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Physical stability and solubility of the thermotropic mesophase of fenoprofen calcium as pure drug and in a tablet formulation

James Patterson, Andrew Bary, Thomas Rades *

Solid State Research Group, School of Pharmacy, University of Otago, Dunedin, New Zealand

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Abstract

The aim of this study was to investigate and compare the physical stability and solubility of the liquid crystalline form of fenoprofen calcium as pure drug and in a proprietary tablet formulation (Nalfon®), and to investigate if a simple heat treatment of a proprietary tablet containing fenoprofen calcium may lead to a physically stable formulation with enhanced dissolution rate and apparent solubility. The liquid crystalline form of fenoprofen calcium (thermotropic mesophase) was prepared by heating the crystalline drug to 125 °C to remove the water of crystallisation. Differential scanning calorimetry investigation revealed an endothermic peak at 89 °C upon heating (liquid crystal formation) attributable to water loss from the crystalline dihydrate. The liquid crystalline order was maintained upon cooling. No interference of tablet excipients with the thermal behaviour of the drug in the tablet formulation was observed. The crystalline dihydrate and liquid crystalline forms of fenoprofen calcium could be differentiated by diffuse reflectance infra-red spectroscopy and X-ray powder diffraction, both as pure drug and in tablet formulation. The supercooled liquid crystal (thermotropic reversed hexagonal phase) alone and in preheated and ground tablets was physically stable when stored in a dry environment or at 33% relative humidities (RH) at both 20 and 40 °C for 2 months. At 40 °C and 75% RH the supercooled mesophase extensively converted to the crystalline dihydrate within 6 days. Liquid crystalline fenoprofen calcium stored at 20 °C and 75% RH showed only partial dihydrate conversion after 2 months of storage. The solubility of the crystalline dihydrate alone and from the tablet formulation was 2.8 ± 0.2 mg/ml and 3.0 ± 0.2 mg/ml (mean $\pm$ s.d.), respectively, (not significantly different), whereas the maximum solubility of the liquid crystal was 5.0 ± 0.3 mg/ml (mean $\pm$ s.d.) and 6.9 ± 0.6 mg/ml (mean $\pm$ s.d.), respectively (significantly different). The difference in maximum solubility between the crystalline dihydrate form of fenoprofen calcium and the fenoprofen calcium mesophase was highly significant, for both the pure drugs and the tablet formulations. The dissolution rate of the liquid crystalline fenoprofen calcium in preheated, intact tablets was significantly lower than that of the crystalline form in non-preheated tablets. Gross visual changes and scanning electron microscopy indicated that the disintegration properties of the tablet may be detrimentally effected by heating the tablet to 125 °C, diminishing the beneficial effect of improved solubility of the liquid crystal. The study has shown that conversion of the crystalline form of fenoprofen calcium to the liquid crystal can enhance the apparent solubility of the pure drug and the drug in presence of tablet

* Corresponding author. Tel.: +64-3-4795410; fax: +64-3-4797034
E-mail address: thomas.rades@stonebow.otago.ac.nz (T. Rades).

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excipients, but that the conversion should be performed before tablet formulation in order to increase dissolution of this poorly water-soluble drug.

Keywords: Fenoprofen calcium; Fenoprofen calcium tablets; Thermotropic liquid crystals; Mesophase; Physical stability; Solubility

1. Introduction

Some pharmaceutical drugs are capable of exhibiting liquid crystalline (mesomorphous) behaviour. Literature reports demonstrate almost exclusively that these drugs form a lyotropic mesophase upon dilution with a polar solvent, usually water. Examples listed by Rades and Müller-Goymann (1992) include salvarsan (nematic mesophase), disodium chromoglycate (nematic and hexagonal mesophase), nafoxidin HCl (hexagonal, cubic, lamellar mesophase) and flufenaminic acid (lamellar mesophase). A series of non-steroidal anti-inflammatory drugs (NSAIDs) including ketoprofen and diclofenac form lyotropic lamellar mesophases in binary systems with water at a certain temperature range (Hamann and Müller-Goymann, 1987; Rades and Müller-Goymann, 1992). Knowledge about the lyotropic mesomorphism of drugs is of considerable interest in dosage form development, as these compounds are likely to interact strongly with phospholipids or other amphiphilic substances able to form lamellar mesophases together with water (Kriwet and Müller-Goymann, 1994).

Thermotropic mesomorphism on the other hand is rarely investigated in pharmaceutical drugs. The few examples that can be found in the literature include the anti-oestrogen compound nafoxidin HCl, which forms a smectic mesophase (Mlodozeniec, 1978) and L-660711 [3-(((3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl) ((3-(dimethylamino)-3-oxo-propyl) thio) methyl) thio) propanoic acid], a leukotriene D4 receptor agonist (unidentified thermotropic mesophase, Vadas et al., 1991). The sodium salt of the NSAID fenoprofen can also form a thermotropic, smectic mesophase (Rades and Müller-Goymann, 1994). Interestingly, nafoxidin HCl, L-660711 and fenoprofen sodium can each form either a thermotropic smectic mesophase or a lyotropic mesophase in certain conditions. Each compound is amphiphilic, showing surfactant properties, thus fulfilling a structural requirement for formation of a lyotropic mesophase and also possess ring systems that are typical structural elements of a thermotropic mesophase (Demus and Zaschke, 1984).

