Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl20

Temperature-Sensitive Permeation of Methimazole through Cyano-biphenyl Liquid Crystals Embedded in Cellulose Nitrate Membranes

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Version of record first published: 31 Aug 2006

To cite this article: Rassoul Dinarvand, Elham Khodaverdi & Fatemeh Atyabi (2005): Temperature-Sensitive Permeation of Methimazole through Cyano-biphenyl Liquid Crystals Embedded in Cellulose Nitrate Membranes, Molecular Crystals and Liquid Crystals, 442:1, 19-30

To link to this article: http://dx.doi.org/10.1080/154214090964870

Mol. Cryst. Liq. Cryst., Vol. 442, pp. 19–30, 2005

ISSN: 1542-1406 print/1563-5287 online
DOI: 10.1080/154214090964870

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In this study, the application of thermotropic liquid crystals (TLCs) embedded in cellulose nitrate membranes as binary thermosensitive drug barriers in response to temperature changes is described. Liquid crystals are physically observed to flow like liquids, but they have some properties of crystalline solids. Two kinds of low-molecular nematic liquid crystals, n-pentyl-cyanobiphenyl (K15) and n-heptyl-cyanobiphenyl (K21), with nematic to isotropic phase-transition temperatures ($T_{n\text{-}i}$) of 36.3°C and 43.3°C, respectively, were chosen to modulate drug release. Triple-layer membranes (TLMs), composed of K15 and K21 as TLCs sandwiched between two layers of cellulose-nitrate (CN) films, were prepared. No TLC leakage was observed through this hydrophilic membrane. TLMs successfully acted as rate-controlling systems, which may also be regarded as time-controlling systems. The transport of methimazole as a low-molecular-weight drug model through the membranes was examined. It was found that changing the environmental temperature below and above the $T_{n\text{-}i}$ of TLCs could modulate methimazole permeation through these composite membranes. These experiments were also repeated with thermal cycling between 30°C and 46°C. The permeation profiles were reversible and followed zero-order kinetics.

Keywords: cellulose nitrate membranes; methimazole; thermotropic liquid crystal; thermoresponsive drug-delivery systems; triple-layer membranes

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INTRODUCTION

Short biological half-life and strong systemic side effects are two major problems associated with many bioactive agents. Regulated drug delivery, more appropriately called stimuli-responsive drug delivery, is a concept in which bioactive agents are delivered at an appropriate rate in response to various stimuli [1]. Disease states may produce biological changes that can be used as stimuli or "triggers" for the onset and offset of the delivery of drugs [2]. A well-known example is insulin, which needs to be delivered when the blood level of glucose is elevated. Another example may be hormones that require rhythmic patterns of their concentrations in the blood. Moreover, drug tolerance, achieved by the long-term continuous use of a sustained release preparation, is always a big problem in clinical therapy [3,4]. To overcome these obstacles, the concept of an intelligent drug-delivery system that acts as both rate-controlling and time-controlling systems has recently been introduced [5]. These self-regulating or auto-feedback drug release systems may be achieved by utilization of stimuli-sensitive materials. Stimuli-sensitive polymeric membranes [6] in drug-delivery systems can act simultaneously as sensors to detect biological conditions or as external controllers of drug-release rates. A wide range of stimuli such as pH changes [7], magnetic fields [8], ultrasound [9], electrical energy [10], chemical changes [11], and temperature changes [12] have been used.

The most extensively considered of these factors is temperature because of its availability and ease of use. Among temperature-modulated polymers, hydrogels have shown interesting characteristics for developing thermoresponsive systems [11]. Certain hydrogels display dramatic changes in their swelling behavior in response to temperature changes. Covalently cross-linked poly-N-isopropylacrylamide (NIPAAm) is perhaps the most extensively studied class of temperature-responsive polymers in drug delivery [12–15]. However, this hydrogel does not have a sharp transition-temperature point and its temperature response is negative. Among temperature-sensitive materials, thermotropic liquid crystals (TLCs) with a sharp transition-temperature point and positive response do not have these drawbacks. Therefore, TLCs are suitable candidates for thermoresponsive drug-delivery systems [16]. The liquid-crystalline phase can exist either in a given temperature or in a given concentration range, which is called thermotropic or lyotropic, respectively. In this study, thermally controlled permeation of a model drug across thermotropic liquid crystals (LCs) with nematic-to-isotropic transition temperature around body temperature is described. LCs have been used in medical

applications such as thermal mapping of skin and breast-cancer detection [17]. Special LC devices can be attached to the skin to show a "map" of temperatures. This is useful because often physical problems, such as tumors, have a different temperature than the surrounding tissue [17].

