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Temperature modulated drug permeation through liquid crystal embedded cellulose membranes

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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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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.

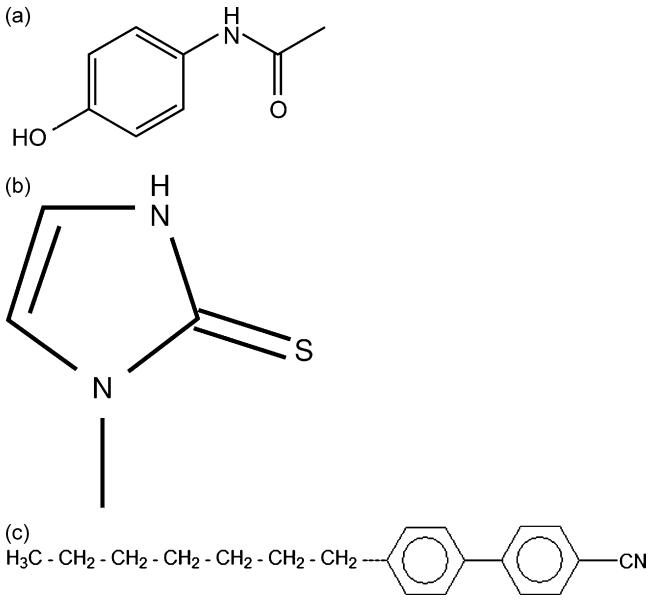

Fig. 1. Chemical structure of: (a) paracetamol ($C_8H_9NO_2$), (b) methimazole ($C_4H_6N_2S$) and (c) *n*-heptyl-cyanobiphenyl (K21).

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.

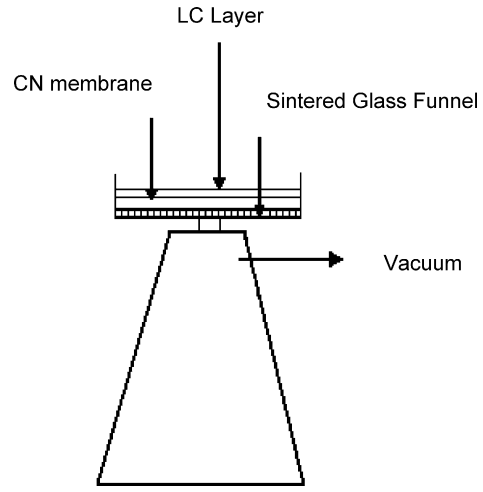

Fig. 2. A simple schematic diagram of the system used for preparation of liquid crystal entrapped cellulose nitrate and acetate membranes.

2.4. Preparation of liquid crystal embedded cellulose nitrate membranes

Cellulose nitrate membranes have a hydrophilic nature (unlike LC materials) therefore the embedding process of liquid crystal molecules is not as easy as CA membranes. In this case the use of vacuum was tried to get LC molecules inside the CN pores. For preparation of LC embedded CN membranes, K21 was warmed up to 46 °C (above its $T_{n–i}$) and an extra volume (more than the porosity of the membrane) of K21 was passed through the CN membranes, previously set on a sintered glass funnel, by means of vacuum. A schematic representation of such system is shown in Fig. 2. The degree of vacuum should be regulated to pull LC into the matrix of the membrane but it should not be very high so that K21 molecules can exit from the other side of the membrane. Weight change of the membranes before and after the soaking process gives the actual amount of K21 embedded within the membranes. To ensure saturation of all membranes with K21, this amount should be in close agreement with the predicted value of weight gain in the membranes regarding to the density of K21, and porosity and thickness of the membranes. For the removal of LC remained on the surface, sheets were washed with distillated water at the end of the process. The textures of membranes were observed by scanning electron microscopy at the end of the process to double-check the LC entrapment. All variations such as degree of vacuum, the temperature of K21, the amount of LC used were the same for all batches of LC embedding CN membranes.

2.5. Scanning electron microscopy (SEM)

The membranes were coated with gold by a SCD 004 sputter coater (Balzers, Germany). The coated membranes were then viewed with a DSM 960A scanning electron microscope (Zeiss, Germany).

2.6. Permeation studies

The effect of temperature on the permeation of two drug models, methimazole ($C_4H_6N_2S$, $M_W = 114.17$) and paracetamol ($C_8H_9NO_2$, $M_W = 151.17$) through LC embedded membranes was measured by determining the amount of drug permeated at different temperatures against time. To determine the solute's permeability, both CA and CN membranes (LC embedded) were clamped in a two-chamber horizontal diffusion cell that had an available permeation area of about 1.98 cm^2 and a half cell volume of about 130 ml. Permeation tests were carried out at different constant temperatures below and above the $T_{n–i}$ of K21 (41.5 °C) for about 12 h. Before each test, LC embedded membranes were soaked in the phosphate buffer solution of the same temperature for at least 2 h.

