ple, theophylline given once daily in the late afternoon reduces the early-morning decrease in peak expiratory flow rate (PEFR) more efficiently than theophylline administered twice daily.[25] In order to apply chronotherapy to the treatment of nocturnal asthma, we have attempted to design a thermoswitchable membrane with a temperature-dependent on-off pulsatile release function to control a once-daily evening dose of the antiasthmatic drug, salbutamol sulfate, with the goal of achieving peak blood concentrations 10-12 h after dosage, and of effectively improving the values of PEF and symptoms of nocturnal asthmatics.

Strategy to Design Thermo-responsive Membranes

The lipid bilayer in the stratum corneum is known to be the main barrier controlling the permeability of drugs.[26] 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.[27] Therefore, phase transition would be one of the most essential functions for biological membranes. Cholesterol is one of the predominant components in biomembranes in most organisms. It is not mesomorphic, but minor changes of substituents in the 3-beta position may lead to cholesteric mesophases. Many studies have described the use of cholesteric liquid crystals in clinical thermometry.[28-29] This is a technique using temperature sensors to detect defects and malfunctions in human beings by reflecting skin temperature patterns from liquid crystal thermography.

Similarly, liquid crystals in polymer membranes might be applicable to modulate permeability, since thermal molecular motion may proceed at distinct changes at the crystal-liquid crystal phase transition temperature. Lipid bilayer-corked capsule membranes have been studied to control the permeability of small molecules from nylon capsules.[30] Liquid crystals embedded in a self-adhesive polymer film have been marketed in medical applications in the form of a tape to obtain the thermal mapping of skin.[28] The major application of membranes in DDSs is to control drug permeation. It has been recently used in transdermal DDSs for topical and systematic therapy. For example, Transderm-Scop and Transderm-Nitro have porous membranes to control the release of scopolamine and nitroglycerin, respectively.[31] However, these transdermal DDSs are not able to release drug in response to the condition of patients. In order to follow the circadian rhythms of human beings, a thermo-responsive membrane relating to changes of body temperature or external thermal stimuli has been designed for timely pulsatile drug delivery. Two types of liquid crystal-embedded membranes have been designed to act as a controlled membrane to develop a transdermal DDS with a thermal stimuli response.

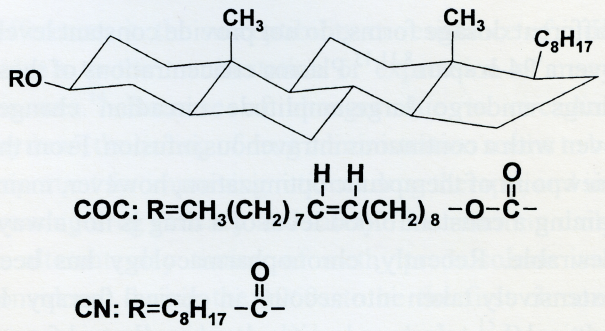

Fig. 4. Molecular structures of cholesteryl oleyl carbonate (COC) and cholesteryl nonanoate (CN).

Thermo-responsive Membranes with an Embedded Single Liquid Crystal

Cholesteryl oleyl carbonate (COC) is one of the most popular cholesterol derivatives used in thermography of medical applications.[28,29] Its structural formula is shown in Fig. 4. COC exhibits a smectic-cholesteric phase transition at 18.3 °C and a cholesteric-isotropic phase transition at 37.5 °C.[32-35] A thermo-responsive membrane was prepared by entrapping COC into a cellulose nitrate or nylon membrane with a vacuum-filtration method at various manufacturing temperatures and then storing it under different conditions. Salbutamol sulfate, an antiasthmatic drug, was used as a model drug. The results demonstrate that the thermal on-off switching membranes can easily be manufactured by the vacuum-filtration method at temperatures above the phase transition temperature of 18.3 °C[36-37] and may achieve high thermo-responsive efficacy using a step-wise temper-