TLCs have been used in different industries but their applications as drug-delivery systems are relatively new. Lyotropic LCs have been used in drug delivery systems before [18]. For example, liquid-crystalline substances with cubic phases, spontaneously formed when amphiphilic lipids are placed in an aqueous environment, have been investigated as drug-delivery systems [19]. A group of fatty-acid esters capable of forming LCs has been identified as a new class of potential bioadhesive substances. From them, a dental gel containing metronidazole (Elyzol® dental gel), which is based on a reversed hexagonal phase, is now available [20]. Also, swelling and enkephalin release from glyceryl monooleate (GMO) as a cubic LC phase has been examined [21]. However, the use of thermotropic LCs as stimuli substances in drug delivery systems has rarely been studied before [22–25]. Lin and coworkers have developed a kind of liquid-crystal-adsorbed membrane in which a cholesteric LC mixture (cholesteryl oleyl carbonate and cholesteryl nonanoate) is used [26]. They demonstrated that this membrane could act as an on–off switch for drug release [3–5]. In our previous work, on–off permeation of hydroxy urea, as a very low-molecular-weight drug model, was examined through thermotropic LC-embedded Poly-HEMA membranes. The TLC molecules used in this study have a rigid head with a flexible tail, which permit them to display the characteristics of a liquid crystal [16]. Because of low porosity of Poly-HEMA membranes, drug permeation through these membranes is expected to be difficult. Therefore, only a low-molecular-weight drug model such as hydroxy urea was chosen for drug-permeation studies [16]. To overcome this drawback, we tested on–off function of K15 and K21 embedded in a more porous membrane, cellulose nitrate, for methimazole permeation. Because of its microporous structure, good mechanical properties, and high hydrophilic characteristics, cellulose nitrate may be regarded as a suitable supporting membrane for TLCs.

EXPERIMENTAL

Materials

n-Pentyl cyano-biphenyl (K15) and n-heptyl cyano-biphenyl (K21) thermotropic liquid crystals were purchased from Merck Co.

(Darmstadt, Germany). Cellulose-nitrate (CN) membranes (pore size 0.22 mm, diameter 49 mm, and thickness 137 μm) were obtained from Whatman (Maidstone, UK). Methimazole (USP 25) was kindly donated by Alhavi Pharmaceutical Co., Iran. All other solvents and reagents used were of analytical grade.

Scanning Electron Microscopy (SEM)

CN membranes were coated with gold with a SCD 004 sputter coater (Balzers, Germany). The coated membranes were viewed with a DSM 960 A scanning electron microscope (Zeiss, Germany). To preserve the original dimensions of the pores and the porous structure of the membranes, dry forms of the membranes were used.

Preparation of LC-Embedded CN Membranes

The triple-layer membrane was prepared by using three discotic CN membranes, two outer monolithic films with a punched middle layer with a 4.9-cm^2 hole (Fig. 1). A known amount of LC (K15 or K21) was loaded into the space between the two outer layers without any air bubble. Then, the membranes were brought into contact as sandwich layers. This system was supported by perforated HDPE mesh films with an effective permeation area of 1.98 cm^2 to ensure a uniform thickness.

