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Study of thermal behaviour of sugar esters

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Abstract

Sugar esters (SEs) are widely used in the pharmaceutical and food industries. They have a wide range of HLB values (1–16), and hence they can be applied as surfactants, or as solubility or penetration enhancers. SEs can be employed in hot-melt technology, because their melting points are low and they decompose only above 220 °C. The aims of this work were to study the thermal properties of SEs and to demonstrate differences between SEs with various HLB values. The results revealed that SEs with high or medium HLB values were vitrified by melting. Their glass transitions (T_g) were determined by modulated differential scanning calorimetry. To visualize the changes in the samples during heating, hot-stage microscopy was used. Hydrophilic SEs were only softened, while lipophilic SEs were melted by heating. After melting and solidification, SEs have partially amorphous layered structures which slowly crystallize in time. Time-dependent solid-state changes (crystalline and amorphous phases) were observed, and analysed by means of differential scanning calorimetry and X-ray powder diffraction.

Keywords: Glass transition; Hot-stage microscopy; Sugar esters; Thermal analysis; X-ray powder diffraction

1. Introduction

Sugar esters (SEs) have been known since 1960s, but they are relatively new materials in pharmaceutical technology. They are tasteless, odourless and non-toxic, and thus they are good emulsifiers for foodstuffs. They are also suitable for medications and cosmetics, because they are non-irritant to the eyes and skin.

SEs are non-ionic surface-active agents consisting of sucrose as hydrophilic group and fatty acids as lipophilic groups, i.e. sucrose fatty acid esters. Sucrose contains 8 hydroxy groups, and it is therefore possible to manufacture SEs with various HLB values by controlling the degree of esterification (Mitsubishi-Kagaku Foods Corporation, 1982; Molinier et al., 2005). Depending on their HLB values, they are available with a range of properties: O/W and W/O emulsifying properties, solubilizing and foaming properties (Husband et al., 1998; Garti et al., 2000), enhancement or inhibition of crystal growth in fat (Awad and Sato, 2002), antibacterial effects (Kato and Arima, 1971), and lubrication and releasing properties (Hahn and Sucker, 1989; Ntawukulilyayo et al., 1993; Otsuka et al., 1998; Marton et al., 2005).

The melting points of most sugars are high, so that preparations by the hot-melt method are problematic (Leuner and Dressman, 2000), but SEs have melting points of 40–79 °C and are very stable to heat, and hence they can be employed to prepare solid dispersions by the melt technology. In fact, it is very important to know the thermal behaviour of these materials, so that the changes in the base materials can be predicted during storage and technological processes such as the preparation of solid dispersions by melting.

The aims of this study were to evaluate the thermal properties of SEs, to observe and analyse the time-dependent solid-state changes (crystalline–amorphous phases) and to demonstrate the differences between SEs with various HLB values. SE samples were chosen by HLB classification system because the ratio of the hydrophilic and lipophilic groups influences their processibility by hot melt technology as well as the bioavailability of the drug material.

2. Materials and methods

2.1. Materials

Ryoto SEs (Mitsubishi-Kagaku Foods Corporation, Japan) are a family of vehicles consisting of sucrose and mixtures of

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Table 1
Data of SEs by Mitsubishi-Kagaku Foods Corporation

Name of SE	Fatty acid	HLB	mp (°C)	Decomposition temperature (°C)
P1670	Palmitate (C16)	16	48	235
S1670	Stearate (C18)	16	56	237
S970	Stearate (C18)	9	56	234
S370	Stearate (C18)	3	58 and 69	238
B370	Behenate (C22)	3	63 and 79	241

mono- to octaesters of fatty acids. According to Aulton (2002), excipients with high HLB (10–18) are hydrophilic (water soluble), with medium HLB (7–9) are water dispersible and with low HLB (0–6) are hydrophobic (oil soluble). SEs with high or moderate HLB can be used in preparation of fast release and SEs with low HLB in preparation of sustained release formulation. So, we selected SEs for study that have high (P1670 and S1670), medium (S970) and low HLB values (S370 and B370). The longer the fatty acid chains in the SEs and the higher the degree of esterification result in the lower the HLB value (Tables 1 and 2).

2.2. Sample preparation

Three types of samples were prepared for the physical evaluation of SEs:

- Untreated samples (U): samples without any special treatment (commercial).
- Freshly solidified samples (F): samples were melted in a porcelain dish in an oven (Factory for Laboratory Equipment, Budapest, Hungary, Labor type 123) from 25 to 100 °C, and then allowed to recrystallize at room temperature.
- Aged samples (A): the freshly solidified samples were stored for up to 1 month at room temperature (20 ± 2 °C) to detect any physical aging effect.
  - A1week: samples stored for 1 week.
  - A4week: samples stored for 4 weeks.

For the comparison of sample properties (e.g. by X-ray), it is important that the particle sizes should be similar. These were therefore determined by sieve analysis (Retsch vibrating apparatus, amplitude: 1, interval: 60 s, time: 5 min, three times). The average particle size of the untreated samples was 100–300 μm. After melting and solidification, the freshly solidified samples were pulverized in a mortar to achieve the same particle size as that of the untreated samples.

Table 2
Data on compositions of different SEs by Mitsubishi-Kagaku Foods Corporation

	P1670	S1670	S970	S370	B370
Monoester (%)	80	77	48	19	15
Diester (%)	17	20	34	33	24
Triester (%)	3	3	14	30	28
Tetraester (%)			4	15	22
Pentaester (%)				3	11

2.3. Derivatography

Fifty milligrams SE and 50 mg inert Al_2O_3 were placed into the platinum container of a Derivatograph-C apparatus (MOM, Hungary). The instrument was calibrated by using $CuSO_4 \cdot 5H_2O$. The TG, DTG and DTA curves were determined. The samples were heated from 25 to 100 °C at a heating rate of 5 °C min^{-1}.

