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Structure and drug release of lamellar liquid crystals containing glycerol

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Abstract

Lamellar lyotropic liquid crystalline (LLC) systems are thermodynamically stable, optically isotropic systems, which are formed with low energy input. New possibilities for the development of controlled drug delivery systems are inherent in these systems due to their stability and special skin-similarly structure. The present aim was to formulate multicomponent LLC systems with a relatively low surfactant content, composed of materials official in the European Pharmacopoeia 4th. Polarizing light microscopic examination of the samples was carried out, together with TEM observation of replicas produced by freeze-fractured technique for the purpose of demonstrating the presence of lamellar LC domains. Our LLC samples contained: Brij 96 (poly-oxyethylene-10-oleyl ether) with water, liquid petrolatum (LP) and glycerol in a given concentration range. The interlamellar repeated distance (d_L) confirming the existence of a regular structure was determined by means of X-ray diffraction. The d_L and G'values of the samples changed according to a maximum curve with increasing glycerol concentration up to 40% (w/w). A prolonged drug release was observed in case of the very water-soluble ephedrine hydrochloride and the same phenomena was observed in the case of tenoxicam, which is practically insoluble in water.

Keywords: Lamellar liquid crystals; Polarizing light microscopy; Cryo-TEM; X-ray diffraction; Oscillating rheology; Controlled drug release

1. Introduction

During the past decade, there has been great interest in lyotropic liquid crystalline systems (LLC) as delivery systems in the cosmetic and chemical industries and also in the field of pharmacy (Attwood and Florence, 1982; Wahlgren et al., 1984; Özer et al., 1991; Vyas et al., 1997; Müller-Goymann, 1998). The reasons for this interest include the extensive similarity of these colloid systems to those in living organisms (Bata, 1986; Chapman, 1991). LLC systems are characterized by the properties of both liquids and solids, i.e. they exhibit in part a structure typical of fluids and also the structured, crystalline state of solids (Müller-Goymann, 1998). Liquid crystal states with various structures, capable of being transformed into each other in a definite sequence under certain circumstances, are also called mesophases (Frieberg et al., 1976; Benton, 1982; Boden, 1994; Hiltrop, 1999). They are usually formed from water and one or two surfactants and possibly cosurfactants, in the definite proportions of the given components, with low energy input or by means of spontaneous structural organization; their production is therefore relatively simple and energy-saving (Benton, 1982; Suzuki et al., 1989). They are thermodynamically stable, and

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can be stored for long periods of time without phase separation. Depending on the concentration of the solvent (generally water or an aqueous solution) and on the polarity of the solvated mesogen, these systems can undergo various phase transformations and structure modifications (Frieberg et al., 1976; Nünberg and Pohler, 1984), therefore their consistency, rheological properties can be changed systematically, as required.

Paasch et al. (1989) carried out a more systematic rheological study of several nonionic surfactant–water lamellar liquid crystalline phases and found, that these phases exhibited shear thinning behavior and yield stresses. More authors (Valdes et al., 1993; Vásquez et al., 1993, 1994) measured the dynamic and steady-shear rheological parameters of the AOT/water liquid crystalline phases. Németh et al. (1998) reported a dynamic rheological method for the identification of pharmaceutically important lamellar phases. Among the main types of LLC systems, mesophases with a lamellar structure that demonstrate the greatest similarity to the intercellular lipid membrane of the skin are primarily recommended for the development of a dermal dosage form (Roux et al., 1994; Vyas et al., 1997).

Through the use of a nonionic surfactant, a reversible increase in the permeability of the stratum corneum can be achieved without irreversible skin irritation. The LLC systems exhibit good penetration, due to the very low interfacial surface tension arising at the oil/water interface (Benton, 1982; Suzuki et al., 1989), and they may facilitate the progressive diffusion of biologically active substances into the skin or systemic circulation (Ziegenmeyer, 1982; Boddé et al., 1986; Cooper and Berner, 1987). They can bring about a considerable increase in the solubility of drugs by means of solubilization, which are either insoluble or slightly soluble in water (Mittal, 1976; Elworthy et al., 1986; Kriwet and Müller-Goymann, 1993; Engström, 1999).

As lamellar liquid crystalline systems contain a major proportion of incorporated water concentrated in the layers between hydrophilic domains, its evaporation is less than in case of traditional o/w creams. Their moisture content is retained for a long time, so that the transepidermal water loss is replaced by long-lasting hydration according to the needs of the skin (Suzuki et al., 1982). Their application elicits a pleasant skin sensation, and they have an ideal consistency and attractive appearance.

The aim of our work was to develop skin compliant lyotropic liquid crystals, with relatively low emulsifier content, to study the structure of the samples by means of polarizing light microscopy, transmission electron microscopy, X-ray diffraction and oscillation rheology measurements. Our aim was to decrease the amount of nonionic surfactants with the use of a short-chain alcohol as cosurfactant, and to increase the dissolving capacity of LLC systems. We studied the effect of increasing concentration of glycerol on the structure of LLC systems. The concentration range of glycerol was 15–40% (w/w). We searched for the relationship between the extent structure of the LLC samples and dynamic rheological properties. We examined the connection between the structure of the samples and drug release of the incorporated model drug with good water-solubility and with practically water insolubility.

