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Temperature effect on the thermal characteristics and drug penetrability of the thermally on-off switching membrane

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Abstract

The aim of this study was to investigate the effects of manufacturing temperature and storage conditions on the thermal properties and drug penetrability of cholesteryl oleyl carbonate (COC)-embedded membranes. The COC-embedded membranes were prepared by a vacuum filtration method at different manufacturing temperatures and then stored at different temperatures. Salbutamol sulphate was used as a model drug across this COC-embedded membrane. It was evident that both manufacturing and storage temperatures significantly affected the characteristics of the membranes. The higher the manufacturing and storage temperatures, especially at 37° C, the greater was the penetration of salbutamol sulphate across the membranes. This phenomenon might due to the smectic-cholesteric phase transition of COC, since crystal fluidity will change in the COC-embedded membranes as a consequence of temperature changes. On the other hand, orientation was also observed to enhance the transport of the molecule at temperatures up the phase transition temperature (T_{sc}) of COC. X-ray diffraction was used to examine the orientation of COC and it was indicated that the intensity of the two most prominent diffraction peaks of COC disappeared as a result of manufacturing and storage temperature below the phase transition temperature of COC. The effect of temperature fluctuation (10 → 25 → 10 → 25° C) on the penetrability changes of salbutamol sulphate was investigated using the COC-embedded membranes. The penetration of salbutamol sulphate at 10° C was initially negligible. When the temperature was changed from 10 to 25° C, increased penetrability of drug was observed. Furthermore, the penetration of drug was further reduced when the temperature was lowered from 25 to 10° C. The penetration rate of salbutamol sulphate was reversibly regulated in response to a step-wise temperature change between 10 and 25° C. In addition, the higher the manufacturing or storage temperature, the better was the alignment of COC in the membranes, making superior regularity for salbutamol sulphate across the membranes. Whether COC-embedded membranes will be capable of controlling the penetrability of salbutamol sulphate during temperature change depends on the manufacturing temperature and storage conditions. Thermally on-off switching membranes can easily be manufactured by the vacuum filtration method at temperatures above the T_{sc} and achieve high thermo-responsive efficacy.

Keywords: Cholesteryl oleyl carbonate; Salbutamol sulfate; Phase transition; Penetrability; Membrane

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1. Introduction

Membrane technology has grown substantially over the past decade and membranes have been widely used for gas separation, filtration and dialysis. Moreover, many controlled-release devices also utilize the film or membrane to encapsulate the active agent and to control the diffusion rate of drug. Through rate-controlling membranes, drug concentrations in blood have been shown to be constant. (Beck et al., 1979; Lawson, 1985; Hisao et al., 1993). Rate-controlling membranes, however, can only maintain a constant release rate. They are not able to release drugs according to the condition of the patients or a preprogrammed schedule. Therefore, a number of investigators recently focused their attentions on the design of self-regulated membranes for drug delivery systems (Okahata et al., 1986; Iwata et al., 1991).

It is well known that the stratum corneum which is composed of lipid, protein and water is the main barrier layer of the skin and the permeability of drugs across the stratum corneum may change due to lipid phase transition (Knutson et al., 1985). On the other hand, 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 (Blok et al., 1976; Fettiplace and Hydon, 1980).

Therefore, the phase transition should be one of the most essential functions for biological membranes. Similarly, liquid crystals in polymer membranes might be applicable to modulate permeability, since a distinct change in thermal molecular motion occurs at the crystal-liquid crystal phase transition temperature. In order to achieve this goal, cholesteric liquid crystals have been successfully embedded in cellulose nitrate membranes in our preliminary study. The objective of this investigation was to examine the effects of manufacturing temperature and storage conditions on the thermal properties and drug penetrability of the liquid crystal-embedded membrane.

