CONTROLLED DRUG DELIVERY THROUGH TAILOR-MADE BLEND POLYMERIC MEMBRANES

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Summary

In this work, we prepare tailor-made membranes by blending sulfonated poly(ether ether ketone) (S-PEEK) and poly(ether sulfone) (PES) polymers, at various ratios. Timolol (TM) is used as a model drug for the investigation of the controlled delivery through these membranes and their application to a transdermal TM patch is discussed.

Introduction

For drugs with short half-lives, transdermal delivery provides a continuous noninvasive mode of administration. For charged drug molecules, the transdermal delivery can be assisted by the application of direct constant current, which drives the drug through the skin by electrostatic repulsion (method called iontophoresis) [1]. An important component of a drug delivery patch is the artificial membrane, which is in contact with the skin and provides controlled drug delivery [2]. In the present work, we study the passive (no current application) and iontophoretic drug transport through tailor-made membranes prepared by blending sulfonated poly(ether ether ketone) (S-PEEK) and poly(ether sulfone) (PES) polymers, at various ratios. The S-PEEK contains negatively charged sulfo-groups, which can be used for the transport of positively charged drugs. When the S-PEEK is blended with the nonconductive PES, its swelling is reduced and the drug delivery can be regulated [3]. Timolol (TM), a nonselective beta-adrenergic blocking agent is used as a model drug molecule. Its pKa is 9.21 and it is therefore positively charged at physiological pH (7.4).

Experimental methods

The poly(ether ether ketone) (PEEK 450PF, Victrex) was sulfonated following the procedure described elsewhere [3]. The polymer blends were prepared by mixing S-PEEK with PES at various weight ratios. Three polymer solutions of 20 wt.% polymer in *N*-Methyl-2-pyrrolidinon (NMP) were prepared: (i) 100% S-PEEK (S-PEEK$_{100}$), (ii) 80% S-PEEK/20% PES (S-PEEK$_{80}$/PES$_{20}$) and (iii) 60% SPEEK/40% PES (S-PEEK$_{60}$/PES$_{40}$). The membranes were prepared by solution casting and evaporation [3]. The membranes after preparation were kept in a phosphate buffer saline (PBS) 0.153 M solution at pH 7.4 and their thickness was measured in the swollen state (Table 1).

Table 1
Membrane characteristics

Membranes	Thickness (μm)	Swelling (%)	Electrical resistance (kΩ cm^2)
S-PEEK$_{100}$	50	89±20	1.1
S-PEEK$_{80}$/PES$_{20}$	46	41±12	40.5
S-PEEK$_{60}$/PES$_{40}$	35	26±8	66.2

The membrane swelling was calculated using the equation: $[(W_{swol}-W_{dry})/W_{dry}]\times 100$, where W_{swol}, W_{dry} is the weight of the membrane in swollen and dry state, respectively. Timolol maleate salt (MW=432.5, Sigma—The Netherlands) was dissolved in PBS. The concentration of TM was in the range of 10–15 mg cm^{-3}. The diffusion cell and the experimental procedure were described in detail elsewhere [2]. In the iontophoretic experiments, we applied a current density up to 0.5 mA cm^{-2}. The electrical resistance of the membranes was measured during the iontophoretic experiments [2] (Table 1). All the experiments were performed at least in triplicate for each membrane. The concentration of TM in the donor and acceptor chamber was determined by HPLC [2]. The steady state flux of TM (J_{ss}, in mg cm^{-2} h^{-1}) through the membrane is expressed as:

$$J_{ss} = K_P C_{TM} \quad (1)$$

where K_P is the TM permeability coefficient and C_{TM} is the concentration of TM in the donor chamber.

Results and discussion

Fig. 1a shows a typical result of the amount of permeated TM through an S-PEEK$_{80}$/PES$_{20}$ membrane vs. time. From the slope, we calculate the J_{ss} and by using Eq. (1), the TM permeability coefficient, K_P. Fig. 1b presents the TM permeability through the blend membranes at various current densities. The error bars represent the average of at least three membrane samples.

