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Study on the release of chlorhexidine base and salts from different liquid crystalline structures

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Abstract

The aim of this study was to investigate the influence of two types of chlorhexidine species, chlorhexidine base and its salts, on the physicochemical features of liquid crystalline systems and on drug transport through lipophilic membranes.

A non-ionic surfactant, Synperonic A7 (PEG7-C13-15) was selected for the preparation of the liquid crystalline systems. Mixtures of different ratios of Synperonic A7 and water were prepared. The liquid crystalline systems were characterized using polarizing microscopy and dynamic oscillatory test. Membrane transport was also examined. The addition of chlorhexidine species to the liquid crystalline system modified the structure of the liquid crystalline system. As a result of the changes of liquid crystalline structures, the drug release of various types of chlorhexidine could be also modified. The combination of the base and salt forms of the drug in one dosage form could eliminate the drug release changes from liquid crystalline systems of dynamically changeable structures.

Keywords: Liquid crystals; Lamellar and hexagonal structure; Chlorhexidine; Chlorhexidine digluconate; Drug release; Polarizing microscopy; Dynamic oscillatory test

1. Introduction

The entire diffusion process of a drug will not be controlled by the biological barriers, e.g. by the skin in the case of dermal application, if the drug-release from the vehicle is the rate limiting step during absorption (Niedner and Ziegenmeyer, 1992). According to this, the receptor organ acts as "perfect sink" for locally applied actives and the conditions of the vehicle influence the permeation of drug, e.g. by its diffusivity inside the system. Earlier works dealt with the mathematical descriptions of these influencing factors (Higuchi, 1960, 1967).

Amphiphilic substances spontaneously tend to self-associate and with increasing concentration they can form highly ordered aggregates, such as lamellar, hexagonal and cubic phases. Using these lyotropic liquid crystalline phases as topical drug delivery systems is favourable because of their high solubilization capacity, thermodynamical stability or broad range of rheological properties. Sustained drug release of hydrophilic substances from cubic and inverse hexagonal structures was observed by several authors (Osborne and Ward, 1995). Swarbrick and Siverly investigated topically applied vehicles containing a micellar liquid phase and liquid crystalline phase (Swarbrick and Siverly, 1992a). The percutaneous absorption of the model drug diminished significantly when the proportion of the liquid crystalline phase increased to more than 5–10% in the vehicle (Swarbrick and Siverly, 1992b).

The acid, base or salt form of the applied drug can interact differently with the vehicle molecules, which might alter the liquid crystalline structure and cause differences in the release property (Müller-Goymann and Frank, 1986; Müller-Goymann and Hamann, 1993). In the case of drug components of similar chemical structure, the liquid crystalline phase change and the permeability coefficient were found to be solute and concentration dependent (Ibrahim, 1989). Mueller-Goymann and Hamann studied the drug release from reversed micellar and from lamellar liquid crystalline systems containing fenoprofen acid and fenoprofen sodium salt. Sustained release was achieved, when phase transformation occurred from the micellar to the lamellar phase (Müller-Goymann and Hamann, 1993). A liquid

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crystalline, controlled release formulation was worked out for periodontal treatment previously (Norling et al., 1992). The appropriate compositions containing metronidazole or metronidazole benzoate were considered for sustained release, which may take place in vivo after phase change initiated by the formulation getting in contact with the gingival fluid. The application of a new type of surfactant, forming liquid crystalline phase was examined for injectable peptid drug delivery. Authors demonstrated the potential utility of these materials as drug depot delivery system (Boyd et al., 2006). According to Lopez et al., the transdermal release studies of saturated colloidal dispersions indicated that pH control of the drug release was marginal (Lopez et al., 2005). The incorporation of compounds into the microgel and the subsequent release depends on the octanol/water partition coefficient and solubility of the respective compound.

The purpose of the present study was to illustrate the applicability of liquid crystalline systems of sensitively changing structures to provide sustained release of drugs using their base and salt forms.

2. Materials and methods

2.1. Materials

Chlorhexidine, chlorhexidine diacetate (Aldrich Chemical Co.) and chlorhexidine digluconate (REANAL, Hungary) were purchased for the study. The non-ionic 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 seven ethyleneoxide units per molecule. Bidistilled water was used in all formulations. Other chemicals and reagents were analytical or HPLC grade.

2.2. Sample preparation

The samples were prepared by heating Synperonic A7, water and drug to 60 °C in closed glass vials and they were stirred until the drug dissolved and clear solutions were obtained. They were cooled down to room temperature. The concentration of the incorporated drug was 4% (w/w).

