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

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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 less 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-embeddded 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; Cholestery 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 (3,5). 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 lattest 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 purhased 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), polytetrafluorolethylene (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

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Table 1. The Detailed Properties of Each Membrane

	CN	Nylon	Anodisc	PTFE	PP	PVDF
Pore size (μm)	0.2	0.45	0.1	0.2	0.1	0.2
Thickness (μm)	133	127	60	178	89	178
Air flow rate (l/m/cm^2, 10 PSI)	2.4	1.8	—	2.0	0.8	1.0
Water flux rate (ml/min/cm^2, 10 PSI)	17.5	16.0	8.0	40.0[a]	1.5[b]	3.5

[a] methanol flow rate.
[b] 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 cm^2 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 responsive 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

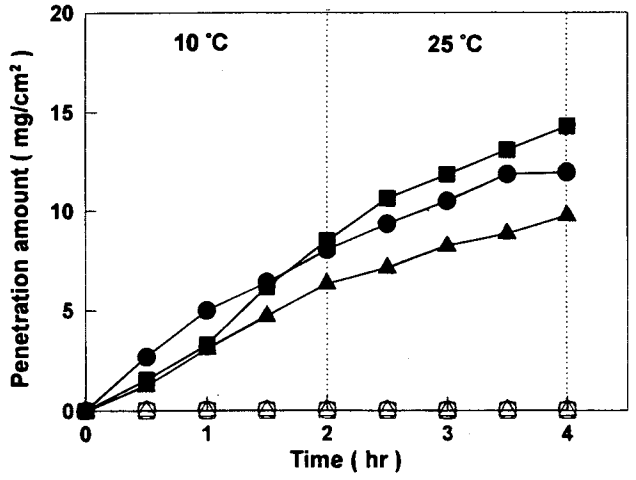

Fig. 1. Permeation profile of salbutamol sulfate across different types of membranes without embedding COC in response to a temperature change. Key: ○, PP; △, PTFE; □, PVDF; ●, CN; ▲, Nylon; ■, Anodisc.

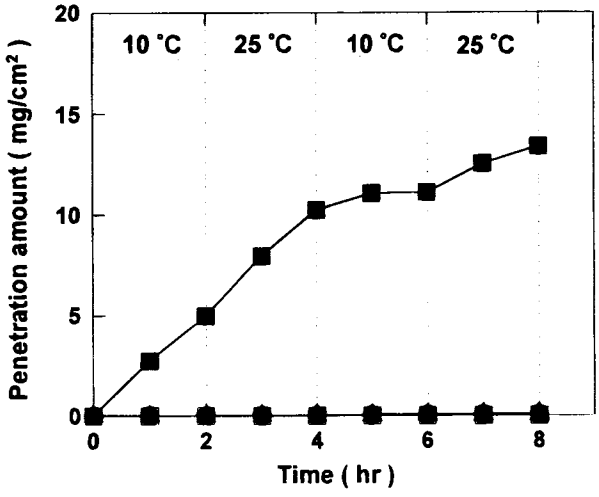

Fig. 2. Permeation profile of salbutamol sulfate across the COC-embedded membranes prepared with 5% COC chloroform solution, in response to a temperature change. Key: ○, PP, △, PTFE; □, PVDF; ●, CN; ▲, Nylon; ■, Anodisc.

Table 2. Water Contact Angle (°) of COC-embedded Membranes

COC (%)	CN	Nylon	Anodisc	PVDF	PP	PTFE
0	0	0	0	121	116	122
5	135	77	0	125	117	129
30	130	80	84	118	104	99