2.4. Differential scanning calorimetry (DSC)

DSC studies were performed with a DSC 821^e (Mettler-Toledo GmbH, Switzerland). The instrument was calibrated by using indium. Samples of 10 mg were heated in a sealed aluminium pan. Measurements were made in an Ar atmosphere at a flow rate of 100 ml min^{-1}. The samples were heated from 25 to 100 °C at a heating rate of 1 °C min^{-1}. For analysis of the recrystallization process, samples were heated up to 100 °C as described above, then cooled down to 25 °C at a rate of 2 °C min^{-1}, and reheated to 100 °C at a heating rate of 1 °C min^{-1}.

The crystallinity index for freshly solidified sample (CI_F) and the aged sample (CI_A) was calculated from the heats of fusion:

$$CI_F\,(\%) = \frac{\Delta H_F}{\Delta H_U} \times 100$$

$$CI_A\,(\%) = \frac{\Delta H_A}{\Delta H_U} \times 100$$

where ΔH_F = normalized enthalpy (J g^{-1}) of freshly solidified sample, ΔH_U = normalized enthalpy (J g^{-1}) of untreated sample, and ΔH_A = normalized enthalpy (J g^{-1}) of aged sample.

Modulated-temperature DSC is a method that allows the relaxation endotherm and glass transition to be separated into non-reversing and reversing signals, respectively. Hence, it is possible to visualize T_g in isolation (Coleman and Craig, 1996; Craig and Royall, 1998; Yu, 2000). In modulated DSC the measurement conditions were as follows: start temperature: 25 °C, heating rate: 1 °C min^{-1}, amplitude: 1 °C, period: 60 s, and end temperature: 75 °C.

2.5. Hot-stage microscopy (HSM)

HSM observations of morphological features and changes during heating were carried out with a Leica MZ6 microscope (Wetzlar GmbH, Germany) equipped with a Leica 350 heating stage and a JVC TK-128OE (Japan) colour video camera. The different types of samples (untreated, freshly solidified and aged) were observed under the microscope by using a scanning speed of 1 °C min^{-1}. Data were imported into a computer and captured images were analysed by using the Leica Q500MC program.

2.6. X-ray powder diffraction (XRPD)

XRPD profiles were taken with a Philips X-ray diffractometer (PW 1930 generator, PW 1820 goniometer). The measurement conditions were as follows: Cu Kα radiation (λ = 0.15418 nm),

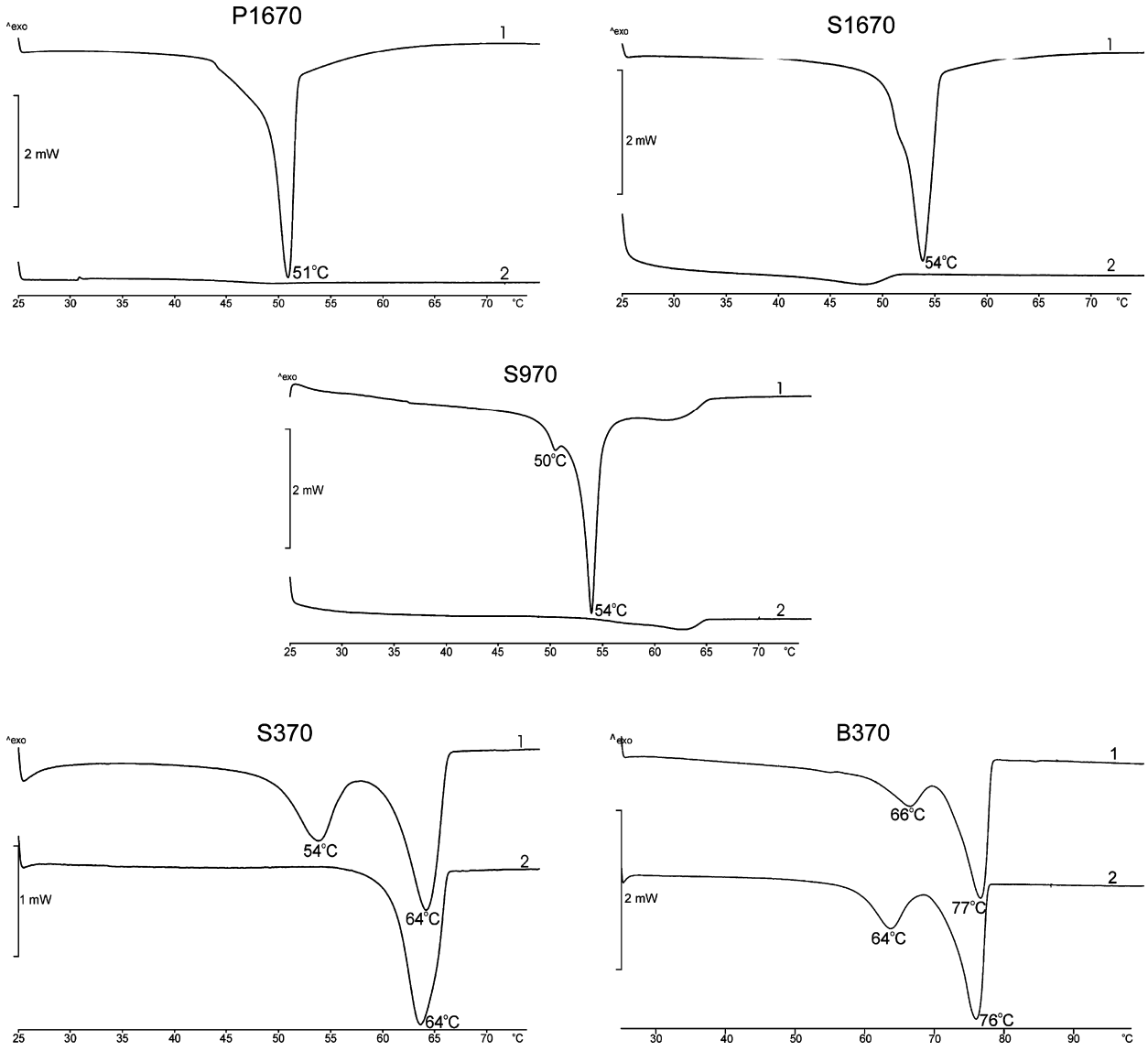

Fig. 1. DSC curves of untreated samples (U); curve 1: first heating; curve 2: second heating.