2.3. Microscopic analysis

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

2.4. Rheology study

The rheological measurements were performed with a Haake RS 80 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 at 25 ± 0.2 °C. Dynamic oscillatory test was carried out with all samples. Firstly, 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.

2.5. Study of permeation of chlorhexidine

The experiments were carried out in a Sartorius Modell-Apparatus (Göttingen, Germany) described earlier (Loth and Holla-Benninger, 1978). The donor chamber of the flow through cell contained 8.0 g of the liquid crystalline sample. The acceptor medium was Britton-Robinson buffer of pH 6.0 ± 0.05. During the study, it was stirred by a Teflon-coated magnetic bar and thermostatted at 32 °C. Cellulose nitrate membrane (Sartorius SM 16754, Göttingen, Germany) impregnated with dodecanol was placed between the two phases. The effective surface area of the membrane was 15.9 cm^2. The amount of chlorhexidine drug was measured in the acceptor phase at predefined time intervals.

2.6. Quantitative determination of chlorhexidine

The chlorhexidine base and salts were analysed spectrophotometrically at 255 nm using a Shimadzu UV-160A (Japan) spectrophotometer. The method gave a linear response over a concentration range of 1–20 μm/ml.

2.7. Surface plot design

Jandel TableCurve 3D (Jandel Scientific Software, Jandel Corporation, San Rafael, USA) was applied for the 3D fitting of the drug release results.

3. Results and discussion

The results of the structural analysis indicate that two different liquid crystalline structures were formed according to the concentration of the applied surface active agent (Synperonic) in the system. At 40% (w/w) Synperonic concentration, hexagonal structure was formed in the case of liquid crystals containing the salts, while the presence of the base form of the drug resulted in a less viscous and less ordered isotropic structure (Fig. 1). The possible reason could be that in the case of the salts the secondary bonds might be stronger between the Synperonic molecules, because chlorhexidine is hydrophilized by acetate and gluconate, and thus cannot interact with the lipophilic part of the surfactant molecules. This could result in a more ordered Synperonic-structure being formed in the presence of the salt forms. Fig. 2 shows the chemical structure of Synperonic and the investigated active ingredients, while Table 1 indicates the water solubility and octanol/water partition coefficients of chlorhexidine and its salts. The low water solubility and high octanol/water partition coefficient refer to the lipophilic character of the base, while the corresponding values of the salt forms indicate the hydrophilizing effect of acetate and gluconate. At 50% (w/w) Synperonic concentration, both lamellar and hexagonal structures are present in the

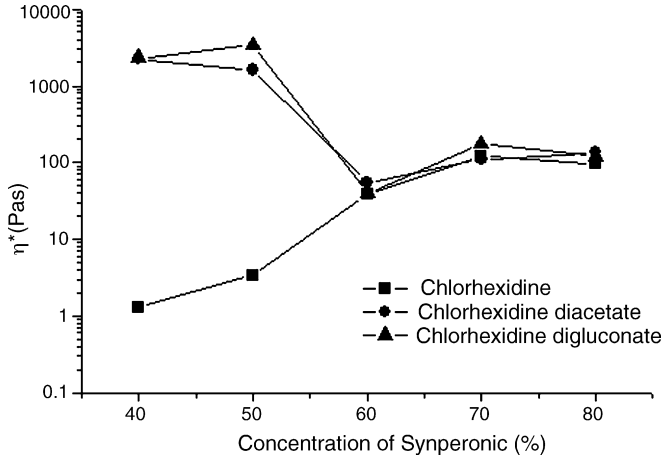

Fig. 1. Complex viscosity (η^*) of the liquid crystalline samples.

system in the case of the salt forms, while in the case of the base only the lamellar structure could be formed. Above 60% (w/w) Synperonic concentration, exclusively the lamellar structure could be built up independently of the type of the drug. The explanation of the latter phenomena could be that along with the higher concentration of the surface active agent, the probability of the interaction between the surfactant molecules increased, leading to the formation of the lamellar structure in all three cases. Table 2 summarizes the visually observed types of liquid crystalline structures as a function of Synperonic concentration in the presence of the base and the salt forms. Our previous studies confirmed these results (Farkas et al., 2000, 2001). The structural changes of liquid crystals as a function of Synperonic concentration could be visualized by polar microscopy (Figs. 3 and 4). Fig. 3 represents the polar microscopic texture of liquid crystalline samples containing 50% (w/w) Synperonic. Fig. 3a illustrates the texture of the same systems containing chlorhexidine gluconate, indicating the more anisotropic structure, while Fig. 3b shows the same system containing the chlorhexidine base. The characteristic Maltese crosses refer to the lamellar structure. Fig. 4a represents the polar microscopic photo of the liquid crystals containing 70% (w/w) Synperonic, thus indicating the formed lamellar structure. Both photos (Fig. 4a and b) show the characteristic Maltese crosses along with the presence of oily streaks.

