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Thermochimica Acta 256 (1995) 151–165

thermochimica acta

Phase equilibria in drug–polymer–surfactant systems ☆

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Abstract

Solid dispersions of griseofulvin were prepared by the melting method with polyethylene glycols (PEGs) of molecular weights 3000, 6000 and 20 000 as carriers, with or without the incorporation of the anionic surfactant sodium dodecyl sulphate (SDS). The state diagrams for griseofulvin and different PEGs with SDS added and the state diagram with PEG 6000 and griseofulvin alone were obtained using X-ray powder diffraction and differential scanning calorimetry. Solid solutions of griseofulvin in both pure polyethylene glycol and polyethylene glycol with SDS incorporated were formed. The pure polymers dissolved less than 3% w/w griseofulvin. When SDS was incorporated in the polyethylene glycols, the solid solubility of griseofulvin increased to 40% w/w in PEG 6000 and to 25% w/w in PEG 3000 and PEG 20 000. The solid solutions of griseofulvin in PEG with SDS incorporated melted close to the melting temperature of the pure PEG phases. Their heat of fusion values differed significantly from those of the solid dispersions.

The effect of different alkali dodecyl sulphates, LiDS, SDS and KDS, forming solid solutions with PEG 3000 and griseofulvin was analysed using oscillating differential scanning calorimetry in the temperature interval −60°C to 80°C. The thermal behaviour of the LiDS-containing solid solution was different from those of SDS- and KDS-containing compounds, with respect to both the C_p (reversible) component and the kinetic (irreversible) component. The enthalpy changes exposed by the ΔH_{C_p} and ΔH_K components were extremely sample-dependent, whereas the conventional ΔH values were constant.

Keywords: Dodecyl sulphate; DSC; Griseofulvin; ODSC; PEG; Phase equilibrium; Solid solution; Ternary system

☆ Presented at the 14th Symposium of Thermal Analysis and Calorimetry, Oslo, Norway, 15–17 June 1994.

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SSDI 0040-6031(94)02172-4

1. Introduction

For hydrophobic drugs, dissolution often becomes the rate-limiting step for absorption and thereby bioavailability. Dispersing a hydrophobic drug in a readily soluble carrier may be one way to increase the dissolution rate. If the drug is dispersed molecularly, i.e. a solid solution is formed, the rate-limiting step in the dissolution process is the dissolution of the carrier. This is also true for solid particulate dispersions up to a certain concentration, above which a decrease in the dissolution generally is seen [1]. The dissolution of dispersions with a higher content of hydrophobic drug can be improved by increasing the solubility of the drug in the carrier. This increase in solubility may be achieved by the use of additives. Knowledge of the phases and structures that emerge when a drug in combination with some additives is dispersed in the carrier are of definite interest for the prediction of the physical and chemical properties of the system. It has been shown [2] that the incorporation of the anionic surfactant sodium dodecyl sulphate can transfer solid particulate dispersions of griseofulvin in PEG 3000 into solid solutions. In dispersions with SDS incorporated in the polymer, the drug molecule is dissolved in the polymer structure via the surfactant molecules to form a solid solution. This is also valid for alkali dodecyl sulphates with counterions other than sodium [3,4].

The aim of the present study was to examine the phase composition and thermal behaviour of dispersions obtained in systems where the hydrophobic drug griseofulvin is dispersed in polyethylene glycol of various molecular weights, with and without incorporation of sodium dodecyl sulphate, and to investigate the reversible and irreversible character of thermal transformations when different alkali dodecyl sulphates are added to a dispersion.

2. Experimental

2.1. Materials

(a) Griseofulvin (GRIS) microsized (Sigma, USA), a hydrophobic drug with the formula $C_{17}H_{17}ClO_6$; purity approx. 97%.

(b) Polyethylene glycols (PEGs) with the formula $HO(C_2H_4\text{-}O)_nH$: PEG 3000 (Sigma, USA) where $n = 70$, average M_w 3350; PEG 6000 (Janssen, Belgium) where $n = 140$, average M_w 5600–7000; PEG 20 000 (Janssen, Belgium) where $n = 450$, $M_r > 17\,000$.

(c) Sodium dodecyl sulphate (SDS) (Sigma, USA), an anionic surfactant with the formula $C_{12}H_{25}SO_4Na$; purity approx. 99%.

(d) Lithium dodecyl sulphate (LiDS) (Sigma, USA), an anionic surfactant with the formula $C_{12}H_{25}SO_4Li$; purity approx. 99%.