40 kV, 35 mA. The basal spacing (d_L) was calculated from the diffraction peaks by using the Bragg equation. The XRPD patterns were determined on untreated, freshly solidified and aged samples.

3. Results

The TG, DTG and DTA curves of untreated samples were determined by investigations with a derivatograph. The TG results showed that the mass loss of samples heated to 100 °C was less than 1%, i.e. the SEs did not include water adsorbed on their surface or any volatile component. In response to heating, endothermic changes were observed in the DTA curves of all the SEs, and more peaks were manifested by SEs with lower HLB values.

To determine the exact melting points, DSC studies were performed. The DSC scans (Fig. 1, curves 1) revealed that the melting points (mp) and melting ranges of P1670 and S1670 and their enthalpies were very similar, while the melting of SEs with lower HLB values was prolonged, with more peaks (Table 3). The probable cause of this was, that the studied SEs with high HLB values included only mono-, di- and triesters, while the SEs with lower HLB values contained tetra- and pentaesters too (Table 2).

The effects of a second heating were also studied. The melted SE in the DSC pan (after the first heating) was cooled to 25 °C

Table 3
Thermal parameters of SEs during first heating

SE	Melting range (°C)	mp (°C)	Total enthalpy (J g^{-1})
P1670	41–62	51	−66.6
S1670	45–62	54	−66.7
S970	36–65	50 and 54	−75.7
S370	45–66	54 and 64	−55.7
B370	51–79	66 and 77	−68.4

at a rate of 2 °C min^{-1}, and then heated again at a heating rate of 1 °C min^{-1} to 100 °C (second heating). The results are illustrated in Fig. 1 by curves 2. The DSC curve of second heating demonstrated that there were no more endothermic changes for P1670, and for S1670 and S970 the changes were negligibly small. Accordingly, the crystal structures of SEs with high (P1670 and S1670) or moderate (S970) HLB values, which can be characterized by melting points (Fig. 1, curves 1) broke down during the first heating and could not recrystallize during cooling. Thus, curves 2 in Fig. 1 (second heating) exhibit the characteristics of amorphous materials. S370 has two endothermic peaks, but during the second heating one peak disappeared and the melting range decreased. B370 seemed to be the most stable material: the melting ranges in the first and second heatings were the same and the shapes of the curves did not change; only the total enthalpy decreased slightly (<5 J g^{-1}) (Table 4).

Table 4
Thermal parameters of SEs during second heating

SE	Melting range (°C)	mp (°C)	Total enthalpy (J g^{-1})
P1670	–	–	–
S1670	–	–	–
S970	–	–	–
S370	54–66	64	−31
B370	52–79	64 and 76	−63.9

Consequently, there was probably a change in the structures of the SEs with high HLB values during heating. According to XRPD investigation, alpha form of the SEs with a hexagonal structure was characterized for all excipients which broke down and built up during the heating and cooling processes. SEs with low HLB values (S370 and B370) had faster recrystallization but the rearrangement of the stucture of SEs with high (P1670 and