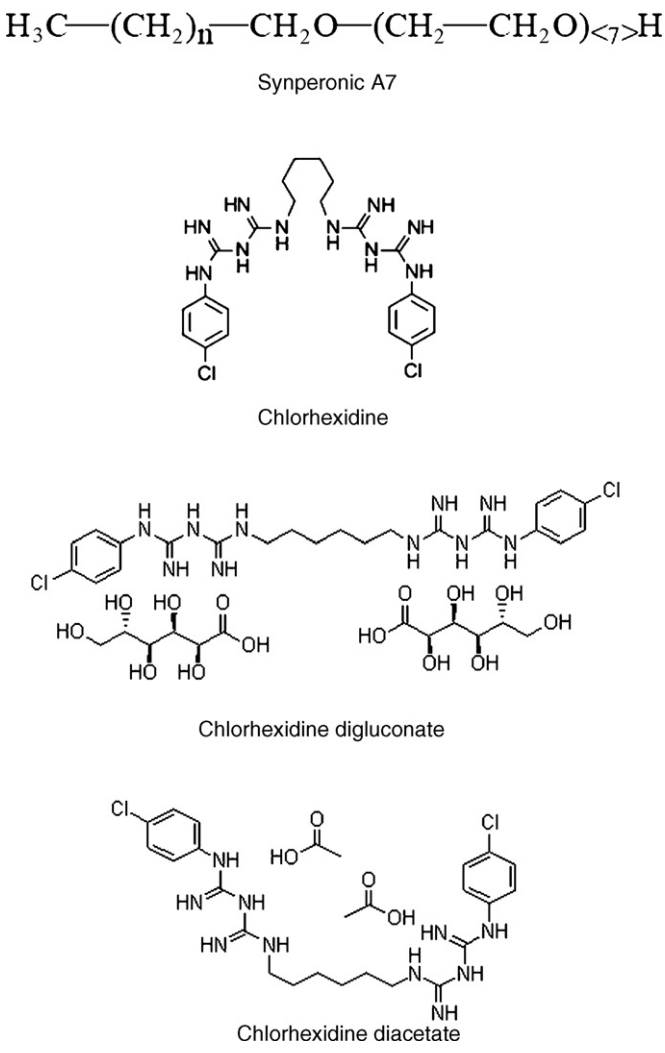

Fig. 2. Chemical structure of Synperonic A7 and the applied active ingredients.

Table 1
Water solubility and octanol/water partition coefficients of the applied chlorhexidine species

	Water solubility (m/V %)	Octanol/water partition coefficient
Chlorhexidine	0.008	0.754
Chlorhexidine diacetate	1.8	0.047
Chlorhexidine digluconate	>70	0.037

As a result of the changes of liquid crystalline structures, the drug release of various types of chlorhexidine could be modified. Fig. 5 represents the surface plot of chlorhexidine and chlorhexidine gluconate release as a function of release time and Synperonic concentration. Fig. 5a indicates that below 50% (w/w) Synperonic concentration, the isotropic and less ordered structure allowed more chlorhexidine base to be released from the liquid crystals compared to the more viscous system containing ordered hexagonal structural elements, which hindered the release of chlorhexidine digluconate (Fig. 5b). As the water-solubility of the latter is somewhat 10,000 times higher than that of the free base, these results suggest that drug release is governed mainly by the structure of the liquid crystal. The extent of drug release is in accordance with the viscosity the systems.

Table 2
Polarizing microscopic structures of liquid crystals

Synperonic (%, w/w)	Chlorhexidine	Chlorhexidine diacetate	Chlorhexidine digluconate
40	Isotropic	Hexagonal	Hexagonal
50	Lamellar	Hexagonal/lamellar	Hexagonal/lamellar
60	Lamellar	Lamellar	Lamellar
70	Lamellar	Lamellar	Lamellar
80	Lamellar	Lamellar	Lamellar