2. Materials and methods

2.1. Materials

Cholesteric oleyl carbonate (COC) was purchased from Sigma Chemical Co. (St. Louis, USA) and used without further purification. Cellulose nitrate membrane (pore size, 0.2 μm; diameter,

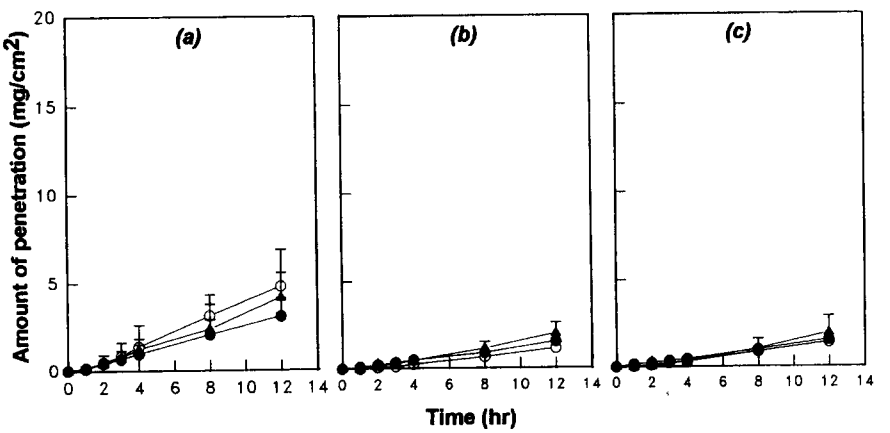

Fig. 1. Effect of different manufacturing and storage temperatures on the penetration of salbutamol sulphate across the COC-embedded membranes at 10° C. Manufacturing temperature: (a) 10° C, (b) 25° C, (c) 37° C; storage temperature: (●) 10° C, (○) 25° C, (▲) 37° C.

25 mm) was obtained from Whatman Ltd (Maidstone, UK). Salbutamol sulphate of pharmaceutical grade was purchased from Huhtamaki OY Pharm. (Helsinki, Finland). All other reagents and chemicals were reagent grade products.

2.2. Preparation of COC-embedded cellulose nitrate membrane

A vacuum filtration method was used to manufacture the COC-embedded membrane. A cellulose nitrate membrane was previously set on a stainless-steel filter holder (Gelman Sci., MI, USA) and a certain amount of COC chloroformic solution at different preparation temperatures (10, 25 or 37° C) was filtered by vacuum. The filter was dried and stored at each of the above temperature for 24 h to obtain the COC-embedded membrane.

2.3. Evaluation of the COC and COC-embedded membrane

2.3.1. Determination of the phase transition temperature of COC

The transition temperature of COC during the heating or cooling process was obtained from DSC thermograms by determination of the sample employing DSC (DSC-910S, TA Instruments, USA) at a scan rate of 5° C/min, under a stream of N_2 gas, from −20 to 50° C and 50 to −20° C, respectively.

2.3.2. In vitro drug penetration study

The in vitro drug penetration was studied using a fluid/fluid diffusion cell (Franz, 1975; Lin et al., 1992). The COC-embedded membrane was carefully mounted in a two-chamber diffusion cell having an available diffusion area of 2.27 cm^2 and a half-cell volume of 15 ml. The penetration study was carried out at 10 or 25° C or 10 and 25° C by step-wise temperature changes of the water bath at predetermined times. 1% of salbutamol sulphate aqueous solution was put into the donor cell, but the receptor chamber was filled only with distilled water. The salbutamol sulphate penetrated was assayed spectrophotometrically at 277 nm. The results were presented as the mean (±S.D.) of three experiments.

2.3.3. X-ray diffraction measurements on cast COC

A certain amount of COC chloroformic saturated solution was cast on a glass sample holder at different temperatures (10 and 37° C), then the glass sample holder was dried at each of the above temperatures for 24 h to obtain the cast COC. The X-ray diffraction measurement of the cast COC was carried out at 10 or 37° C and the