(e) Potassium dodecyl sulphate (KDS) (Sigma, USA), an anionic surfactant with the formula $C_{12}H_{25}SO_4K$; purity minimum 95%.

2.2. Methods

2.2.1. Preparation of solid dispersions

Various solid dispersions of griseofulvin in the three carriers with and without the addition of 2% w/w SDS were prepared by the melting method in a Carbolite furnace HRF 7/22 with a Eurotherm 818P Programmer at a temperature of 170°C for PEG 3000 and 190°C for PEG 6000 and 20 000. The samples were brought to room temperature by fast cooling (50–100°C s^{-1}) and after at least 24 h the dispersions were pulverized and sieved to obtain the 300–500 μm fraction.

2.2.2. X-ray diffraction

Phase analysis was made by X-ray powder diffraction using a STOE position-sensitive detector (PSD) system (Germany) with Ge monochromatized Cu $K\alpha_1$ radiation. A linear detector covering 7° at 155 mm distance was operated in a scanning mode. The detection limit for the X-ray diffraction equipment is $\geq 2\%$ w/w for griseofulvin in the investigated systems. All phases present could be identified by means of characteristic non-overlapping peaks.

2.2.3. Differential scanning calorimetry

Various PEG dispersions and solid solutions (3.5–5.0 mg) were analysed using a Mettler DSC 20 differential scanning calorimeter (Switzerland). A heating rate of 10°C min^{-1} was selected in the temperature range 25–240°C in an atmosphere of nitrogen with the samples kept in aluminium pans. The calorimeter was calibrated with an indium standard. The results are presented as mean values with the standard deviations based on at least three determinations.

2.2.4. Oscillating differential scanning calorimetry

Some PEG 3000 dispersions were also analysed using an oscillating Seiko DSC 220 differential scanning calorimeter SSC/5200H (Japan). The samples (4–8 mg) were kept in aluminium pans in an atmosphere of nitrogen. An amplitude of 4°C and a frequency of 0.02 Hz were selected in the oscillating mode together with a heating rate of 5°C min^{-1} in the temperature range −80–255°C. The calorimeter was calibrated with indium, tin and lead as standards. The results are presented as mean values with the standard deviations based on three determinations.

3. Results and discussion

3.1. Phase equilibria in griseofulvin–polyethylene glycol dispersions with and without the incorporation of sodium dodecyl sulphate

3.1.2. Solid state solubility

Four representative X-ray powder diffractograms are presented in Fig. 1(a)–(d) showing the effect of the addition of sodium dodecyl sulphate. Diffractograms 1(a) and (b) show the pattern of pure PEG 6000 and pure griseofulvin, prepared in the

same way as the dispersions. Fig. 1(c) shows the diffractogram of the dispersion of 20% w/w griseofulvin in PEG 6000, where the major characteristic peaks of griseofulvin are clearly seen. In the corresponding sample with 2% w/w SDS incorporated in the polymer phase (Fig. 1(d)), none of these diffraction peaks are present. The diffractogram is essentially identical with that of pure PEG 6000. A summary of the phase analysis is presented in Table 1. In the PEG dispersions with 3% w/w griseofulvin or more, both PEG and griseofulvin are present as pure phases. This is valid for all three polymers. With an addition of 2% w/w SDS, the solubility of griseofulvin increases in all three PEGs, but the solid solutions formed have a varying solubility limit of the drug in the carrier depending on the PEG molecular weight. In PEG 3000, PEG 6000 and PEG 20 000 with SDS added, the amount of griseofulvin dissolved is 25%, 40% and 25% w/w respectively.

