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Adsorption of Binary Liquid Crystals onto Cellulose Membrane for Thermo-Responsive Drug Delivery

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Abstract. A thermo-responsive membrane was developed by adsorbing the binary liquid crystals (LC) onto the cellulose nitrate membrane. The binary LC mixture is consisted of 36% cholesteric oleyl carbonate (COC) and 64% cholesteryl nonanoate (CN). The physico-chemical and the thermo-responsive properties of this binary LC adsorbed-membrane were examined. The results indicate that the adsorption behavior of binary LC mixture on the cellulose membrane was quick and reached to the equilibrium about 10 min, and linearly correlated with the increase of LC concentration used. The hydrophilic membrane was hydrophobicized after adsorption of binary LC mixture. The focal conic fan textures of binary LC mixture were observed from the surface of cellulose membrane. Due to the obedience and reproducibility of the binary LC used, the binary LC mixture-adsorbed membrane continuously exhibited an on-off thermo-responsive sensitivity to control the drug penetration.

Keywords: adsorption, liquid crystal, membrane, thermo-responsive, penetration, drug delivery

Introduction

Recently, the concept of chronotherapy has been considerably adopted for the clinical therapy (Levi, 1996; Lemmer, 1997). The rational chronotherapy is the regimen of drug administration according to biological rhythm to maximize pharmacological effects and minimize side effects. The ideal drug delivery system not only performs or pumps with constant or programmable delivery rates, but also delivers a drug at a definite time responding to signals from the human body when physiologically needed (Bruguerolle, 1998). This pulsatile drug delivery is similar to biological rhythms in human body, it can empirically modulate drug release at the predetermined time (D'Emanuele, 1996), resulting in better drug therapy by avoiding the side effect and tolerance of drug.

In our previous studies (Chen et al., 1996; Lin et al., 1996a, 1996b, 1998, 2000a, 2000b), a novel thermo-responsive liquid crystal (LC)-embedded membrane has been successfully developed with a pulsatile function in response to thermal stimuli. The on-off thermo-responsive function of this LC-embedded membrane was conducted by altering the repeated temperature cycle. A vacuum-filtration method was applied to embed a single or binary cholesteric LC into the cellulose nitrate or nylon membrane to have a pulsatile on-off drug release behavior. Since the cholesteric LC used in these investigations possessed a hydrophobic property, it must dissolve in trihalomethanes such as chloroform before use. The vacuum-filtration method is too complicated for manufacturing, due to, the exposure chances to chloroform. Due to the severe toxicity of chloroform (Plaa, 2000; Delic et al., 2000), the occupational exposure to the organic solvent should be prevented. Thus a method other than vacuum-filtration must be considered. In our preliminary study, the adsorption method is a hopeful candidate, which not only may easily operate but also can prepare the membrane with thermo-responsive function.

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The purpose of this study is to develop a novel thermo-responsive membrane by adsorbing the binary LC onto the cellulose nitrate membrane. The physico-chemical properties and the thermo-responsive efficacy of this binary LC adsorbed-membrane were examined.

Materials and Methods

Materials

Cholesteric oleyl carbonate (COC) and cholesteryl nonanoate (CN) were purchased from Sigma Chem. Co. (St. Louis, MO, USA) and used without further purification. Cellulose nitrate membrane (pore size: 0.2 μm, diameter: 25 mm) was obtained from Whatman Limited (Maidstone, England). Salbutamol sulfate was used as a model drug and purchased from Huhtamaki OY Pharm. (Helsinki, Finland). All other reagents and chemicals were of reagent grade.

Adsorption Study

Nine pieces of cellulose membrane were immersed in each 20 ml of different chloroform binary LC concentrations (10–25%, w/v) in a sealed dish, respectively. The weight ratio of binary LC mixture is 36% COC : 64% CN (Lin et al., 2000b). At the prescribed intervals, all the membranes were taken off and vacuum-dried at 25°C for 30 min. The weight of each membrane was accurately weighed, and mean was obtained ($n = 9$).

Fabrication of the Binary LC Mixture-Adsorbed Membrane

The binary LC-adsorbed membrane was prepared by an adsorption method. A cellulose nitrate membrane was immersed in the above different concentrations of binary LC (36% COC : 64% CN) mixture in a sealed dish at 25°C for 10 min, respectively. The membrane was withdrawn, vacuum dried at 25°C, and stored at 25°C for in vitro penetration study.