Thermotropic mesophases form upon heating of crystalline substances and thus, unlike lyotropic mesophases, do not require the presence of a solvent for their formation. It has been estimated that 5% of all organic compounds exhibit thermotropic mesomorphism (Schülke, 1987). As transfer of heat energy to the substance cannot be avoided in many processes in pharmaceutical manufacture, it appears possible that mesophases may be formed upon handling or processing of drugs. It is possible that these mesophases (like a metastable polymorphic form of a drug) do not transform back into the crystalline state once the heat energy is no longer exerted onto the drug. In that respect, the thermotropic liquid crystalline form of a drug may be regarded as a special polymorphic form. (This however, should not be confused with the fact that it is possible for a substance to form several thermotropic liquid crystalline phases (Demus and Richter, 1978), i.e. that there is also a 'true' mesomorphic polymorphism.) There is thus a need to investigate the ability of drugs to form mesophases, just as there is a need to characterise the crystalline polymorphism of drugs. On the other hand, if the mesophase does not transform back to the thermodynamically stable crystalline state, the free energy of the drug is increased, which may give rise to an increased dissolution rate and possibly an enhanced apparent solubility of the drug. In that respect, formation of a supercooled thermotropic liquid crystalline form

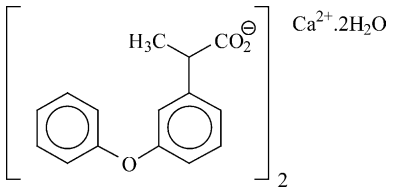

Fig. 1. Structural formula of fenoprofen-calcium dihydrate.

of a drug may be regarded as a process comparable to the formation of a supercooled amorphous form of a drug. As the drug in the supercooled mesophase is in an energetic minimum (albeit not the primary minimum) this may be a more stable supercooled state than if the drug was present in an amorphous form.

In an earlier study, it could be shown that the calcium salt of fenoprofen (Fig. 1), because of its low aqueous solubility, does not form a lyotropic mesophase or even a micellar solution, but can exist in a thermotropic liquid crystalline form. This mesophase can be prepared by 'open' heating of the crystalline dihydrate form of the drug to drive off the water of crystallisation (Rades and Müller-Goymann, 1994; Rades et al., 1996). The mesophase has the appearance of a solid-like material, which does not flow, until pressure is exerted onto the sample (Rades and Müller-Goymann, 1994), indicating that the mesophase may be better understood and differentiated from solids and liquids in terms of its molecular order, rather than viscosity.

The low water solubility of the crystalline dihydrate of fenoprofen calcium could potentially be improved by transformation into a supercooled thermotropic mesophase (Rades et al., 1996), analogous to the formulation of glassy, amorphous solids, by melting and quench cooling of crystalline drugs (Forster et al., 2001). The objective of the current work was to investigate and compare the physical stability and solubility of the liquid crystalline form of fenoprofen calcium alone and in a ground proprietary tablet formulation (Nalfon®), and to investigate if a simple heat treatment of a proprietary tablet containing fenoprofen calcium leads to a physically stable formulation with enhanced dissolution rate and apparent solubility.

2. Experimental

2.1. Materials

Fenoprofen calcium dihydrate (6.4% H_2O) was purchased from Sigma Chemical Co and was used as received. Nalfon® tablets (Eli Lilly) contain 600 mg fenoprofen (Mw: 241.3) as calcium dihydrate (694.6 mg). The total average weight of a tablet is 949 mg (s.d. = 3 mg; $n = 20$), thus the tablets contain approximately 73% (w/w) active ingredient. The main excipients present in Nalfon® tablets are calcium phosphate and cornstarch (Physicians Desk Reference, 1998). The film coating on the Nalfon® tablets was mechanically removed before use. All other chemicals were at least reagent grade.

Transformation of crystalline fenoprofen calcium to the liquid crystalline form was carried out by heating the dihydrate in open vials (pure drug or tablet ground in a mortar and pestle) in an oven to 125 °C for 45 min (preheating). Following preheating, samples were cooled in an ice bath for 1 min and then in a freezer to −84 °C for 10–15 min, before being brought back to room temperature. Samples were then ground again in a mortar and pestle and stored under various conditions (see below).

2.2. Physico-chemical characterisation of samples

The thermal behaviour of the fenoprofen calcium samples was characterised using differential scanning calorimetry (DSC). Samples (3–4 mg) were heated from 20 °C to 180 °C at a heating rate of 5 °C/min in aluminium sample pans with the lids pierced to allow evaporation of the water of crystallisation.

Diffuse reflectance infrared spectroscopy (DRIFTS) spectra of the samples were obtained using a Bio-Rad FTS 175C infrared spectrophotometer, fitted with a diffuse reflectance accessory (Pike Technology Easidiff). Samples were diluted to 5% (w/w) in KBr (Sigma Chemical Co.) and gently ground in a mortar and pestle. All samples were measured in triplicate.