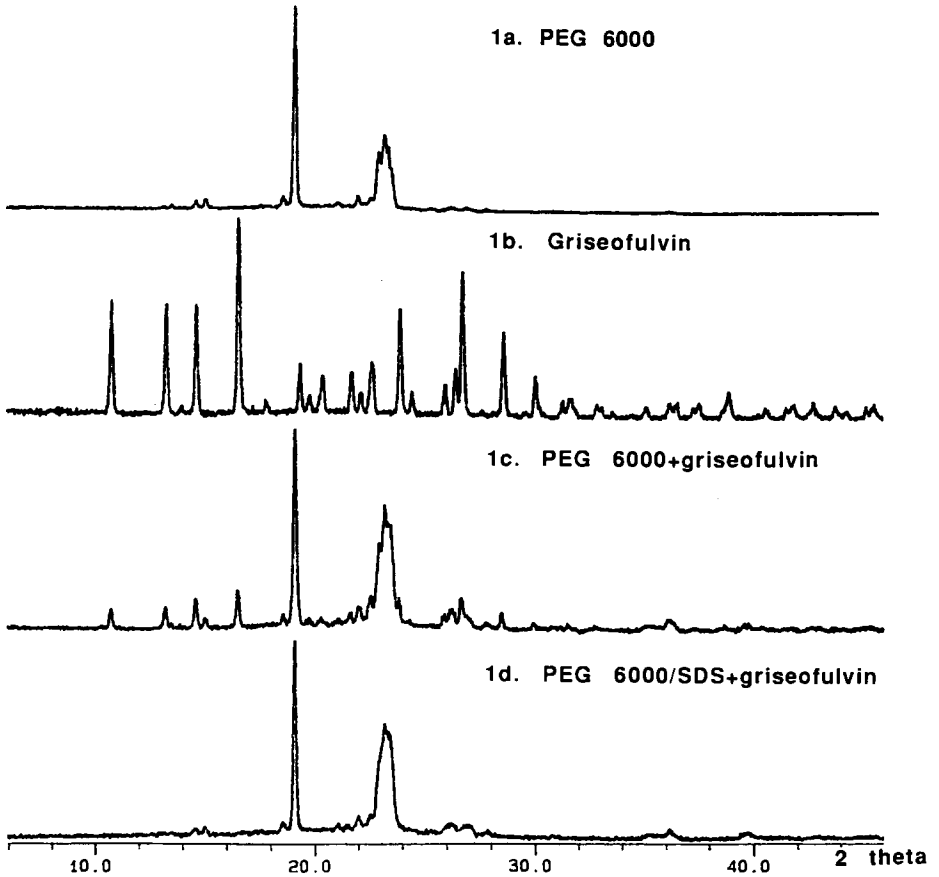

Fig. 1. X-ray powder diffractograms of (a) polyethylene glycol (PEG) 6000, (b) griseofulvin (GRIS), (c) solid dispersion of 20% w/w griseofulvin in PEG 6000, (d) solid solution of 20% w/w griseofulvin in PEG 6000 with 2% w/w sodium dodecyl sulphate (SDS) incorporated.

Table 1
X-ray powder diffraction phase analysis of dispersions and solid solutions in the griseofulvin–polyethylene glycol (PEG)–alkali dodecyl sulphate (MDS) systems

Sample	Phases observed
PEG* + 2% griseofulvin	$(PEG^*)_{1+w}$ griseofulvin$_w$
PEG* + 3% griseofulvin	$(PEG^*)_{1-w}$ griseofulvin$_w$ + PEG* + griseofulvin
PEG 3000/SDS + 25% griseofulvin	$(PEG\ 3000/SDS)_{1-x}$ griseofulvin$_x$
PEG 3000/SDS + 30% griseofulvin	$(PEG\ 3000/SDS)_{1-x}$ griseofulvin$_x$ + PEG 3000/SDS + griseofulvin
PEG 6000/SDS + 40% griseofulvin	$(PEG\ 6000/SDS)_{1-y}$ griseofulvin$_y$
PEG 6000/SDS + 45% griseofulvin	$(PEG\ 6000/SDS)_{1-y}$ griseofulvin$_y$ + PEG 6000/SDS + griseofulvin
PEG 20 000/SDS + 25% griseofulvin	$(PEG\ 20\,000/SDS)_{1-z}$ griseofulvin$_z$
PEG 20 000/SDS + 30% griseofulvin	$(PEG\ 20\,000/SDS)_{1-z}$ griseofulvin$_z$ + PEG 20 000/SDS + griseofulvin
PEG 3000/MDS + 10% griseofulvin	$(PEG\ 3000/MDS)_{1-x}$ griseofulvin$_x$ [4]

Key: PEG* represents PEG 3000, PEG 6000 or PEG 20 000, $(PEG^*)_{1-w}$ griseofulvin$_w$ is the solid solution of griseofulvin in PEG*, (PEG/SDS) represents pure PEG and pure SDS or a solid solution of the surfactant in PEG combined with the pure phases [3], $(PEG/SDS)_{1-m}$ griseofulvin$_m$ (where $m = x, y, z$) is the solid solution of griseofulvin in PEG with SDS incorporated, $(PEG/MDS)_{1-x}$ griseofulvin$_x$ is the solid solution of griseofulvin in PEG with MDS incorporated.