Drug Permeation through Triple-Layer Membranes

The composite membrane was carefully mounted in a specially built double-chamber drug-permeation apparatus that had an available area of about 1.98 cm^2 and a half-cell volume of 130 mL. Before each

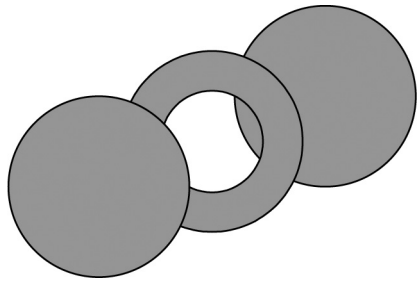

FIGURE 1 Schematic drawing of the triple-layer CN membrane.

test, both the donor and receptor chambers were completely filled with distilled water and left 2 h to allow LCs to reach their equilibrium points. The system was spectrophotometrically checked for any LC leakage. Permeation studies were carried out at different constant temperatures (30, 37, 43, and 46°C) below and above the phase-transition temperature of the LCs (K15, K21). The nematic-to-isotropic phase-transition temperatures ($T_{n\text{-}i}$) of K15 and K21 were 36.3°C and 43.3°C, respectively. Methimazole was chosen as the drug model. Because of the low molecular weight of LCs, methimazole, a lower-molecular-weight drug model, was chosen because its permeation is not limited by factors such as small pore size of LCs. For this purpose, 1% of drug aqueous solution was put into the donor cell and the receptor chamber was filled with drug-free distilled water of the same pH. The solution of each compartment was stirred at 100 rpm to eliminate the boundary-layer effect. To create a special constant temperature, a thermostated water bath with temperature fluctuations of ±0.1°C (Memmert, Germany) was used. Aliquots of 4 mL were taken out and the same amount of distilled water was substituted. Final sample in each experiment was extracted with 3 mL of dichloromethane and then examined for LC leakage with UV-spectrophotometer (Scinco, S-1300) at 306 nm for K15 and 310 nm for K21. The amount of methimazole permeated through the system was assayed spectrophotometrically at 251 nm. The amount permeated was then plotted against the time. Permeation coefficients of K21 and K15 at different temperatures were obtained from the slope of permeation curve at each temperature using the $M = PSC_d t$ equation [27], in which M is the amount permeated, P is the partition coefficient of the composite membranes at different temperatures, S is the available area for drug permeation, C_d is the drug concentration in donor cell, and t is the time.

The role of CN membranes without LCs in drug permeation was also determined by application of distilled water–embedded membrane at the same temperatures. The result of each point is expressed as mean ± standard deviation (SD) of three determinations, generally.

Drug Permeation through the Triple-Layer Membranes with Thermal Cycling

The effect of thermal cycling on the permeation of methimazole through the triple-layer membranes was also investigated. The experimental method was similar to that described previously, except that the temperature fluctuated between 30°C and 46°C in predetermined intervals.

The permeation of methimazole through a control embedded membrane with thermal cycling was also investigated.

RESULTS AND DISCUSSION

Figure 2 shows the SEM images of CN membranes. Microporous and sponge-like structure of CN membranes can be seen in the figures. These microporous films facilitate better drug permeation, so the LC

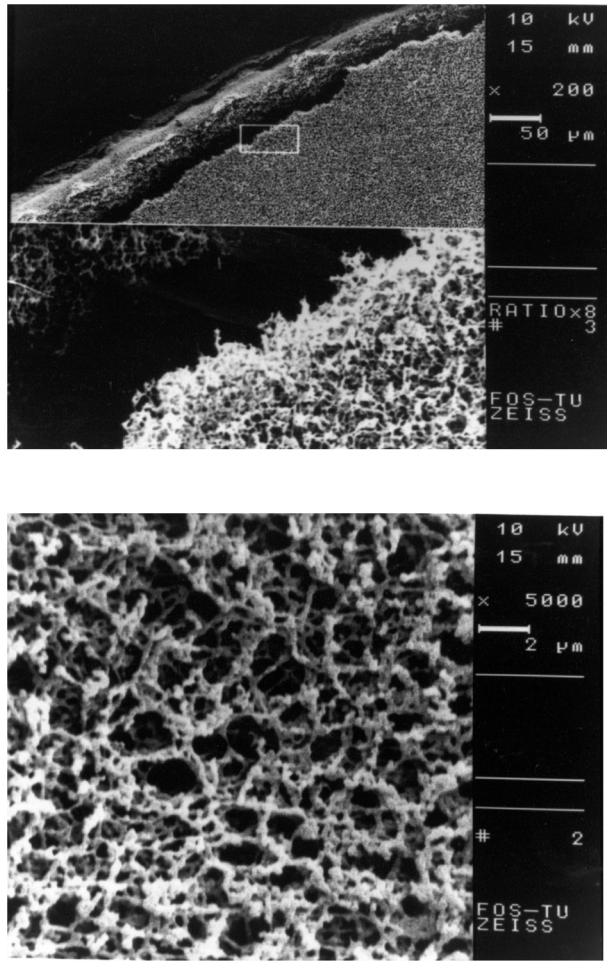

FIGURE 2 SEM images of (a) the surface and (b) cross section of the CN membrane.