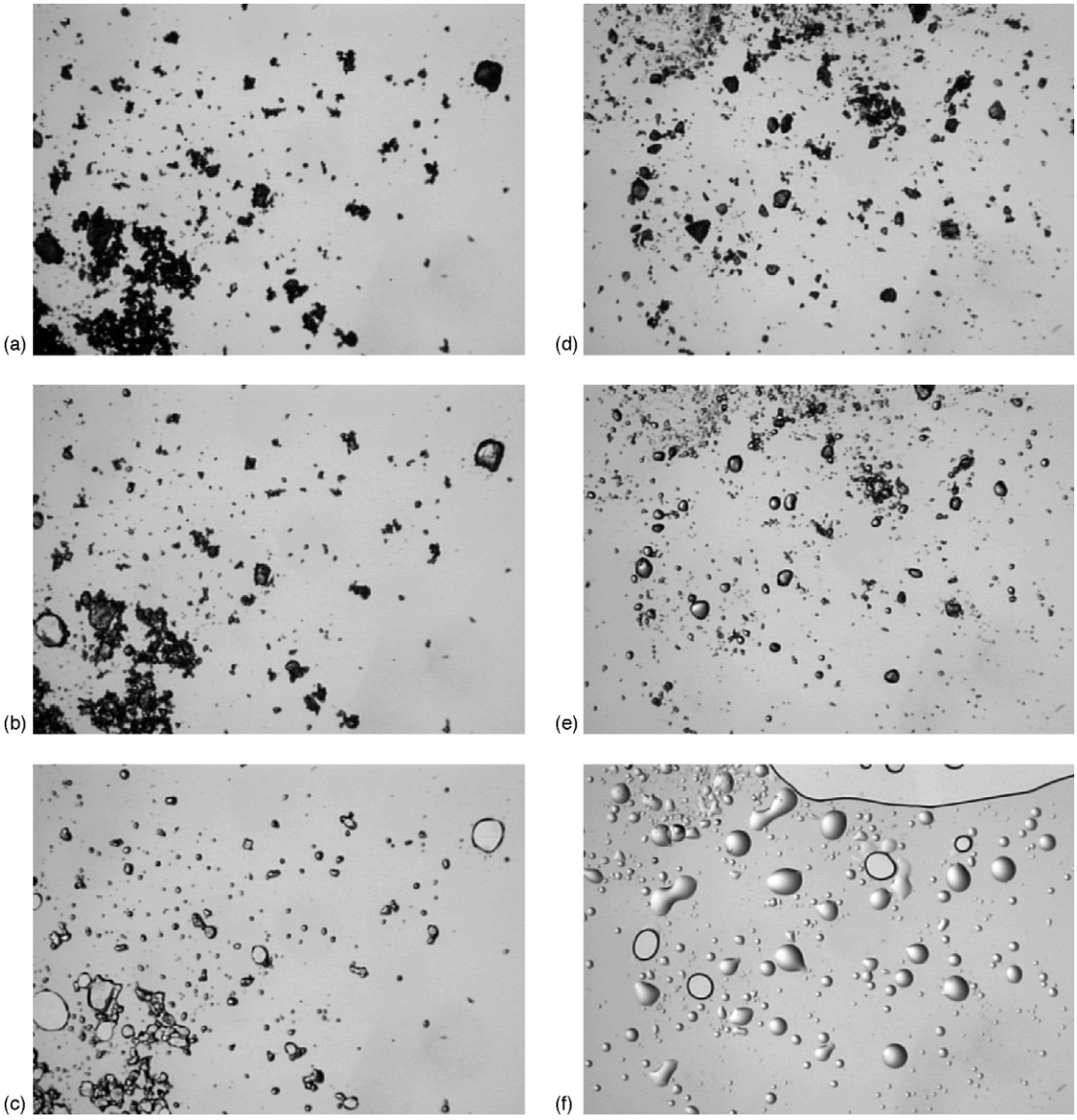

Fig. 2. HSM pictures of untreated S1670 at 25 °C (a), 65 °C (b) and 100 °C (c), and of untreated S370 at 25 °C (d), 70 °C (e) and 100 °C (f).

S1670) or moderate (S970) HLB values was very long. So, this led to an amorphous state. Amorphous materials can be characterized with the glass transition temperature (T_g) instead of the melting point. The determination of T_g by the conventional DSC method is difficult, because T_g is often concealed by or overlapped with other thermal events which take place in parallel. The results of our MTDSC measurements revealed that SEs with high (P1670 and S1670) or moderate (S970) HLB values undergo a glass transition, which coincides with the melting points of the materials (Table 5).

To visualize the changes in the samples during heating, HSM was used. This technique is complementary to DSC and may help in the interpretation of the DSC results. The photographs in Fig. 2 shows the morphology of SEs with high (S1670) or low (S370) HLB values before heating (at 25 °C) and after their melting (S1670: 65 °C, and S370: 70 °C). While SEs with high HLB values (e.g. S1670) only became soft, but did not flow, lipophilic SEs (e.g. S370) melted. SEs with high or medium HLB values did not melt during the first heating; their melting points detected in the DSC curves were truly their glass transitions (Table 5).

Table 5
Melting points and glass transitions during first and second heatings

	First heating		Second heating	
	mp (°C)	T_g (°C)	mp (°C)	T_g (°C)
P1670	51	–	–	50
S1670	54	–	–	51
S970	50 and 54	–	–	53
S370	54 and 64	–	64	–
B370	66 and 77	–	64 and 76	–