membranes in response to the change in temperature. These membranes were prepared with 5% COC chloroform solution. Salbutamol sulfate was found unable to penetrate through these COC-embedded membranes, except Anodisc. Such results might be explained by the contact angle of membrane, as indicated in Table 2. In general, hydrophilic drugs readily penetrate hydrophilic membranes. Penetration studies using hydrophilic drugs through hydrophobic membranes, however, have been unsuccessful. This is primarily due to weak partition and low diffusivity of the hydrophilic drug through the hydrophobic membrane (18). It could be near zero for hydrophilic membranes (CN, nylon and Anodisc) but about 120° for hydrophobic membranes (PP, PTFE and PVDF). Once hydrophilic membranes were prepared with 5% COC chloroform solution, the contact angle of water became 135.6°, 77.3° and 0° for CN, nylon and Anodisc COC-embedded membranes, respectively. CN and nylon membranes became hydrophobicize by COC and thus became difficult for hydrophilic salbutamol sulfate to penetrate through. Inorganic Anodisc, a membrane with nondeformable honeycomb pore structure, offers a number of advantages over conventional polymeric materials in filtration such as wide solvent compatibility and low protein adsorption. Similarly, the adsorption of COC on Anodisc is low enough for hydrophilic salbutamol sulfate to readily penetrate across this hydrophilic membrane. However, the Anodisc membrane embedded with COC was also hydrophobicized when the concentration of the solution prepared increased to above 30% of that COC. From SEM observation, the surface of Anodisc was completely covered by COC (Fig. 3). It seemed impossible for salbutamol sulfate to permeate through this COC-embedded membrane. However, it is worthy to study that the permeability behavior of hydrophobic drug through the COC-emmbeded membrane.

Effect of COC Concentration on the Drug Permeation Through COC-embedded Hydrophilic Membranes by Exchanging Temperature Between 10°C and 25°C

Since salbutamol sulfate can only penetrate across the hydrophilic membranes, the effect of COC concentration used on the permeation behavior of drug through COC-embedded hydrophilic membranes was investigated, as shown in Fig. 4. These COC-embedded hydrophilic membranes were prepared with 0.5%, 3%, 20%, and 30% COC chloroform solution, respectively. The perme-

