4-h cycle time, the penetration rate of salbutamol sulfate was about 0.225 ± 0.074 mg/cm^2 per hour at 25 °C and 0.009 ± 0.02 mg/cm^2 per hour at 10 °C. However, the penetration rate at 25 °C was about 0.087 ± 0.015 mg/cm^2 per hour but at 10 °C was about 0.01 ± 0.002 mg/cm^2 per hour in the 24-hr cycle time.[40] A constant penetration rate with each time cycle indicates that the COC-embedded membrane continuously maintained its thermo-related sensitivity even with repeated use.

A reservoir compartment such as an aqueous solution or a semisolid dosage form has been combined with the COC-embedded membrane. The influence of the pH of an aqueous solution and of a semisolid preparation on the on-off pulsatile penetration behavior of salbutamol sulfate through the thermo-responsive COC-embedded membrane is very critical. Fortunately, the on-off function of this COC-embedded membrane is not influenced by the pH of the medium. On the other hand, pH dependence of the ionization of salbutamol and the viscosity of the gel base as well as the interaction between salbutamol and carbopol might change the amount and rate of salbutamol sulfate

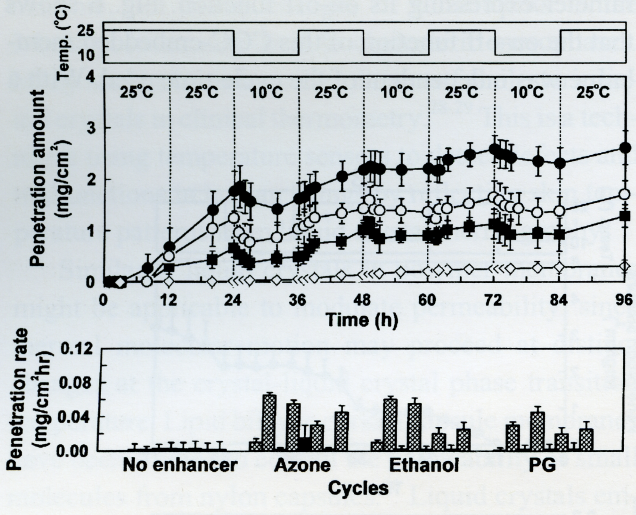

Fig. 7. Penetration profile and rate of salbutamol sulfate from a gel formula containing different skin-penetrating enhancers across a COC-embedded membrane applied to nude mice skin in reponse to temperature exchange cycles.[42] Skin-penetrating enhancers: ●, azone; o, ethanol; ■, PG; ◊, no enhancer.

penetrating across the COC-embedded membrane.[41]

We must be concerned about whether the skin-penetrating enhancers commonly used in transdermal DDSs may alter the structure of COC to change the on-off switching function of COC-embedded membranes. With application of COC-embedded membranes to intact skin, moreover, the long-term maintenance of the on-off switching function of this COC-embedded membrane, needs to be verified. Fig. 7 shows that the on-off switching penetration behavior of salbutamol sulfate from gel formulas through the COC-embedded membrane, with or without application to excised nude mice skin, was not influenced by the use of skin-penetrating enhancers such as azone, ethanol, or propylene glycol (PG).[42-43] These data conclude that these skin-penetrating enhancers do not alter the structure of COC embedded in membranes to change the thermo-responsive on-off switching penetration behavior of drugs. This finding suggests the usefulness of COC-embedded membranes for thermal control of drug delivery.

Thermo-responsive Membranes with Embedded Binary Liquid Crystals

A thermo-responsive membrane entrapping a single liquid crystal has been successfully developed with a pulsatile function in response to thermal stimuli. Investigations have studied the thermophysical properties of the liquid crystal, temperature effects and fabricating methods, types, pore sizes and properties of the membrane used, cycle time of temperature, pH of preparations, and types of skin-penetrating enhancers. The on-off thermo-responsive function of this single liquid crystal-embedded membrane was assessed by altering a repeated temperature cycle between 10 and 25 °C. Although COC-embedded membranes with rate-controlled and thermo-responsive function are easily be prepared by a vacuum-filtration method to achieve high reversible thermo-response efficacy by choosing COC concentrations properly, the phase transition temperature of COC is not near body temperature. This thermo-switchable membrane can still not be used for transdermal drug delivery systems in practice.