X-ray powder diffraction (XRPD) was performed using a Phillips PW1050 powder diffract-

ometer equipped with a Cu kα tube (λ: 1.5419 Å). Analysis was carried out at room temperature at 40 kV/20 mA with 50 steps/degree and 1 s/step. Samples were gently ground in a mortar and pestle and filled into aluminium pans, which served as sample holders. The surface of the samples was carefully smoothed using a razor blade. No pressure was exerted onto the sample. To investigate the shape of the particles after grinding the resulting powders were viewed by scanning electron microscopy and found to be almost isodiametric. The crystalline samples of the pure drug and the ground tablets before heat treatment were agglomerates of very small primary particles, which also appeared to be iso-diametric. Sample preparation and particle shape should therefore decrease likelihood of preferred orientation of the particles in the sample holder. Samples were scanned from 3° to 28° 2θ, for both the drug in the crystalline dihydrate form and in the liquid crystalline form. XRPD was used qualitatively to confirm the transformation of fenoprofen calcium dihydrate to a liquid crystal and to identify the type of the mesophase, and semi-quantitatively to determine the proportion of fenoprofen calcium as the liquid crystal in the samples upon storage (see below). The thermotropic mesophase of fenoprofen calcium could be investigated by wide angle XRPD, as the rod diameter of the reversed hexagonal phase was so small that the resulting scattering angles were larger than 3° 2θ.

Scanning electron microscopy (Cambridge S360 SEM) was performed at 5 and 10 kV. Samples were sputter coated with approximately 80 nm gold/palladium prior to observation (Bio-Rad E 5100).

2.3. Chemical and physical stability

Samples of fenoprofen calcium dihydrate alone or powdered tablet formulation were heated to 125 °C for various time periods (30 to 180 min) and then cooled to room temperature. Samples were then dissolved in 100 ml of 20% ethanol in HPLC water and analysed by stability indicating HPLC. The system consisted of a Jasco 880-PU pump delivering a mobile phase of acetonitrile, water and glacial acetic acid (0.58:0.38:0.04) at 1.0 ml per min through a Phenomenex 250×4.6 mm^2 Luna 5 μ C18 column. Column effluent was monitored for fenoprofen at 280 nm using a Shimadzu SPD 10A UV detector.

The physical stability of the liquid crystal over 60 days was determined at 20 and 40 °C at dry conditions and at relative humidities (RH) of $30 \pm 3\%$ and $75 \pm 3\%$. Samples were stored over activated silica gel (dry) or saturated solutions of $MgCl_2 \cdot 6H_2O$ (30% RH) or NaCl (75% RH). Samples for analysis by XRPD were collected at ten time-points during storage.

For a semi-quantitative estimation of the conversion of the liquid crystal to the crystalline dihydrate, a calibration curve was established from binary mixtures of crystalline fenoprofen calcium dihydrate or powdered tablet and the ground, supercooled liquid crystal using XRPD, by determining the intensity of the peak at 6.4° 2θ, which is characteristic for the crystalline dihydrate. The peak at 6.4° 2θ was not obscured by peaks from the tablet excipients. In the binary mixtures no significant overlap between the peak of interest (at 6.4° 2θ) and the main peak of the liquid crystalline form of the drug (at 5.4° 2θ) was observed, as initially the peak of the liquid crystalline form was very defined. However, upon storage of the samples the peak at 5.4° 2θ became broader, and some overlap (albeit minor) of the two peaks may have occurred. Such an overlap will have led to a small overestimation of the area of the crystalline peak and therefore an overestimation of the amount of crystalline form of the drug in the various formulations. The method used here to quantify the conversion of the liquid crystalline form of fenoprofen calcium to the dihydrate is thus only semi-quantitative, allowing determination of the start and relative extent of recrystallisation, but may slightly overestimate the actual degree of crystallinity in the samples.

2.4. Solubility and dissolution of samples

The solubility of the crystalline dihydrate and liquid crystalline fenoprofen calcium over 120 min at 25 ± 0.2 °C was determined from the supernatant of aqueous suspensions containing fenoprofen calcium alone or in the powdered tablet

formulation. Suspensions were prepared by adding the equivalent 0.23 mmol of fenoprofen to 16 ml HPLC water and stirred by a magnetic stirrer. The amount of fenoprofen calcium added to the suspensions was well in excess of the previously reported solubility of the crystalline dihydrate and liquid crystalline forms of fenoprofen calcium (2.5 mg/ml (Ward and Schirmer, 1977) and 5.3 mg/ml (Rades et al., 1996), respectively). At various intervals, a sample was drawn and filtered through a 0.45 μm nylon filter (Syntex), diluted 1:20 with HPLC water and analysed by HPLC, as described above.

The dissolution properties of the tablets containing the drug as the crystalline dihydrate or liquid crystal (tablets preheated as described above) were determined using USP dissolution apparatus I. All dissolution profiles were determined using 1 l of 0.2 M phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C. The paddle speed was 80 rpm. Samples (5 ml) were taken at various timepoints and filtered through a 0.45 μm nylon filter before analysis by HPLC. In all studies, the tablets containing each form ($n = 3$) were intact with the film coating removed.