layer is the main rate-controlling barrier in these systems. Moreover, hydrophilic CN membranes do not permit lypophilic LC leakage.

As can be seen in Figs. 3 and 4, the difference in methimazole permeation through membranes at above and below the $T_{n\text{-}i}$ of TLCs is significant. Methimazole-permeation rate at the temperatures above the $T_{n\text{-}i}$s was much higher than those at temperatures below the $T_{n\text{-}i}$s of the TLCs ($P < 0.004$ for K21 and $P < 0.002$ for K15). This can be described according to the characteristics of LCs. The distinguishing characteristic of the liquid-crystalline state is the tendency of the molecules (mesogens) to point along a common axis, called the director. In the solid state, molecules are highly ordered and have little translational freedom. This is in contrast to molecules in the liquid phase, which have no intrinsic order. The characteristic orientational order of the liquid-crystalline state is between the traditional solid and liquid phases. Fewer pores exist between the molecules compared with those in isotropic liquids. Also the movement of molecules at a crystalline state is much more limited compared with those in an isotropic state [28]. This phenomenon may act as an on–off switch for drug permeation through the membranes [16]. It should be noted that methimazole permeation through this system did not cease completely because the TLCs are in a nematic phase below their $T_{n\text{-}i}$s. As

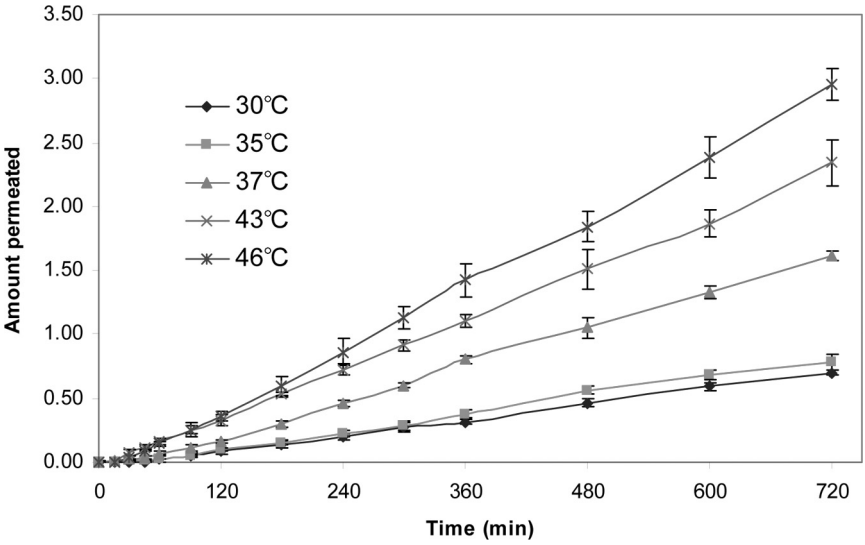

FIGURE 3 Methimazole permeation through K15-embedded CN membranes at different temperatures below and above the phase-transition temperature of the LC ($n = 3$).