2. Materials and methods

2.1. Materials

The nonionic surfactant was poly-oxyethylene-10-oleyl ether (ICI Hungary Ltd., Budapest, Brij 96), official in USP XXIV NF. The ICI product was used without transformation. The liquid petrolatum (LP), glycerol as short-chain alcohol and distilled water are official in the European Pharmacopoeia 4th. Distilled water was produced by double distillation in glass equipment. Tenoxicam as practically water-insoluble, ephedrine hydrochloride as good water-soluble drugs were used, which are official in the European Pharmacopoeia 4th.

2.2. Sample preparation

The samples were produced by heating the mixture of the lipophilic phase and of the surfactant to 60 °C. Distilled water was heated up to 60 °C was then added during constant stirring at 500 r/s (Ikamag RET-G magnetic stirrer). Stirring was continued until the mixture cooled down to room temperature, and great care was taken to prevent water-evaporation during formulation and storage (Nürnberg and Friess,

1990). The systems were first stored at room temperature for 1 week before investigation, until the subsequent spontaneous structural organization had finished. In case of the drug-containing samples, the practically water-insoluble drug was added to the lipophilic phase than they were mixed with distilled water. The good water-soluble drug was first dissolved in distilled water than this solution was added to the oil–surfactant mixture.

2.3. Microscopic analysis

The phase boundaries were examined by direct optical measurements (Hartshorne, 1974) using polarizing light microscopy (Leica Q 500 MC Image Analyser system) at a magnification of 500× and 1000×. The optical observation of the structure was supplemented by the transmission electron micrograph of the replicas produced by freeze-fractured technique (Müller et al., 1980; Goodman and Clunie, 1974) at a magnification of 18,000× (BA 400D, Balzers).

2.4. X-ray diffraction

The d_L values between the lamellar LC domains were determined by means of X-ray diffraction (Phillips PW 1820 diffractometer), which confirmed that the drug-free samples and drug-containing systems had an organized structure. The samples were first stored at the room temperature for a week, then placed in a copper sample holder and covered with Mylar foil. X-ray diffractograms were then measured at room temperature (25 °C) in the inclination angle range $2\theta = 1$–5°. The d_L values reflecting the extent of the structure were determined via the Bragg equation (Fontell, 1974):

$$n\lambda = 2d_L \sin\theta \quad (1)$$

where λ is the used wavelength, d_L the interlamellar repeated distance between successive identical crystal planes, θ the diffraction angle and n is "the order of the reflection".

2.5. Dynamic oscillatory tests

Dynamic oscillatory measurements, described by Németh et al. (1998), were used to identify the lamellar LC domains. The Haake RheoStress 1 Rheometer, equipped with a cone-plate sensor (diameter of 35 mm), and a cone angle of 1° was used. The thickness of the sample in the middle of the sensor was 0.048 mm. Samples were kept at 32 ± 0.2 °C under saturated water vapor during the measuring process. The linear viscoelastic region was at first determinated by measuring the complex modulus versus stress at a low (0.036 Hz) frequency, 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 measured parameters were defined as follows:

$$G^* = \frac{\tau_0}{\gamma_0}$$

$$G' = G^* \cos\delta$$

$$G'' = G^* \sin\delta$$

$$\mu^* = \frac{G^*}{\omega}$$

where γ_0 is the strain amplitude, τ_0 the stress amplitude, G^* the complex modulus, ω the angular velocity, G' the storage (elastic) modulus, G'' the loss (viscous) modulus, δ the phase shift angle, and μ^* is the complex viscosity (Schramm, 1994).

2.6. Drug release study

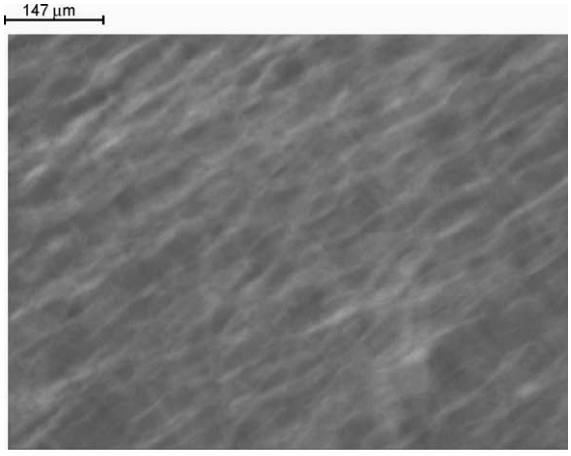
The rate and extent of drug release was measured by an autosampling system containing vertically diffusion cells (Hanson Microette autosampling system), which method is official in the USP XXIV. The drug release profile was determinated at 32 ± 0.5 °C using phosphate buffer of pH 5.4 (by McIlvaine), special cellulose-acetate membrane filters, which are official in the USP XXIV, were used; diameter: 0.45 μm, thickness: 150 μm, surface area: 0.008 cm^2. The measurements of the drug released were carried out with an ATI UNICAM UV-Vis Spectrometer. The absorbance maximum of ephedrine hydrochloride was at 260 nm and solubilized tenoxicam was determined at 370 nm.