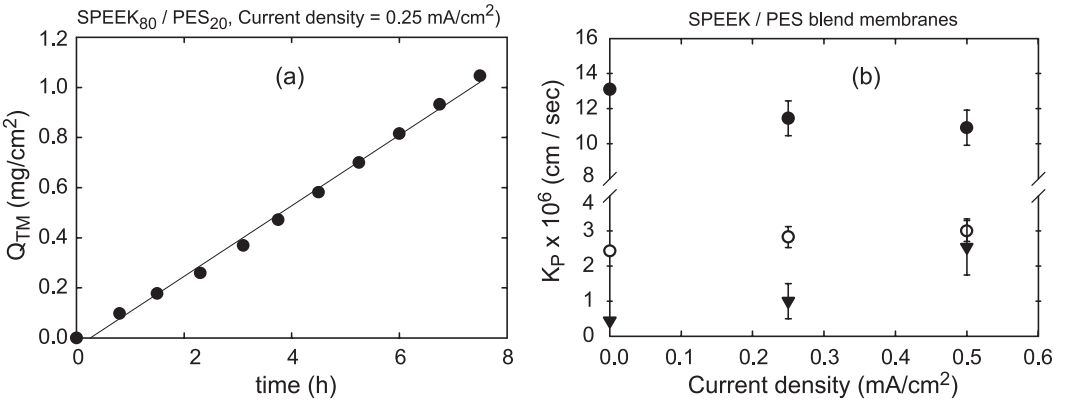

Fig. 1. (a) Typical result of TM transport through the S-PEEK$_{80}$/PES$_{20}$ membrane. C_{TM}=13.9 mg cm^{-3}. (b) The TM permeability through the S-PEEK$_{100}$ (full circles), S-PEEK$_{80}$/PES$_{20}$ (open circles) and S-PEEK$_{60}$/PES$_{40}$ (full triangles) blend membranes.

For passive diffusion, the blending of S-PEEK with PES gives the opportunity to regulate the TM delivery in a broad range (TM permeability in the range: 0.4–13×10^{-6} cm/s). For the S-PEEK$_{100}$ and S-PEEK$_{80}$/PES$_{20}$ membranes, the transport of TM is high due to the high membrane swelling (Table 1). In addition, the application of electrical current does not have a significant effect on the TM delivery. For these membranes, the contribution of passive diffusion greatly outweighs the contribution of electrical current thereby making the TM transport with and without applied current indistinguishable. For the S-PEEK$_{60}$/PES$_{40}$ membrane, however, the transport of TM increases significantly due to the current application (Figs. 1b and 2). Interestingly, the effect of the electrical current on the TM transport through this membrane is comparable to that for the TM transport through pig stratum corneum (SC) [4] and human skin [5] (Fig. 2). The latter is a very interesting finding because the S-PEEK$_{60}$/PES$_{40}$ membrane can be considered for two applications:

(i) As a membrane in a TM iontophoretic transdermal patch. In this case, it will act as a safe guard for the TM transport and control the delivery if for any reason the skin is compromised.

(ii) As a possible substitute for the human or pig skin for the in vitro tests with TM.

It is finally important to note that during the iontophoretic experiments, the electrical resistance of the blend membranes increases significantly. Especially for the S-PEEK$_{80}$/PES$_{20}$ and S-PEEK$_{60}$/PES$_{40}$ membranes, it reaches rather high values (Table 1). This phenomenon, which is not observed for the PBS alone (blank solution, when no TM is used), can be attributed to the ion-pairing effect between the positively charged and bulky TM molecules and the sulfo-groups of the S-PEEK resulting in the decrease of the membrane conductivity [6].

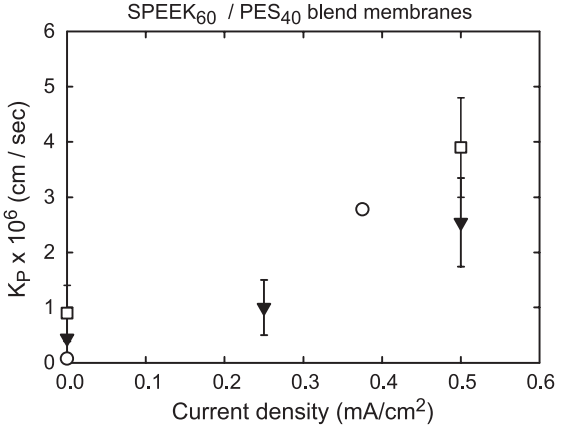

Fig. 2. Effect of current density upon the TM permeability through the S-PEEK$_{60}$/PES$_{40}$ membrane (triangles), pig SC (squares, [4]) and human skin (circles, [5]).

Conclusions

The controlled delivery of TM through various S-PEEK/PES blend membranes was investigated. The presence of PES in the blend reduces the swelling of S-PEEK resulting in the regulation of the TM transport. The application of electrical current increases the TM delivery only for the $S\text{-}PEEK_{60}/PES_{40}$ membrane. For this membrane, the TM transport at various current densities is similar to that for the pig SC and human skin reported in the literature.

Acknowledgements

The European Community is acknowledged for the financial support of this work, which is part of the ACTRADEL project within the 5th RTD Framework program.

References

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