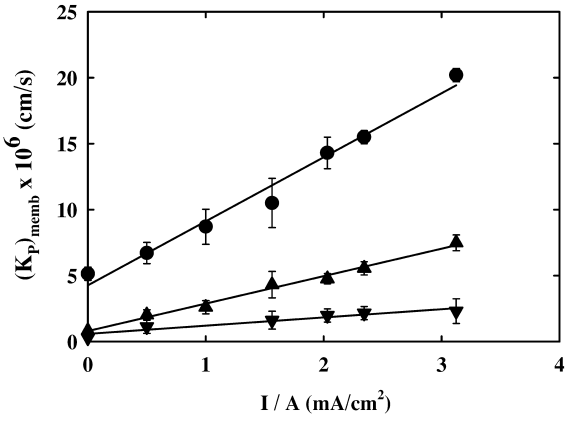

Fig. 4. Results of the relation of membrane permeability with applied electrical current density during transport of TM through: NF-PES-10 (●), NF-45 (▲) and UTC 70 (▼) micro-porous membranes.

are frequently used in controlled release drug delivery systems [7]. Cotran™ 9702 and 9728 have already been used in reservoir patches for the delivery of hydrocortisone (MW=362.5), estradiol (MW=272.4), progesterone (MW=314.5) and testosterone (MW=288.4). Passive permeability of the above molecules through Cotran™ membranes has been reported in the range of $(0.02–0.06)\times10^{-6}$ cm/s (3M Medica at: www.mmm.com), which is in good agreement with the results obtained in this work with the similar sized molecule of TM.

For Cotran™, CM2 and FKB ion-exchange membranes, no difference for the TM permeability has been found between passive diffusion and iontophoresis. For the CM2 membrane, low electrical resistance has been measured. In contrast, for both Cotran™ and the FKB cation-exchange membranes, the electrical resistance was very high. For the FKB membrane, we have observed a gradual increase in the system's electrical resistance in time. This could be due to material fouling [9c].

For silicone rubber membranes no passive or iontophoretic permeability of TM could be detected. Moreover, in the case of iontophoresis, extremely high electrical resistance was measured. This is due to the material's notable hydrophobicity. Practically, no swelling of it was observed in aqueous solutions.

In the light of all the above findings, it can be concluded that the application of dense membranes in the iontophoretic TM delivery does not seem appropriate {although $(K_P)_{memb}/(K_P)_{skin}<0.2$}. The TM permeability through these membranes during passive diffusion and iontophoresis is the same and most of them have very high electrical resistance. Therefore, no further research on dense membranes has been carried out.

3.2. Adsorption of TM to the membranes

The adsorption of TM to all porous membranes was measured. When membranes of the same material, but of variable MWCO were available, TM adsorption was measured for the membrane with the lowest MWCO.

The average amount of TM adsorbed to the porous membranes at 37 °C, except Mill F-0.025 μm, was low (in the range of 0.02–0.33 mg/cm^2) and almost independent of the TM concentration. In contrast, the adsorption of TM to Mill F-0.025 membranes was increasing with TM concentration. Typical results of TM adsorption to the membranes at TM concentration of 25 mg/ml are presented in Table 3 and typical adsorption isotherms of TM to NF-PES-10 and Mill F-0.025 membranes, at 37 °C are presented in Fig. 5. No definite explanation can be given for the higher adsorption of TM to the Mill F-0.025 than

Table 3
Adsorption of TM to the membranes

Membrane	Thickness h (μm)	TM adsorption (mg/cm^2)
Meso-porous		
Mill F-0.025 μm	94	2.86±0.69
CT-10 kDa	100	0.20±0.11
Dialysis-5 kDa	55	0.02±0.01
PES-30 kDa	116	0.06±0.05
PSf-100 kDa	100	0.33±0.17
CA-10 kDa	93	0.18±0.10
Micro-porous		
NF-CA-30	318	0.12±0.08
NF-PES-10	290	0.28±0.14
NF 45	142	0.05±0.01
UTC 70	186	0.12±0.01
LFC 1	140	0.15±0.01

Concentration of TM: 25 mg/ml.

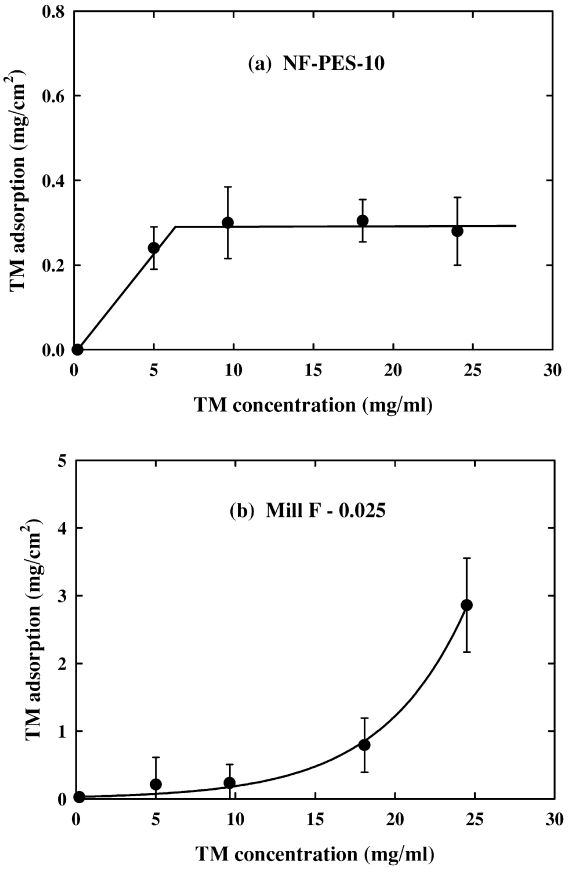

Fig. 5. Typical adsorption isotherms of TM at 37 °C for (a) NF-PES-10 and (b) Mill F-0.025 membranes.