3. Results and discussion

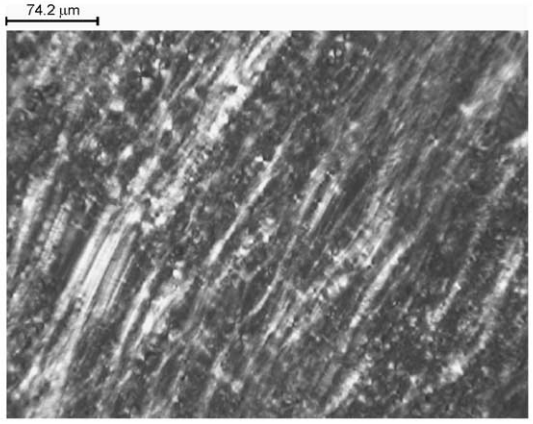
The first step in the development of the dosage form was to determine the emulsifier and water ratio

Table 1
Compositions of two-, three- and four-component samples investigated

Sample number	Brij 96/water proportion	Brij 96% (w/w)	Glycerol % (w/w)	Liquid petrolatum % (w/w)	Distilled water % (w/w)
I	1:1	50	–	–	50
II	4:3	57.2	–	–	42.8
III	3:2	60	–	–	40
IV	2:1	66.6	–	–	33.3
V	3:1	75	–	–	25
VI	4:1	80	–	–	20
1	2:1	60	–	10	30
2	3:2	45	15	10	30
3	17:12–(4:3)	42.5	17.5	10	30
4	4:3	40	20	10	30
5	1:1	30	30	10	30

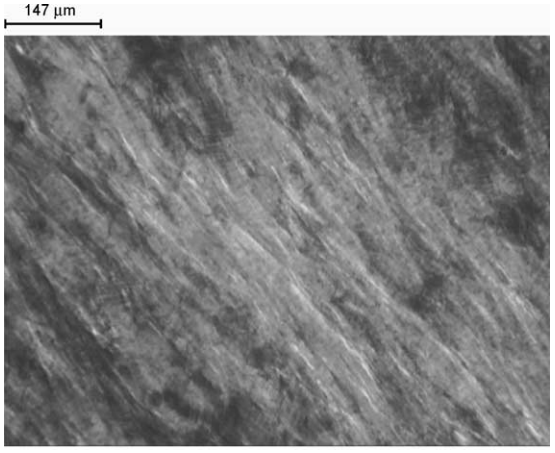


(A)



(B)

Fig. 1. (A) Polarizing microscopic picture of the sample II at magnification of 500×. (B) Polarizing microscopic picture of sample IV with Maltese crosses at magnification of 1000×.



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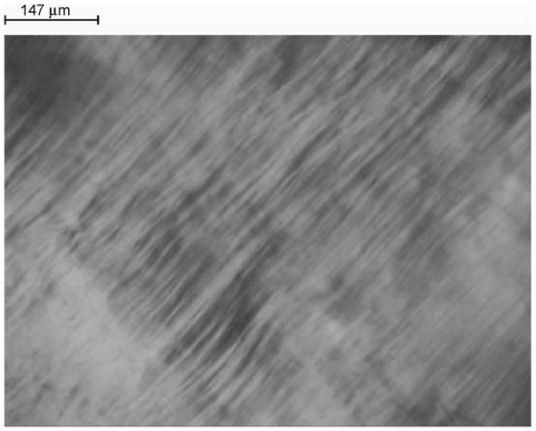


(B)

Fig. 2. (A) Polarizing microscopic picture of sample 1 at magnification of 500×. (B) Polarizing microscopic picture of sample 2 at magnification of 500×.

Fig. 3. Transmission electron micrograph of the four-component sample 3 made by freeze-fractured technique at magnification of 18,000×.

where the liquid crystalline structure formed. The poly-oxyethylene-10-oleyl ether ether forms liquid crystals with water. The surfactant content was relatively high in these samples (over 50% (w/w)). To achieve a much more skin compliant composition we decreased the surfactant concentration by using a glycerol as cosurfactant and to increase the dissolving capacity of the systems we used LP. It was found that these excipients did not bring a considerable decrease in the presence of liquid crystalline domains.

The domains were examined by polarizing light microscope. The binary systems and the compositions of the three- and four-component lamellar liquid crystals with different surfactant/cosurfactant ratios are summarized in Table 1.

The existence of the biaxial lamellar liquid crystalline character of these systems was confirmed by polarizing light microscopy at a magnification of 500× and 1000×.

Polarization microscopy of these two-component systems, containing various proportions of nonionic surfactants and water, revealed a LLC pattern with a characteristic ribbon structure in polarized light (Fig. 1A and B). Fig. 1A (sample II) depicted biaxial lamellae with a melted hydrophobic part, where the Brij 96/water ratio was 4:3. In this case the hydrocarbon chains were in a crystalline (frozen) state and these chains made an angle other than 90° with the plane of the lamellae. When the ratio of Brij 96 and water in the binary sample was 2:1, the lamellar liquid crystal became uniaxial (sample IV), as shown by the crystal pattern resembling a Maltese cross in Fig. 1B (Frieberg, 1985).

The binary systems were transformed into ternary systems with the addition of LP (in case of sample 1), while the lamellar liquid crystalline structure was retained (shows Fig. 2A). The use of glycerol as a coemulsifier (in case of sample 2) allowed a decrease in surfactant concentration, while the sample structures were remained (see in Fig. 2B).