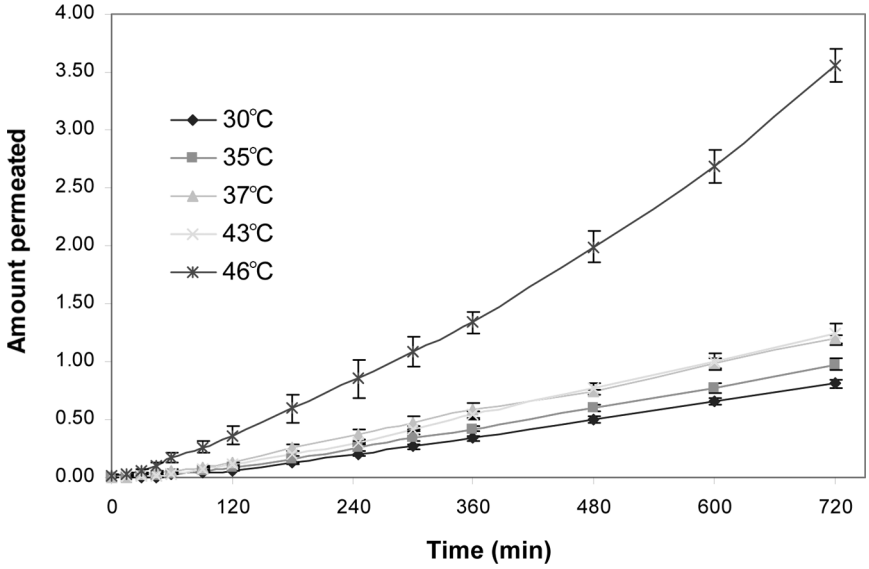

FIGURE 4 Methimazole permeation through K21-embedded CN membranes at different temperatures below and above the phase-transition temperature of the LC ($n = 3$).

described before, this phase has the least positional ordering compared with the other liquid-crystalline phases. Therefore, a complete on–off control of drug permeation is not expected with these nematic TLCs [28]. Also, as can be seen in Figs. 3 and 4, the lag time for drug permeation through the liquid-crystalline embedded membranes is very small. This might be mainly attributed to the hydrophobic liquid-crystalline layer delaying the permeation of the hydrophilic methimazole. No lag time was observed when membranes without LCs were used.

Figure 5 indicates that methimazole permeation through CN membranes without TLCs was not temperature dependent. It means methimazole diffusion does not differ significantly with temperature changes.

Figures 6 and 7 show methimazole permeation through K15- and K21-embedded membranes in the temperature cycles between 30°C and 46°C, below and above the phase-transition temperatures of TLCs. As can be seen, the drug-permeation rate at 46°C was markedly higher than the permeation rate at 30°C, and this pattern of drug permeation was reversible. Reversibility in thermoresponsivity is a main factor for an efficient on–off drug-delivery system.

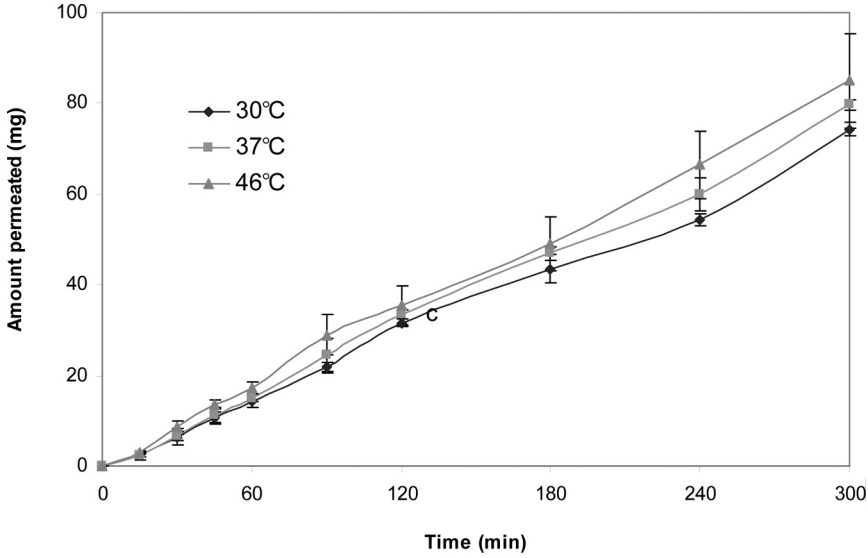

FIGURE 5 Methimazole permeation through CN membranes without any LC embedding ($n = 3$).