3. Results and discussion

3.1. Physico-chemical characterisation of samples

Open heating of drug alone or in the powdered tablet formulation in the DSC revealed an endothermic peak with a maximum at 89 °C (onset: 72 °C) as the only thermal event between 20 and 180 °C. This endotherm corresponds to water loss of the crystalline dihydrate and formation of the liquid crystal, and confirms the findings of an earlier study using modulated DSC (Rades et al., 1996). Cooling and subsequent re-heating of the samples yielded no endothermic peaks, indicating that the liquid crystalline form is maintained upon cooling. The peak onset and maximum observed during heating of the drug alone or in the tablet formulation were not significantly different, indicating that the excipients did not show any detectable thermal conversions in the temperature range studied. The specific enthalpy of the thermal event in the tablet formulation was approximately 30% lower than in the pure drug (≈ 90 J/g and ≈ 120 J/g, respectively) attributable to the excipients in the tablet formulation. It can therefore be stated that the excipients did not have a measurable influence on the phase transition of the crystalline dihydrate to the thermotropic mesophase.

Characteristic DRIFTS spectra of the crystalline and the liquid crystalline form of fenoprofen calcium were obtained for both, the drug alone and in the tablet formulation. The major differences between the DRIFTS spectra of the drug in the crystalline and liquid crystalline state were found in the region 1200–1280 cm^{-1} where the symmetric ether stretching is expected, as well as in the region 800 cm^{-1} corresponding to aromatic out of plane vibrations. This confirms data from an earlier investigation in which FTIR was used to determine the vibrational spectra of the drug alone in crystalline and liquid crystalline states (Rades et al., 1996).

The DRIFTS spectra of the drug in the crystalline and liquid crystalline state were characteristic, both for drug alone and in the tablet formulation (Fig. 2). Interestingly, it can be seen from Fig. 2 that the excipients present in the tablet formulation did not have a strong influence on the appearance of the DRIFTS spectra of the tablet compared to those of the pure drug, in both the crystalline and supercooled liquid crystalline state, i.e. that the spectra of the tablet formulations appeared almost unchanged compared to those of pure drugs. DRIFTS thus allows a fast, qualitative identification of the state of the drug both as the pure drug substance and in tablet formulation. Current work in our laboratory is aiming to evaluate the use of DRIFTS to quantitatively determine the state of the drug in the presence of tablet excipients.

The DRIFTS spectra of the liquid crystalline drug appear less well defined compared to spectra of the drug in the crystalline dihydrate state (e.g. in the spectral regions around 1450–1500 cm^{-1}, 1200–1400 cm^{-1}, 900–750 cm^{-1}). A similar observation has been made by Forster et al. (2001), comparing the spectra of several drugs in the crystalline and amorphous, glassy state (nifedipine, lacidipine, indomethacin and tolbutamide).

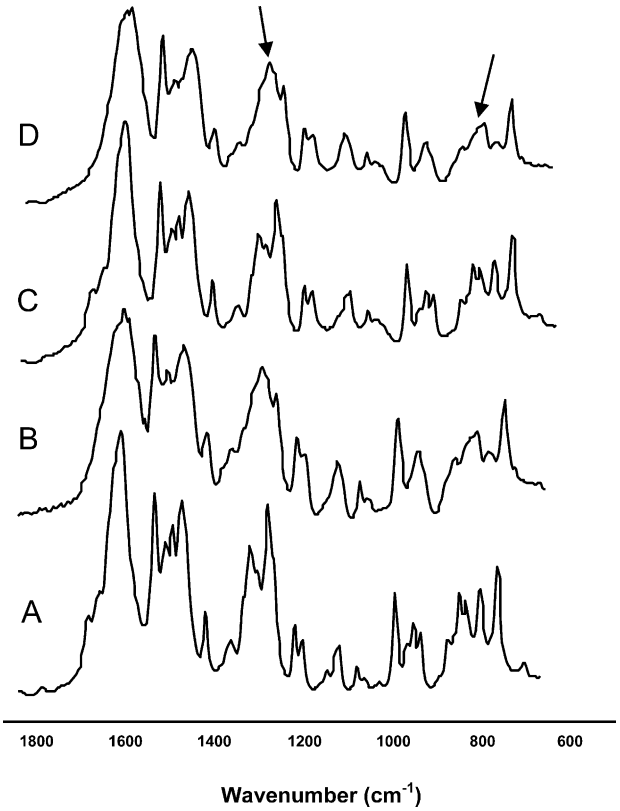

Fig. 2. DRIFTS spectra of fenoprofen calcium (A) drug alone, crystalline; (B) drug alone, supercooled liquid crystal; (C) tablet formulation, crystalline; (D) tablet formulation, supercooled liquid crystal. Arrows indicate the regions of major differences between the DRIFTS spectra of the crystalline and liquid crystalline drug.

Thus, although DRIFTS is a method that determines properties of molecules on a molecular level (Brittain, 1995), the definition of the DRIFTS spectra may, to some extent, reflect the degree of order in the sample.

