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ScienceDirect
International Journal of Pharmaceutics 339 (2007) 213–221
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Temperature modulated drug permeation through liquid crystal embedded cellulose membranes

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Received 24 May 2006; received in revised form 26 February 2007; accepted 6 March 2007
Available online 12 March 2007

Abstract

Stimuli-sensitive membranes may act as "on–off switches" or "permeability valves", producing patterns of pulsatile release, where the period and rate of mass transfer can be controlled by external or environmental triggers. In this study, cellulose nitrate (CN) and cellulose acetate (CA) monolayer membranes containing thermotropic liquid crystals (LC) were developed as thermoresponsive barriers for drug permeation. A low molecular thermotropic LC, *n*-heptyl-cyanobiphenyl (K21), with nematic to isotropic phase transition temperature ($T_{n–i}$) of 41.5 °C was chosen to modulate drug permeation. Methimazole and paracetamol as hydrophilic and hydrophobic drug models were used, respectively. It was found that upon changing the temperature of the system around the $T_{n–i}$, both cellulose membranes without LC showed no temperature sensitivity to drug permeation, whereas the results for LC entrapped membranes exhibited a distinct jump in permeability when temperature was raised to above the $T_{n–i}$ of the liquid crystal for both drug models. On the other hand, drug permeation through these LC embedded membranes can be thermally modulated. Thermoresponsive drug permeation through the membranes was reversible, reproducible and followed zero order kinetics. Liquid crystal embedded cellulose acetate membranes showed more temperature sensitivity than liquid crystal embedded cellulose nitrate membranes, apparently due to higher LC loading in their porous matrix compared to CN membranes. The pattern of on–off permeation through LC embedded membranes was more distinguished for methimazole compared to that of paracetamol, seemingly due to its lower molecular weight.

Keywords: Thermoresponsive drug delivery; Composite membrane; Thermotropic liquid crystals; Methimazole; Paracetamol

1. Introduction

Current approaches to the development of drug delivery systems are based typically on the premise that relationship between the plasma concentration and therapeutic effect of a drug is invariant with time. It has been recognized for some time, however, that this approach may not be appropriate for certain drugs and it has been suggested that therapeutic efficacy may be improved by the utilization of triggered, pulsed and programmed delivery systems (D'Emanuele, 1996; Kost and Langer, 2001). The fabrication of such smart systems requires the use of stimuli-sensitive materials (Bussemer et al., 2001). Among these materials, liquid crystals (LC) have attracted attentions due to their sharp, positive, reversible and multi-stimuli responses. Studies on lyotropic LCs in drug delivery goes back to some years ago (Wahlgren et al., 1984; Makai et al., 2003). However, the concept of using thermotropic LCs as stimuli-sensitive materials in responsive drug delivery systems is new and only few works have been carried out in this field (Dinarvand and Ansari, 2003). Studies on photochromic azobenzene LCs as controlled release drug delivery systems have shown that cellulose nitrate membranes embedded with two different commercially available LCs of this category are reversibly thermoresponsive and the rate of drug transport through them was dependent on the amount of LC deposited on the membrane (Watson et al., 1999, 2001). Another thermoresponsive membrane was developed by adsorbing the binary cholesteric LCs, 36% cholesteryl oleyl carbonate (COC) and 64% cholesteryl nonanoate (CN) solved in an organic solvent into the cellulose nitrate membranes (Lin et al., 2002a). Ng et al. (2001) prepared

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doi:10.1016/j.ijpharm.2007.03.004

a thermoresponsive membrane using absorption techniques with an appropriate molar ratio of two saturated straight chain alkanes, docosane ($C_{20}H_{42}$) and eicosane ($C_{22}H_{46}$) with melting points of 44.4 and 36.7 °C, respectively. In our previous works, triple layer polymeric membranes containing cyanobiphenyl liquid crystals were successfully developed (Dinarvand et al., 2005, 2006). In this study, a kind of monolayer composite membrane is prepared in which *n*-heptyl cyanobiphenyl (K21), as the liquid crystalline (LC) material, embedded in the matrix of cellulose membranes. Manufacturing and using a monolayer membrane is much simpler than triple layer polymeric membranes. *N*-Heptyl cyanobiphenyl liquid crystal is a thermotropic LC with a nematic to isotropic phase transition temperature ($T_{n–i}$) of about 41.5 °C close to the body temperature. Due to the low melting point of K21, there is no need to use any solvent as used for the cholesteric LCs by Lin et al. (2002a,b).