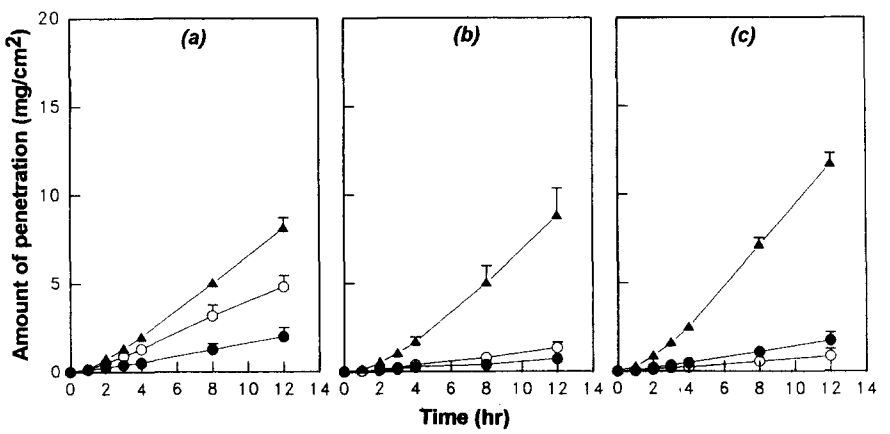

Fig. 2. Effect of different manufacturing and storage temperatures on the penetration of salbutamol sulphate across the COC-embedded membranes at 25° C. Manufacturing temperature: (a) 10° C, (b) 25° C, (c) 37° C; storage temperature: (●) 10° C, (○) 25° C, (▲) 37° C.

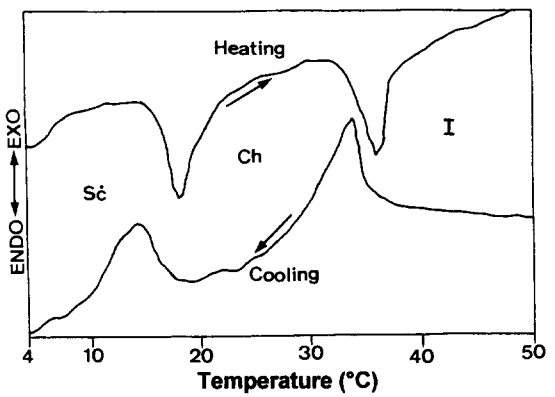

Fig. 3. DSC thermogram of cholesteryl oleyl carbonate (COC).

pattern was recorded by using a X-ray diffractometer (Siemens, Diffractometer D5000, Japan) with Cu-Kα radiation.

3. Results and discussion

It is known that orientation can cause remarkable changes in the transport properties of a polymer membrane These changes can result in enhancement or weakening of the barrier or separation properties of products to be used in barrier packaging or membrane separation applications (Chau and Raspor, 1990). The orientation was found to reduce the transport rate when transport occurred mainly perpendicular to the direction of orientation. In contrast, transport may be enhanced if orientation and transport are in the same direction. The properties of liquid crystal-embedded membranes are sensitive to the fabrication processes. The monodomain orientation of a liquid crystal in a membrane may be achieved by using the vacuum filtration method and controlling the temperature adequately. The penetration rate of salbutamol sulphate across membranes at 10° C is shown in Fig. 1. Obviously, the penetration rate depends on the treatment of the membranes. When COC-embedded membranes were manufactured at 10° C, the penetration rate of the drug was greater than that manufactured at 25 and 37° C. The penetration profiles of drug are very slow and similar in comparison with a preparation temperature between 25 and 37° C. On the other hand, the penetration rate is unaffected by whether the membranes are stored at 10, 25 and 37° C. This suggests that the storage temperature had no apparent effect on the penetration of drug across the membrane at 10° C, the penetration rate being predominantly governed by the manufacturing temperature. However, for the penetration of drug across the membranes at 25° C, both the manufacturing temperatures and storage conditions have significant effects as shown in Fig. 2. The higher the manufacturing and storage temperatures, especially at 37° C, the greater is the penetration of salbutamol sulphate across membranes. This phenomenon might due to the phase transition and orientation of COC. Because the smectic-cholesteric phase transition temperature (T_{sc}) of COC is 18.3° C during heating and 15.8° C for the cholesteric-smectic transition during cooling (Fig. 3), the crystal fluidity changes in the COC-embedded membranes as a consequence of temperature changes. The thermal molecular motion of COC was frozen and the alignment of COC in the membrane was poor, when the manufacturing temperature was below T_{sc}. Defects might occur during such fabrication processes. Defects in COC-embedded membranes would lead to the rapid permeation of salbutamol sulphate across such membranes at 10° C. On the other hand, orientation was also