Contact Angle of the Binary LC Mixture-Adsorbed Membrane

The contact angle of the binary LC mixture-adsorbed membrane was determined by a Goniometer (Type G-l, Erma Optical Work Ltd., Tokyo, Japan) using sessile drop method with distilled water. Determination was repeated 6 times for each membrane to obtain mean value.

Microscopic Observation

Surface modification of the binary LC mixture-adsorbed membrane was observed with an optical microscopy (Olympus, BH2, Tokyo, Japan).

In vitro Drug Penetration Study

In vitro drug permeation was studied using a fluid/fluid diffusion cell (Chen et al., 1996; Lin et al., 1996a, 1996b, 1998, 2000a). The binary LC mixture-adsorbed membranes were carefully mounted in a two-chamber diffusion cell having an available diffusion area of 2.91 cm^2 and a half-cell volume of 15 ml. The permeation study was carried out by repeatedly exchanging the temperature cycle (30°C $\Leftrightarrow$ 37°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 amount of salbutamol sulfate permeated was assayed spectrophotometrically at 277 nm. The penetration rate was obtained from the slope of permeation curve at each period. The results were presented as mean $\pm$ standard deviation (S.D.) of three experiments.

Results and Discussion

Physico-Chemical Properties of the Binary LC Mixture-Adsorbed Membrane

The results for the adsorption of binary LC mixture on cellulose nitrate membrane are shown in Fig. 1. It clearly indicates that the adsorption behavior of binary LC mixture on the cellulose membrane was quick and reached to the equilibrium about 10 min. Moreover, the amount of LC adsorbed was linear with the increase of LC concentration used. This suggests that the greatest adsorption capability of LC on cellulose membrane was dependent on the concentration of LC used.

The contact angle was used to examine the surface modification of the cellulose nitrate membrane after adsorption of the binary LC mixture. It was found that the membrane did not contain the binary LC mixture, its contact angle of water was near zero. Once the binary

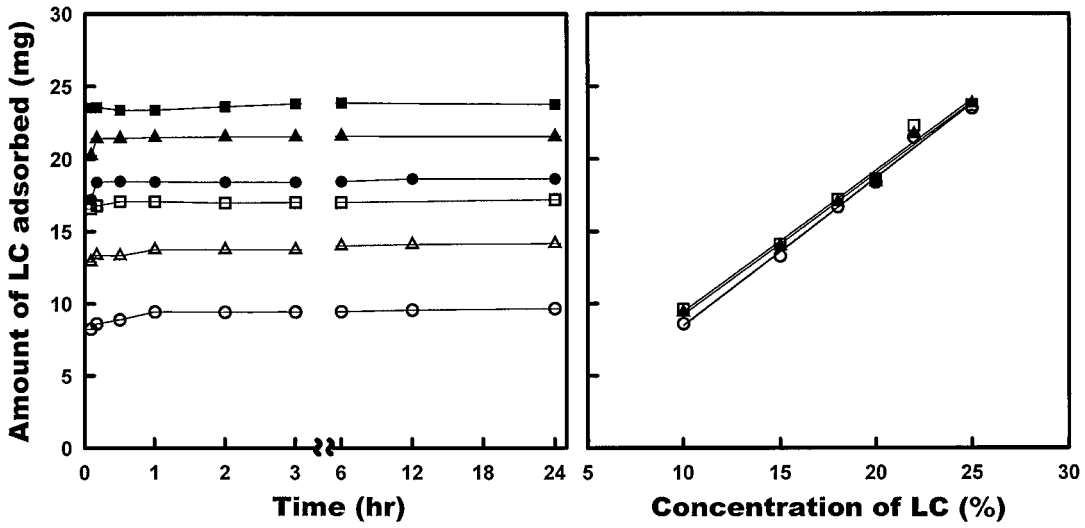

Figure 1. The adsorption behavior of binary LC mixture adsorbed on cellulose membrane and its relationship with the LC concentration used Key: Concentration of binary LC mixture used. ○: 10%; △: 15%; □: 18%; ●: 20%; ▲: 22%; ■: 25%.

LC mixture was adsorbed on the membrane, even in a small amount, the contact angle of water increased significantly to $85 \pm 2^{\circ}$, which was also found in our previous studies (Chen et al., 1996; Lin et al. 1995). This indicates that the hydrophilic membrane was hydrophobicized by the adsorption of binary LC mixture. The surface modification of membrane after LC absorption was also found from the optical microphotographs, as shown in Fig. 2. Obviously, focal conic fan textures of cholesteric phase of binary LC mixture were observed on the surface of cellulose membrane. This implies that the binary LC mixtures were exactly loaded on the cellulose nitrate membrane.