The existence of lamellar phases was confirmed by transmission electron microscopy on replicas

Table 2
Measured interlamellar repeated distance (d_L), intensity values and dynamic rheological parameters: storage (G'), loss (G'') and complex modulus (G^*) of liquid crystalline samples

Sample number	Distilled water % (w/w)	Short-chain alcohol % (w/w)	$d_{L_{1,2}}$[a] (nm)	Intensity (counts)	G'[b] (Pa)	G''[b] (Pa)	G^*[b] (Pa)
I	50	–	3.18 (3.97)	5538.7 (505)	45300	8690	62400
II	42.9	–	3.09	2092.9	15800	6330	10980
III	40	–	3.06	4066.4	18100	2110	10000
IV	33.3	–	2.94	9374.4	2150	312	21300
V	26	–	2.79	6079.3	1593	158	1780
VI	20	–	4.95 (4.032)	2353.9 (2109)	2381	206	2395
1	30	–	3.18	2331.7	7380	3100	5430
2	30	15	3.5	551.0	36200	1830	40300
3	30	17.5	5.22 (3.15)	435.5 (699.8)	125131	4870	8643
4	30	20	4.46	306.5	46400	4700	32300
5	30	30	4.22	275.6	1770	5210	11800

[a] Interlamellar repeated distance was measured at inclination angle range $2\theta = 1$–$5°$.
[b] The applied stress amplitude (τ) was 2.5 Pa.

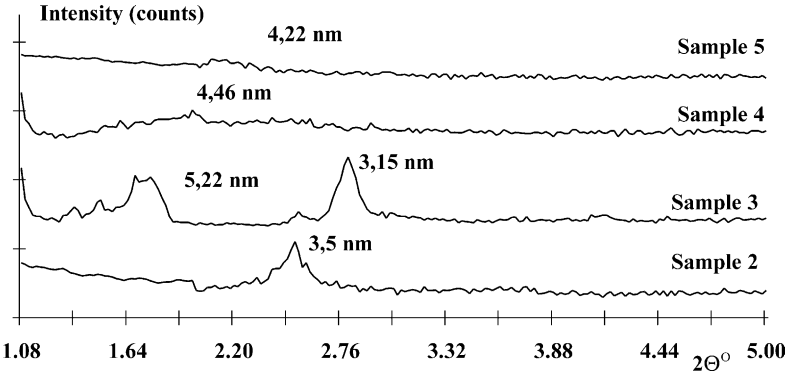


Fig. 4. X-ray diffractograms of three- and four-component samples 2–5.

produced by freeze-fractured technique. Fig. 3 shows the texture of four-component lamellar liquid crystalline sample 3.

The existence of regularly organized structures was demonstrated by the X-ray diffraction measurements, chosen as an indirect method of structure confirmation, for two-, three- and four-component samples. The majority of the samples manifested first-order Bragg reflections of very high intensity, thereby proving the structure formed by regularly organized domains. These structures with one-dimensional periodicity had the diffuse reflection with spacing corresponding to 3–5 nm, they showed sharp reflection in the low-angle region. The intensity fell off steeply for the higher orders and because of the aqueous system only the first reflection was visible, although the d_L values measured in binary systems were almost one order of magnitude higher than those found for multicomponent compositions. The structures of the two-component sample II and that of the four-component sample 3 showed two sharp reflections with d_L values in the ratio of 1:1/2 that oriented lamellae within the samples parallel to each other. Fig. 4 depicts diffractograms of three- and four-component lamellar liquid crystalline samples. The interlamellar repeated distances (d_L) and intensity values of two-, three- and four-component samples without model drugs are summarized in Table 2.

The liquid crystalline structure can be characterized by its dynamic rheological behavior. Oscillating

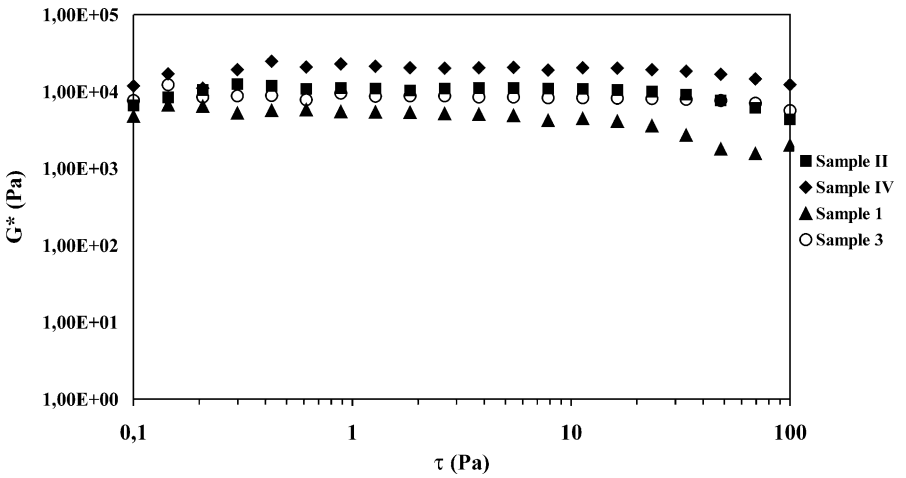


Fig. 5. Complex moduli (G^*) of samples II, IV, 1 and 3.

rheological measurements offer the possibility to identify the lamellar phase, which is the most convenient for dermal and transdermal drug delivery systems (Németh et al., 1998).

We measured the dynamic rheological parameters of surfactant/water, surfactant/water/LP and surfactant/water/LP/glycerol systems. The frequency-dependent storage and loss moduli were found to be characteristic to the lamellar phase in the linear viscoelastic region, so the linear viscoelastic region should be established first.

Results of such a test were plotted as G^* versus amplitude. This range was limited to that amplitude range for which G^* was constant. The sample was deformed under these conditions that leading to the breakdown of the internal temporary bounds of molecules or aggregates. Shear thinning took place and a major part of the introduced energy has been irreversibly lost.

The typical curves of the complex moduli versus stress at a constant low frequency ($f = 0.036$ Hz) of two-, three- and four-component LLC systems are demonstrated in Fig. 5.