to the other porous membranes. The Mill F-0.025 membrane is a mixed cellulose acetate–cellulose nitrate membrane and since the adsorption of TM to the pure cellulose acetate membranes is relatively low (Table 3) the increased adsorption of TM to the Mill F-0.025 membrane could be due to a high adsorption of TM to the cellulose nitrate part.

3.3. Transdermal delivery of TM for systemic use

Based on the permeability results presented earlier, the LFC 1 micro-porous membrane seems to be the most suitable for a membrane controlled TM delivery system. In addition, this membrane has low electrical resistance and the TM adsorption to it is very low.

At steady state, the rate of TM administration through LFC 1+skin should be equal to the rate of its elimination in plasma:

$$A(J_{ss})_{total} = C_{ss}\,CL \Leftrightarrow A\,C_{donor}(K_P)_{total} = C_{ss}\,CL \quad (4)$$

where $(J_{ss})_{total}$ is the steady state flux through LFC 1+skin, C_{ss} is the steady state TM concentration in the plasma (in ng/ml) and CL is the TM clearance (the rate of TM elimination divided by the TM plasma concentration, in l/h) [14]. For an individual of 75 kg weight, the TM clearance has been reported at approximately 35 l/h [15]. The TM daily dose depending on the disease and treatment varies between 10 and 60 mg (TM–Rx List Monographs, at: www.rxlist.com) and therefore the estimated constant TM concentration in the plasma should be in the range of 12–71 ng/ml [16]. From the above parameters, using Eqs. (1) and (4) and by assuming C_{donor} = 40 mg/ml, the size of the LFC 1 membrane for the achievement of the above TM plasma concentration range at various current densities was calculated (Table 4). For this calculation, a linear relation was used to estimate the $(K_P)_{skin}$ of TM at various current densities and was found combining the results of Karikkannan et al. [8] (at I/A=0 and 0.375 mA/cm^2) and Fatouros and Bouwstra (at I/A=0.5 mA/cm^2, unpublished results, personal communication). The TM permeability through the LFC 1 membrane at various current densities was found in this work. Based on our calculations, the therapeutic plasma TM concentration is achievable by using the LFC 1 membrane in realistic sizes and by application of current densities lower than 0.5 mA/cm^2 (Table 4).

Table 4
Predicted characteristics of a TM transdermal iontophoretic patch prepared by application of the LFC 1 membrane

Membrane	I/A (mA/cm^2)	$(K_P)_{skin}\times10^6$ (cm/s)	$(K_P)_{memb}\times10^6$ (cm/s)	A (cm^2)
LFC 1	0.13	0.92	0.38	11–64
	0.25	1.69	0.53	7–43
	0.38	2.50	0.64	6–33
	0.50	3.40	0.86	5–27

4. Conclusions

The average TM iontophoretic permeability through porous membranes was found in the range of $(0.86–90.7)\times10^{-6}$ cm/s. Their electrical resistance (0.12–3.08 kΩ cm^2) was much lower than the electrical resistance commonly reported during iontophoresis with human skin (16–50 kΩ cm^2).

For meso-porous membranes, the TM permeability without and with current application was practically the same. No change has been observed even with the application of higher currents. Compared to skin, all meso-porous membranes have much higher TM permeability. Application of these membranes would make the transdermal TM delivery system skin controlled.

For almost all micro-porous membranes, a significant transport contribution of iontophoresis was observed, being more pronounced when higher currents were applied. Most micro-porous membranes have TM iontophoretic permeability lower than skin. When the LFC 1 membrane is applied to the transdermal delivery system, it will mainly control the TM delivery. In this case, the TM dose of 10–60 mg/day can be delivered using membrane sizes of 5–64 cm^2 and by application of current densities between 0.13 and 0.5 mA/cm^2.

The average TM permeability through dense membranes was significantly lower compared to porous membranes [$(0.02–0.08)\times10^{-6}$ cm/s]. The application of dense membranes in iontophoretic TM delivery is not appropriate {although $(K_P)_{memb}/(K_P)_{skin}<0.2$} because the TM permeability during passive diffusion and iontophoresis is the same and most of these membranes have very high electrical resistance.

The adsorption of TM to the porous membranes was mainly low (0.02–0.33 mg/cm^2) and almost independent of the TM concentration. The TM adsorption to the Mill F-0.025 membrane was significantly higher than to the others.

Based on our results, the optimum membrane for a transdermal TM delivery system is the LFC 1 microporous membrane. This membrane mainly controls the TM delivery, it has very low electrical resistance and the TM adsorption to it is low. The therapeutic plasma TM concentration is achievable by application of this membrane in realistic sizes and by application of current densities lower than 0.5 mA/cm^2.

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