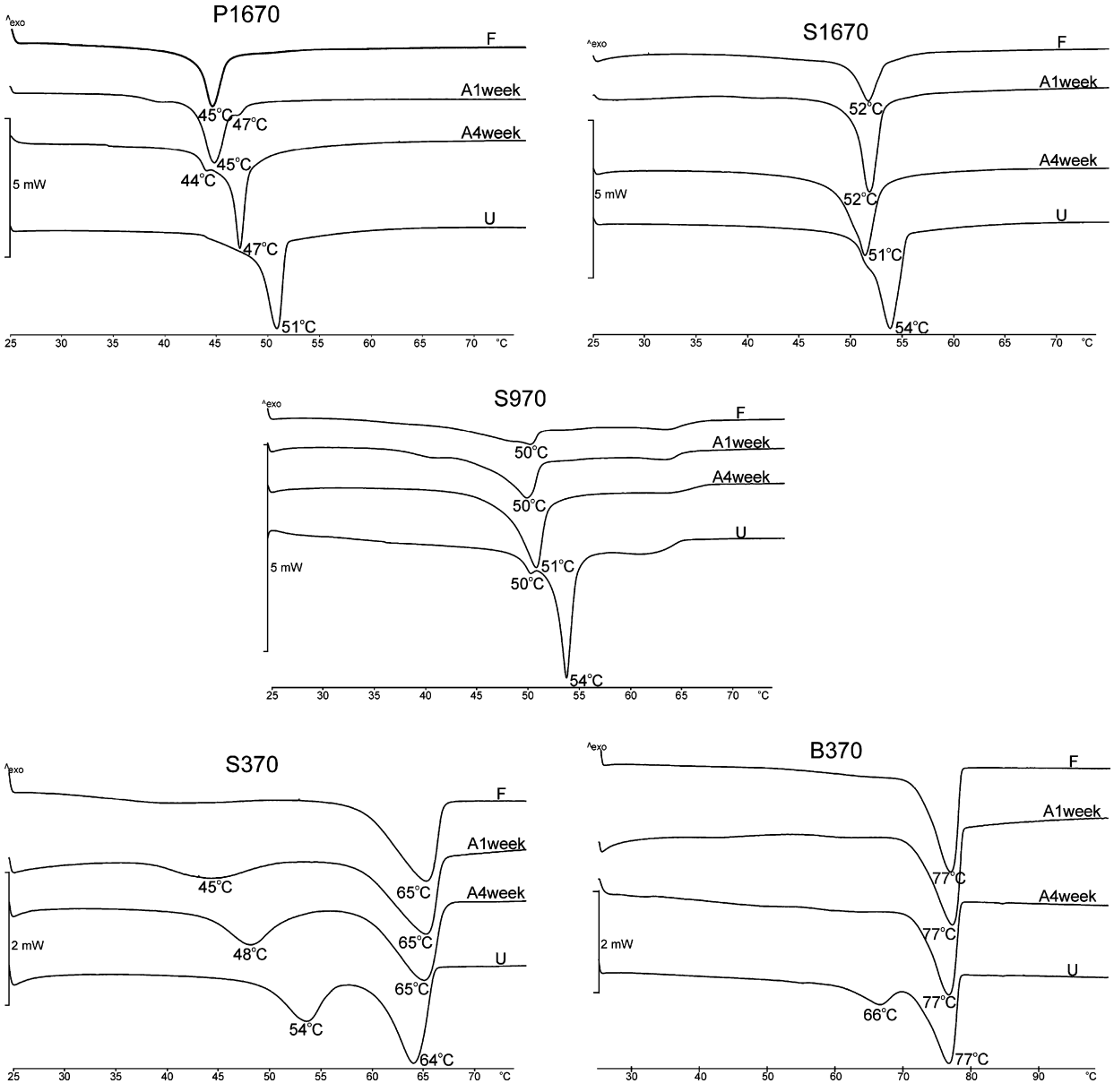

Fig. 3. DSC heating curves of SEs obtained from untreated (U), freshly solidified (F), and aged (A1week and A4week) samples.

During the preparation of the melts the SEs with high (P1670 and S1670) or moderate (S970) HLB values did not become fluid even at 100 °C, in contrast with the lipophilic (S370 and B370) SEs, as expected from the HSM study (Fig. 2c and f). If we wish to prepare a solid dispersion of a drug with a high melting point, this can be a problem if SEs with high HLB values are used, as their melts do not flow.

With respect to the processing, it is important to know whether the changes in structure of these materials are irreversible, or whether the original morphology of the samples is recovered in time. To study this, melts of SEs were prepared and their changes in time were examined in comparison with the initial state. The melting ranges of freshly solidified (F) and aged (A1week or A4week) samples were measured, their normalized enthalpies were compared with the enthalpy of the untreated sample (U), and the crystallinity index (CI) was calculated.

The melting behaviour of samples after melting and solidification differed from that of untreated samples, and it changed in time (Fig. 3 and Table 6). The freshly solidified (F) P1670 started to melt 2 °C earlier than the untreated (U) sample and its melting also finished earlier. In the DSC curve of the solidified sample, a small peak appeared after 1 week (A1week), which was not characteristic of the untreated sample (U). After 1 month (A4week), the sizes of the two peaks had changed: the melting point had drawn nearer to that for the untreated sample, but was lower; on the other hand, the enthalpy determined by the melting range was the same as that for the untreated sample. The melting points of the freshly solidified (F) and aged (A1week and A4week) S1670

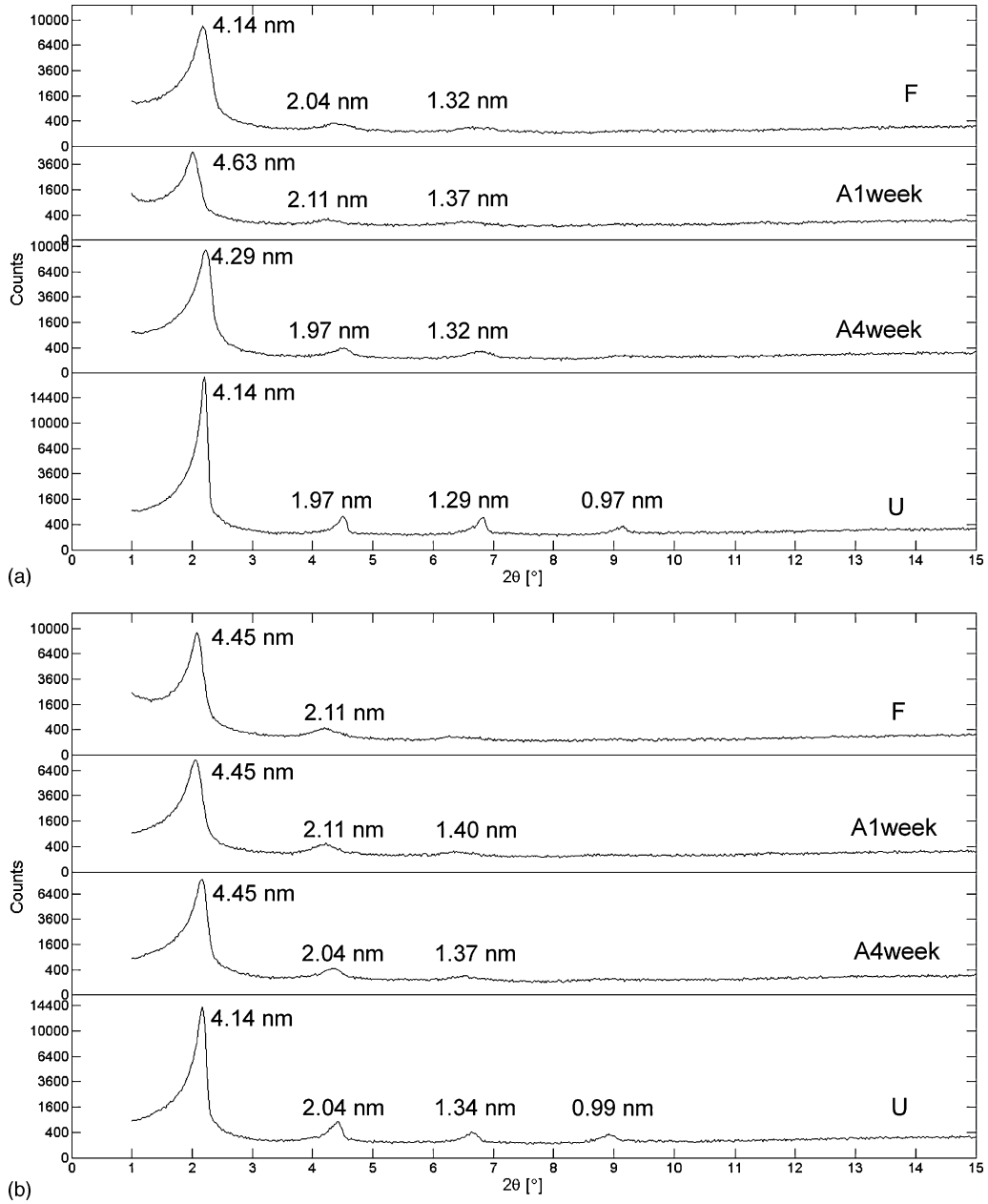

Fig. 4. X-ray patterns of SEs with high HLB values, obtained on untreated (U), freshly solidified (F) and aged (A1week and A4week) samples (a) P1670, (b) S1670.