One percent of drug buffer solution (phosphate buffer, pH 7.4) was put into the donor cell, but receptor chamber was filled with drug free buffer solution with the same pH. The diffusion cell immersed in thermostated water bath with temperature fluctuations of ±0.1 °C (Memmert, Germany). The solution of each compartment was stirred at 100 rpm to eliminate boundary layer effects. At different time intervals, an aliquot of 4 ml was removed and replaced with the same volume of blank phosphate buffer solution. The amount of drug permeated through the membrane was monitored over time by UV absorbance measurement at 251.1 and 243 nm for methimazole and paracetamol, respectively. The amount permeated was plotted against time. The tests were generally performed in triplicates. The permeation rate is obtained from the slope of permeation curve at each temperature. To see if the K21 has remained inside the pores and has not leaked out, LC embedded membranes were weighted before and after the permeation experiments.

The permeation study was also examined for both drugs and both LC embedded membranes by regulating the temperature between 30 and 46 °C alternatively (below and above the $T_{n–i}$ of K21) to investigate the reversibility and reproducibility of the temperature dependence of drug permeation through the membranes. Permeation coefficients of LC embedded membranes are obtained from the slope of permeation curves at each temperature. All permeation tests were performed in triplicates.

3. Results and discussion

3.1. Scanning electron microscopy

Fig. 3 shows the SEM images of K21 embedded CN membrane (a); K21 embedded CA membrane (b); CA membranes without LC embedding (c), respectively. The entrapment of K21 in the spongy-like matrix of the cellulose membranes can be clearly observed.

3.2. Drug permeation at constant temperatures

3.2.1. Permeation through LC entrapped CA membranes

Figs. 4 and 5 show the permeation of methimazole through LC entrapped and blank CA membranes, respectively. As it can be seen methimazole permeation through LC entrapped CA membranes at temperatures above liquid crystal's $T_{n–i}$ (41.5 °C) increases substantially compared to that at temperatures below

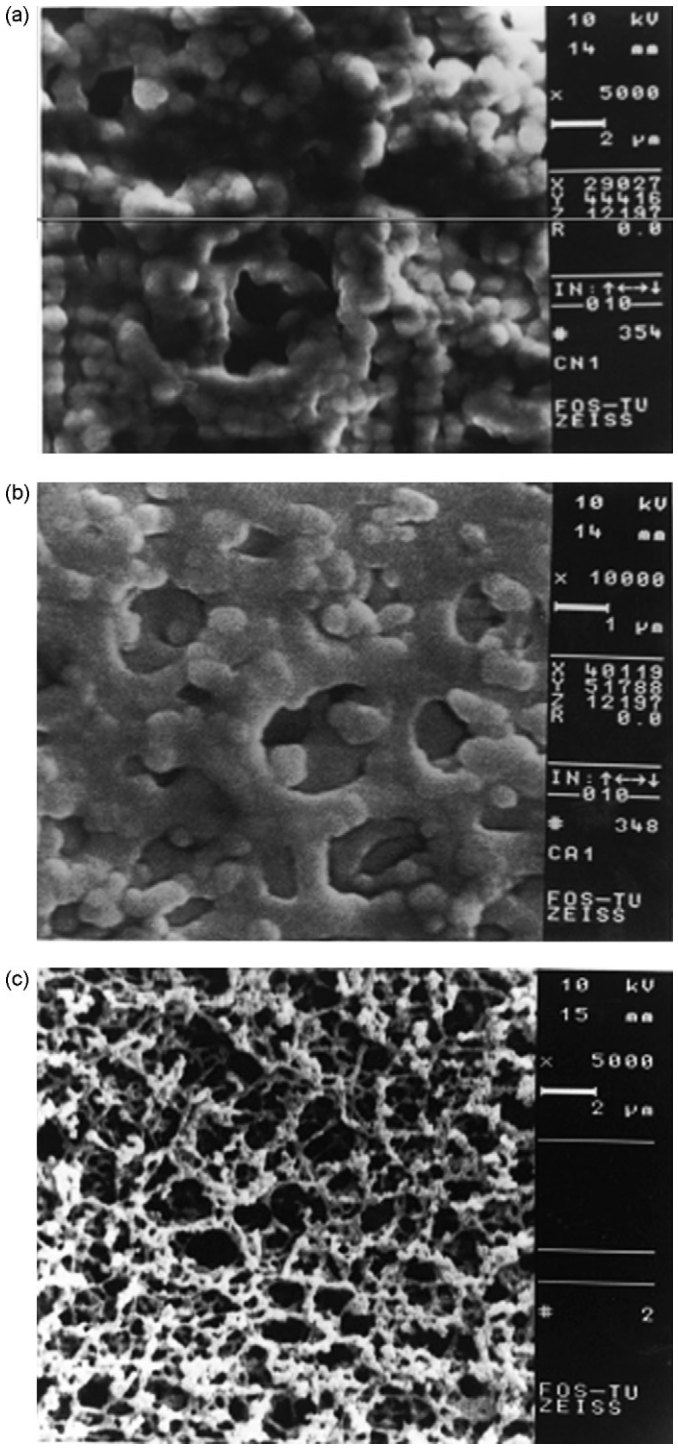

Fig. 3. SEM images of a cellulose membrane: (a) CN membrane without LC, (b) LC entrapped CN membrane and (c) LC entrapped CA membrane.

