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Transdermal timolol delivery from a Pluronic gel

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Summary

In this work, the transdermal timolol (TM) delivery from a Pluronic F127 (PL) gel reservoir was investigated. Both gel concentration and the artificial membrane are used to regulate the TM delivery through pig stratum corneum (SC). At low PL concentrations and for high pore size membranes, the SC mainly controls the TM delivery. At high PL concentrations and for low pore size membranes, the contribution of the system (gel + artificial membrane) to the TM delivery becomes significant.

Introduction

In iontophoresis, the application of constant electrical current enhances the transdermal transport of a charged drug molecule due to electro-repulsion. The electric field imposes a force on the drug molecule, which adds to the pure passive diffusion or the concentration gradient [1,2]. During iontophoresis, the skin permeability also increases due to changes in the structure of the skin caused by current flow [3]. In commercial transdermal systems, the drug is often incorporated in a gel reservoir. The gel reservoir functions either only as storage of the drug or it contributes to the control of the delivery, too. In this work, TM is incorporated into Pluronic® F127 (PL). The passive and iontophoretic delivery of TM from the gel through porous artificial membranes alone and in combination with pig stratum corneum (SC) are studied. Based on these results, the contribution of the gel, membrane and SC to the control of the TM delivery is evaluated aiming to the development of a TM iontophoretic transdermal delivery system.

Experimental

Timolol maleate salt was purchased from Sigma (The Netherlands) and Pluronic® F127 (MW 12,600) from BASF (The Netherlands). The membrane manufacturers provided the Polyflux®, PES-30 and NF-PES-10 artificial membranes (see Table 1). The Institute of Animal Science and Health (ID-Lelystad, The Netherlands) kindly provided the pig skin and the SC was obtained following the procedure described in [4].

Pluronic solutions of concentration 20–35% (w/w) in TM-citrate and/or phosphate buffer saline (PBS) solution [citrate: 0.148 M at pH 4.7, PBS: 0.153 M solution, at pH 7.4) at 4 °C were prepared. At these concentrations, a stable thermo-reversible gel was formed at room temperature (21±2 °C). The Pluronics are amphiphilic copolymers consisting of hydrophilic ethylene oxide (EO) and hydrophobic propylene oxide (PO) blocks arranged in the structure: $(EO)_x$–$(PO)_y$–$(EO)_x$. At high PL concentrations, the molecules aggregate and form micelles, a process which is dependent upon temperature. The PL gel is formed due to the micellar entanglements and packing and it is more entangled at higher PL concentrations [5]. TM was positively charged (pK_a of TM is 9.21). In all experiments, the TM concentration (C_{donor}) was in the range of 15–20 mg/ml.

All transport experiments (passive diffusion and iontophoresis) were performed in a continuous flow through diffusion cell (details in [6]). Circulating water at 37 °C controlled the temperature of the acceptor chamber (containing PBS). For the transport experiments, TM gel was applied in the anodal chamber and gel without TM in the cathodal chamber. The SC was fragile and it was supported by a dialysis membrane (Dialysis-5, Table 1). In a previous study [7], we found no contribution of this membrane to the overall TM permeability. In iontophoresis, current density of 0.5 mA/cm^2 was applied using Ag plate electrode and Ag/AgCl as driving electrodes in the anodal and cathodal compartment, respectively. All transport experiments were performed for 8–10 samples for each membrane or pig SC. The concentration of TM was determined by HPLC [6]. The steady state TM flux (J_{ss}, mg cm^{-2} h^{-1}) is expressed as:

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

where K_P is the system's permeability coefficient.

Results and discussion

The passive and iontophoretic transport of TM from the PL gel through all artificial membranes is investigated. For

Table 1
Artificial membranes used in this work.

Membrane	Material	MWCO (kDa)	Manufacturer
Dialysis-5	Neutral cellulose	5	Diachema — Germany
Polyflux®	Polyarylethersulfone	10	Gambro — Germany
PES-30	Polyethersulfone	30	Sartorius — Germany
NF-PES-10	Polyethersulfone	Unknown	Nadir — Germany

these systems, the amount of TM transporting through the membranes is linear with time and the TM permeability is calculated using Eq. 1. Fig. 1 presents the effect of PL concentration upon the permeability of TM through the membranes. The permeability decreases with the increase of PL gel concentration due to the increased entanglement of the PL gel at high concentration. For the 20% (w/w) PL concentration, the TM transport increases slightly due to the current application, mainly for the NF-PES-10 membrane (Fig. 1B). However at higher PL concentration, an increase of TM permeability due to the electrical current for the Polyflux® and PES-30 membranes is observed too (Fig. 1B).