In the samples with just polymer and SDS, the diffraction patterns were essentially identical with those of the pure PEG phases [3]. This suggests that SDS is periodically distributed in a molecular form in the polymer structure in all three PEGs, forming a solid solution [5]. Also lithium and potassium dodecyl sulphate create solid solutions when 2% w/w is added to PEG 3000 [4].

3.1.3. Melting

The thermograms of the pure PEGs, the dispersions and the solid solutions show a characteristic endothermic peak close to the melting range of the polymer phase. For the dispersions, a small divergence from the baseline is seen in the interval 115–220°C. This peak represents a value on the liquidus curve in the state diagram while the first peak indicates where the melting process starts. In Fig. 2, the thermograms of two representative samples are presented. In the dispersion without SDS added, a second peak appears at approx. 175°C, while in the sample containing surfactant, no such deviation from the baseline can be seen. With the addition of SDS to the PEG–griseofulvin dispersions, the heat of fusion values decrease significantly for all three PEGs. Some of the heat of fusion values obtained for the PEG 6000 systems are presented in Table 2(a) and (b). For the solid solution with 20% w/w griseofulvin dissolved in PEG 6000/SDS, for instance, the heat of fusion is 124 J g^{-1}. The corresponding value for the dispersion without SDS added is 161 J g^{-1}. The state diagrams of griseofulvin and different polyethylene glycols with and without SDS added are presented in Fig. 3.

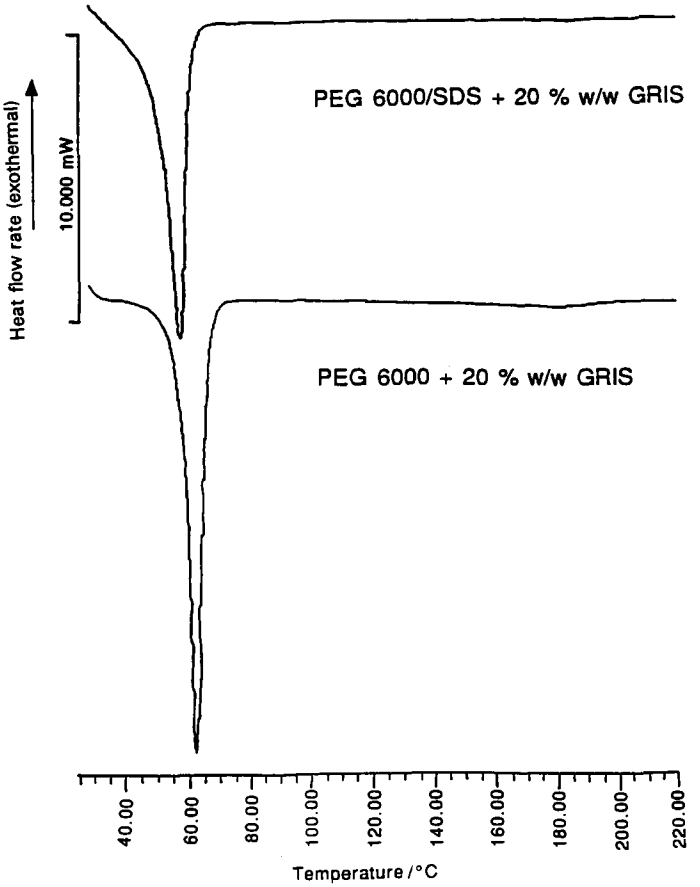

Fig. 2. DSC curves of the preparations with 20% w/w grisoefulvin (GRIS) in polyethylene glycol (PEG) 6000 with and without 2% w/w sodium dodecyl sulphate (SDS) added.

3.2. Thermal behaviour of griseofulvin–PEG 3000 dispersions with incorporation of varying alkali dodecyl sulphates by ODSC

The thermograms of the samples are presented in Fig. 4(a)–(d) and Fig. 5(a)–(d).

3.2.1. The interval −60–20°C

The conventional thermogram in Fig. 4(a) demonstrates that the LiDS-containing solid solution undergoes a transformation at approx. −30°C. In the SDS- and KDS-containing compounds, the changes with temperature are less distinct and moved to higher temperatures. From the kinetic component (see Fig. 4(c)) of the DSC signal, it is found that the changes are mainly irreversible. The C_p (reversible) components are very small in all compounds (Fig. 4(b)). In the LiDS compound, the transformation might, however, include a T_g transition.