$T_{n–i}$ of the LC. However, as it can be seen in Fig. 5, permeation of methimazole through control membranes (CA membranes without LCs) shows no significant differences upon changes in temperatures below and above the phase transition temperature of K21 (41.5 °C).

On the other hand, in all temperatures, drug permeation through control membranes was not thermoresponsive. This supports the idea that molecular inherent diffusivity change of

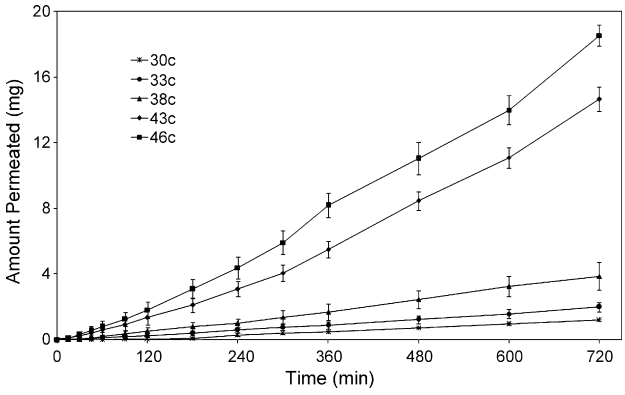

Fig. 4. Methimazole permeation through K21 embedded CA membranes at different temperatures below and above the phase transition temperature of the LC ($n = 3$).

methimazole in terms of temperatures below and above the $T_{n–i}$ of K21 is small and the LC component of membranes provides thermoresponsive control of drug permeation through LC embedded membranes. Another point which is seen in these figures is that methimazole permeation through control CA membranes is much greater than that through the LC embedded membranes. This shows that the presence of liquid crystal molecules within the pores of the polymeric membranes limits the drug permeation as expected. Fig. 6 shows the permeation of paracetamol through LC embedded CA membrane at different temperatures. It can be seen that paracetamol permeation through LC entrapped CA membranes at temperatures above liquid crystal's $T_{n–i}$ (41.5 °C) increases substantially compared to that at temperatures below it. The permeation pattern of paracetamol through blank CA membrane (without LC) was similar to that of methimazole (data not shown here). Permeation coefficients of paracetamol and methimazole through LC entrapped CA membranes at different temperatures are shown in Fig. 7. Permeation coefficients of both drug molecules through the membranes are seen to increase by several orders of magnitude at temperatures above the phase transition temperature of K21 (41.5 °C).

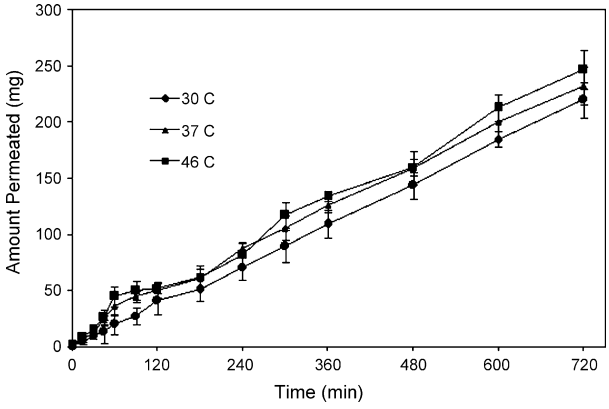

Fig. 5. Methimazole permeation through blank CA membranes (without LCs) at different temperatures below and above the phase transition temperature of K21 ($n = 3$).

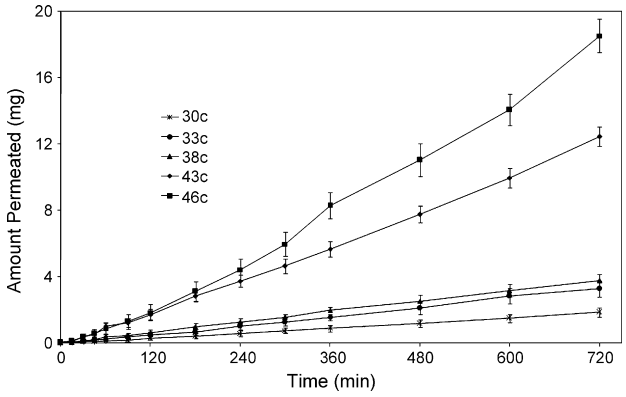

Fig. 6. Paracetamol permeation through K21 embedded CA membranes at different temperatures below and above the phase transition temperature of K21 ($n = 3$).