The average TM permeability from a liquid solution through pig SC alone is $3.9\pm0.9\times10^{-6}$ cm/s [7]. For PL concentration up to 20% (w/w) and for the Polyflux® or PES-30 high pore size membranes, the TM permeability is much higher than through the SC and we expect that if these systems are applied in combination with pig SC, the TM transdermal system will be SC controlled. At higher PL concentrations (30–35% (w/w)), the TM permeability through the membranes and SC is comparable and both the system (gel+membrane) and the SC will contribute to controlling the TM delivery. For the NF-PES-10 membrane and for the whole range of PL gel concentration, the gel+membrane will have a significant role in the control of TM delivery, which will be more pronounced at high PL concentrations.

To confirm the prediction, we performed TM transport experiments from the TM-PL 30% (w/w) system through the combination of NF-PES-10 membrane and pig SC. The application of pig SC in combination with the NF-PES-10 membrane decreases the TM passive and iontophoretic permeability in comparison to the NF-PES-10 membrane alone proving the significant role of the SC to the TM delivery (see Table 2).

For the PL 30% (w/w)/NF-PES-10 system, we do not find significant differences in the TM transport at pH 7.4 or 4.7 (Table 2). Furthermore, the decrease of NaCl concentration in the gel from 8 to 4 g/l seems to have no effect upon the TM permeability. Recently, it was reported [8] that for the iontophoretic delivery of propranolol (a beta blocking agent, like TM), the major charge carrier was the Cl^- moving from beneath the skin into the anodal chamber. It seems that also in our case, the competition of the counter ion (Cl^-) mainly determines the overall TM transport efficiency and not the competition of the co-ion (Na^+) present in the donor.

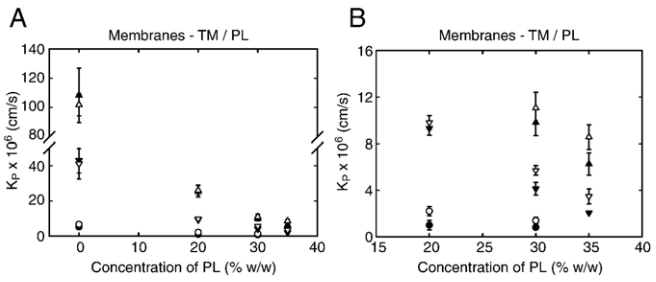

Fig. 1. (A) Effect of the PL gel concentration upon the TM permeability through the artificial membranes: Polyflux® (triangles up), PES-30 (triangles down) and NF-PES-10 (circles). (B) Zoom of (A) at high PL concentrations. Filled symbols: passive diffusion. Open symbols: iontophoresis.

Table 2
Passive and iontophoretic permeability of TM from a PL 30% (w/w) gel through the NF-PES-10 membrane alone and combination of the NF-PES-10 membrane with pig SC.

PL 30% (w/w)	$K_P \times 10^6$ (cm/s)	
	Passive diffusion	Iontophoresis
NF-PES-10		
PBS, pH 7.4, 8 g/l NaCl	0.8±0.1	1.4±0.3
PBS, pH 7.4, 4 g/l NaCl	0.6±0.4	1.1±0.4
Citrate, pH 4.7, 8 g/l NaCl	1.2±0.5	1.5±0.1
NF-PES-10+pig SC		
Citrate, pH 4.7, 8 g/l NaCl	0.1±0.1	0.6±0.3

Conclusions

For the PL gel reservoir, both the gel concentration and the artificial membrane can be used as "tools" to regulate the TM delivery. At low PL concentrations and for high pore size membranes (Polyflux®, PES-30), the SC mainly controls the TM delivery. At high PL concentrations and for low pore size membranes (NF-PES-10), the contribution of the device (gel +artificial membrane) to the TM delivery is significant.