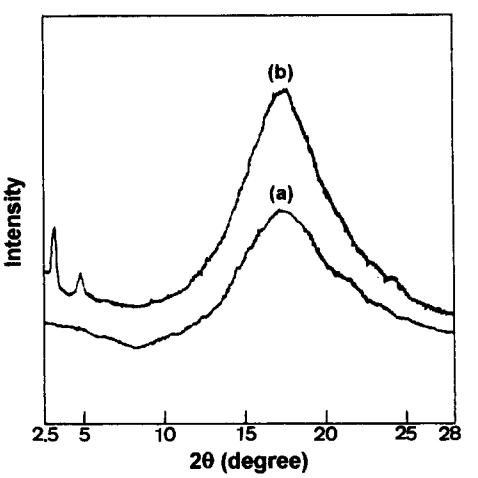

Fig. 4. X-ray diffraction intensity curve for cholesteryl oleyl carbonate. (a) Manufactured and stored at 10° C; (b) manufactured and stored at 37° C.

observed to enhance the transport of molecules at temperature up to T_{sc}. The better the orientation of COC in cellulose nitrate membranes for manufacturing temperature above the T_{sc}, the greater is the penetration of COC across the membranes. Moreover, alignment will be promoted for storage temperatures above T_{sc}. In order to examine the degree of orientation of COC in the membrane, an X-ray diffraction study was carried out at 10 or 37° C. COC was cast on glass to mimic its behavior in membranes. Fig. 4 shows the X-ray diffraction patterns of cast COC that had been manufactured and stored above (37° C) and below (10° C) T_{sc}, respectively. Only a broad band corresponding to the melting of the alkyl chains (Ohta et al., 1992) was obtained in Fig. 4a. However, two narrow reflections in the low-angle region which correspond to the lamellar structure are observed in Fig. 4b as a result of manufacturing and storage temperature above T_{sc}. From Fig. 4, it is evident the orientation of COC

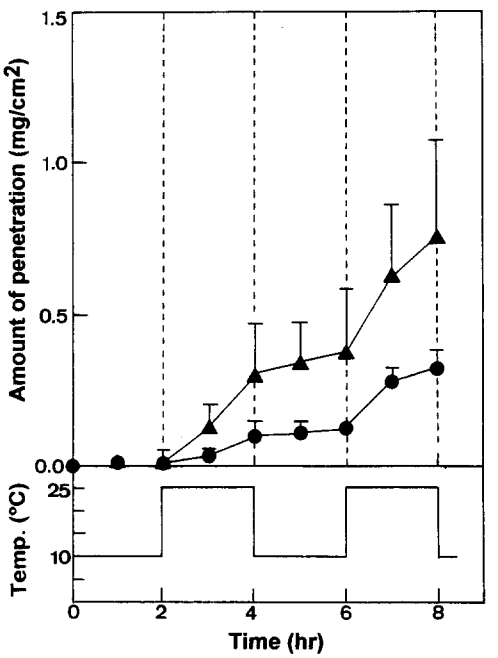

Fig. 5. Penetration profile of salbutamol sulphate across COC-embedded membranes, manufactured at 37° C and stored at different temperatures, in response to a temperature change. Storage temperature: (●) 10° C, (▲) 37° C.

