Permeation Behavior of Salbutamol Sulfate Through Hydrophilic and Hydrophobic Membranes Embedded by Thermo-responsive Cholesteric Oleyl Carbonate

Shan-Yang Lin,1,4 Yih-Yih Lin,2,3 and Ko-Shao Chen2

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Purpose. To investigate the suitability of hydrophilic or hydrophobic membranes for use as potential thermo-responsive drug delivery system.

Methods. Liquid crystal was embedded in membranes using vacuum filtration method to control the penetration rate of salbutamol sulfate. Cholesteryl oleyl carbonate (COC) with smectic-cholesteric phase transition temperature near 18°C was used as a model liquid crystal.

Results. It indicates only hydrophilic salbutamol sulfate can penetrate through the hydrophilic membranes embedded with or without COC, in which the permeation is mainly governed by the adsorption of COC. However, the hydrophilic drug do not pass through the hydrophobic membranes even if not embedded with COC. The void volume of the membrane also influences the penetration of salbutamol sulfate. The higher thermo-response efficacy of the COC-embedded membranes can be explained not only by the permeability through matrix part of the membrane but also by higher thermal motion of the COC molecules due to above the phase transition temperature.

Conclusions. A COC-embedded membrane with rate-controlled and thermo-responsive function is easily prepared by vacuum filtration method. High reversibly thermo-responsive function can be achieved by choosing membrane and COC concentration properly.

KEY WORDS: thermo-responsive membrane; penetration; Cholesteric oleyl carbonate; salbutamol sulfate.

INTRODUCTION

Medical chronobiology has been concerned with biologic rhythms and other bioperiodic influences on human diseases during drug therapy (1–2). Thus the fact that the maintenance of a constant drug concentration in the blood after application of any controlled release preparations to achieve the therapeutic optimization is doubtful. Recently the chronopharmacology has been extensively taken into account in clinical therapy. In particular, tolerance of nitroglycerin released from the long-term used transdermal patch with zero-order release kinetic has been found (3–4). To prevent the occurrence of tolerance, some drugs such as nitrates, antibiotics and steroids may require rhythmic patterns of drug concentration (5). It therefore seems attractive and effective method to combine homeostasis theory and biologic rhythm concept to design an intelligent drug delivery system (DDS) that not only acts as a rate-controlling system but also delivers the drug when it is required. To achieve this goal, we attempt to design a thermo-switchable membrane for the use in drug delivery system.

A number of investigations have confirmed the usefulness of membranes in regulating the delivery rate of pharmaceutical or veterinary drugs (6–7). In general, the rate of drug permeation is affected by several factors such as medium viscosity, drug size and the intrinsic properties of membranes. The latter plays an especially predominant role in controlling the diffusion rate of solutes. Since diffusion is usually the governing mechanism for membrane-moderated controlled drug release devices, the solubility and diffusivity of drug in the membrane are of great importance. It is well known that the lipid bilayer in the stratum corneum is the main barrier layer to control the permeability of drug by changing the lipid phase transition (8). Moreover, biological membranes are also capable of reversible structural modification in a liquid crystalline state, and their permeation and selectivity are closely associated with the gel-liquid crystal phase transition (9–10). Therefore, the phase transition would be one of the most essential functions for biological membranes. Similarly, liquid crystal in polymer membranes might be applicable to modulate permeability, since a distinct change in thermal molecular motion occurs at crystal liquid crystal phase transition temperature. In order to achieve this goal, cholesteric liquid crystal has been successfully embedded in cellulose nitrate membrane to thermally control the drug permeation (11–15), it is still unknown whether hydrophilic or hydrophobic membrane is the best choice of preparation. The aim of this study is to investigate the suitability of various types of on-off switching membranes in controlling drug penetration.

EXPERIMENTAL

Materials

Cholesteric oleyl carbonate (COC) was purchased from Sigma Chem. Co. (St. Louis, USA) and used without further purification. The phase transitional temperature of COC was about 18°C (11–12). Six commercially available membranes (diameter: 25 mm) were used. Hydrophilic membranes—cellulose nitrate (CN, pore size: 0.2μm) and nylon (pore size: 0.45 μm) were obtained from Whatman Limited (Maidstone, England), and inorganic Anodisc membrane (pore size: 0.1μm) was obtained from Gelman Science Limited (Ann Arbor, Michigan). Hydrophobic membranes, including polypropylene (PP, pore size: 0.1μm), polytetrafluorethylene (PTFE, pore size: 0.2μm) and polyvinylidene difluoride (PVDF, pore size: 0.2μm), were purchased from Gelman Science Limited (Ann Arbor, Michigan). The detailed properties of each membrane are listed in Table 1. Salbutamol sulfate of pharmaceutical grade was purchased from Huhtamaki OY Pharm., (Helsinki, Finland). All the other reagents and chemicals were reagent grade products.