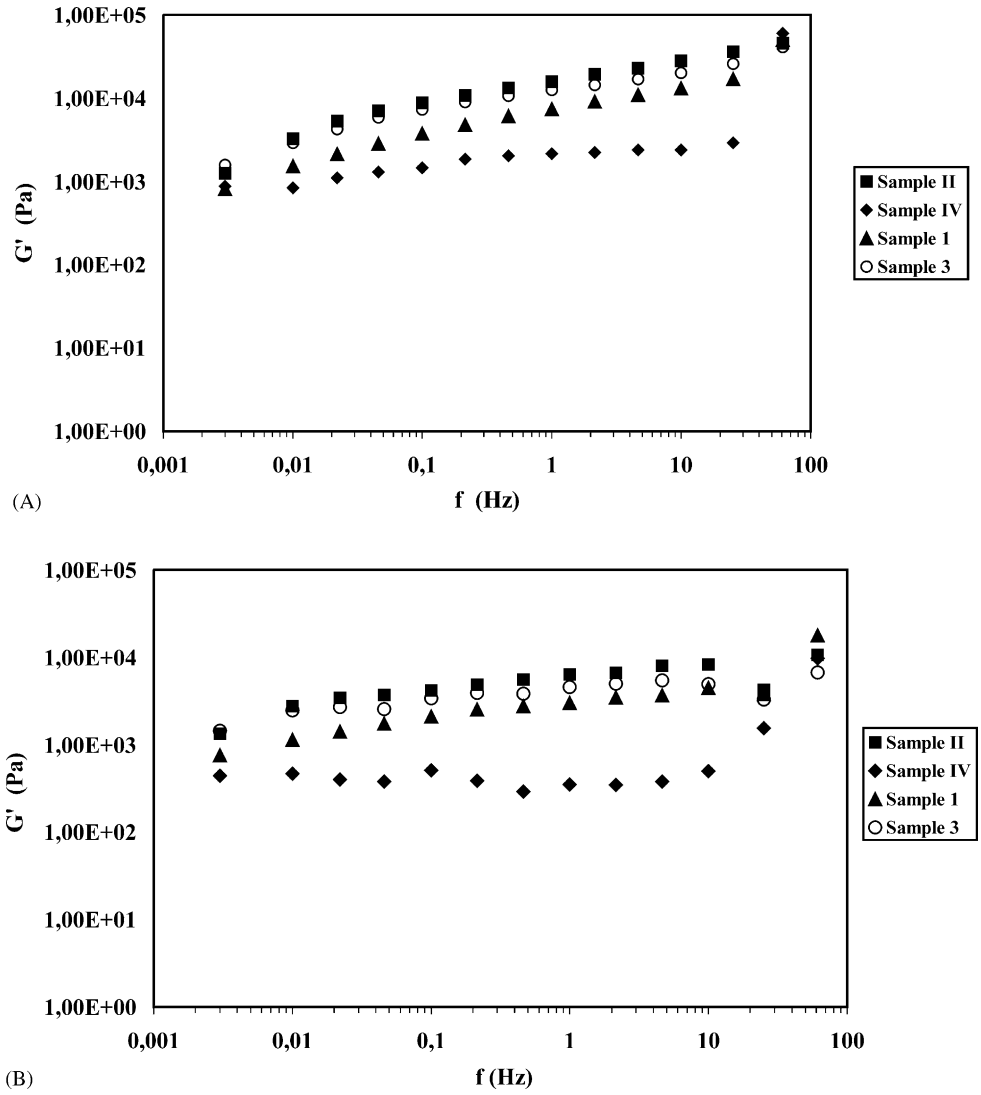


Fig. 6. (A) Storage moduli (G') of samples IV, II, 1 and 3. (B) Loss moduli (G'') of samples IV, II, 1 and 3.

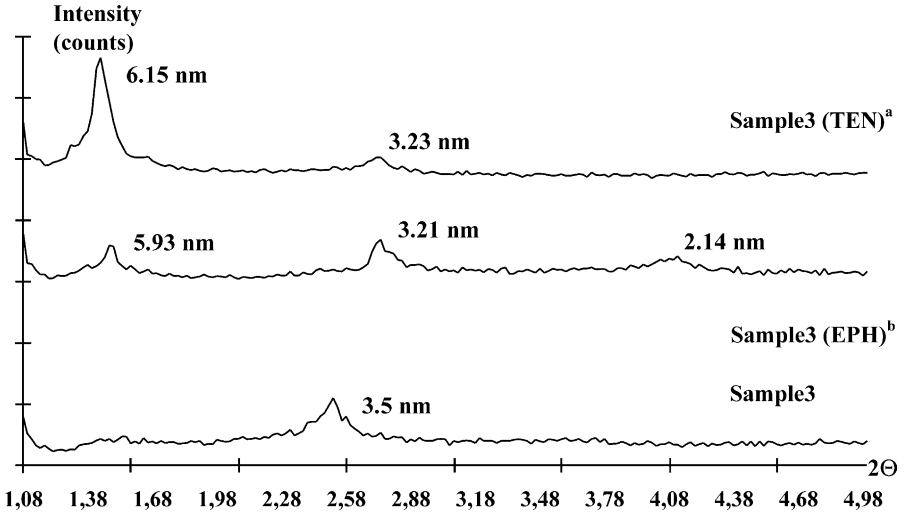


Fig. 7. X-ray diffractograms of sample 3 containing 1% (w/w) of ephedrine hydrochloride (EPH) and 1% (w/w) of tenoxicam (TEN). Interlamellar repeated distance (d_L) was measured at inclination angle range $2\theta = 1$–5°. [(a)]Sample 3 (TEN): sample 3 containing 1% (w/w) of tenoxicam. [(b)]Sample 3 (EPH): sample 3 containing 1% (w/w) of ephedrine hydrochloride.

