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The effect of liquid crystalline structure on chlorhexidine diacetate release

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Abstract

The aim of this study was to examine different liquid crystalline preparations containing chlorhexidine diacetate and to find connection between their structure and the kinetic of drug release. Nonionic surfactant, Synperonic A7 (PEG_7–C_{13-15}) was selected for the preparation of the examined liquid crystalline systems. Mixtures of different ratios of Synperonic A7 and water were produced. By increasing the water content of the systems, lamellar and hexagonal liquid crystal structures were observed. For the analysis of the prepared liquid crystalline systems polarising microscopy, rheology study, differential scanning calorimetry and dynamic swelling tests were carried out. The chlorhexidine diacetate release was examined by Franz-type vertical diffusion cell apparatus. The chlorhexidine diacetate release from hexagonal liquid crystalline preparations was characterised by zero-order release kinetics, while the drug release from lamellar liquid crystalline systems was described by anomalous (non-Fickian) transport. The results indicate that the drug release kinetic is strongly dependent on the liquid crystalline structure.

Keywords: Liquid crystals; Hexagonal and lamellar structure; Release kinetics

1. Introduction

Dermatological preparations may achieve local, penetration or systemic effect of the active ingredient according to the therapeutical requirements. It may be assured by appropriate compositions and place of application. The required effective concentration of drug at the site of action is determined by the upper layer of the epidermis and by the colloidal structure of the vehicle, also. The liquid crystalline structure of the vehicle can act as a diffusional barrier and consequently controls the rate of drug release (Mueller-Goymann and Frank, 1986; Tiemessen et al., 1988).

Liquid crystalline mesophases have been investigated as modern formulations by many authors (Wahlgren et al., 1984; Willimann et al., 1992; Westesen et al., 1995).

In the presence of a surface-active agent and solvent, different types of aggregate structures can form over a wide range of compositions. Cubic,

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hexagonal lamellar and micellar phases can be observed in most cases, which differ from each other in their mechanical properties. Mesophases have enhanced physical stability due to their viscoelastic behaviour (Tyle, 1989).

If the semisolids are viscoelastic in nature it is valuable, both theoretically and practically, to examine them in their rheological ground state where the method of testing does not significantly alter the structure (Davis, 1969). Oscillatory tests were found useful for the analysis of different liquid crystalline phases (Barry and Eccleston, 1973; Cordobés et al., 1997; Németh et al., 1998). Colloidal structure of pharmaceutical systems not only determines the viscoelastic properties but affects the drug release, as well.

For analysing the structure and interaction between the components, DSC measurements can be used. Several authors (Rosenholm and Hakala, 1978; Tyle, 1989) found it evident from the specific heat measurements that there is a difference in structural ordering due to the formation of various mesomorphic phases. Important information could be derived from these data on the factors governing the formation and stabilisation of the phases.

The main objectives of this work were to examine the prepared liquid crystalline systems, containing chlorhexidine diacetate, by different physico-chemical methods — polarising microscopy, rheology, differential scanning calorimetry, dynamic swelling test — and to find a connection between their structure and the kinetics of drug release.

2. Materials and methods

2.1. Materials

Chlorhexidine diacetate (Aldrich Chemical) was chosen as a model drug. Concentration of the drug was 5%w/w in all formulation. The applied carrier was a mixture of nonionic surfactant and water, which forms a liquid crystalline phase.

The nonionic surfactant, Synperonic A7 was a gift of ICI Surfactants. It is an alcohol ethoxylate type surfactant of a mixture of C_{13} and C_{15} alkyl chain in the ratio of 6,6:3,4 and of an average of 7 ethyleneoxide units per molecule. Distilled water was used in formulations, the concentration varying from 20–70% (w/w).

2.2. Sample preparation

The samples were prepared by heating the surfactant, water and drug to 60°C in closed glass vials and they were homogenised by shaking until the drug dissolved and clear solutions were obtained. The resulting solutions were cooled to room temperature. Care was taken that no air bubbles got into the samples. The mixtures were stored at room temperature for 1 week before measurements were taken.