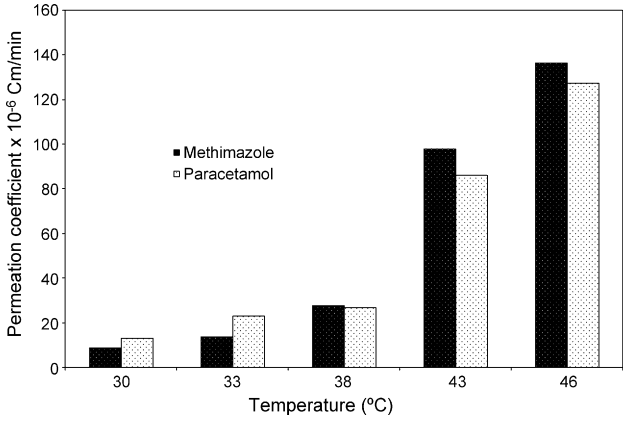

Fig. 7. Methimazole and paracetamol permeation coefficients through K21 embedded CA membranes at different temperatures below and above the phase transition temperature of K21 ($n = 3$).

3.2.2. Permeation through LC embedded CN membranes

Figs. 8 and 9 show the methimazole permeation through LC entrapped and blank CN membranes, respectively. The results for paracetamol permeation through LC entrapped CN membrane is shown in Fig. 10. As expected the permeation of methimazole through blank CN membranes (without LCs) show

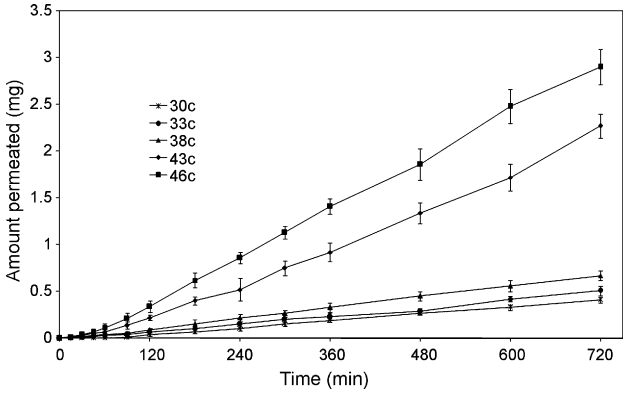

Fig. 8. Methimazole permeation through K21 embedded CN membranes at different temperatures below and above the phase transition temperature of the LC ($n = 3$).

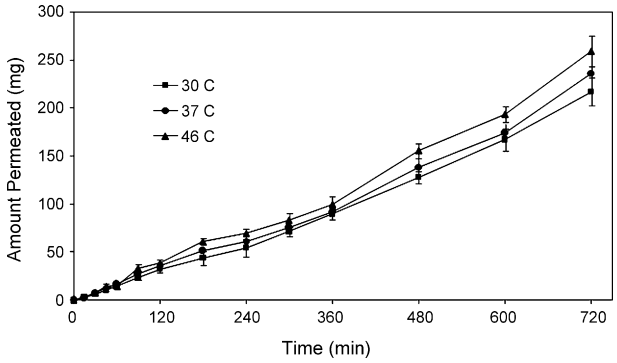

Fig. 9. Methimazole permeation through blank CN membranes (without LCs) at different temperatures below and above the phase transition temperature of K21 ($n = 3$).

no significant differences upon changes in temperatures below and above the $T_{n–i}$ of K21 (Fig. 9). The same was true for methimazole (data not presented here). It can be seen that the permeation of both methimazole and paracetamol through LC embedded CN membranes at temperatures above the nematic to isotropic phase transition temperature of K21 increases substantially compared to that at temperatures below K21 $T_{n–i}$ (41.5 °C).

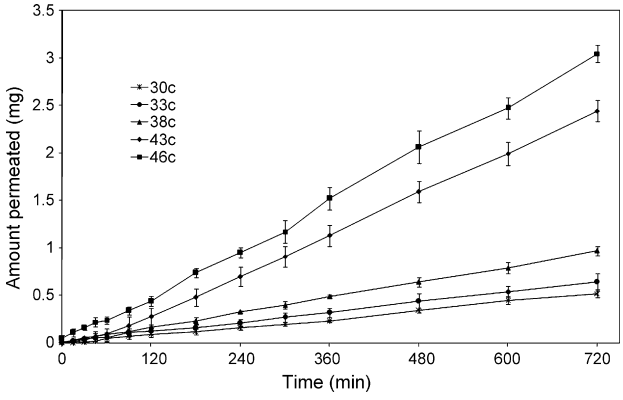

Fig. 10. Paracetamol permeation through K21 embedded CN membranes at different temperatures below and above the phase transition temperature of the LC ($n = 3$).