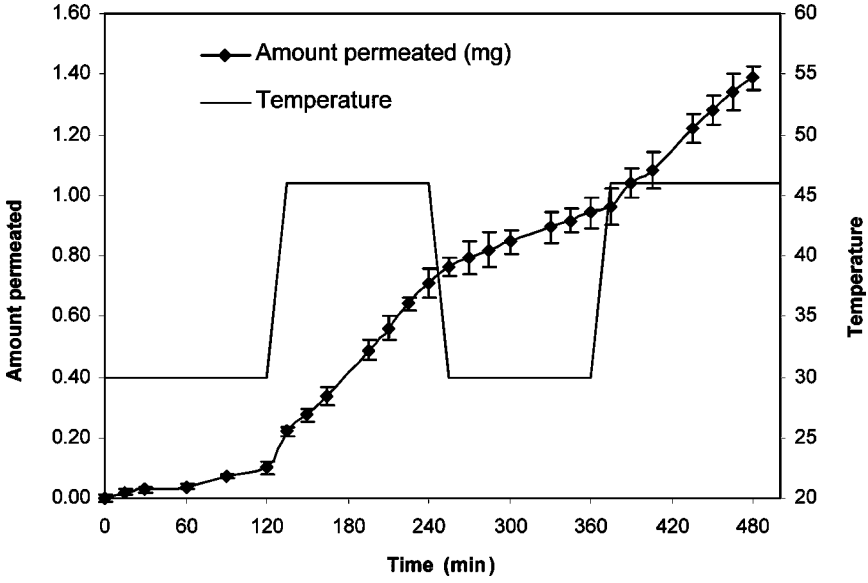

FIGURE 6 Methimazole permeation through K15-embedded CN membranes with thermal cycling between 30°C (below the phase-transition temperature of the LC) and 46°C (above the phase-transition temperature of the LC) ($n = 3$).

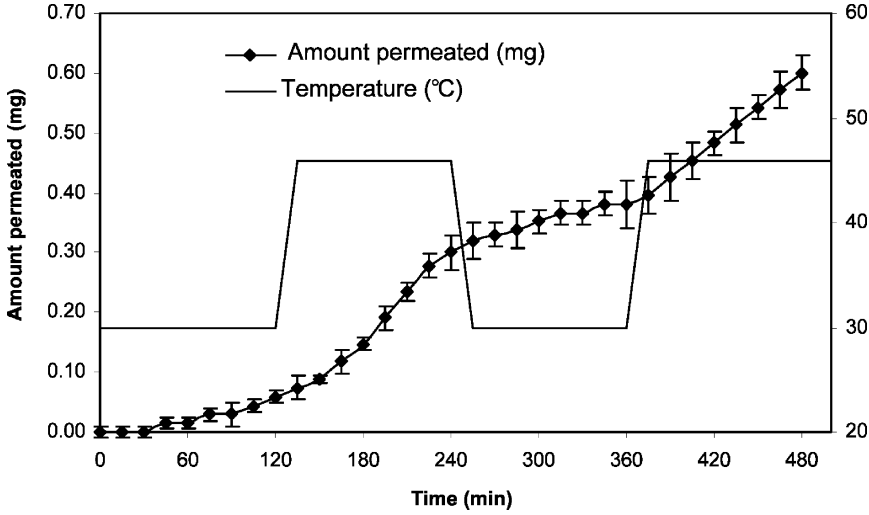

FIGURE 7 Methimazole permeation through K21-embedded CN membranes with thermal cycling between 30°C (below the phase-transition temperature of the LC) and 46°C (above the phase-transition temperature of the LC) ($n = 3$).

Figure 8 shows the permeation of methimazole through control membranes at temperatures cycled between 30°C (below $T_{n\text{-}i}$s) and 46°C (above $T_{n\text{-}i}$s). The membranes without LCs, as expected, did not exhibit thermoresponsive on–off control of drug permeation.

The permeation coefficient of methimazole through TLC-embedded membranes at different temperatures is shown in Fig. 9. Again, a significant difference between drug permeation at temperatures below and above the $T_{n\text{-}i}$s of the TLCs can be observed.