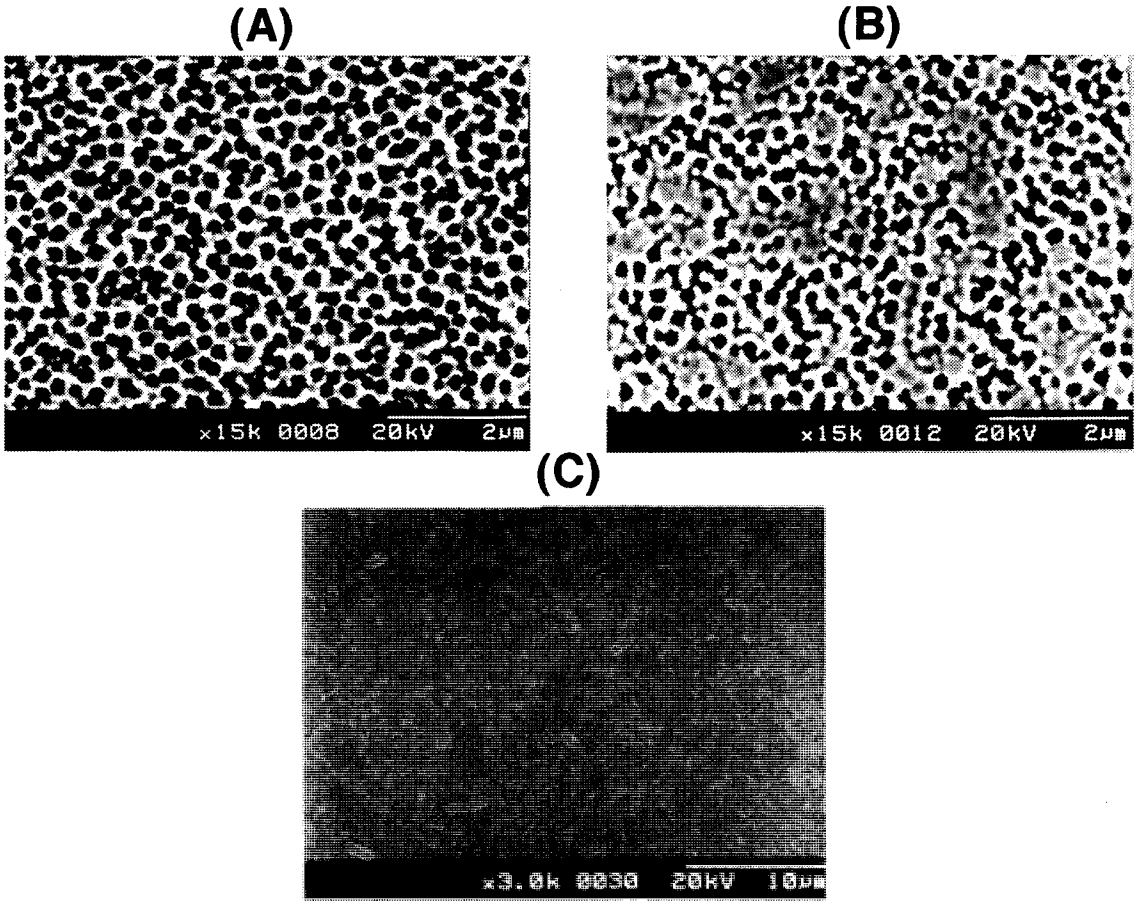

Fig. 3. Scanning electron micrographs of COC-embedded Anodisc membranes prepared with different COC chloroform solutions. Key: (A) 0%, (B) 5%, (C) 30%

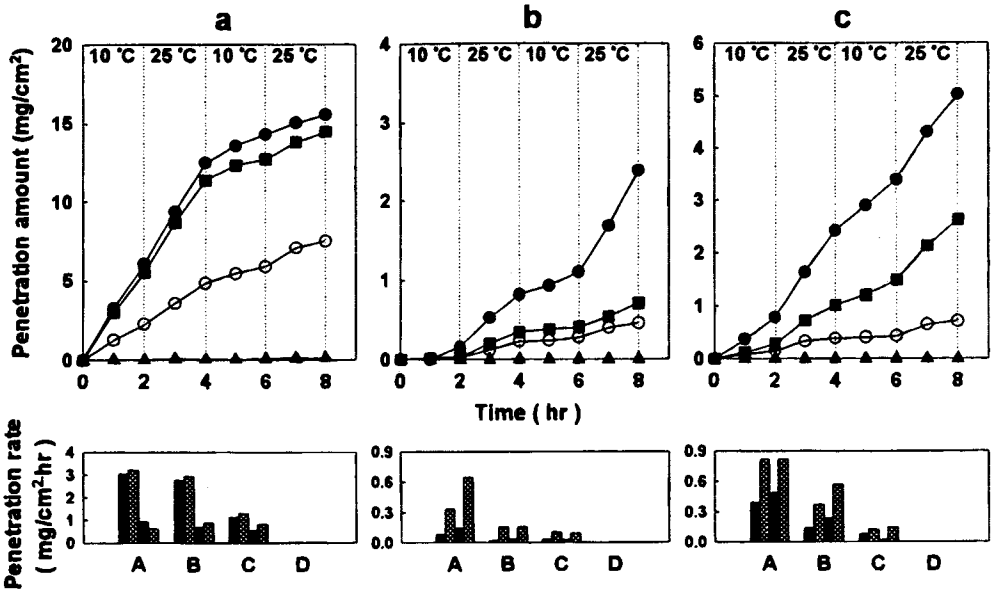

Fig. 4. Permeation profile and permeation rate of salbutamol sulfate across COC-embedded membranes prepared with different COC chloroform solutions, in response to a temperature change. Key: (a) Anodisc; (b) CN; (c) Nylon A, ●: 0.5%; B, ■: 3%; C, ○: 20%; D, ▲: 30%.

