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An Examination of the Drug Transport Properties of Liquid Crystal Embedded Membranes

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Cellulose nitrate membranes were embedded with two different commercially available liquid crystals and the transport of a model drug through the membranes was examined spectrophotometrically. It was found that upon changing the temperature of the system, membranes without liquid crystal showed no temperature dependent drug transport properties. Membranes embedded with liquid crystal however, showed a distinct temperature variation in the drug release. It was found that the rate of drug transport was dependent on the amount of liquid crystal deposited on the membrane and by cycling the temperature of the system, pulsatile drug release could be achieved.

Keywords: liquid crystal; drug release; pulsatile delivery; membrane transport; thermo-responsive

INTRODUCTION

It is thought that if drugs can be delivered in a controlled, modulated manner, in accordance with the body's needs, then the side effects associated with many drugs and conditions may be reduced or

eliminated altogether (1). For example, the therapeutic effect of certain new peptide and protein based drugs is optimum when delivery mirrors the discontinuous release profiles of endogenous peptides and proteins (2). Controlled drug delivery systems which show responsive release are therefore vital for optimum therapy.

The ideal responsive drug delivery system is one with a short response time which can be engineered to produce significant increases in drug release in response to a relatively small, controllable, external stimulus. LCs are promising candidates for this application. They are multifunctional materials, responding to a number of different external stimuli, and the diffusion properties of a drug solute within a LC system can potentially be controlled by manipulation of the phase type and the macroscopic alignment of the self assembling system.

The use of lyotropic LCs as sustained drug release media is well established (3,4), but this study is one of very few (5,6,7) to examine the feasibility of using thermotropic LCs as *responsive* drug delivery systems, which can deliver varying amounts of drug upon application of an external stimulus.

MATERIALS AND METHODS

All the membranes used in this study were based on Whatman cellulose nitrate (CN) membrane filters, with a nominal pore size of 0.3μm, a diameter of 47mm and a thickness of 0.13mm. The thermotropic LCs used were 8CB, a standard smectic LC, and TM1001, a thermochromic

mixture that displays a body temperature cholesteric phase. Salicylic acid was used as a model drug. All the materials were purchased from Merck and used as supplied.

The LC membranes used in the studies were prepared by filtering solutions of either TM1001 or 8CB in chloroform through the CN membrane. Varying the concentration of the solution enabled the fabrication of membranes with between 150 mg to 3 mg of adsorbed LC. There was no mass loss of the membranes after being stored in air for up to a month, nor was there any mass loss in membranes immersed in water and salicylic acid solution for up to a week. The solutions used to store the membranes were checked spectrophotometrically for the presence of LC, but no peaks were observed. It is therefore unlikely that there is any leakage of the LC from the membrane.

The membranes were positioned in a glass two-compartment diffusion cell with inner chambers made from PTFE, with an available surface area for drug transport of 8.55 cm^2. The donor cell was filled with 130 cm^3 of 0.025% w/v salicylic acid solution, and the receptor chamber filled with 130 cm^3 of distilled water, both chambers were then agitated using 160rpm stirrers. The cell was made watertight by the addition of silicone grease, and the complete cell was immersed in a thermostatic water bath to enable the temperature of the system to be varied to induce phase transitions in the liquid crystal embedded on the membrane. 3ml samples were taken every half hour from the receptor chamber, assayed spectrophotometrically at 298nm to determine the salicylic acid concentration, and replaced in the receptor compartment.

RESULTS AND DISCUSSION

Membrane Characterisation

The phase transition temperatures of the LC materials used were determined using polarising microscopy and Differential Scanning Calorimetry. DSC measurements on the LC embedded membranes, showed slight depressions (up to 2°C) on the transition temperatures when compared with the bulk samples, and new phase transition temperatures were assigned for the LC membranes as follows:

8CB Membrane: $K \xrightarrow{18^{\circ}C} S_A \xrightarrow{32^{\circ}C} N \xrightarrow{39^{\circ}C} I$

TM1001 Membrane: $S_A \xrightarrow{25.5^{\circ}C} Ch \xrightarrow{42.5^{\circ}C} I$

This transition temperature depression is commonly found for liquid crystals in confined geometries (8).