It can be stated that each of the samples have linear viscoelasticity in 1–10 Pa range of applied stress amplitude, 2.5 Pa was therefore chosen as applied stress where we measured the rheological properties as the function of the frequency (0.100–100 Hz). Typical curves of the samples 1–5 with lamellar mesophases as a function of frequency can be seen in Fig. 6A and B.

The systems were more elastic than viscous in this frequency-range, the storage moduli were higher than the loss moduli. These curves indicated the presence of lamellar structure because the storage moduli are higher by about one order of magnitude than the loss moduli and the loss moduli show a minimum. Other phases like hexagonal phase and inverse micellar phase show completely different curves as a function of the frequency. This explanation is based on the work of Németh et al. (1998).

The most characteristic rheological parameters of two-, three- and four-component samples can be seen in Table 2.

These samples kept their liquid crystalline structures after the incorporation of the model drugs in a concentration of 1% (w/w).

The sample 3 was defined as the most promising lamellar composition at 17.5% (w/w) glycerol concentration. The comparison of the results obtained with the two indirect structure-examination methods showed that sample 3 had the greatest d_L value and the highest storage modulus values (G'), which indicate that the sample had more elastic than viscous character. We selected the four-component sample 3 which had an ideal consistency and attractive appearance, and its application on the skin elicited a pleasant sensation either.

Table 3
Drug release parameters of three- and four-component samples containing ephedrine hydrochloride[a] (EPH) and tenoxicam[a] (TEN)

Sample number	Q^b (μg/cm^2)	D^c (μg cm^{-2}/min)	R^{2d}
1 TEN	207.327	17.969	0.9995
2 TEN(LC)[e]	308.788	26.567	0.9999
3 TEN(LC)[e]	390.973	33.982	0.9980
4 TEN	225.884	19.982	0.9993
5 TEN	551.927	48.065	0.9993
1 EPH	239.17	0.6058	0.9166
2 EPH (LC)[e]	316.59	0.6140	0.9378
3 EPH (LC)[e]	383.22	0.5968	0.9446
4 EPH (LC)[e]	374.31	0.5194	0.9395
5 EPH	537.01	181.28	0.8817

[a] Drug concentration was 1% (w/w).
[b] Q: total amount of released drug after 6 h.
[c] D: diffusion coefficiens.
[d] R^2: correlation coefficiens.
[e] LC: samples with lamellar liquid crystalline structures containing drugs.

The X-ray diffractograms of the sample 3 because it containing drugs, presented in Fig. 7, showed sharp reflections with d_L values in the ratio 1:1/2 in case of tenoxicam, and 1:1/2:1/3 in case of ephedrine hydrochloride. These compositions kept their lamellar structure. There was a further increase in the d_L values, which was caused by the incorporation of tenoxicam and ephedrine hydrochloride partly into the lamellar space and partly they are located at the given polarity part of the amphiphilic surfactant molecules.

The samples containing drugs were confirmed to retain their lamellar LC structure by the oscillatory rheological measurements, as shown in Fig. 8A and B.

In case of the three- and four-component samples containing water and LP in a constant weight ratio, the values of the d_L changed according to a maximum curve with the increase of the concentration of glycerol 0–30% (w/w). The phenomena can be seen in Fig. 9A.

We examined the effect of the glycerol as a cosurfactant in concentrations between 0 and 30% (w/w) on the storage (G') and loss moduli (G'') in each type of our systems at a constant water/LP ratio (1:3). The values of storage and loss modulus versus glycerol concentration at a constant frequency (1 Hz) can be seen in Fig. 9B. The storage modulus (G') went through a maximum value with increasing surfactant