Porous substrates can be modified to produce membranes with variable and controllable permeability. Responsive materials can be either physically placed in the pores or covalently attached to the pore surfaces. The porous substrate acts as an inert and, usually impermeable physical support, while the pore-filling, responsive materials, such as polymers, cross-linked hydrogels and LCs, respond to external stimuli to control drug diffusion (Ng et al., 2001). Two different types of cellulose membranes, cellulose nitrate (CN) and cellulose acetate (CA), with porous spongy like matrixes were used in this study. It has already been shown that liquid crystal molecules can physically be adsorbed within the pores of the cellulose membranes (Lin et al., 2002b).

Such thermoresponsive LC embedded membranes are much permeable to drug molecules at temperatures above 41.5 °C. One can envisage to use this triggerable drug delivery system that releases drug only above a certain temperature as a drug reservoir system. One of the rationales for such thermoresponsive system may be the potential for their use in chemotherapeutics delivery under local hyperthermia. The synergistic effect of chemotherapy and hyperthermia has already been established (Gofrit et al., 2004).

2. Experimental

2.1. Materials

N-Heptyl cyanobiphenyl (K21) as a thermotropic liquid crystal was purchased from Merck Co. (Darmstadt, Germany). Cellulose nitrate membranes (pore size 0.22 μm, diameter 49 mm, thickness 125 μm, porosity 63.9%) were obtained from Whatman (Maidstone, UK). Cellulose acetate membranes (pore size 0.45 μm, diameter 47 mm, thickness 100 μm, porosity 71.4%) were obtained from Macherey–Nagel (Duren, Germany). Methimazole and paracetamol (USP 25) were kindly donated by Sobhan Pharma Co., Iran, and Alhavi Pharma Co., Iran, respectively. All other solvents and reagents used were of analytical grade. The chemical structures of *n*-heptyl cyanobiphenyl, methimazole and paracetamol are shown in Fig. 1.

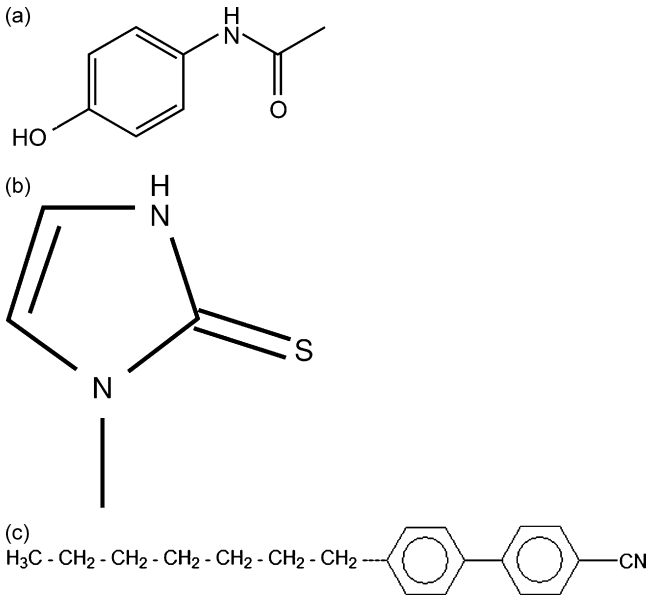

Fig. 1. Chemical structure of: (a) paracetamol ($C_8H_9NO_2$), (b) methimazole ($C_4H_6N_2S$) and (c) *n*-heptyl-cyanobiphenyl (K21).

2.2. Determining the porosity of CN and CA membranes

Three dry CN and CA membranes weighed carefully. Then the membranes were submerged in distillated water. In different time interval, they were taken out from the media and padded with clothing and weighed again. After reaching to equilibrium, the difference between weights of soaked membranes and dry ones give the amount of liquid filled the pores. The porosity is then calculated by dividing the volume of the liquid absorbed by the membrane by the total volume of the membrane.

$$\%\text{Porosity} = \frac{\text{Maximum volume of liquid absorbed to the membrane}}{\text{Total volume of the membrane}}$$

2.3. Preparation of liquid crystal embedded cellulose acetate membranes

Cellulose acetate membranes have a hydrophobic nature (similar to LC materials). For preparation of liquid crystal embedded cellulose acetate membranes, the disk-like CA sheets were soaked in *n*-heptyl cyanobiphenyl (K21) previously warmed to above the nematic–isotropic phase transition of K21 (41.5 °C). At above this temperature, LC molecules are at isotropic phase and can therefore move around freely and distributed within the membranes pores easier. Lin et al. (2002a) showed that with preparing membranes in temperatures above the $T_{n–i}$ of LC materials, a higher temperature sensitivity can be achieved. At different time intervals, membranes were taken out and weighed after the extra amount of LC on their surfaces were removed. Reaching to a constant weight means that the membranes are saturated with K21. For the removal of LC remained on the surface, sheets were washed with distillated water at the end of the process. Scanning electron microscopy was applied to see the embedding result of K21 in the membrane matrix.