Drug Transport Studies

The rate of drug transport through CN membranes with no LC embedded was determined as a control. Figure 1 shows a typical profile and it can be seen that there is no change in the rate of drug release as the temperature of the system is increased. Figure 2 shows a plot of the amount of drug transferred through a membrane embedded with 7.24 mg of 8CB. (Plots of a similar form were seen for membranes embedded with TM1001). The release shows a marked change as the temperature of the system is increased; the release rates being 0.010 mg/hr, 0.043 mg/hr, 0.095 mg/hr, 0.133 mg/hr and 0.273 mg/hr at temperatures of 15°C, 27°C, 37°C, 45°C and 55°C respectively.

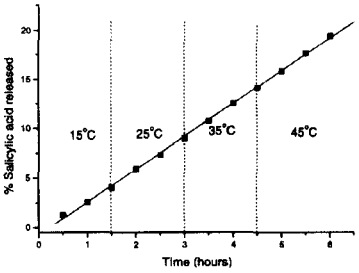


FIGURE 1 The amount of drug transferred through a 0.3μm CN membrane.

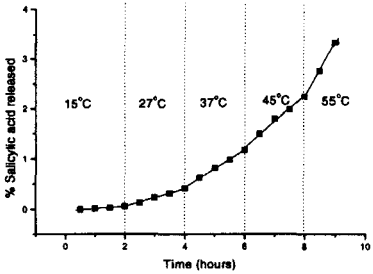
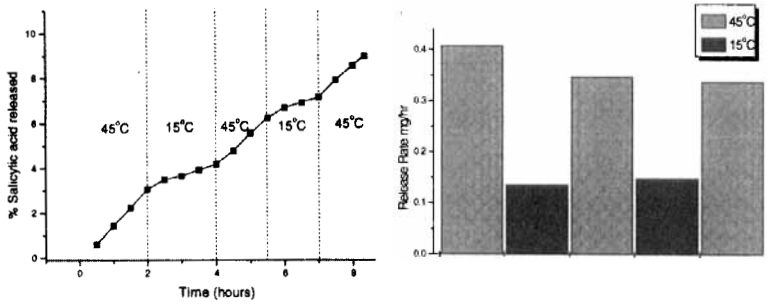


FIGURE 2 The drug transfer through a CN membrane embedded with 7.24mg of 8CB

This is an increase in drug release in a ratio of 1:4.3 between the crystal and smectic phase, 1:2.2 between smectic and nematic phase, 1:1.4 between the nematic and isotropic phase and 1:2.1 between 45°C and 55°C. At both 45°C and 55°C the system is isotropic, so it appears that the release rate changes are due to viscosity changes that occur in the LC as the temperature of the system is increased. These rises are practically constant between all phases, with the exception of the crystal to smectic phase measurements. Many materials display changes in viscosity upon heating, but LCs can display very pronounced viscosity changes over very small temperature increases, and for this reason are promising candidates for a diffusion controlled device of this type.

In order to examine the membrane integrity, the drug transport experiment was repeated under exactly the same conditions but this resulted in a noticeably different release profile. The release effectively showed no temperature dependence suggesting that the membranes lose their responsiveness to temperature over time.

A new membrane was prepared with 12.93mg of 8CB, and the effect of pulsing the temperature on the drug transport examined. Figure 3 clearly shows that pulsatile release is possible using this system. The rate of drug transfer is increased twofold upon increasing the temperature and can be modulated satisfactorily. These changes are seen more clearly in the bar chart shown in figure 3b.



(a) (b)

FIGURE 3 The amount of drug transferred through 0.3μm CN membranes, embedded with 12.93mg of 8CB

A membrane with 48.75mg of 8CB deposited on it was used to examine the effect of temperature cycling on the drug release (figure 4). It can be seen that the release rates in the second heating run are somewhat lower than those previously obtained and there appears to be a loss of temperature sensitivity upon repeated cycling.