Penetration of Drug through the Binary LC Mixture-Adsorbed Membrane

Our previous studies have found that the binary mixture of 36% COC and 64% CN had two endothermic peaks at 35.1°C and 65.8°C in DSC curve (Lin et al., 2000b). The former peak was due to the solid-cholesteric transition and the latter peak was responded to the cholesteric-isotropic transition (Griffen and Porter, 1973; Tai and Lee, 1990). Thus in order to evaluate the thermo-responsive efficacy of this binary LC mixture-adsorbed cellulose membrane, the penetration study was in vitro performed by a system with stepwise change in temperature cycle between 30°C ("off" state) and 37°C ("on" state).

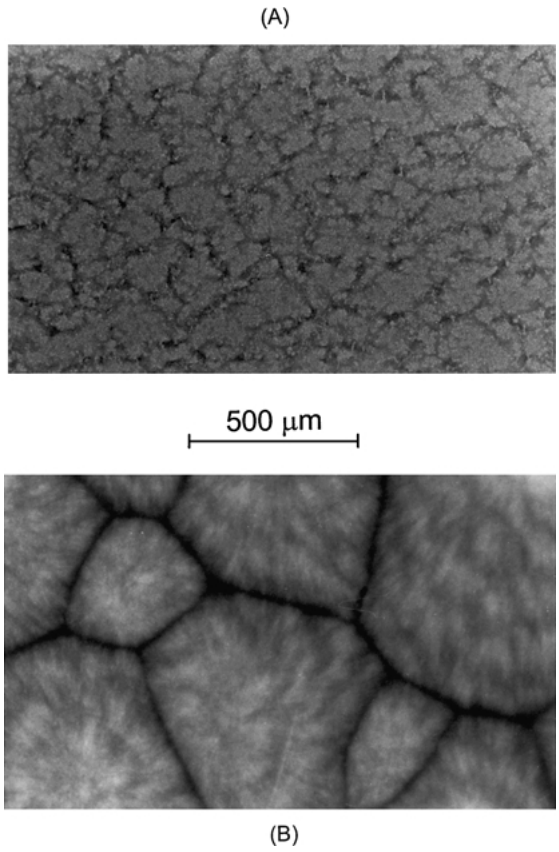

Figure 2. (A) LC-free membrane, (B) LC-adsorbed membrane.

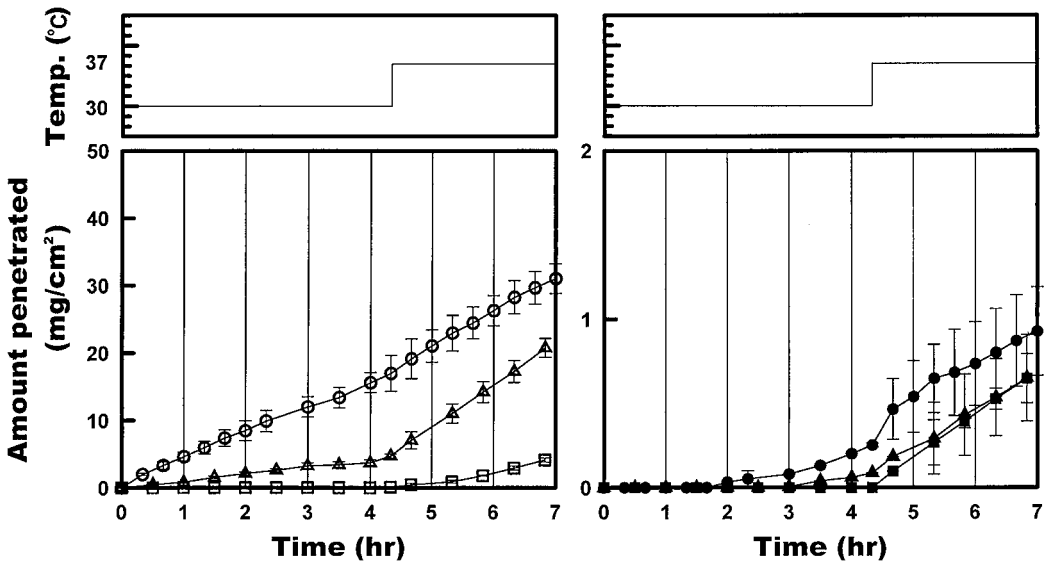

Figure 3. In vitro penetration profile of salbutamol sulfate through the binary LC mixture-adsorbed new membrane at 30°C for 4 hrs and then changed to 37°C for 3 hrs. Key: Concentration of binary LC mixture used. ○: 10%; △: 15%; □: 18%; ●: 20%; ▲: 22%; ■: 25%. The bars indicate the mean ($n = 3$) ± standard deviation.