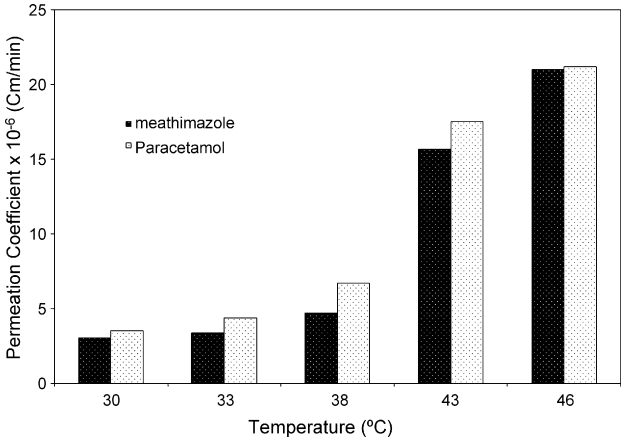

Fig. 11. Methimazole and paracetamol permeation coefficient through K21 entrapped CN membranes at different temperatures below and above the phase transition temperature of K21 ($n = 3$).

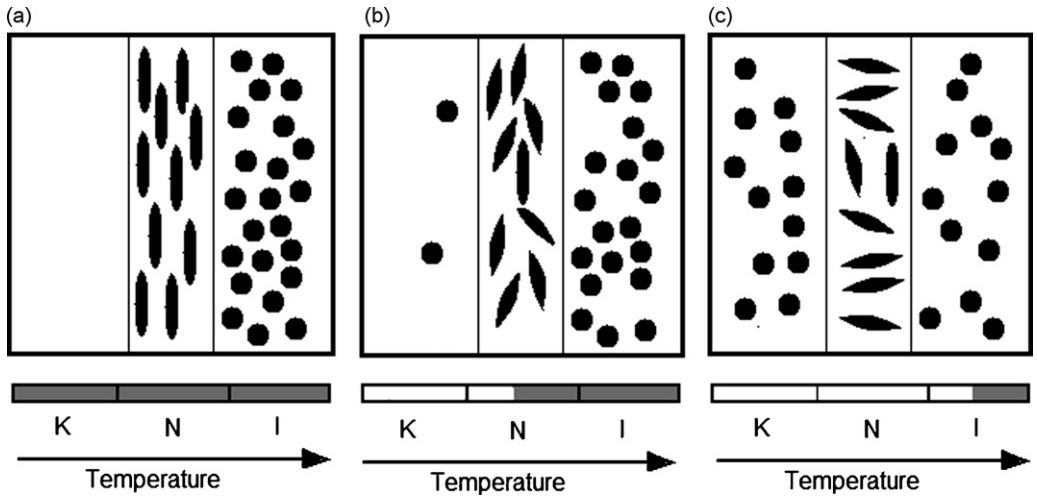

Fig. 12. A schematic diagram of temperature sensitivity of the liquid crystal embedded polymeric membranes: K, crystal; N, nematic phase; I, isotropic phase.