2.3. Microscopic analysis

The texture of the samples was observed by polarising microscope (HUND, Germany). The measurements were carried out at room temperature. Magnification: 200–400 ×.

2.4. Rheology study

The rheological measurements were performed with Haake RS 100 apparatus. A cone-plate sensor was used having a diameter of 20 mm, and a cone angle of 4°. The thickness of the sample in the middle of the sensor was 0.134 mm. Samples were kept on 25°C ± 0.2 under saturated water vapour for the duration of the measurements.

Dynamic oscillatory test was carried out with all samples. First the linear viscoelastic region was determined by measuring the complex modulus versus stress at a given frequency (0.1 Hz) and then 2.5 Pa was chosen as a stress amplitude which was found to be in the linear viscoelastic region in all cases. The storage and loss moduli were examined as a function of the applied frequency.

2.5. Dynamic swelling test

The water uptake of the liquid crystalline systems was examined gravimetrically. The sample was weight into the donor phase of the diffusion

cell sealed by semipermeable membrane. The cell was measured at analytical accuracy and then was brought into contact with the water-containing chamber. At appropriate time intervals the weight of the cell was measured after removing excess water.

2.6. Differential scanning calorimetry

The measurements were carried out with Mettler TA 4000 System. Liquid crystalline samples (3–9 mg) were weighed in aluminium pans and immediately sealed by press. The reference was an empty pan. The samples were rapidly cooled by liquid nitrogen to −120°C and then heated to 70 and 90°C, respectively. The heating rate was 10 K/min. The heat flow rate was measured as a function of the temperature.

2.7. Drug release study

A vertical diffusion cell (developed by Franz (1975)) was used for the drug release experiments. The donor phase contained 1 g of the liquid crystalline sample and was sealed with parafilm to prevent evaporation. The acceptor medium was Britton–Robinson buffer of pH 6.0 ± 0.05 and it was stirred by teflon-coated magnetic bar. A Cuprophan membrane (AKZO 150M, Membrana GmbH) was placed between the two phases, which was impermeable to the surfactant molecules. The effective surface area of membrane was 2.01 cm^2. The measurement was carried out at 30°C for 6 h. Four mililitre aliquots were taken from the buffer medium at prearranged time intervals and were replaced by fresh buffer solution. The taken fractions of the dissolution medium were continuously changed with fresh buffer and low concentration of diffused drug ensured sink conditions.

2.8. Quantitative determination of chlorhexidine diacetate

UV spectrophotometer (Shimadzu UV-160A, Japan) was used for the determination of chlorhexidine diacetate concentrations of different samples. The absorbance was measured at 255 nm. The method gave a linear response over a concentration range of 1–20 μm/ml.

3. Results and discussion

Fig. 1 illustrates the loss and storage moduli of the liquid crystal systems measured at a frequency