ation study was conducted with a system having temperature cycle between 10°C and 25°C. Anodisc membrane prepared with 0.5% or 3% COC chloroform solution did not exhibit any pulsatile release function, but its permeation rate could be thermally controlled when 20% COC chloroform solution was used. On the other hand, CN and nylon membranes exhibited pulsatile pemeation function while they were prepared with 0.5%, 3%, or 20% COC chloroform solution. Although the same order of the permeation rate of salbutamol sulfate was obtained, the reversibly thermo-responsive efficacy seemed to be more pronounced in membranes adsorbing with higher amount of COC. In the region of adsorbing less COC, only a little amount of COC could embed into membranes. It was thus difficult to achieve high thermo-responsive efficacy. The higher thermo-responsive efficacy can be explained not only by less permeability through matrix part of the membrane (<18°C) but also by higher thermal motion of the COC molecules (>18°C). When COC increased to 30% of the solution, the penetration of salbutamol sulfate through these composite membranes became impossible because the surface of membranes is completely covered with COC.

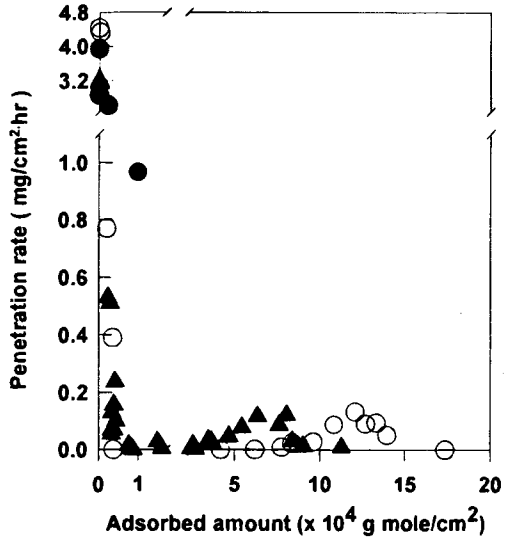

Fig. 5. Effect of adsorbed amount of COC on the permeation rate of salbutamol sulfate through COC-embedded membranes. Key: ●, Anodisc; ○, CN; ▲, Nylon.

Effect of Adsorption of COC on the Permeation Rate of Drug at 25°C

The effect of COC adsorption on the permeation rate of salbutamol sulfate through COC-embedded membrane at 25°C is shown in Fig. 5. Apparently, similar permeation behavior of salbutamol sulfate through these membranes confirmed the adsorption of COC as the predominant factor of the drug permeation. Since Anodisc membrane is so fragile to form cracks during the manufacturing process, especially at higher COC content, thus the evaluation of the COC-embedded Anodisc membrane was only done at low COC content. It is very interesting to find that the permeation rate of salbutamol sulfate decreased suddenly with the increasing adsorption of COC at the initial stage and then decreased gradually untill the membranes turned impermeable. The drug permeation started again when the adsorption of COC kept increasing and finally stopped with excess amount of COC because the hydrophilic membrane had been hydrophobicized. The aggregation of COC in turn created some channels to improve the permeation of salbutamol sulfate. When the surface of membranes was completely covered by COC, drug permeation was impossible. The surface topography and internal texture of the COC-embedded nylon membranes in Fig. 6 can confirm and consistent with the above results.