Conversion of a crystalline substance into a liquid crystalline state, and possibly the type of the liquid crystal formed, can be determined by XRPD. Typical XRPD pattern of liquid crystals only show peaks in the small angle range of the diffractogram, indicating for instance the regular distances of the molecules in the layered order (i.e. the monolayer thickness) of a smectic thermotropic liquid crystal, or in the bilayer structure (i.e. the bilayer thickness) of a lyotropic lamellar mesophase. With the exception of higher ordered liquid crystals (Gray and Goodby, 1972), the wider angle range on the diffractogram only shows a halo, indicating the lack of order in the lateral distances of the molecules in the majority of liquid crystals. In an earlier study (Rades and Müller-Goymann, 1994), the type of thermotropic liquid crystal formed by fenoprofen calcium was identified by the characteristic peak pattern in the low angle region of the X-ray diffractogram of both a heated and a supercooled fenoprofen calcium mesophase. The relative ratios between the crystalline spacings (calculated from the peak positions of the diffractogram using the Bragg equation) were found to be $1:1/\sqrt{3}:1/\sqrt{4}:1/\sqrt{7}$, indicating that the fenoprofen calcium mesophase has a hexagonal order (Luzzati et al., 1960). Due to packing constraints and the absence of water in the thermotropic mesophase, the liquid crystal can only be of a reversed hexagonal nature, that is, the polar headgroups are pointing towards the inside of the rods. The hexagonal nature of the fenoprofen calcium mesophase was confirmed by freeze-fracture electron microscopy, from drug samples heated to 250 °C (Rades et al., 1996). In the current study, the crystalline spacings of the supercooled liquid crystalline form could be confirmed as characteristic for a (reversed) hexagonal packing (Table 1), which is unusual for thermotropic mesophases, but has been described for example for the calcium soap of stearic acid (Spegt and Skoulios, 1960).

The diffraction pattern was found to be similar in the angle range 3–16° 2θ for both, the liquid crystalline form of the drug alone and in the preheated tablet formulation, with the exception of a peak at 11.5° 2θ that can be attributed to an excipient peak in the tablet formulation (Fig. 3). This implies that the excipients don't interact with the drug in the liquid crystalline state, as this most likely would have led to a change in the rod diameter, and thus the diffraction pattern of the drug.

Interestingly, the diffraction pattern of the liquid crystal began to change following storage at 33 or 75% RH. The peak with the highest intensity at 5.2° 2θ began to broaden and to decrease in intensity upon storage whilst the higher order peaks at 8.7–9° 2θ, 10.1–10.2° 2θ and 13.5–

Table 1
Peak positions in X-ray diffractograms and calculated crystalline spacings (experimental and predicted values) for the fenoprofen calcium mesophase of the pure drug and the fenoprofen calcium mesophase in preheated and ground tablet formulations

Fenoprofen calcium mesophase (pure drug)			Fenoprofen calcium mesophase (preheated tablet formulation)		
Predicted d value for hexagonal order	d (nm)	$2^\circ\ \theta$	Predicted d value for hexagonal order	d (nm)	$2^\circ\ \theta$
	1.70	5.2		1.71	5.2
0.98	1.01	8.7	0.98	0.99	9.0
0.85	0.88	10.1	0.87	0.87	10.2
0.64	0.66	13.5	0.64	0.64	13.7

Conversion from peak positions ($2^\circ\ \theta$) to spacings (d) was calculated using to the Bragg equation: $n\lambda = 2d \sin\theta$; with $n = 1$ and λ (wavelength of the monochromatic X-ray radiation) = 0.154 nm. Prediction of spacings was performed according to the expected relative ratios for the spacings of a liquid crystal with hexagonal order ($1{:}1/\sqrt{3}{:}1/\sqrt{4}{:}1/\sqrt{7}$), according to Luzzati et al. (1960).

13.7° 2θ were no longer clearly detectable (Fig. 3, diffractogram (B). At the same time, no new peaks could be detected, for example at 6.4° 2θ, the position of a high intensity peak in the diffractogram of the crystalline dihydrate (Fig. 3, diffractogram (C)). These findings indicate that the liquid crystal takes up water prior to its conversion to the crystalline state. The water molecules are most