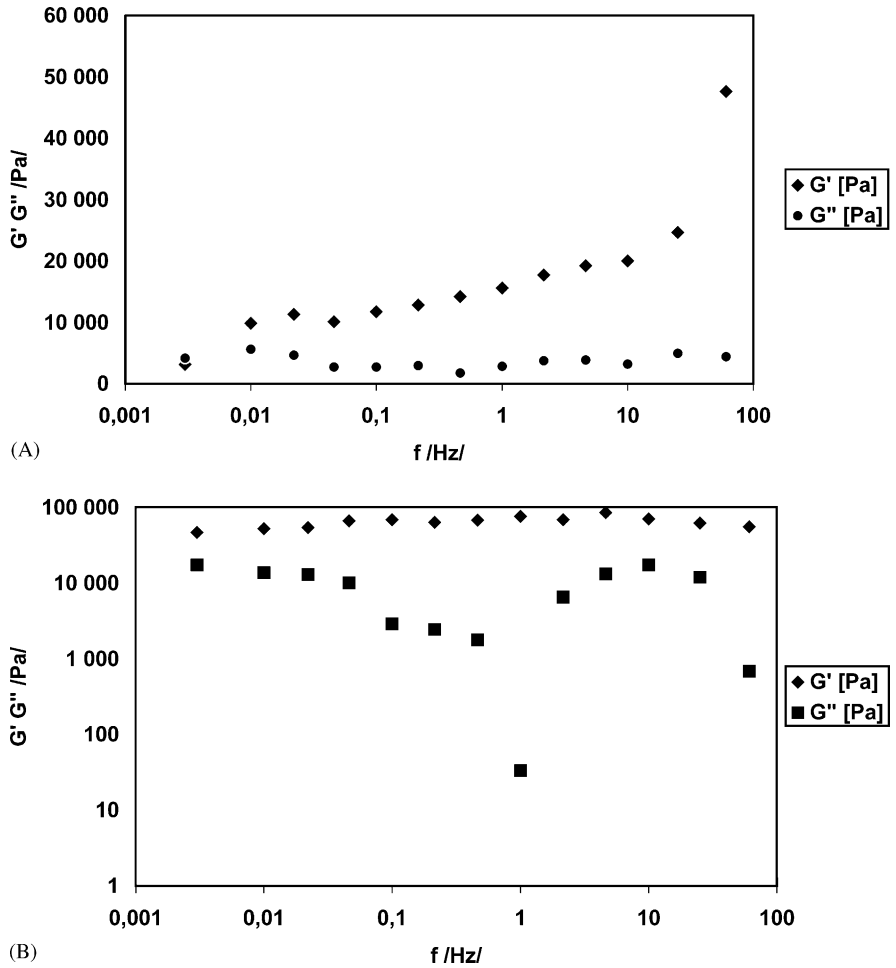
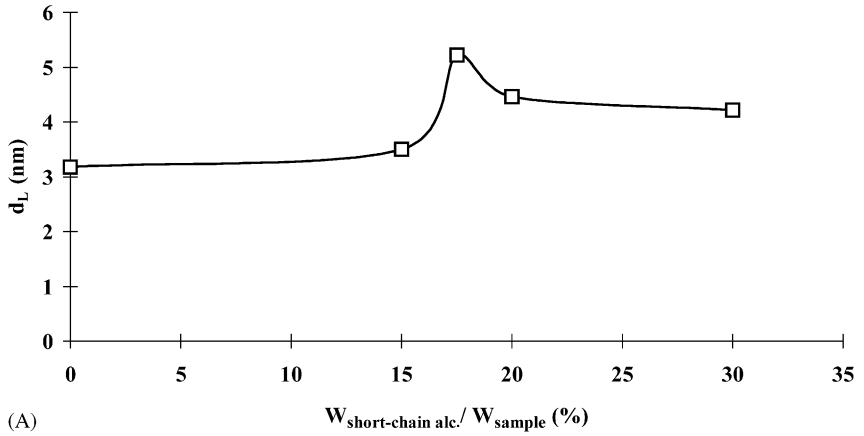


Fig. 8. (A) Storage (G') and loss moduli (G'') of four-component sample 3 containing 1% (w/w) of ephedrine hydrochloride. (B) Storage (G') and loss moduli (G'') of four-component sample 3 containing 1% (w/w) of tenoxicam.



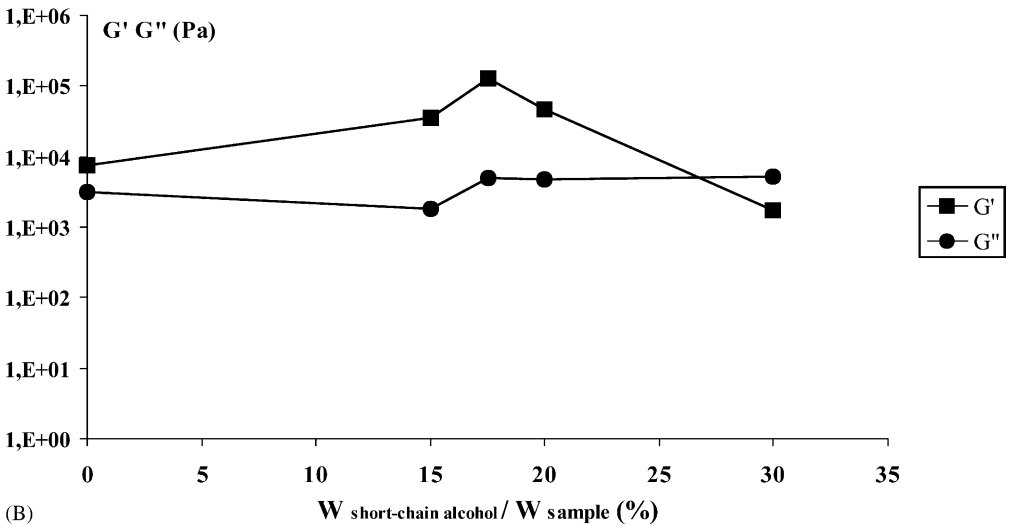


Fig. 9. (A) Effect of glycerol content on the values of interlamellar repeated distance (d_L) of three- and four-component samples. (B) Effect of glycerol content on the values of storage (G') and loss modulus (G'') of three- and four-component samples.

concentration, the loss moduli (G'') fitted to a minimum curve. Typical parameters of the drug release study are summarized in Table 3.

Approximately the same amount of the incorporated drugs were released after 6 h from both sample-groups containing the very water-soluble ephedrine hydrochloride and the water-insoluble tenoxicam (Fig. 10A and B).

The drug release of ephedrine hydrochloride showed a first-order kinetic. A fast drug release was observed followed by a slow release in case of samples 2–4 containing glycerol 15–20% (w/w). Zero-order release kinetic was measured in case of sample 5 because the higher glycerol content should be caused its softer consistency.