Table 2(a)
Heat of fusion values and peak temperatures with standard deviations in the range 35–240°C for the ternary system griseofulvin (GRIS)–polyethylene glycol (PEG) 6000–sodium dodecyl sulphate (SDS)

Sample (–)	Range in °C	T_p in °C	ΔH in J g^{-1}
PEG 6000+			
2% SDS	35–80	60.3 ± 0.2	180.6 ± 4.0
	80–240	181.6 ± 6.0	
+ 5% GRIS	35–80	59.8 ± 0.1	170.5 ± 3.9
	80–240	173.3 ± 6.0	
+ 10% GRIS	35–80	58.6 ± 0.1	150.0 ± 4.4
	80–240	172.2 ± 9.6	
+ 20% GRIS	35–80	54.9 ± 0.3	123.8 ± 6.2
	80–240	174.4 ± 7.9	
+ 50% GRIS	35–80	43.5 ± 0.0	56.0 ± 3.4
	80–240	83.2 ± 0.0	
+ 80% GRIS	35–80	42.5 ± 0.5	68.1 ± 5.6
	80–240	213.0 ± 0.0	

Table 2(b)
Heat of fusion values and peak temperatures with standard deviations in the range 35–240°C for the binary system griseofulvin (GRIS)–polyethylene glycol (PEG) 6000

Sample	Range in °C	T_p in °C	ΔH in J g^{-1}
PEG 6000	35–80	60.0 ± 0.1	181.7 ± 3.1
	80–240	–	
+ 5% GRIS	35–80	60.6 ± 0.2	170.7 ± 3.0
	80–240	174.4 ± 12.6	
+ 10% GRIS	35–80	60.6 ± 0.1	172.9 ± 4.7
	80–240	131.6 ± 3.4	
+ 20% GRIS	35–80	60.5 ± 0.2	160.9 ± 2.3
	80–240	74.4 ± 0.9	
+ 50% GRIS	35–80	59.4 ± 0.1	135.6 ± 6.8
	80–240	202.1 ± 1.0	
+ 80% GRIS	35–80	47.4 ± 0.2	101.1 ± 11.9
	80–240	214.5 ± 0.1	
GRIS	35–80	–	116.8 ± 1.8
	80–240	219.8 ± 0.1	