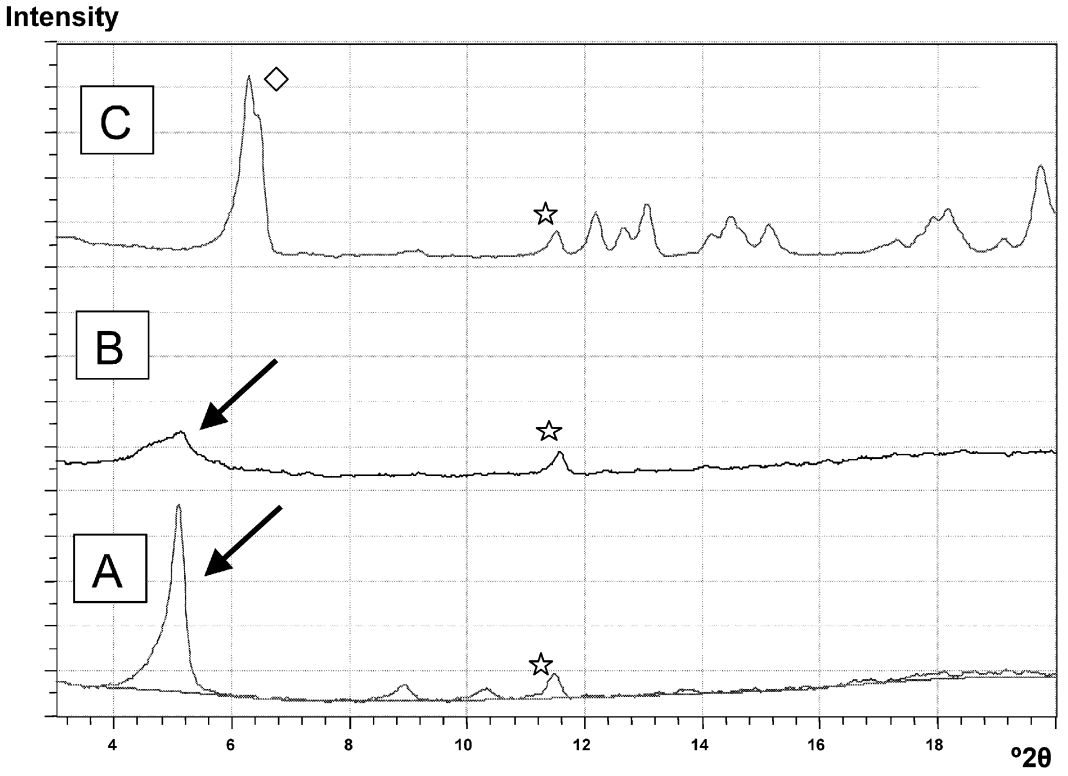

Fig. 3. XRPD diffractogram of (A) fenoprofen calcium tablets, heated to 125 °C for 45 min, and stored at room temperature under dry conditions; (B) fenoprofen calcium tablets, heated to 125 °C for 45 min and stored at 20 °C/33% RH for 7 weeks; (C) fenoprofen calcium tablets (no preheating). Arrows indicate the main peak of the hexagonal thermotropic liquid crystal; the diamond indicates the main peak of the crystalline dihydrate and the star indicates an excipient peak.

likely bound at or near to the polar head group of the fenoprofen molecule. This may lead to a less well defined reversed hexagonal order with some variability in the rod diameter or the distance of two neighbouring rods. According to Usselmann (1987) the distance (a) of two neighboring rods is related to the spacing (d) that corresponds to the first order peak position, by the equation: $a = (2/\sqrt{3})d$.

Variability in the intensity and area of the characteristic liquid crystal peaks was a major limitation in determination of the ratio of liquid crystalline fenoprofen calcium to the crystalline dihydrate. Therefore the magnitude of the characteristic peak of the crystalline dihydrate at 6.4° 2θ was used to estimate the ratio both as drug alone and in the tablet formulation (Section 2.3).

3.2. Chemical and physical stability

Fenoprofen calcium showed no sign of degradation after heating to 125 °C for up to 3 h in the solid state. HPLC analysis revealed no significant decrease in the fenoprofen peak or the appearance of any peaks attributable to its degradation products.

The stability of the liquid crystal under various storage conditions was monitored for 60 days. No conversion to the crystalline dihydrate was observed when liquid crystalline fenoprofen calcium alone and in the tablet formulation was stored over silica gel or 35% RH, at 20 and 40 °C. At 40 °C and 75% RH samples were still completely liquid crystalline after 4 days, although the peak corresponding to the liquid-crystalline order at 5.4° 2θ already was broadened and decreased in intensity. At the next time-point (6 days), the samples had converted almost completely to the dihydrate form (87% for the pure drug and 94% for the tablet formulation). After 8 days this value had increased to 92 and 96%, respectively. Recrystallisation therefore took place after a lag time, during which water-uptake occurred, which however, did not lead to a conversion form mesophase to dihydrate. Once conversion started, it lead to an almost complete transformation at 40 °C.

Liquid crystalline fenoprofen calcium alone and in the tablet stored at 20 °C and 75% RH showed approximately 6 and 24% conversion, respectively, after 60 days.

Although it has to be borne in mind that these results are only semi-quantitative, they nevertheless highlight the importance of both humidity and temperature on the conversion of the liquid crystal to the crystalline dihydrate form:

- At low humidity (dry or 35% RH) the liquid crystalline form of the drug is stable, irrespectively of the fact that the drug was present in pure form or in a tablet formulation.
- At high humidity, conversion is faster and occurs to a greater extend, if the temperature is increased (20 vs. 40 °C), again irrespectively of the fact that the drug was present in pure form or in a tablet formulation.
- At high humidity and low temperature, it appears that conversion of the liquid crystalline form occurred to a larger extent in the tablet formulation than in the pure drug (24 vs. 6%). This may be due to the excipients acting as heterogeneous nuclei for the transformation of the reversed hexagonal rods to the crystalline dihydrate form. The interaction therefore occurs on a particulate level.

These findings indicate that a high humidity is a necessary prerequisite for the conversion of the supercooled liquid crystal to the crystalline form. This is not surprising, as the crystalline form of fenoprofen is a dihydrate. It is however, interesting to notice that the supercooled liquid crystal cannot transform to a non-hydrate crystalline form of the drug.

3.3. Solubility and dissolution of samples

The solubility of the crystalline dihydrate form of fenoprofen calcium was 2.8 ± 0.2 mg/ml (mean ± s.d.) and 3.0 ± 0.2 mg/ml (mean ± s.d.) for the crystalline drug in tablets. This difference however, was not statistically significant ($P > 0.05$). The maximum solubility of the fenoprofen calcium mesophase was 5.0 ± 0.3 mg/ml (mean ± s.d.) and 6.9 ± 0.6 mg/ml (mean ± s.d.) for the pure mesophase and the drug in the preheated tablets, respectively. This difference was statistically sig-

nificant ($P < 0.05$). The reason for this discrepancy is most likely that the drug recrystallised from the supersaturated solution more easily, i.e. at a lower degree of supersaturation, in the absence of the excipients (see below).