CONCLUSIONS

A COC-embedded membrane with rate-controlled and thermo-responsive function was prepared using vacuum filtra-

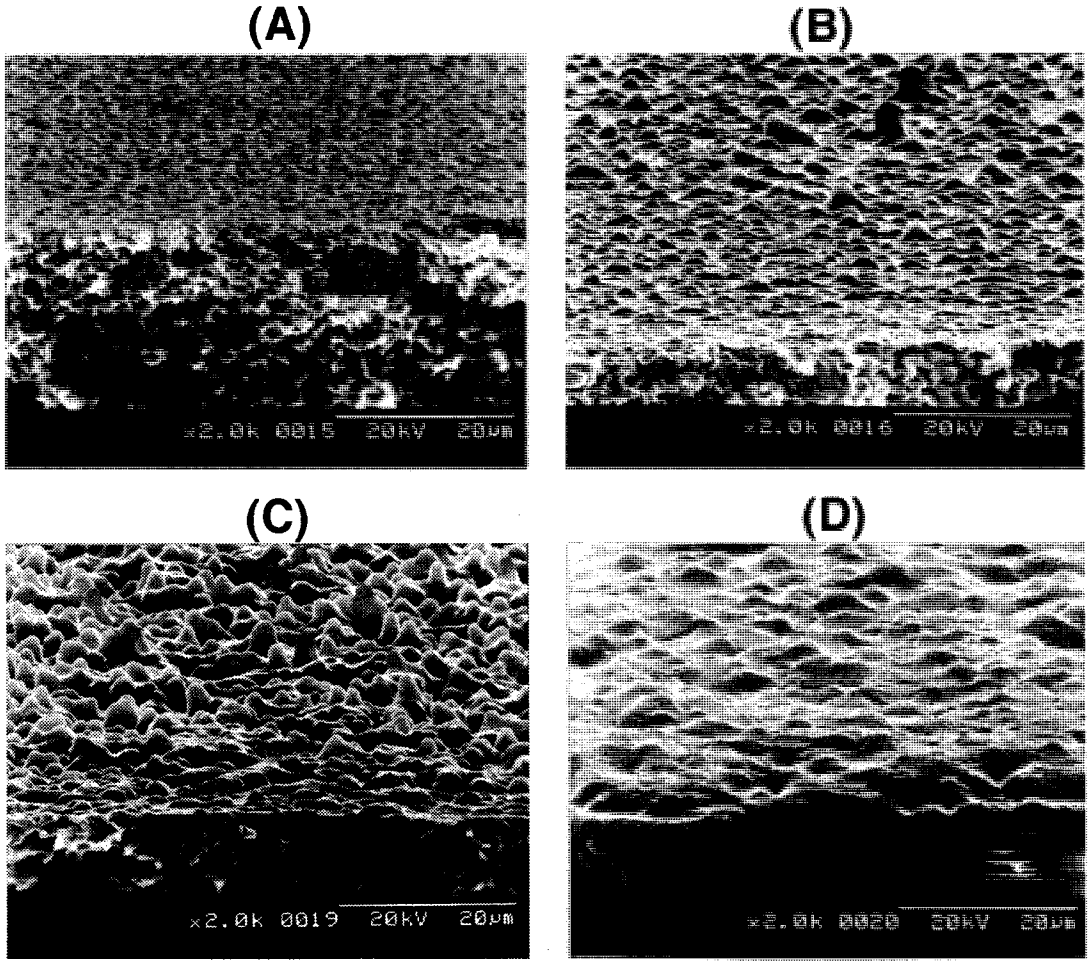

Fig. 6. Effect of adsorbed amount of COC on the scanning electron micrographs of nylon membranes. Key: Amount of COC ($\times 10^{-4}$ g mole/cm^2) (A) 0.4, (B) 1.6, (C) 3.7, (D) 7.0.

tion method. Membrane properties and the adsorption of COC play an important role in controlling solute permeation. This thermo-switchable membrane can be used for the development of drug delivery system. The penetration rate of hydrophobic drug through the COC-embedded membranes will be evaluated in future.