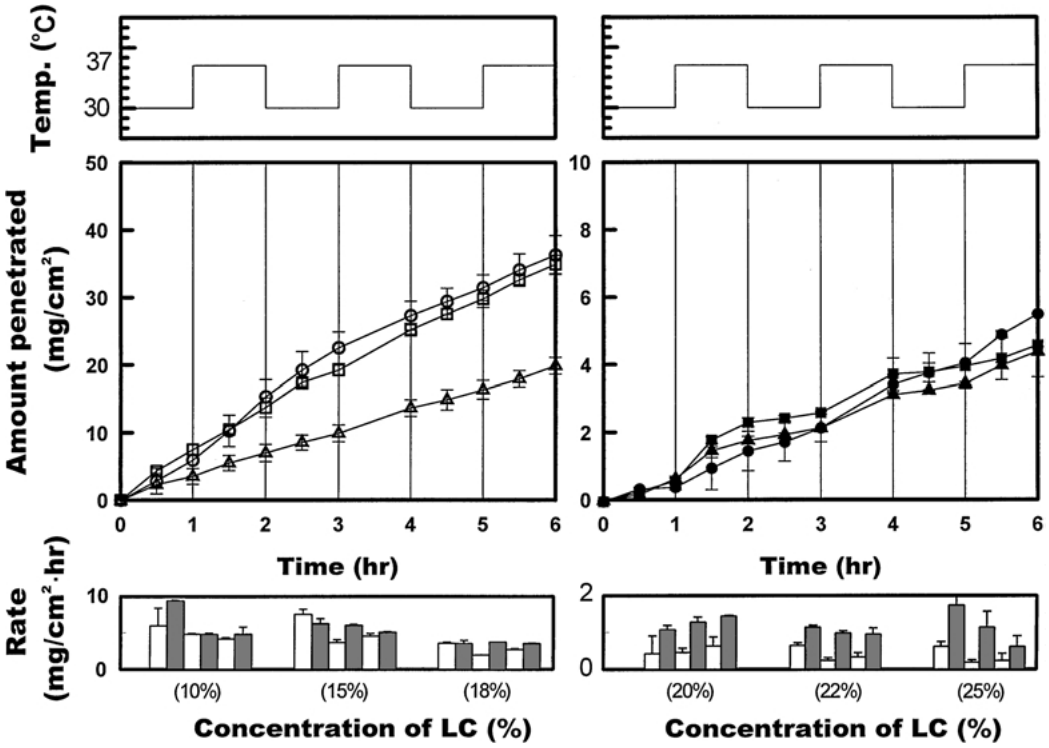

Figure 4. In vitro penetration profile and rate of salbutamol sulfate across the 7 hrs-penetrated membrane (Fig. 3) in response to temperature cycles of 30°C and 37°C. Key: Concentration of binary LC mixture used. ○: 10%; △: 15%; □: 18%; ●: 20%; ▲: 22%; ■: 25%. The bars indicate the mean ($n = 3$) ± standard deviation.

Figure 3 shows the penetration profile of salbutamol sulfate through the binary LC mixture-adsorbed membrane at 30°C for 4 hrs and then changed to 37°C for 3 hrs. Obviously, when the drug penetration study was carried out at 30°C, which was below the phase transition temperature of 35.1°C, the penetrated amount of drug through this binary LC mixture-adsorbed membrane is lower. Furthermore, the higher the concentration of binary LC mixture used the slower the penetrated amount of drug obtained. Once the temperature was changed from 30 to 37°C, which was above the phase transition temperature of 35.1°C, the penetration of drug increased significantly. The marked increase in drug penetration might be caused by activation of thermal molecular motion of liquid crystal on the membrane and/or an enhancement of pore formation around the domain of liquid crystal (Kajiyama et al., 1982; Washizu et al., 1984). This implies that the binary LC mixture-adsorbed membrane had a thermo-responsible property.