Table 6
Effects of treatment and storage of SEs

		Melting range (°C)	Enthalpy (J g^{-1})	CI (%)
P1670	F	39–56	−37	55.6
	A1week	37–52	−42.3	63.5
	A4week	35–61	−66.6	100
	U	41–62	−66.6	100
S1670	F	39–60	−35.7	53.5
	A1week	38–61	−49.6	74.4
	A4week	38–62	−64.3	96.4
	U	45–62	−66.7	100
S970	F	33–68	−30	39.6
	A1week	35–68	−52.9	69.9
	A4week	34–68	−63.8	84.3
	U	36–65	−75.7	100
S370	F	59–67	−35.2	63.2
	A1week	38–69	−50.3	90.3
	A4week	39–69	−55.7	100
	U	45–66	−55.7	100
B370	F	55–78	−57.5	84.1
	A1week	56–79	−63.6	93
	A4week	55–78	−66.4	97.1
	U	51–79	−68.4	100

were decreased by 2 °C as compared with that of the untreated sample, but the shape of the curve did not change considerably: it was characterized by one sharp peak. S970 crystallized very slowly after melting and solidification; in contrast with the other SEs, its CI was not 100% restored after 1 month (Table 6). The melted S370 had only one endothermic peak after solidification (F), but after 1 week (A1week) the other peak characteristic of the untreated sample appeared. The melting started 7 °C earlier, and thus the melting range was increased as compared with that for the untreated sample. For B370, one of the two peaks likewise disappeared after melting and solidification (F), and did not appear even after 1 week (A1week) or 1 month (A4week) later. However, the normalized enthalpy nearly reached the enthalpy of the untreated sample (Table 6). It is probable that, similarly to other fatty acid derivatives, SEs transform from one polymorph to another during storage (Hagemann, 1988; Siekmann and Westesen, 1994; Sutananta et al., 1994; Hamdani et al., 2003; Schubert et al., 2005).

After storage for 1 month (A4week), the heats of fusion of aged samples drew near to the enthalpy of the untreated sample, which means that the structures of all the SEs are apparently restored in time. This is in accordance with the finding of Laine et al. (1988), that solidified triglycerides have partially amorphous layered structures, which gradually crystallize during storage. DSC measurements indicated that, even if the total enthalpies of aged samples reached the enthalpy of the untreated sample, the shape of the DSC curves was different from that of the curve of the initial material, i.e. the original structure was not recovered.

Hence, even if the molecular dispersion of a drug in SEs is successful, it is not sure that this advantageous state can be maintained, because the structure of the SE is continuously changing.

To confirm the DSC results, X-ray analysis was performed on untreated (U), freshly solidified (F) and aged (A1week and A4week) samples. The DSC curves of P1670 and S1670 were similar (Fig. 1, curve 1), and the same can be said about their X-ray diffraction patterns (Fig. 4a and b, U). Both SEs have ordered structures: four distinct peaks (P1670: $2\theta = 2.2°$, 4.5°, 6.8° and 9.2°; S1670: $2\theta = 2.2°$, 4.4°, 6.6° and 8.9°) and nearly the same basal spacing (these are given in Figs. 4–6, in nm), characteristic of stearic acid. S970 has a more complex structure: it contains more di- and triester, and also a little tetraester. Moreover, S370 and B370 include pentaester too (Table 2). In consequence of the presence of these components, the characteristic diffrac-

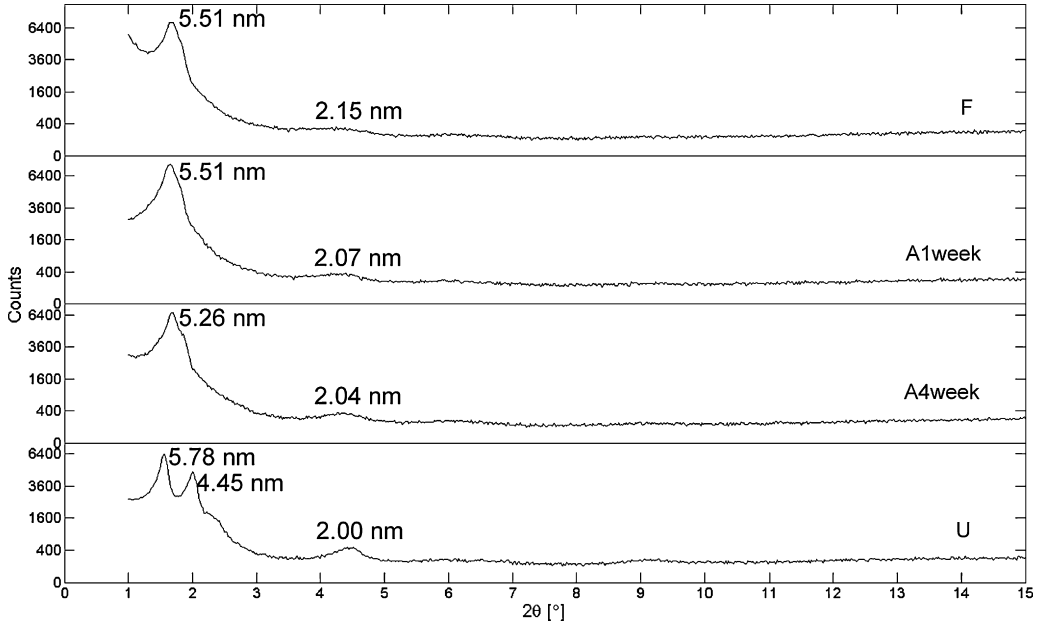

Fig. 5. X-ray patterns of S970, obtained on untreated (U), freshly solidified (F) and aged (A1week and A4week) samples.