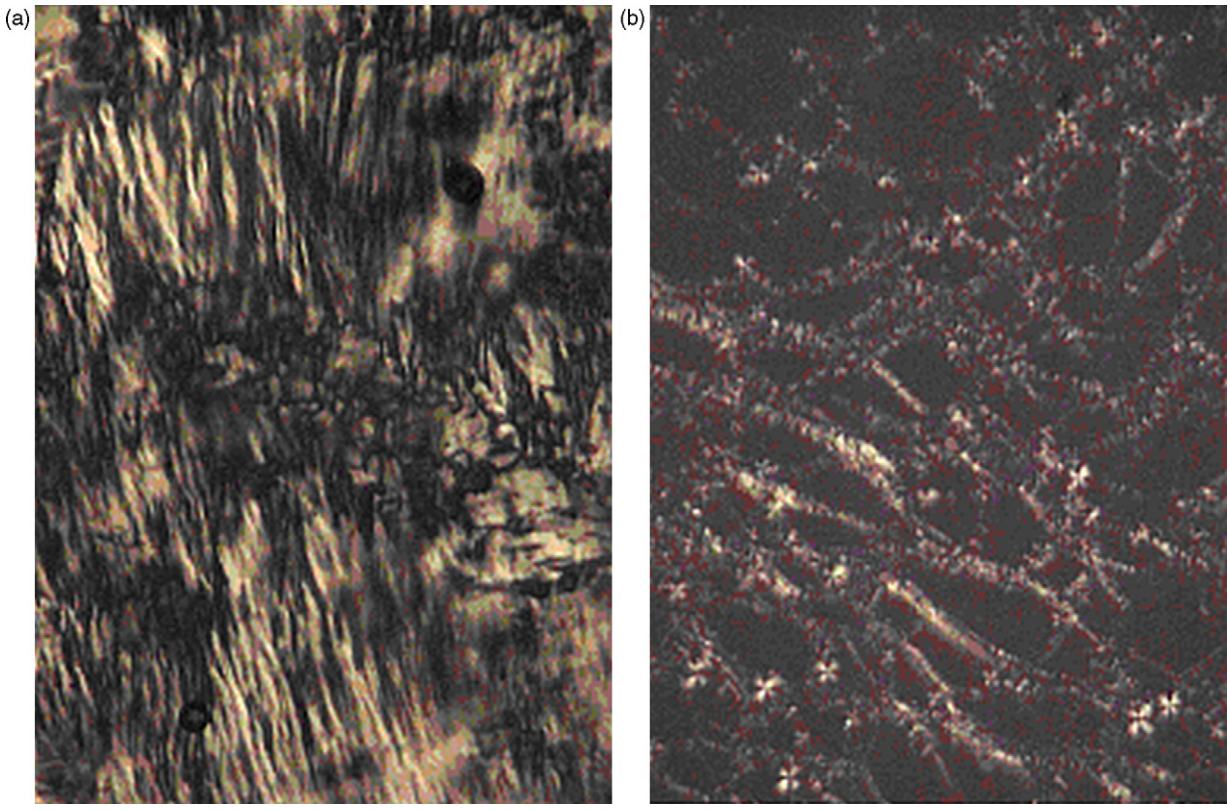

Fig. 3. Polarizing microscopic pictures of liquid crystals containing 50% (w/w) Synperonic and (a) chlorhexidine digluconate and (b) chlorhexidine base.