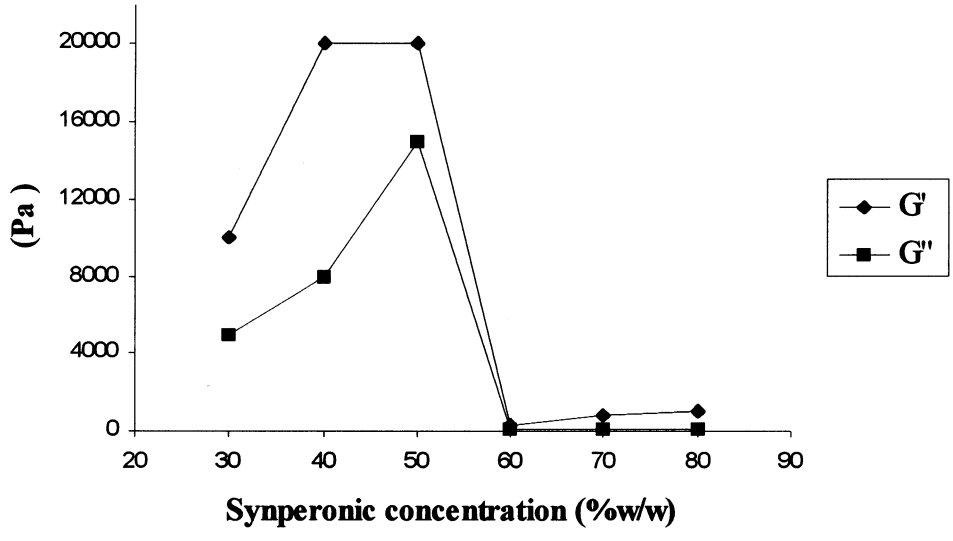

Fig. 1. Loss (G″) and storage (G′) moduli of the prepared liquid crystalline samples.

Table 1
Microscopic and rheological characteristics of liquid crystalline systems as a function of synperonic A7 concentration

Synperonic (%w/w)	Structure	Loss tangent (tan δ)	Phase lag δ (°)
30	Hexagonal	0.474	25.38
40	Hexagonal	0.375	20.57
50	Hexagonal/Lamellar	0.627	32.09
60	Lamellar	0.369	21.60
70	Lamellar	0.124	7.05
80	Lamellar	0.104	5.96

of 1 Hz. Table 1 summarises the loss tangent (tan δ) and the calculated phase lag (δ) values of the prepared liquid crystalline systems. Depending on the Synperonic concentration the structure of the liquid crystalline system, observed by polarising microscope, was changed. In the case of 30–40% w/w Synperonic concentrations the liquid crystalline system showed hexagonal structure, while in the case of 60–80% w/w Synperonic concentration its appearance showed lamellar structure. Fifty percent w/w Synperonic concentration resulted in mixed hexagonal–lamellar systems which was visible under polarising microscope, although no attempt was made to determine the proportion of the hexagonal and lamellar phases in the prepared systems. Lamellar phases are less viscous than hexagonal phases even though they contain less water. A phase lag of 0° would be produced by a perfectly elastic material whereas a perfect fluid would give a phase lag of 90° (Aulton, 1988). As a result of the increasing Synperonic content of the liquid crystalline system, the phase lag values decreased which indicates that the system of lamellar structure became more elastic. Table 2. summarises the thermoanalytical characteristics of the prepared liquid crystalline systems. Four transitions (Hatakeyama and Quinn, 1994) — glass transition, cold crystallisation, melting, liquid crystalline-isotropic transition — can be distinguish on the thermograms of the examined liquid crystalline systems (Fig. 2). The glass transition temperature (T_g) did not show structure dependent change. There were not significant differences between the glass transition values of the first heating and that of the second one. Along with the increasing Synperonic concentration, the water content of the liquid crystalline systems decreased. The measured melting enthalpy values confirm this fact. The enthalpy of the hexagonal liquid crystalline-isotropic transition is significantly greater than that of the lamellar liquid crystalline-isotropic transition. This phenomenon can be explained by the differences between the structural mobility of the hexagonal and that of the lamellar phases. In hexagonal phase, the hexagonally packed cylindrical aggre-

Table 2
Thermoanalytical characteristics of the prepared liquid crystalline systems[a]

Synperonic %w/w	Glass transition T_g (°C)		Melting enthalpy ΔH (J/g)		Liquid crystalline-isotropic transition	
	1st heating	2nd heating	1st heating	2nd heating	T (°C)	ΔH (J/g)
30	−67.7	−68.2	177.3	173.3	51.2	0.8
40	−67.0	−67.0	116.0	110.3	44.7	1.6
50	−67.1	−68.3	102.6	81.9	36.9	0.6
60	−72.1	−69.4	75.3	68.8	–	–
70	−70.5	−70.4	57.4	54.1	–	–
80	−69.4	−70.3	47.0	44.6	40.5	0.6

[a] Average of two parallels; RSD <5%.

gates can move freely only along their length while the parallel layers of the lamellar phase can slide over each other (Clint, 1992). Considerable activation energy required to lift a plane of cylinders over another plane and down into the next energy minimum in the hexagonal phases.