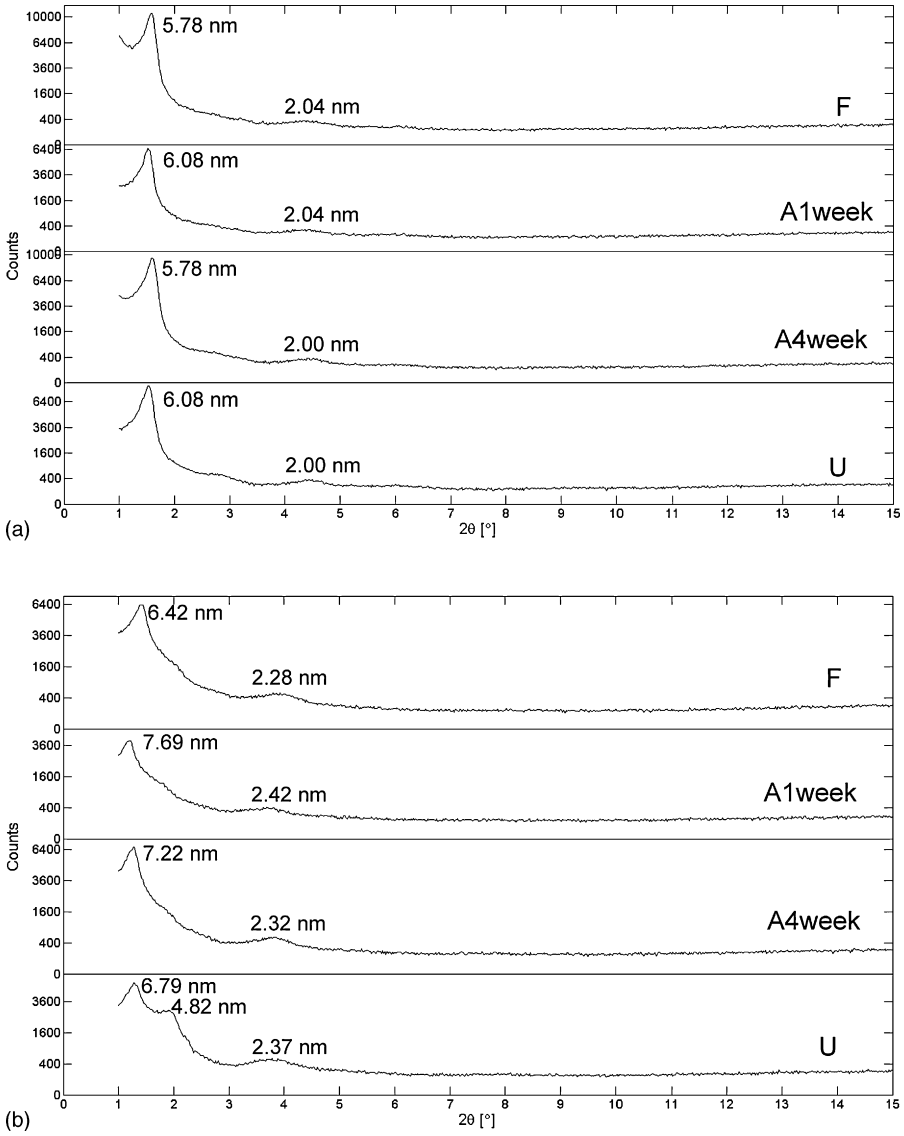

Fig. 6. X-ray patterns of SEs with low HLB values, obtained on untreated (U), freshly solidified (F) and aged (A1week and A4week) samples; (a) S370, (b) B370.

tion peaks disappeared from the X-ray diffractograms and the interlayer spacings increased. The untreated S970 (Fig. 5, U) had three ($2\theta = 1.6°$, 2° and 4.4°), S370 (Fig. 6a, U) had two ($2\theta = 1.5°$ and 4.5°), and B370 (Fig. 6b, U) had three ($2\theta = 1.3°$, 1.9° and 3.9°) characteristic peaks. After melting and solidification, the structures of all the SEs were changed, the basal spacings and counts were modified and in almost all cases one of the characteristic peaks had disappeared, which was probably induced by the polymorphism of the fatty acids. In the diffractograms of melted P1670 and S1670, only three peaks were observed in comparison with the untreated sample, where four peaks were found. The P1670 peak at 9.2°, and the S1670 peak at 8.9° disappeared (Fig. 4a and b). The peak intensities decreased (practically only the first signal could be seen) and the basal spacings increased. Of the three peaks of untreated S970, after melting and solidification the second signal ($2\theta = 2°$) had disappeared and was not recovered even 1 month later (Fig. 5). The X-ray pattern of S370 (Fig. 6a) did not exhibit such a large change in counts as for SEs with high HLB values, but the basal spacings were modified in this case too. The change in degree of crystallinity for B370 was smaller, and the count fluctuation was slight, but the second signal ($2\theta = 1.9°$) disappeared and the morphology of the untreated sample was not restored (Fig. 6b). These X-ray observations are in accordance with the DSC results, since the shapes of the DSC curves changed continuously, the melting range varied after treatment and the original shape of the curve (characteristic of the untreated sample) was not regained even after storage for 1 month.

4. Discussion

The aims of this work were to study the thermal properties of SEs and to evaluate their applicability in hot-melt technology. SEs with various HLB values can be used to influence (increase or decrease) the rate of dissolution of drugs, and hence to change the development of the effect. Due to their low melting points,

they are promising carriers for the melting method. For this reason, we searched for a relation between their thermal behaviour and HLB values.