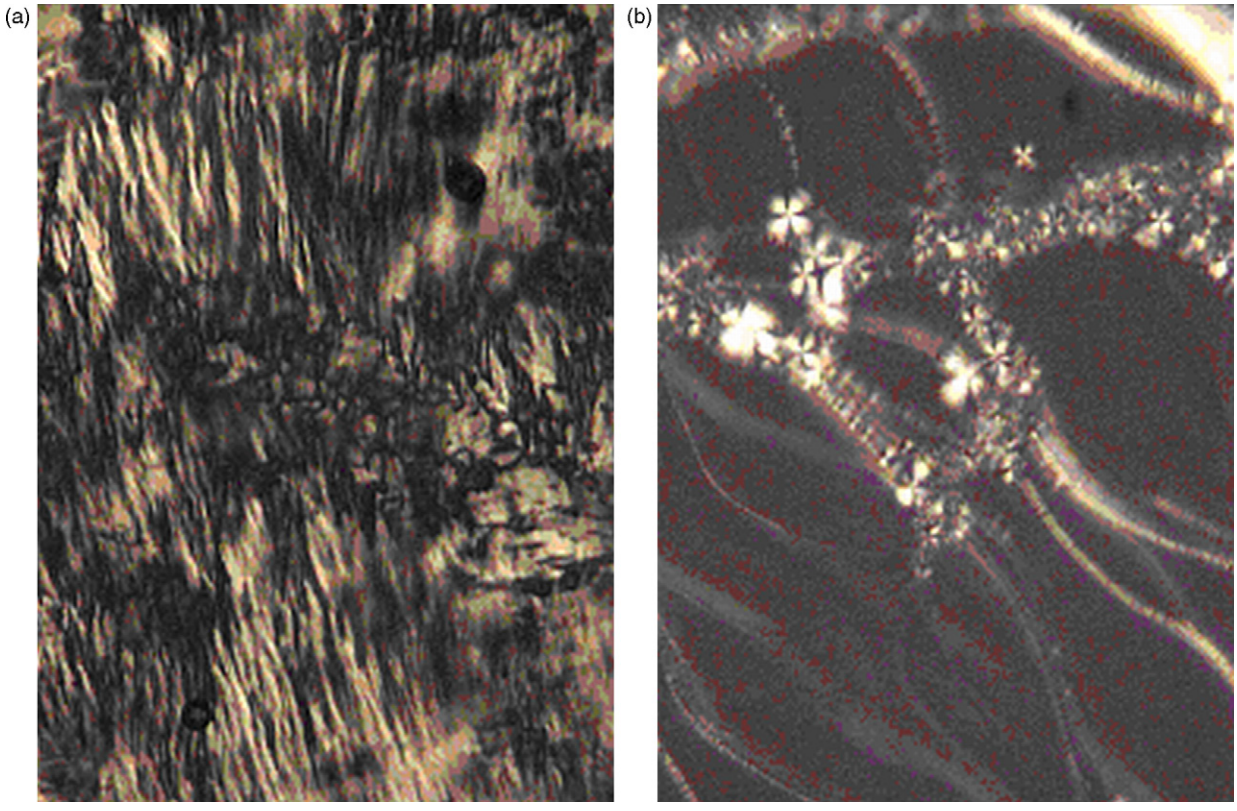

Fig. 4. Polarizing microscopic pictures of liquid crystals containing 70% (w/w) Synperonic and (a) chlorhexidine digluconate and (b) chlorhexidine base.

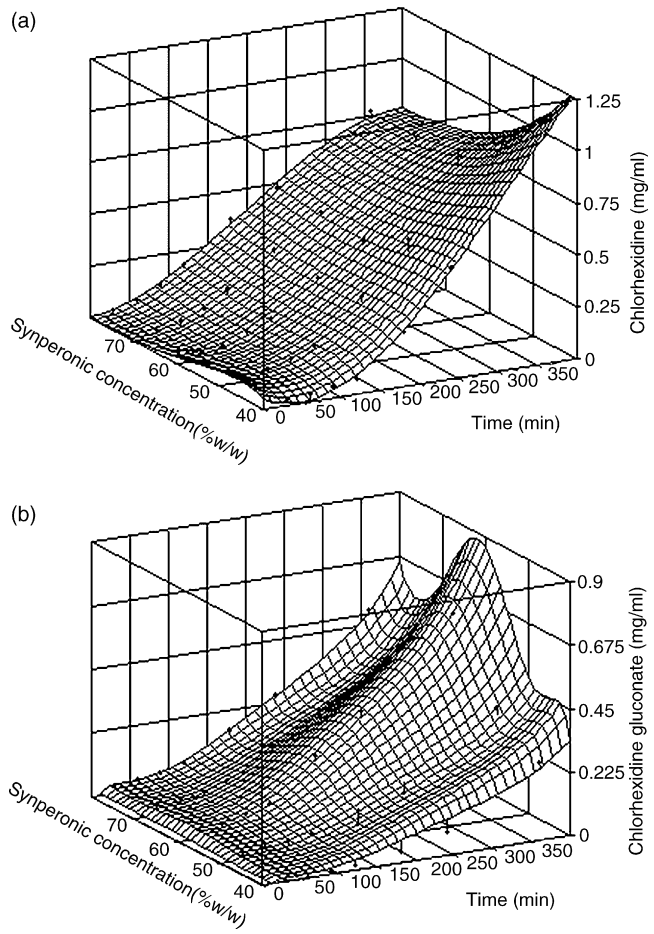

Fig. 5. Surface plots of released drug concentration from the liquid crystalline systems as a function of Synperonic concentration and time. The samples contain (a) chlorhexidine and (b) chlorhexidine digluconate.

4. Conclusion

Based on the structural changes caused by different concentrations of the surface active Synperonic in the liquid crystals and the presence of the base and salt forms of the drug, the combination of chlorhexidine and one of its salts in one dosage form could eliminate the drug release changes from liquid crystalline systems sensitively reacting on the alteration of the environment, e.g. water absorption.

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