The difference in maximum solubility between the crystalline dihydrate form of fenoprofen calcium and the fenoprofen calcium mesophase was highly significant, for both the pure drugs and the tablet formulations ($P < 0.01$). This strong increase in fenoprofen calcium solubility by conversion to a liquid crystalline form can be attributed to the raised free energy arising from the decreased molecular order in the liquid crystal.

The solubility of fenoprofen calcium alone in the liquid crystalline state returned to that of the dihydrate after approximately 30 min, indicating that a thermodynamically unstable enhanced apparent solubility had occurred (Fig. 4). The solubility of the drug in preheated tablet formulations however, remained higher than the solubility of the dihydrate for a longer period of time (Fig. 5). This result indicates that the tablet excipients might interact with the dissolved drug and to some extent prevent the recrystallisation of the drug. As this interaction takes place in solution, it most likely occurs on a molecular level. Further investigations should focus on the nature of the potential interaction between the drug in solution and the excipients.

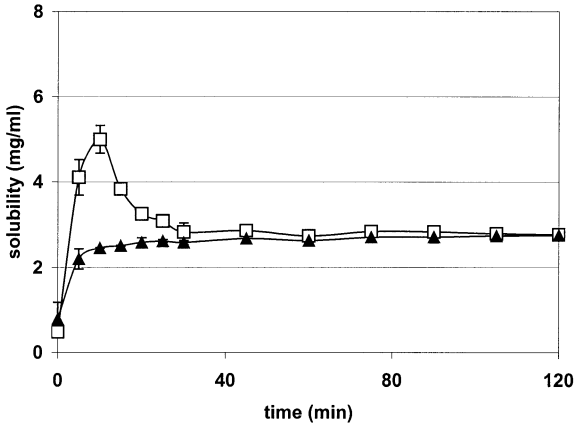

Fig. 4. Solubility vs. time profile for crystalline (▲) and supercooled liquid crystalline (□) fenoprofen calcium as the

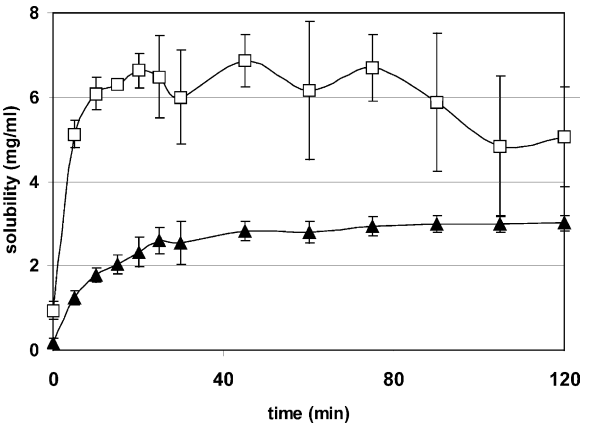

Fig. 5. Solubility vs. time profile for crystalline (▲) and supercooled liquid crystalline (□) fenoprofen calcium in the tablet formulation. Points represent mean ± s.d., $n = 3$.

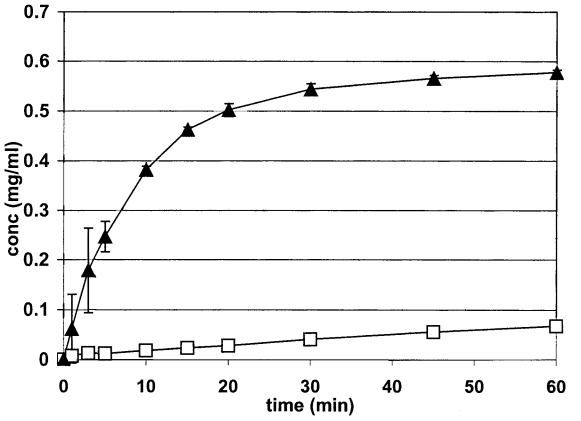

Fig. 6. Dissolution profile of crystalline (▲) and supercooled liquid crystalline (□) fenoprofen calcium in the tablet formula-

The increase in solubility of fenoprofen calcium by conversion to the liquid crystal however, did not correspond to an increase in the dissolution rate of the liquid crystalline drug from intact, preheated tablets. Heating of whole tablets to produce the liquid crystal lead to a considerable decrease in the dissolution rate (Fig. 6). Upon heating, the appearance of the tablets was considerably altered and SEM micrographs indicated that cavities had formed inside the tablet, possible attributable to evaporation of water from the crystalline dihydrate upon its conversion to the