The results of DSC and HSM revealed that SEs with high (P1670 and S1670) or moderate (S970) HLB values have a glass transition temperature (T_g) instead of a melting point. They soften during heating, whereas SEs with low HLB values (S370 and B370) melt and then quickly recrystallize from their melts. However, the original structure does not return either for SEs with high or moderate, or for SEs with low HLB values: after melting and solidification, their melts continuously change. The DSC scans and X-ray patterns of samples stored for up to 1 month do not display the same picture as that for the untreated samples. There are other excipients which are used in hot melt technology and change during aging. Shimpi et al. (2004) and Sutananta et al. (1995) studied the effect of preparation condition and storage on the rate of drug release from the hydrophobic Gelucire and they reported an increase in drug release caused by phase transformation. Saers et al. (2002) examined the effect of storage on drug dissolution from solid dispersions with PEG 3000 or xylitol and observed that the dissolution rate of drug was unchanged during storage. These results demonstrate that changes in morphology must be considered during research and development. This is especiall important as concerns molecular dispersed materials (amorphous state) in SEs. In consequence of the changes in structure, a drug can partially or completely assume a crystalline form, which can entail a lower dissolution rate or the appearance of an undesirable polymorph form.

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References

Aulton, M.E., 2002. Pharmaceutics, The Science of Dosage form Design, 2nd ed. Churchill Livingstone, Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, Toronto, p. 96.

Awad, T., Sato, K., 2002. Acceleration of crystallisation of palm kernel oil in oil-in-water emulsion by hydrophobic emulsifier additives. Colloids Surf. B 25, 45–53.

Coleman, N.J., Craig, D.Q.M., 1996. Modulated temperature differential scanning calorimetry: a novel approach to pharmaceutical thermal analysis. Int. J. Pharm. 135, 13–29.

Craig, D.Q.M., Royall, P.G., 1998. The use of modulated temperature DSC for the study of pharmaceutical systems: potential uses and limitations. Pharm. Res. 15, 1152–1153.

Garti, N., Aserin, A., Faunn, M., 2000. Non-ionic sucrose esters microemulsions for food applications. Part 1. Water solubilization. Colloids Surf. A 164, 27–38.

Hagemann, J.W., 1988. Thermal behaviour and polymorphism of acylglycerides. In: Garti, N., Sato, K. (Eds.), Crystallization and Polymorphism of Fats and Fatty Acids. Marcel Dekker, New York, USA, pp. 29–67.

Hahn, L., Sucker, H., 1989. Solid surfactant solutions of active ingredients in sugar esters. Pharm. Res. 6, 958–960.

Hamdani, J., Moës, A.J., Amighi, K., 2003. Physical and thermal characterisation of Precirol® and Compritol® as lipophilic glycerides used for the preparation of controlled-release matrix pellets. Int. J. Pharm. 260, 47–57.

Husband, F.A., Sarney, D.B., Barnard, M.J., Wilde, P.J., 1998. Comparison of foaming and interfacial properties of pure sucrose monolaurate, dilaurate and commercial preparations. Food Hydrocolloids 12, 237–244.

Kato, A., Arima, K., 1971. Inhibitory effect of sucrose ester of lauric acid on the growth of Escherichia coli. Biochem. Biophys. Res. Commun. 42, 596–601.

Laine, E., Auramo, P., Kahela, P., 1988. On the structural behaviour of triglycerides with time. Int. J. Pharm. 43, 241–247.

Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.

Marton, S., Anner, A., Csoka, G., 2005. Increased solubility applying solid-in-solid solutions. Eur. J. Pharm. Sci. 25S1, S155–S157.

Mitsubishi-Kagaku Foods Corporation, 1982. Ryoto Sugar Ester Technical Information. Nonionic surfactant/Sucrose fatty acid ester/Food additive.

Molinier, V., Fenet, B., Fitremann, J., Bouchu, A., Qeneau, Y., 2005. PFGSE-NMR study of the self-diffusion of sucrose fatty acid monoesters in water. J. Colloid Interf. Sci. 286, 360–368.

Ntawukulilyayo, J.D., Bouckaert, S., Remon, J.P., 1993. Enhancement of dissolution rate of nifedipine using sucrose ester coprecipitates. Int. J. Pharm. 93, 209–214.

Otsuka, M., Ofusa, T., Matsuda, Y., 1998. Dissolution improvement of water-insoluble glybuzole by co-grinding and co-melting with surfactants and their physicochemical properties. Colloids Surf. B 10, 217–226.

Saers, S.E., Nyström, C., Aldén, M., 2002. Physicochemical aspects of drug release. XVI. The effect of storage on drug dissolution from solid dispersions and the influence of cooling rate and incorporation of surfactant. Int. J. Pharm. 90, 105–118.

Schubert, M.A., Schicke, B.C., Müller-Goymann, C.C., 2005. Thermal analysis of the crystallisation and melting behaviour of lipid matrices and lipid nanoparticles containing high amounts of lecithin. Int. J. Pharm. 298, 242–254.

Shimpi, S., Chauhan, B., Mahadik, K.R., Paradkar, A., 2004. Preparation and evaluation of diltiazem hydrochloride-Gelucire 43/01 floating granules prepared by melt granulation. AAPS PharmSciTech. 5, 43, http://www.pharmscitech.com/journal.

Siekmann, B., Westesen, K., 1994. Thermoanalysis of the recrystallization process of melt-homogenized glyceride nanoparticles. Colloids Surf. B 3, 159–175.

Sutananta, W., Craig, D.Q.M., Newton, J.M., 1994. The effects of ageing on the thermal behaviour and mechanical properties of pharmaceutical glycerides. Int. J. Pharm. 111, 51–62.

Sutananta, W., Craig, D.Q.M., Newton, J.M., 1995. An investigation into the effect of preparation condition and storage on the rate of drug release from pharmaceutical glycerides bases. J. Pharm. Pharmacol. 47, 355–359.

Yu, L., 2000. Amorphous pharmaceutical solids: preparation, characterization and stabilization. Adv. Drug Deliv. Rev. 48, 27–42.