Preparation of COC-embedded Membranes

COC-embedded membrane was prepared via vacuum filtration. Membranes were mounted individually on the stainless steel filter holder (Gelman Sci., MI, USA). A certain amount
Drug Penetration Through Thermo-responsive Membrane

Table 1. The Detailed Properties of Each Membrane

<table>
<thead>
<tr>
<th></th>
<th>CN</th>
<th>Nylon</th>
<th>Anodisc</th>
<th>PTFE</th>
<th>PP</th>
<th>PVDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pore size (µm)</td>
<td>0.2</td>
<td>0.45</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
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<tr>
<td>Thickness (µm)</td>
<td>133</td>
<td>127</td>
<td>60</td>
<td>178</td>
<td>89</td>
<td>178</td>
</tr>
<tr>
<td>Air flow rate</td>
<td>2.4</td>
<td>1.8</td>
<td>—</td>
<td>2.0</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>(l/min/cm², 10 PSI)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Water flux rate</td>
<td>17.5</td>
<td>16.0</td>
<td>8.0</td>
<td>40.0</td>
<td>1.5</td>
<td>3.5</td>
</tr>
<tr>
<td>(ml/min/cm², 10 PSI)</td>
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</tbody>
</table>

* methanol flow rate.
* isopropanol flow rate.

of COC chloroform solution at 37°C was filtrated using reducing pressure. The filter was then dried at 37°C and stored at 25°C for 24 hrs to obtain the COC-embedded membrane.

Evaluation of Different Types of COC-embedded Membranes

**Adsorption of COC on Different Type of Membranes**

The adsorption of COC on different types of membranes was evaluated by gravimetric method.

**Contact Angle of Each COC-embedded Membrane**

The contact angle of different types of COC-embedded membranes was measured by a Goniometer (Type G-1, Erma Optical Work Ltd, Japan) using sessile drop method with distilled water. Determination was repeated 5 times for each membrane to obtain mean value and standard deviation (S.D.).

**Scanning Electron Microscopy Study**

The surface topography and internal texture of these COC-embedded membranes were observed with a scanning electron microscopy (SEM, Hitachi S-2400 Japan).

**In Vitro Drug Permeation Study**

In vitro drug permeation was studied using a fluid/fluid diffusion cell (16–17). The COC-embedded membranes were carefully mounted in a two-chamber diffusion cell having an available diffusion area of 2.27 cm² and a half-cell volume of 15 ml, and pre-equilibrated with the pure medium for 1 day prior to use. The permeation study was carried out at 25°C or by repeatedly exchanging the temperature cycle (10°C ⇄ 25°C) of the water bath at predetermined intervals. One percent of salbutamol sulfate aqueous solution was put into the donor cell, but the receptor chamber was filled only with distilled water. The penetration rate was obtained from the slope of permeation curve at each period. The amount of salbutamol sulfate permeated was assayed spectrophotometrically at 277 nm. The results were presented as mean ± (S.D.) of three experiments.

RESULTS AND DISCUSSION

**Permeation Behavior of Drug Through Membranes Without COC**

In order to evaluate whether membranes without COC have thermo-responsive function, the permeation study was performed by a system with temperature cycling between 10°C and 25°C. The permeation profiles of salbutamol sulfate through these membranes without COC in response to a temperature change are shown in Fig. 1. It clearly indicates that we could not find any pulsatile release function. Salbutamol sulfate was hardly to penetrate through the porous PP, PTFE or PVDF membranes. Because of the hydrophobic property of these three membranes that makes the hydrophilic drug difficult to penetrate through the lipophilic membranes (18–20). In other words, the hydrophilic drug cannot permeate through the hydrophobic membrane, and the hydrophilic membranes without COC cannot induce any thermal-related change in rate of drug permeation.

**Permeation Behavior of Drug Through COC-embedded Membranes**

Figure 2 shows the permeation profiles of salbutamol sulfate through the COC-embedded hydrophilic or hydrophobic