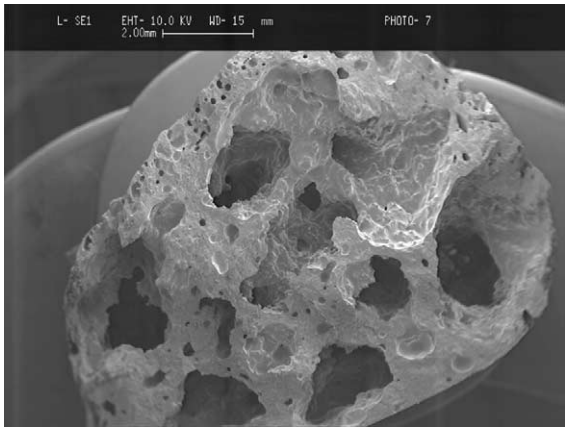

Fig. 7. SEM micrograph of a fenoprofen calcium tablet, preheated to 125 °C for 45 min.

mesophase (Fig. 7). It also appeared that the particles in the tablet formulation had fused together upon heating thus changing the disintegration behaviour of the preheated tablets compared with non-preheated tablets. Whilst non-preheated tablets completely disintegrated within 5 min after contact with the dissolution medium, preheated tablets remained intact for the duration of the dissolution study. The overall decrease the dissolution rate of the liquid crystalline form of fenoprofen calcium in tablets may therefore be due to reduced disintegration.

4. Conclusion

Whilst the behaviour of fenoprofen calcium dihydrate towards heat treatment is not different if the drug is present alone or together with excipients, some differences became apparent in the physical stability of the mesophase at high humidity. The reverse hexagonal thermotropic liquid crystal of fenoprofen calcium is only stable at 20 and 40 °C if humidity is low (dry or 33% RH). At high humidity the supercooled mesophase transformed more readily to the crystalline dihydrate in the presence of excipients. The solubility of the liquid crystalline drug in preheated tablet formulations remained higher for a longer period of time than from the pure supercooled mesophase. Nevertheless, in both cases conversion to the liquid crystalline form strongly improves the apparent solubility of fenoprofen calcium. This enhanced apparent solubility however, does not correlate with an increased dissolution rate of the drug in preheated, intact tablets. Conversion of the crystalline form of fenoprofen calcium to the liquid crystal should be performed before tablet formulation in order to increase dissolution of this poorly water-soluble drug.

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References

Brittain, H.G., 1995. Physical Characterisation of Pharmaceutical Solids. Marcel Dekker, New York.

Demus, D., Richter, L., 1978. Textures of Liquid Crystals. Verlag-Chemie, Weinheim, New York.

Demus, D., Zaschke, H., 1984. Flüssige Kristalle in Tabellen II. Verlag für Grundstoffindustrie, Leipzig.

Forster, A., Hempenstall, J., Rades, T., 2001. Characterisation of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers. J. Pharm. Pharmacol. 53, 303–315.

Gray, G.W., Goodby, J.W.G., 1972. Smectic Liquid Crystals—Textures and Structure. Leonard Hill, Glasgow.

Hamann, H.J., Müller-Goymann, C.C., 1987. Lyotroper Mesoprophismus von Arzneistoffen unter besonderer Berücksichtigung der Profene. Acta Pharm. Technol. 33, 67–73.

Kriwet, K., Müller-Goymann, C.C., 1994. Mutual interactions between diclofenac diethylamine and phospholipids-investigation on the microstructure of the arisen systems. Pharmazie 49, 187–191.

Luzzati, P.V., Mustacchi, H., Skoulios, A., Husson, F., 1960. La structure des colloides d'association. I. Les phases liquide-cristallines des systemes amphiphile-eau. Acta Cryst. 13, 660–667.

Mlodozeniec, A.R., 1978. Thermodynamics and physical properties of a lyotropic mesophase (liquid crystal) and micellar solution of an ionic amphiphile. J. Soc. Cosmet. Chem. 29, 659–683.

Physicians Desk Reference, 1998. Media Economics Company, Montvale, NJ, pp. 85 7–859.

Rades, T., Müller-Goymann, C.C., 1992. Structural investigations on the liquid crystalline phases of fenoprofen. Pharm. Pharmacol. Lett. 2, 131–134.

Rades, T., Müller-Goymann, C.C., 1994. Melting behaviour and thermotropic mesomorphism of fenoprofen salts. Eur. J. Pharm. Biopharm. 40, 277–282.

Rades, T., Padmadisastra, Y., Müller-Goymann, C.C., 1996. Thermal behaviour and solubility of fenoprofen calcium. Pharmazie 51, 846–851.

Spegt, P., Skoulios, A., 1960. Structure des phases mésomorphique du stéarate de calcium anhydre. CR Acad. Sci. 251, 2199.

Schülke U., 1987. Synthese und Untersuchung von flüssigkristallinen, semiflexiblen Hauptkettenpolymeren, Thesis, Technical University of Darmstadt, Germany.

Usselmann B., 1987. Beitrag zur Strukturaufklärung topischer Zubereitungen mit Fettalkoholpolyethylenglycolethern und Cholesterol als Tensiden. Ph.D. Thesis, Technical University of Braunschweig, Germany.

Vadas, E.B., Toma, P., Zografi, G., 1991. Solid state transitions initiated by water vapor sorption of crystalline L-660,711, a leukotriene D4 receptor agonist. Pharm. Res. 8, 148–155.

Ward, C.K., Schirmer, R.E., 1977. Fenoprofen Calcium. In: Flory, K. (Ed.), Analytical Profiles of Drug Substances, vol. 6. Academic Press, New York, pp. 161–182.