Figure 5 shows a plot of the results obtained for three different membranes embedded with varying amounts of 8CB.

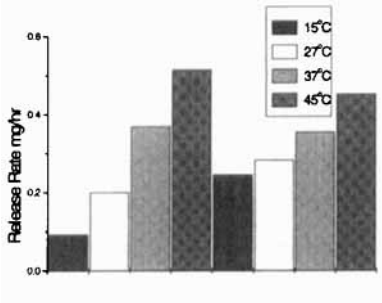


FIGURE 4 Release rates for a membrane embedded with 48.75mg of 8CB.

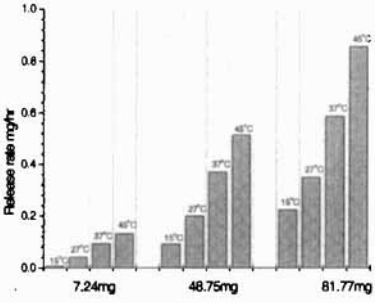


FIGURE 5 The rates of release for three different 8CB embedded membranes.

Although the addition of LC onto the membranes results in a decrease in the rate of release, *increasing* the loading of LC actually increases the rate at which drug diffuses through the membrane. It is likely therefore that the main diffusion mechanism in the control membranes is directly though the pores, rather than by partitioning into the CN membrane. As small amounts of LC are added to the membranes, the pores are obstructed and the release rate decreases as the solute diffuses through both the CN membrane and the LC. As increasing amounts of LC are added to the membrane, the release rates increase, presumably since the drug can now partition predominantly into the LC phase. It appears that for certain drugs, it may be possible to achieve specific release rates by careful consideration of the membrane and LC used.

The greatest increase in release rates is between the crystalline and LC phase transition. The most pronounced changes in release with changing temperature are seen for the membranes with least LC embedded on them. For example, the ratio of release rates between the

crystal and isotropic phase is 1:13 for the membrane with 7.24mg of liquid crystal deposited on it, 1:6 for the membrane with 48.75 mg of liquid crystal and 1:4 for the membrane with 81.77mg of 8CB.

The work presented herein raises a number of interesting questions, which leave much scope for further studies. The loss of membrane thermal responsiveness is probably the main issue to be addressed. A new experimental set-up is being designed to ensure water tightness of the system without the use of silicone grease to rule out the possibility of this affecting the LC. Alternatively, the reduction in thermal responsiveness may be due to the LC aligning in the pores after thermal cycling. The diffusion properties of LCs show a marked anisotropy and different membrane geometries or pore sizes may impose a different type of alignment on the LC and may offer a greater degree of control over drug transport. Other drugs will also show different diffusion properties and offer opportunities for further study.

The materials used in this study, whilst interesting model compounds, would not be clinically acceptable. Further investigations can be made into LCs which show suitable transition temperatures for use in the body and are biocompatible. It would be possible, for example, to use a LC material, which has a much smaller range over which the phases are present. In this way, large changes in release could be achieved, (e.g., by going from a crystal to nematic phase), by inducing a temperature change of only a few degrees.

It is thought that the changes in release rates are primarily due to the viscosity changes that the LC undergoes as it is heated. Once the

long-term sensitivity loss problems are resolved, it would be interesting to investigate the release over very small temperature intervals, such as every degree, to see if there actually are large changes in drug transport just prior to and after a given phase transition.

CONCLUSIONS

This paper presents an *in vitro* study of a LC drug delivery system, which has been shown to display thermoresponsive properties. While there were problems encountered with the systems examined in this work, such as lack of reproducibility, the results reported herein demonstrate that it is possible to change the rate of transport of a drug through a LC embedded membrane and these systems merit further study. Drug delivery devices based on LCs present interesting new possibilities as thermo-responsive drug delivery systems.

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