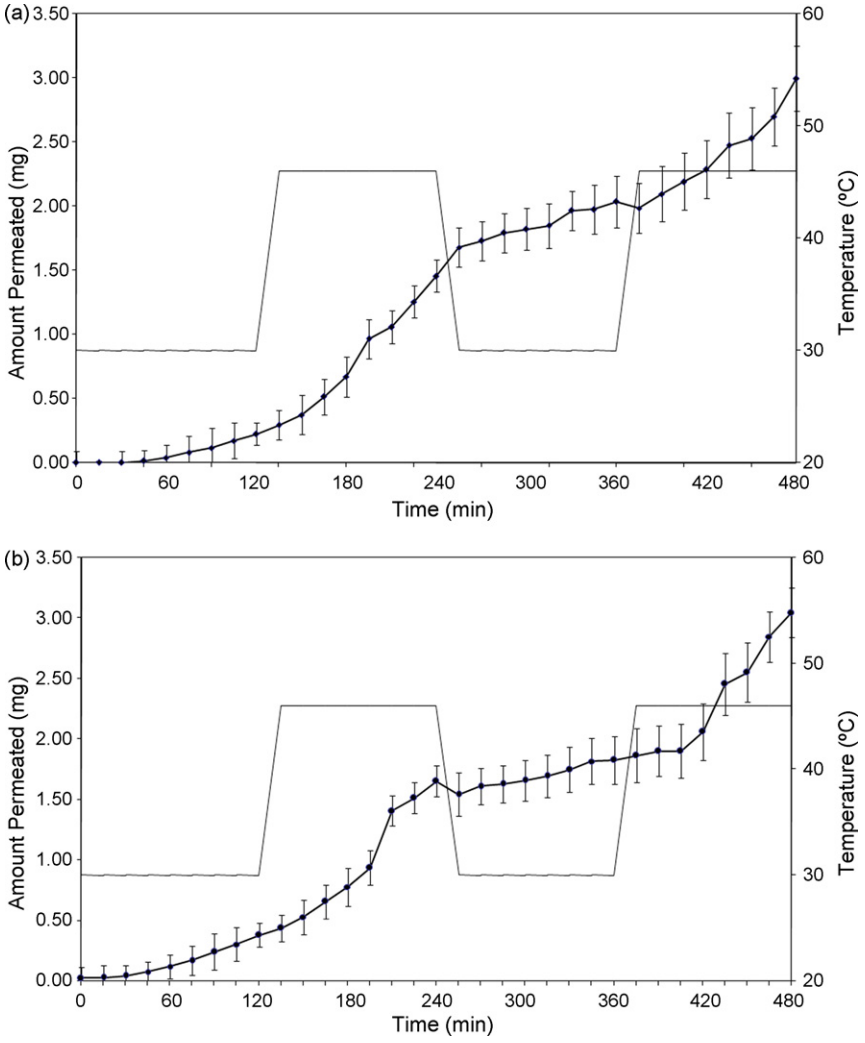

Fig. 13. Methimazole (a) and paracetamol (b) permeation through K21 embedded CA membranes with thermal cycling between 30 °C (below the phase transition temperature of K21) and 46 °C (above the phase transition temperature of K21) ($n = 3$).

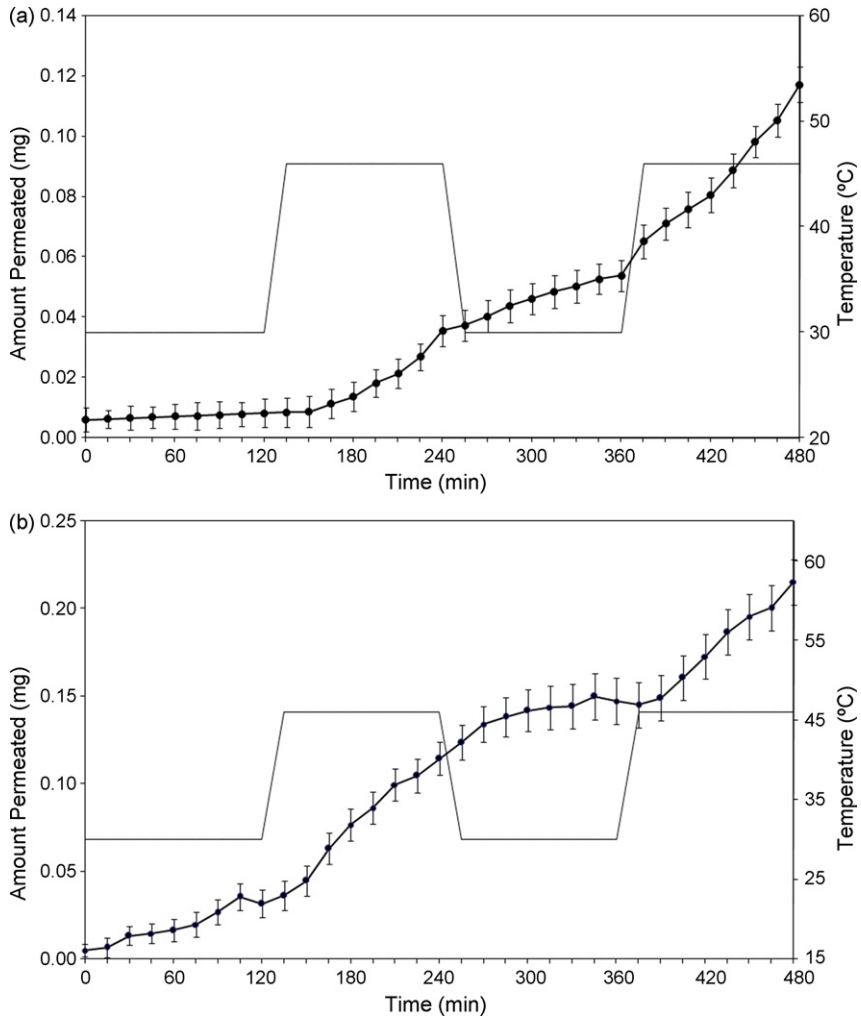

Fig. 14. Methimazole (a) and paracetamol (b) permeation through K21 embedded CN membranes with thermal cycling between 30 °C (below the phase transition temperature of K21) and 46 °C (above the phase transition temperature of K21) ($n = 3$).