In order to evidence the thermo-reversible reproducibility of this binary LC mixture-adsorbed membrane, the above membranes after 7 hrs-penetration study were used again to perform the penetration study but step-wise changed the temperature cycle between 30°C and 37°C, as shown in Fig. 4. It is evident that the penetration behavior of drug through this reused membrane was different from the results of Fig. 3. Particularly, there was no thermo-reversible on-off function for the membrane prepared by lower concentration of binary LC mixture. However, the thermo-reversible on-off function was found for the membrane prepared by >20% concentration of binary LC mixture used. The 22% and 25% seem to be the most suitable concentrations for preparing the thermo-responsive membrane. This suggests that the penetration rate of salbutamol sulfate through this reused membrane was still thermo-reversibly regulated in response to the temperature change. When a new binary LC mixture-adsorbed membrane was used for drug penetration, a different result was found, as shown in Fig. 5. Obviously, the penetration rate of drug was reduced for new membrane, particularly for the membrane prepared by the concentration of binary LC mixture >20%. Like the reused

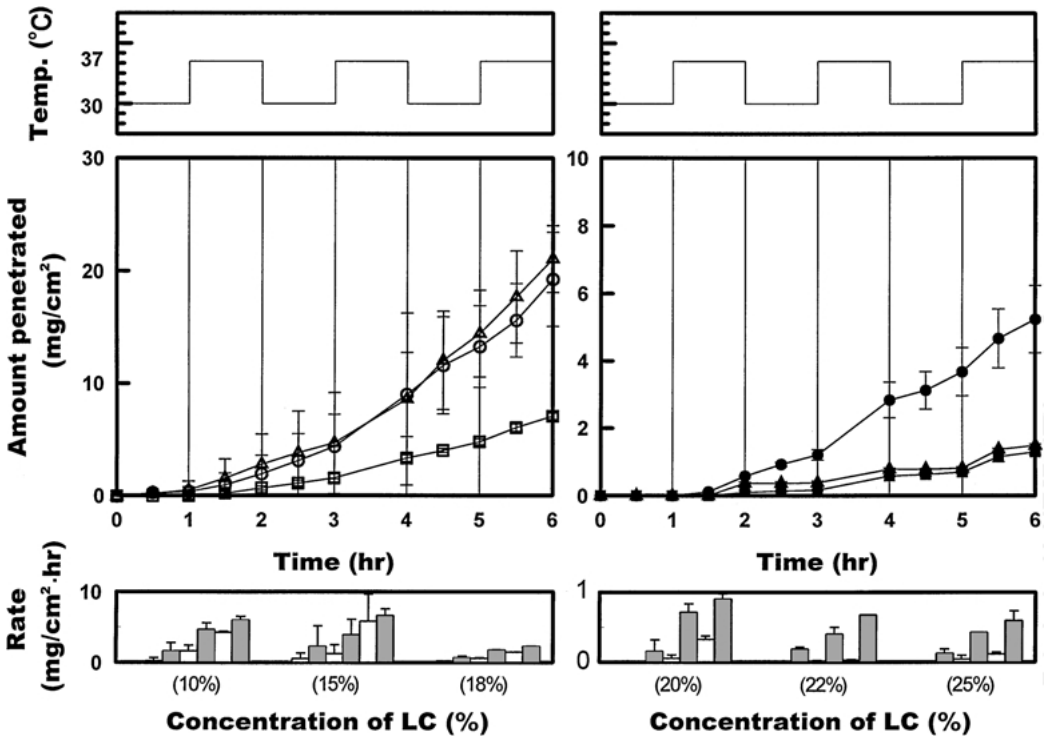

Figure 5. In vitro penetration profile and rate of salbutamol sulfate across the binary LC mixture-adsorbed new membrane in response to temperature cycles of 30°C and 37°C. Key: Concentration of binary LC mixture used. ○: 10%; △: 15%; □: 18%; ●: 20%; ▲: 22%; ■: 25%. The bars indicate the mean ($n = 3$) ± standard deviation.

membrane, the thermo-reversible on-off function was also found for the membrane prepared by the higher concentration (>20%) of binary LC mixture used.

It should be noted that the reused membrane had a faster and higher penetration rate in the first temperature cycle of 30°C ("off" state), which was significantly different from the new membrane. After the first temperature cycle, however, the drug penetration slowed down and reverted to maintain the constant rate in the "on" state but was minimized in the "off" state. The LC seems to return to the natively thermal property. This phenomenon implies that the LC used exhibited obedient and reproducible characteristics to temperature response. A new membrane started from the "off" state, it exactly obeyed the temperature response to control the drug penetration. This reveals that the obedience and reproducibility of the binary LC used and also suggests the usefulness of the binary LC mixture-adsorbed membrane continuously held the thermo-responsive sensitivity.

In conclusion, the present result indicates that the binary LC (36% COC : 64% CN) mixture-adsorbed membrane was sensitive and reproducible to the temperature response, and was able to have rate-controlled and thermo-responsive function.

Acknowledgments

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