Chlorhexidine diacetate release from the systems of different crystalline structures can be described with good correlation by the following semiempirical equation:

$$M_t/M_\infty = kt^n \quad (1)$$

where M_t is the released solute at time 't', M_∞ is the released solute at infinite time 't_∞', k is a constant characteristic of the system, n is an exponent characteristic of the mode of transport of the solute.

The computer package Microsoft Excel 7.0, solver function was applied for the nonlinear parameter estimation. Table 3. shows the parameters of the applied model and Fig. 3. represents the chlorhexidine diacetate release from the hexagonal (Fig. 3a) and lamellar (Fig. 3b) liquid crystalline systems. The release exponent (n) — indicative of the mechanism of drug release — is approximately 1.0 in the case of hexagonal crys-

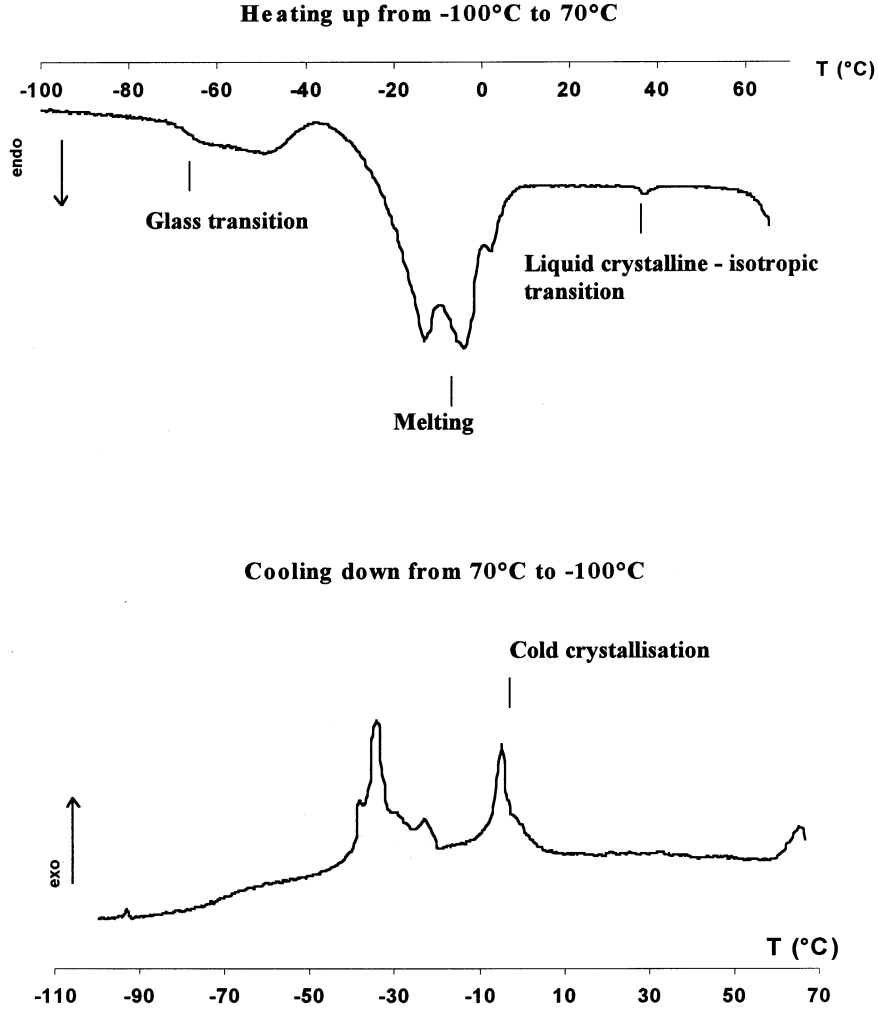

Fig. 2. DSC curve of liquid crystalline system containing 50% Synperonic A7 and 5% chlorhexidine acetate.