Permeation coefficients of paracetamol and methimazole through K21 embedded CN membranes at different temperatures are shown in Fig. 11. Permeation coefficients of both drug models through the membranes is increased by several orders of magnitude at temperatures above the $T_{n–i}$ of K21 (41.5 °C). As the temperature of K21 increases, it changes to the nematic phase (N) and then to isotropic (I) which the molecules can move at all directions easily. On a microscopic level, the rod like K21 molecules are locked in place and aligned when sample is at crystalline (K) phase. The molecules are still aligned and ordered at nematic (N) phase but with slight freedom of movement at one direction. When the liquid crystal becomes isotropic at temperatures above the $T_{n–i}$ (41.5 °C), the molecules are free to translate and rotate at any directions. Disruption in the orientation and transforming from anisotropic liquid crystal to an isotropic liquid provides more rooms for drug molecules to permeate (Fig. 12). Ratto (1993) observed the same behavior. They prepared a polymer–liquid crystal composite membrane consisting of a sulfonic perfluorinated ionomer, Nafion, and a nematic liquid crystal, 4-cyano-4′-*n*-hexylbiphenyl in polymer by swelling methods. Preliminary oxygen and nitrogen permeation through this system jumps by some five orders of magnitude at the crystal-nematic transition of this composite membrane.

As it can be seen in Figs. 7 and Fig. 11, drug permeation coefficients through LC entrapped CA membranes are more thermoresponsive than that through LC entrapped CN membranes. However, this difference is not very considerable. It can be explained by the fact that CA membranes have greater porosity than CN membranes. This causes more LC to be loaded on them compared to CN membranes. Watson et al. (1999, 2001) and Nozawa et al. (1991a,b) showed that the amount of LC deposited on the membranes has a significant effect on the temperature sensitivity of the membrane. They showed that the higher the porosity is, the more LC will be filled in the porous matrix and the bigger temperature sensitivity will be expected.

At the present study, LC material is filled inside the pores of CN and CA membranes. Temperature sensitivity in the monolayer LC embedded membranes showed a small dependency on the molecular size and hydrophilicity of drug models. This can be attributed to the difference between molecular size of drug models and LC materials. K21 molecules are in the cate-

gory of low molecular weight liquid crystals. Therefore, one reason for better on–off permeation of methimazole through the membranes may be due to its smaller M_W (114.17 g/mol) compared to paracetamol (151.17 g/mol). Another reason may be the hydrophilicity of methimazole compared to paracetamol. These hypotheses are supported by our previous findings (Dinarvand and Ansari, 2003; Dinarvand et al., 2005) in which it was demonstrated that a low molecular weight drug model such as hydroxyurea (M_W 78 g/mol) showed a temperature sensitive permeation better than methimazole (M_W 114.17 g/mol) through thermotropic liquid crystal embedded membranes. In a previous study the drug permeation through triple layer membranes in which a uniform layer of LC sandwiched between two sheets of CN membranes was investigated. A high dependence of drug transport through those membranes on the molecular size of the drug models was observed (Dinarvand et al., 2006). In this study, the lower dependence of drug transport through C embedded membrane may be attributed to the lack of a uniform layer of LC like the one existed in former membranes.

Weights of LC embedded membranes before and after each experiment was measured to detect any loss of LC during the permeation experiment. No significant changes in the weights of membranes before and after experiments were observed. It shows that LC molecules are kept into the pores and are not washed out from the membrane at all. Lin et al. (1996) prepared cholesteryl oleyl carbonate embedded CN membranes for studying thermoresponsive permeation. They also showed that there is no weight loss for the membranes though the LC material when physically absorbed on CN membranes.

3.3. Temperature sensitivity of the monolayer LC embedded cellulose membranes with thermal cycling

Figs. 13 and 14 show the permeation profile of methimazole and paracetamol through K21 entrapped CA and CN membranes, respectively, with thermal cycling between 30 °C (below the $T_{n–i}$ of K21) and 46 °C (above the $T_{n–i}$ of K21).

These permeation profiles clearly indicate that the permeation of methimazole and paracetamol is much faster at 46 °C (above the $T_{n–i}$ of K2) compared to that at 30 °C (below the $T_{n–i}$ of K21) and this near on–off drug permeation is repeatable.

These figures indicate not only the temperature responsive permeation of methimazole and paracetamol through LC embedded membranes, but also reversibility and reproducibility of temperature response for both drugs through both LC embedded CA and CN membranes. This confirms that changing the orientation of LC molecules in response to temperature changes is fairly quickly reversible. The reproducibility of the permeation experiments carried out with thermal cycling is not as high as the permeation experiments carried out at constant temperatures. This may be due to the slight differences in the heating and cooling of the membranes between each individual permeation experiment carried out with thermal cycling.