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REFERENCES

1. M. H. Smolensky and G. E. D'alonzo, Medical chronobiology: Concepts and applications. *Am. Rev. Respir. Dis.*, **147**:s2–s19 (1993).
2. B. Bruguerolle and B. Lemmer, Recent advances in chronopharmacokinetics: Methodological problems. *Life Sci.*, **52**:1809–1824 (1993).
3. J. T. Flaherty, Nitrate tolerance: A review of the evidence. *Drugs*, **37**:523–550 (1989).
4. C. Cowan, J. Bourke, D. Reid and D. G. Julian, Tolerance to glyceryl trinitrate patches: Prevention by intermittent dosing. *Br. Med. J.*, **294**:544–545 (1987).
5. H. L. Fung, Pharmacokinetic determinants of nitrate action. *Am. J. Med.*, **76** (supp. 6A):22–26 (1984).
6. C. L. Lee, K. L. Ulman and K. R. Larson, Kinetics and thermodynamics of drug permeation through silicone elastomers IV. Effect of polymer backbone structure, *Drug Devel. Indus. Pharm.*, **12**:369–383 (1986).
7. S. T. Hwang, R. J. Shea, K. H. Moon and R. G. Bunge, Permeation of testosterone through silicone rubber membranes. *Invest. Urol.*, **8**:245–253 (1970).
8. K. Knutson, R. O. Pott, D. B. Guzek, G. M. Golden, J. E. McKie, W. J. Lambert and W. I. Higuchi, Macro- and molecular physical considerations in understanding drug transport in the stratum corneum. *J. Control. Release*, **2**:67–87 (1985).
9. M. C. Blok, L. L. van Deenen and J. De Gier, Effect of the gel to liquid crystalline phase transition on the osmotic behavior of phosphatidylcholine liposomes. *Biochim. Biophys. Acta*, **443**:1–12 (1976).
10. R. Fettiplace and D. A. Hydon, Water permeability of lipid membranes. *Physiol. Rev.*, **60**:510–550 (1980).
11. Y. Y. Lin, K. S. Chen and S. Y. Lin, Thermophysical property of cholesteryl oleyl carbonate determined with microscopic FTIR/DSC system. *J. Chin. Chem. Soc.-Taipei*, **42**:865–868 (1995).
12. Y. Y. Lin, K. S. Chen and S. Y. Lin, Temperature effect on the thermal characteristics and drug penetrability of the thermally On-off switching membrane. *Int. J. Pharm.*, **124**:53–59(1995).

13. S. Y. Lin, Y. Y. Lin and K. S. Chen. A thermoswitchable membrane for drug delivery. *Drug Delivery,* **2**:123–127 (1995).
14. Y. Y. Lin, K. S. Chen and S. Y. Lin, Development and investigations of a thermo-responsive cholesteryl oleyl carbonate-embedded membrane. *J. Control. Release,* accepted (1996).
15. K. S. Chen, Y. Y. Lin and S. Y. Lin, Penetration behavior of salbutamol sulfate through thermo-responsive nylon membrane containing liquid crystal. *Drug Delivery System,* **11**:55–61 (1996).
16. T. Z. Franz, Percutaneous absorption on the relevance of in vitro data. *J. Invest. Dermatol.,* **64**:190–195 (1975).
17. S. Y. Lin, S. J. Hou, T. H. S. Hsu and F. L. Yeh, Comparisons of different animal skins with human skin in drug percutaneous penetration studies. *Meth. Find. Exp. Clin. Pharmacol.,* **14**:645–654 (1992).
18. S. J. Lee, K. B. Tamie and S. W. Kim, Ion-paired drug diffusion through polymer membranes. *Int. J. Pharm.,* **47**:59–73 (1987).
19. M. M. Ghannam, K. Tojo and Y. W. Chien, Kinetics and thermodynamics of drug permeation through silicone elastomers (1) Effect of penetrant hydrophilicity. *Drug Devel. Indus. Pharm.,* **12**:303–325 (1986).
20. M. M. Ghannam, K. Tojo and Y. W. Chien, Kinetics and thermodynamics of drug permeation through silicone elastomers (1) Effect of penetrant lipophilicity. *Drug Devel. Indus. Pharm.,* **12**:327–348 (1986).