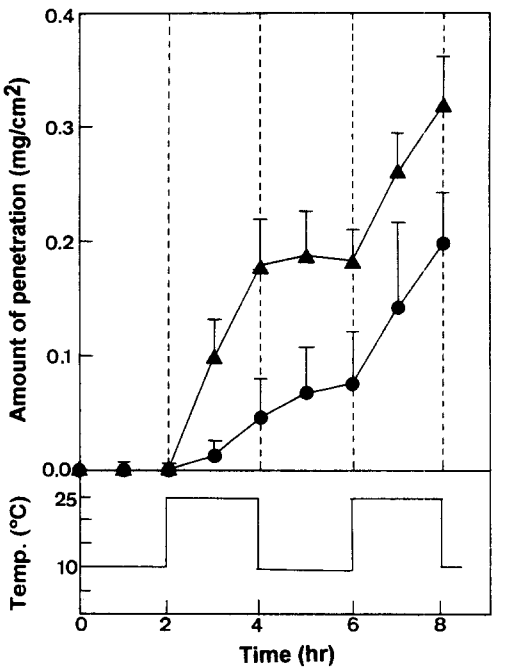

Fig. 6. Penetration profile of salbutamol sulphate across COC-embedded membranes, manufactured at 10° C and stored at different temperatures, in response to a temperature change. Storage temperature: (●) 10° C, (▲) 37° C.

can be improved by manufacturing and storage temperatures.

The penetration rate of salbutamol sulphate might be regulated in response to the temperature change based on the thermal responsiveness and oriented aggregation of COC-embedded membranes. Therefore, the effect of temperature fluctuation (10 → 25 → 10 → 25° C) on the penetrability changes of salbutamol sulphate was investigated using the COC-embedded membranes. The effects of manufacturing and storage temperatures on the penetration profile of salbutamol sulphate across COC-embedded membrane, in response to a temperature change, are shown in Fig. 5 and 6. When COC-embedded membranes were manufactured and stored at 37° C (above T_{sc}), the penetration of salbutamol sulphate at 10° C was initially negligible, attributed not only to the lag time but also to the thermal molecular motion of COC being frozen. When the temperature was changed from 10 to 25° C, increased

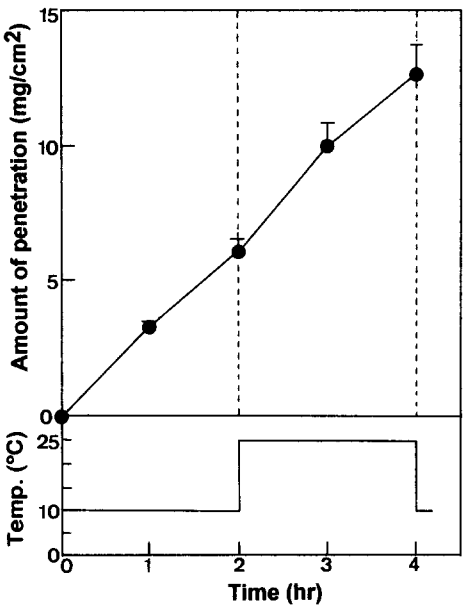

Fig. 7. Penetration profile of salbutamol sulphate across membranes without COC in response to a temperature change.

penetrability of drug was observed. In this region, the penetrability of salbutamol sulphate increased markedly, possible as a result of the activation of thermal molecular motion in the membrane and/or the enhancement of pore formation. Furthermore, the penetration of drug was further reduced when the temperature was lowered from 25 to 10° C. The penetration rate of salbutamol sulphate was reversibly regulated in response to a step-wise temperature change between 10 and 25° C. Similar results can be obtained with membranes manufactured at 37° C then stored at 10° C (below T_{sc}) or manufactured at 10° C then stored at 37° C. On the other hand, regularity was also exhibited when COC-embedded membranes were manufactured and stored at 10° C, however, only to a limited extent. Thus, the higher the manufacturing or storage temperature, the better is the alignment of COC in the membranes, as clearly demonstrated by the previous discussion, showing the superior regularity for salbutamol sulphate across the membranes. The penetration of salbutamol sulphate across free membranes with a step-wise temperature change between 10 and 25° C is shown in Fig. 7. Apparently, the penetration rate of salbutamol sulphate cannot be controlled by temperature change. In contrast, in the case of membranes with COC, the penetration rate at 25° C was greater than that at 10° C.

In conclusion, the COC-embedded membrane with thermo-responsive penetrability of salbutamol sulphate is mainly dependent on the manufacturing temperature and storage conditions. This suggests that the thermal characteristics of COC-embedded membranes play an important role. Thermally on-off switching membranes can readily be prepared by the vacuum filtration method at temperatures above T_{sc} and achieve high thermo-responsive efficacy.

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