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Evaluation of irinotecan drug-eluting beads: A new drug–device combination product for the chemoembolization of hepatic metastases

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Summary

Irinotecan drug eluting beads (DEB) were characterized in vitro with regard to their properties as a chemoembolization agent. Drug plasma levels and histopathology were performed in a porcine model of hepatic arterial embolisation and compared to intra-arterial bolus injection of drug, resulting in a reduction in peak plasma levels with DEB. A good correlation between in vitro and in vivo drug release was obtained. These data support the use of irinotecan DEB for the chemoembolization of hepatic metastases.

Introduction

Colorectal carcinoma (CRC) is the third leading cause of death from cancer in both males and females in the western world. 5-Fluorouracil-based chemotherapy has been the cornerstone of treatment of metastatic CRC for more than 40 years, and new drugs such as irinotecan and oxaliplatin with a definite activity have recently broadened the options for treatment. In addition, there is renewed interest in local delivery of chemotherapy to the liver in an attempt to increase the effectiveness of these drugs against liver metastases [1,2]. One approach to local therapy is the use of transarterial chemoembolization (TACE), which involves administration of chemotherapeutic agents directly within the feeding artery of hypervascular tumors, followed by a subsequent step to occlude the vessel with an embolic device [3,4]. As such, the tumor is starved of its oxygen and nutrient supply and the washout of the drug is minimized.

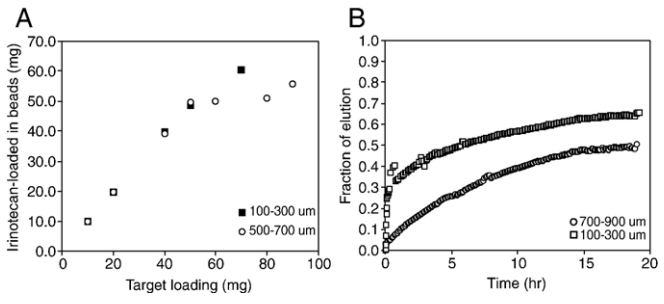

Fig. 1. (A) Actual vs target drug loading of beads; (B) Drug elution profiles using a T-apparatus.

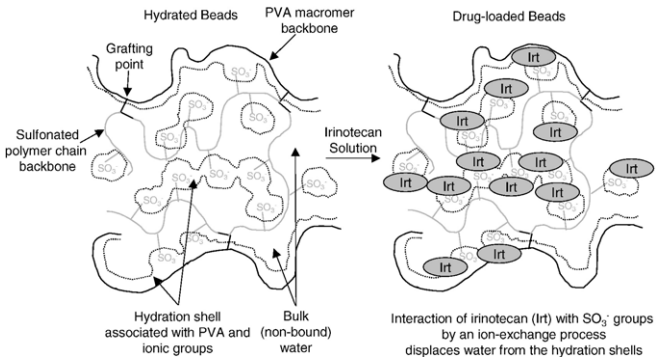

Fig. 2. Mechanism of irinotecan (Irt) loading within the sulfonated hydrogel beads.

Irinotecan drug eluting beads (DEB) combine the drug with the embolization device and can be administered intra-arterially in the same manner as TACE. This drug–device combination may offer the possibility of precisely controlling the release and dose of the drug into the tumor bed. This study presents both in vitro and in vivo characterization with respect to how the drug influences the physical properties and handling of the device, and how the device matrix is able to modulate release of the drug over a therapeutically-meaningful timeframe.

Experimental methods

The DEB were prepared by combining embolization beads (DC Bead™, Biocompatibles UK Ltd) with irinotecan hydrochloride solution (Campto®, Pfizer). The resulting irinotecan DEB were characterized in vitro with respect to size, compressibility, suspension, microcatheter deliverability and drug elution by T-apparatus. Porcine hepatic arterial embolization was performed in 4 groups of animals ($n=5$/group): 100–300 μm control beads, 100–300 μm irinotecan DEB, 700–900 μm irinotecan DEB and intra-arterial injection of drug alone. Plasma samples were taken over 90 d and histopathology performed at 30 d and 90 d.

Results and discussion

In vitro characterization

The rate of drug uptake was seen to be bead size dependent, the smaller beads loading more quickly due to increased surface area to volume ratio. The maximum loading of bound drug was shown to be around 50–60 mg irinotecan/ml beads for all sizes (Fig. 1(A)).