As the permeation of methimazole and paracetamol through LC embedded membranes does not stop at temperature below the phase transition of the liquid crystal, thus complete on–off control of drug permeation is not achieved. Drug permeation at 30 °C, may be the result of drug diffusion mechanism when the liquid crystals are at nematic phase which allows for the movement of the LC molecules at one direction.

4. Conclusion

New composite membranes capable of positive temperature sensitive for the modulation of drug transport through the membrane were developed. The approach adopted was to develop the liquid crystal entrapped membranes using two commercially available membranes namely cellulose nitrate and cellulose acetates with good mechanical strength that would act as an adsorbent media for the thermotropic liquid crystal molecules. The permeability of composite membranes to drug models increased by several orders of magnitude when the temperature of the systems was increased above the $T_{n–i}$ of the liquid crystal. Temperature sensitive permeation of both drug models through both membranes was reversible, reproducible and followed zero order kinetics. Methimazole permeation through LC entrapped CA membranes showed a higher temperature modulation.

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References

Bussemer, T., Otto, I., Bodmeier, R., 2001. Pulsatile drug-delivery systems. Crit. Rev. Ther. Drug Carrier Syst. 18, 433–458.

D'Emanuele, A., 1996. Responsive polymeric drug delivery systems—meeting the patient's needs. Clin. Pharmacokinet. 31, 241–245.

Dinarvand, R., Ansari, M., 2003. Temperature modulated permeation of hydroxy urea through thermotropic liquid crystals embedded in poly-HEMA. J. Membr. Sci. 223, 217–226.

Dinarvand, R., Khodaverdi, E., Atyabi, F., 2005. Temperature-sensitive permeation of methimazole through cyanobiphenyl liquid crystals embedded in cellulose nitrate membranes. Mol. Cryst. Liq. Cryst. 442, 19–30.

Dinarvand, R., Khodaverdi, E., Atyabi, F., 2006. Thermoresponsive drug delivery using liquid crystal embedded cellulose nitrate membranes. Drug Deliv. 13, 1–6.

Gofrit, O.N., Shapiro, A., Pode, D., Sidi, A., Nativ, O., Leib, Z., Witjes, J.A., van der Heijden, A.G., Naspro, R., Colombo, R., 2004. Combined local bladder hyperthermia and intravesical chemotherapy for the treatment of high-grade superficial bladder cancer. Urology 63, 466–471.

Kost, J., Langer, R., 2001. Responsive polymeric delivery systems. Adv. Drug Del. Rev. 46, 125–148.

Lin, Y.Y., Chen, K.S., Lin, S.Y., 1996. Development and investigation of a thermo-responsive cholesteryl oleyl carbonate-embedded membrane. J. Control. Release 41, 163–170.

Lin, S.Y., Lin, H.L., Li, M.J., 2002a. Adsorption of binary liquid crystals onto cellulose membrane for thermo-responsive drug delivery. Ads. J. Inter. Ads. Soc. 8, 197–202.

Lin, S.Y., Lin, H.L., Li, M.J., 2002b. Manufacturing factors affecting the drug delivery function of thermoresponsive membrane prepared by adsorption of binary liquid crystals. Eur. J. Pharm. Sci. 17, 153–160.

Makai, M., Csanyi, E., Nemeth, Z., Palinkas, J., Eros, I., 2003. Structure and drug release of lamellar liquid crystals containing glycerol. Int. J. Pharm. 256, 95–107.

Ng, C.C., Cheng, Y.-L., Saville, B.A., 2001. Thermoresponsive polymer membrane for the local delivery of drugs. J. Sex, Reprod. Med. 1, 21–27.

Nozawa, I., Suzuki, Y., Sato, T., Sugibayashi, K., Morimoto, Y., 1991a. Preparation of thermo responsive membranes. J. Biomed. Mater. Res. 25, 577–588.

Nozawa, I., Suzuki, Y., Sato, T., Sugibayashi, K., Morimoto, Y., 1991b. Preparation of thermo responsive membranes. J. Biomed. Mater. Res. 25, 543–554.

Ratto, J.A., 1993. Investigation of a liquid crystal dispersed in an ionic polymeric membrane. Chem. Mater. 5, 1570–1576.

Wahlgren, S., Lindstrom, A.L., Friberg, S.E., 1984. Liquid crystals as a potential ointment vehicle. J. Pharm. Sci. 73, 1484–1486.

Watson, S.J., Gleeson, H.F., D'Emanuele, A., Serak, S., Grozhik, V., 1999. A study of photochromic azobenzene liquid crystals as controlled release drug delivery systems. Mol. Cryst. Liq. Cryst. 331, 2235–2242.

Watson, S.J., Gleeson, H.F., D'Emanuele, A., 2001. An examination of the drug transport properties of liquid crystal embedded membranes. Mol. Cryst. Liq. Cryst. 367, 3223–3231.