Table 3
Drug release parameters of Eq. (1)

Synperonic %w/w	n	k (x10^{-3})	Correlation coefficient
30	0.979	4.99	0.9983
40	1.007	3.98	0.9994
50	0.988	4.48	0.9998
60	0.892	7.77	0.9992
70	0.853	9.33	0.9998
80	0.753	15.63	0.9994

talline structure, consequently the drug release rate is independent of time. This case corresponds to zero-order release kinetics. Drug release from this system is controlled by the dynamic swelling behaviour of the hexagonal phase. In the case of lamellar crystalline structure, anomalous (non-Fickian) transport occurs and the release exponent is greater than 0.5 and smaller than 1.0 ($0.5 < n < 1$).

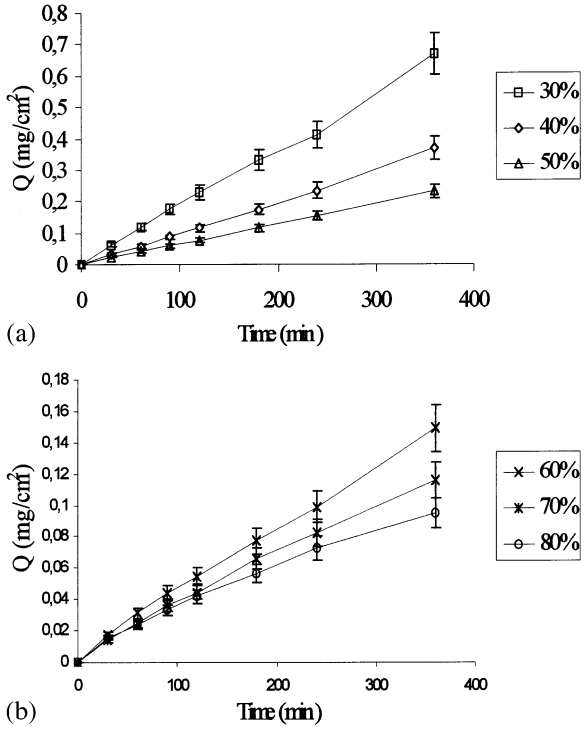

Fig. 3. Chlorhexidine diacetate release from hexagonal (a) and from lamellar (b) liquid crystalline systems (Average of 3 parallels ± SD).

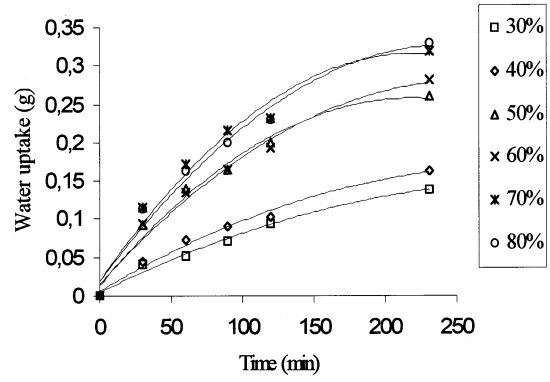

Fig. 4. The water uptake of liquid crystalline systems of different Synperonic A7 concentrations as a function of time (Average values, $n = 3$).

Fig. 4. illustrates the water absorption curves of different liquid crystalline systems. The results indicate that the less ordered lamellar liquid crystalline structure (60–80% Synperonic content) enables rapid water uptake. As a result of the rapid water uptake the swollen liquid crystalline system inhibits the further drug release (Fig. 3a, b). The chlorhexidine diacetate release from the lamellar liquid crystalline systems were more than three times less compared to the hexagonal mesophases.

4. Conclusions

Our results indicate that the liquid crystalline structure has a decisive impact on the drug release characteristics, consequently on the bioavailability of the preparations.

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