The release of tenoxicam corresponded to zero-order release kinetic. The highest amount of released tenoxicam was measured from sample 5 with the highest diffusion coefficient. The other glycerol-containing sample showed slower drug release, because during drug release measurements a controlling effect was observed, when the lamellar liquid crystalline structures were present.

This phenomenon can be explained as follows: the water amount present in the lamellar liquid crystal systems was sufficient for dissolving the very soluble

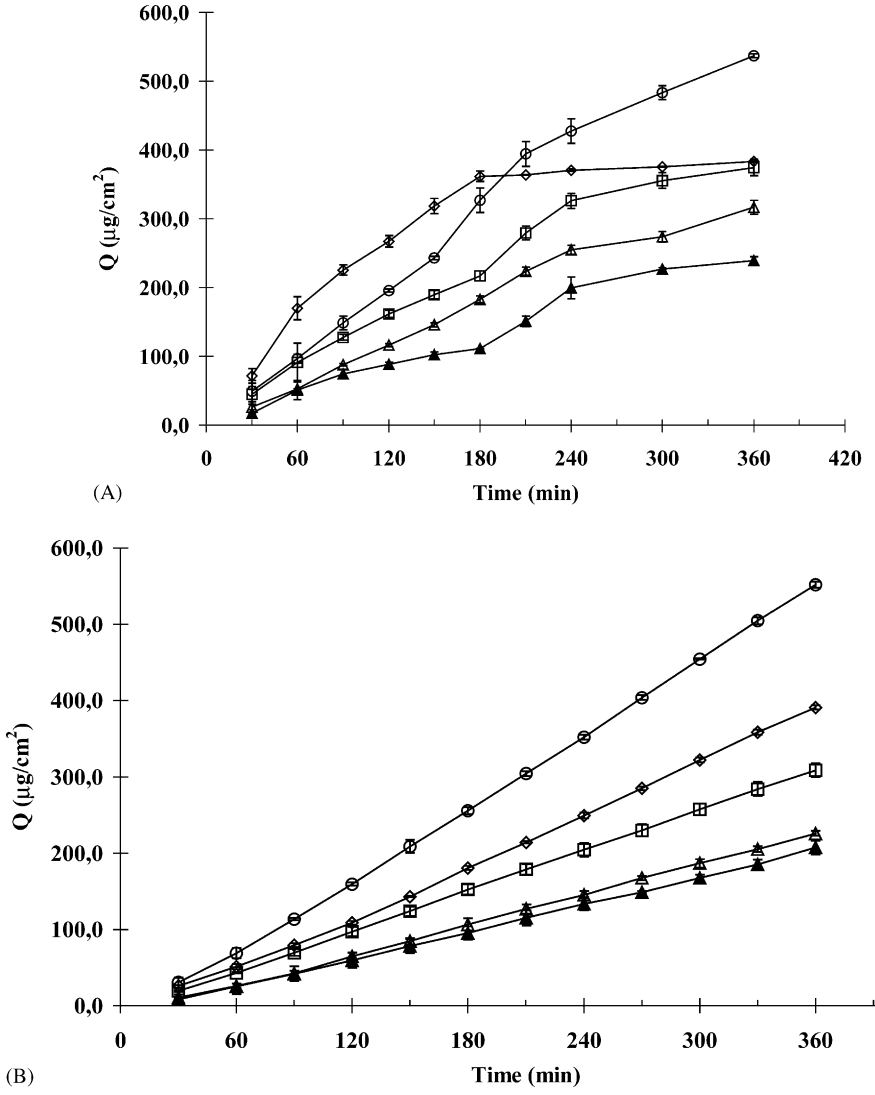


Fig. 10. (A) Ephedrine hydrochloride release from different three- and four-component samples. Sample 1 (▲), sample 2 (△), sample 3 (◇), sample 4 (□), sample 5 (○) (average of three parallels ± S.D.). (B) Tenoxicam release from different three- and four-component samples. Sample 1 (▲), sample 2 (△), sample 3 (◇), sample 4 (□), sample 5 (○) (average of three parallels ± S.D.).

ephedrine hydrocloride. Tenoxicam as a practically insoluble drug was completely solubilized in the selected systems. An increase in the interlamellar distance (d_L) was detected in case of both incorporated model drugs, meaning that the drugs were partly built between the lamellar space, and partly located at the given polarity part of the amphiphilic surfactant molecules.

4. Conclusion

This research has revealed that poly-oxyethylene-10-oleyl ether is a proper surfactant suitable for the formation of lamellar liquid crystals with water. The samples with the composition Brij 96/glycerol/LP/distilled water formed stable, well-tolerable lyotropic lamellar liquid crystals.

The surfactant content could be decreased to 30% (w/w) by adding the glycerol as a cosurfactant. The applied LP, glycerol and model drugs with low concentration did not result in a significant change in the structure of the lamellar liquid crystals; this was supported by X-ray diffraction, confirming the results of polarizing microscopy, transmission electron microscopy and parameters of dynamic rheological measurements.

The lamellar d_L values of the regularly structured samples changed with the increase of the concentration of glycerol according to a maximum curve, similarly to the values of the storage modulus (G') obtained with oscillatory rheological measurement.

Samples containing ephedrine hydrochloride and tenoxicam in a concentration of 1% (w/w) also retained their organized lamellar structure, which was confirmed both with X-ray diffraction and oscillatory rheological tests.

Our experiments ensured, that the developed lamellar liquid crystalline systems were proper not only for incorporating of a poorly water-soluble drug, but were adequate for achieving a prolonged drug release in case of very water-soluble drug.

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