As can also be seen in Fig. 9, that permeation coefficient of methimazole through K21-embedded membranes is slightly more than that for K15-embedded membranes in temperatures both below and above their $T_{n\text{-}i}$s. This can be attributed to the molecular weight of LCs ($MW_{k15} = 249.36$, $MW_{k21} = 277.41$). The larger the molecules, the bigger holes there are between them and the more amount of drug can permeate through the membrane [22].

In conclusion, liquid-crystalline materials are unique in their properties and uses. As research into this field continues and as new applications are developed, LCs will play an important role in modern technology. In this study, we investigated the application of TLCs as on–off drug modulators. For this purpose, two thermotropic LCs (K15 and K21) with nematic-to-isotropic transition temperatures of about

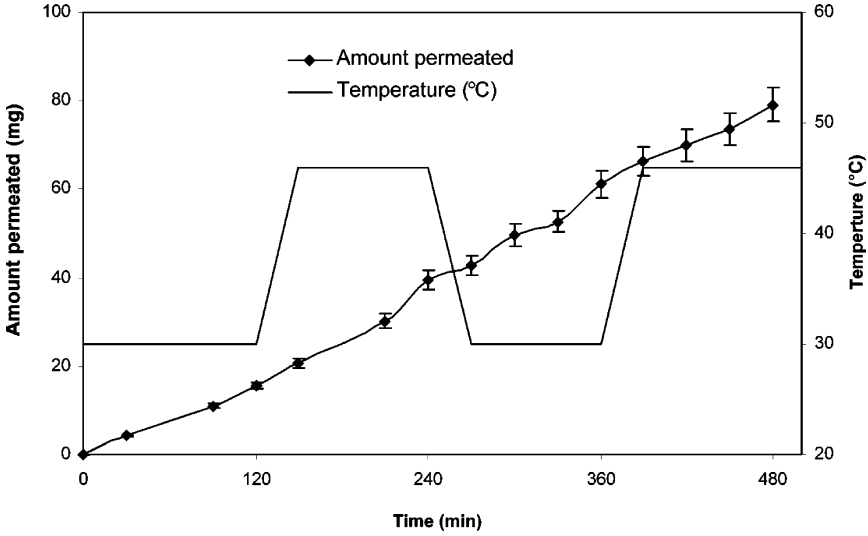

FIGURE 8 Methimazole permeation through the CN membranes without any LC embedding with thermal cycling between 30°C and 46°C ($n = 3$).

body temperature were chosen. The TLCs were sandwiched between two layers of CN membranes. Methimazole permeation through these composite membranes was shown to be thermoresponsive. The results

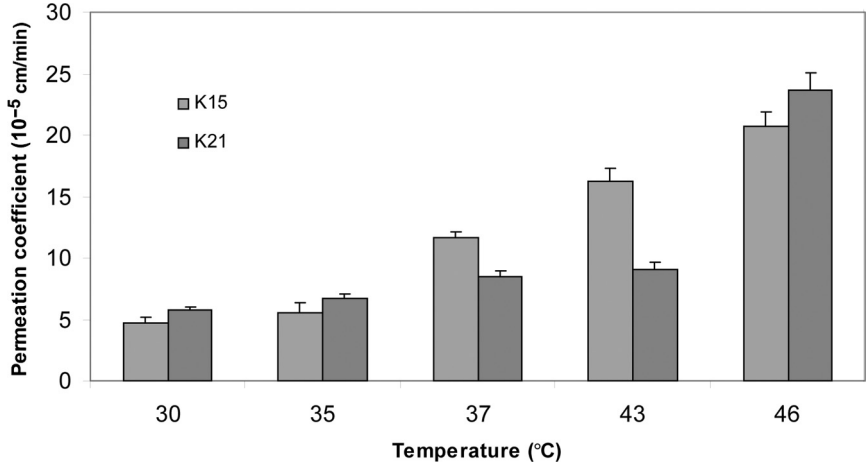

FIGURE 9 Permeation coefficient of K15- and K21-embedded CN membranes for methimazole at different temperatures below and above the phase-transition temperature of the LCs ($n = 3$).

indicate that the TLCs can act as on–off temperature-modulated drug-delivery systems.

ACKNOWLEDGMENT

The authors are grateful for the financial support granted by Tehran University of Medical Sciences to this study.

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