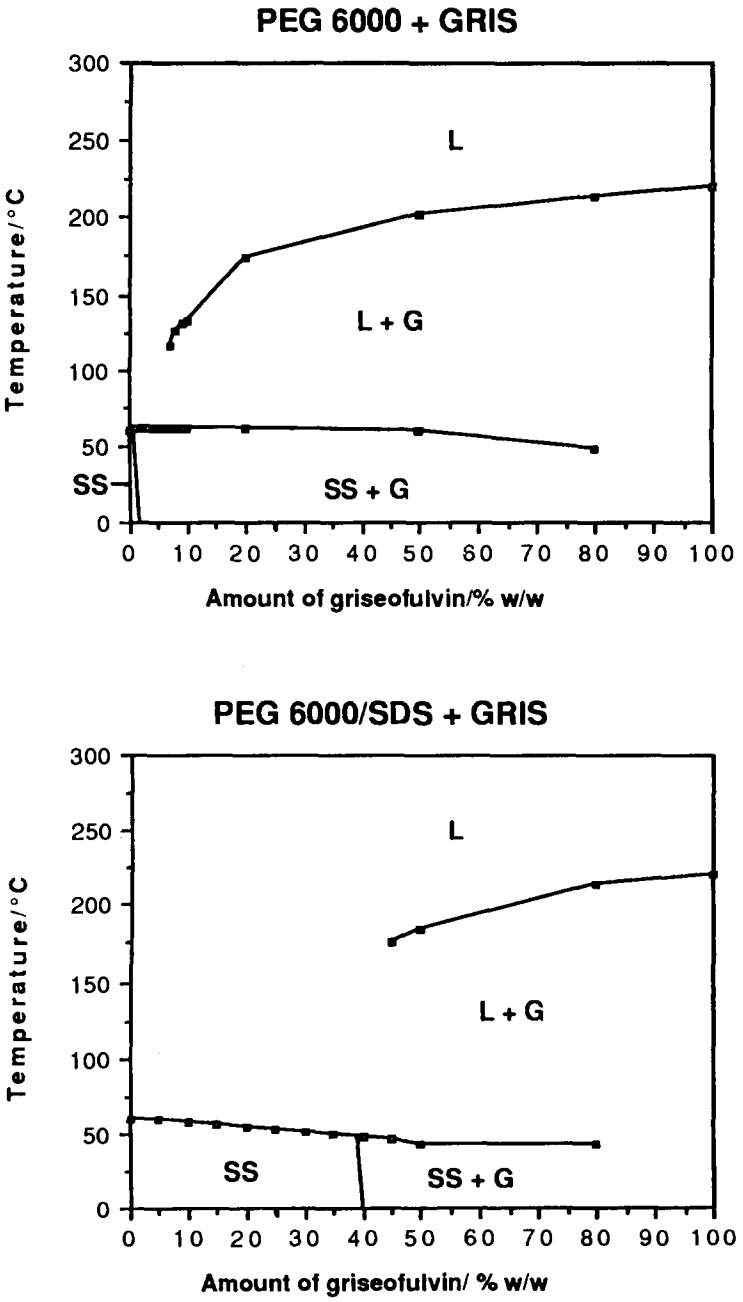

Fig. 3. (continued on next page).

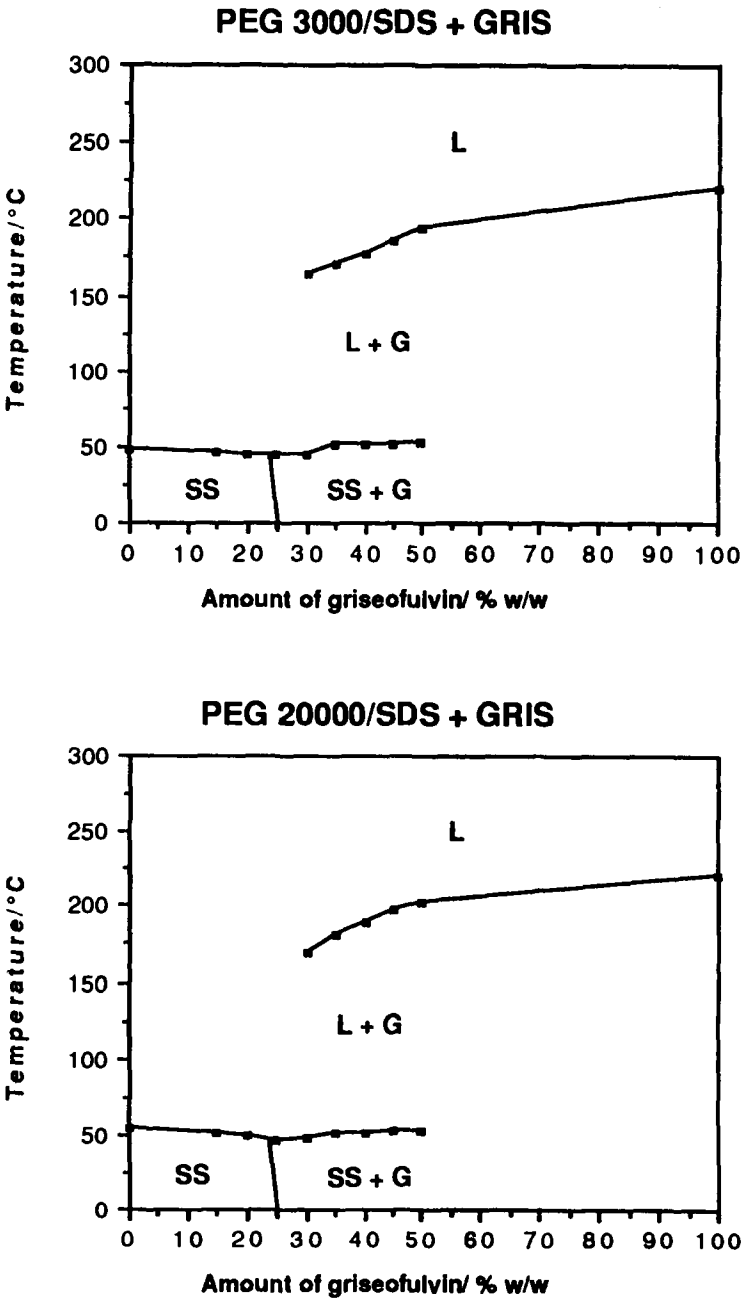

Fig. 3. State diagrams of binary and ternary drug–polymer–surfactant systems: SS, solid solution; G, griseofulvin (GRIS); L, liquid phase.

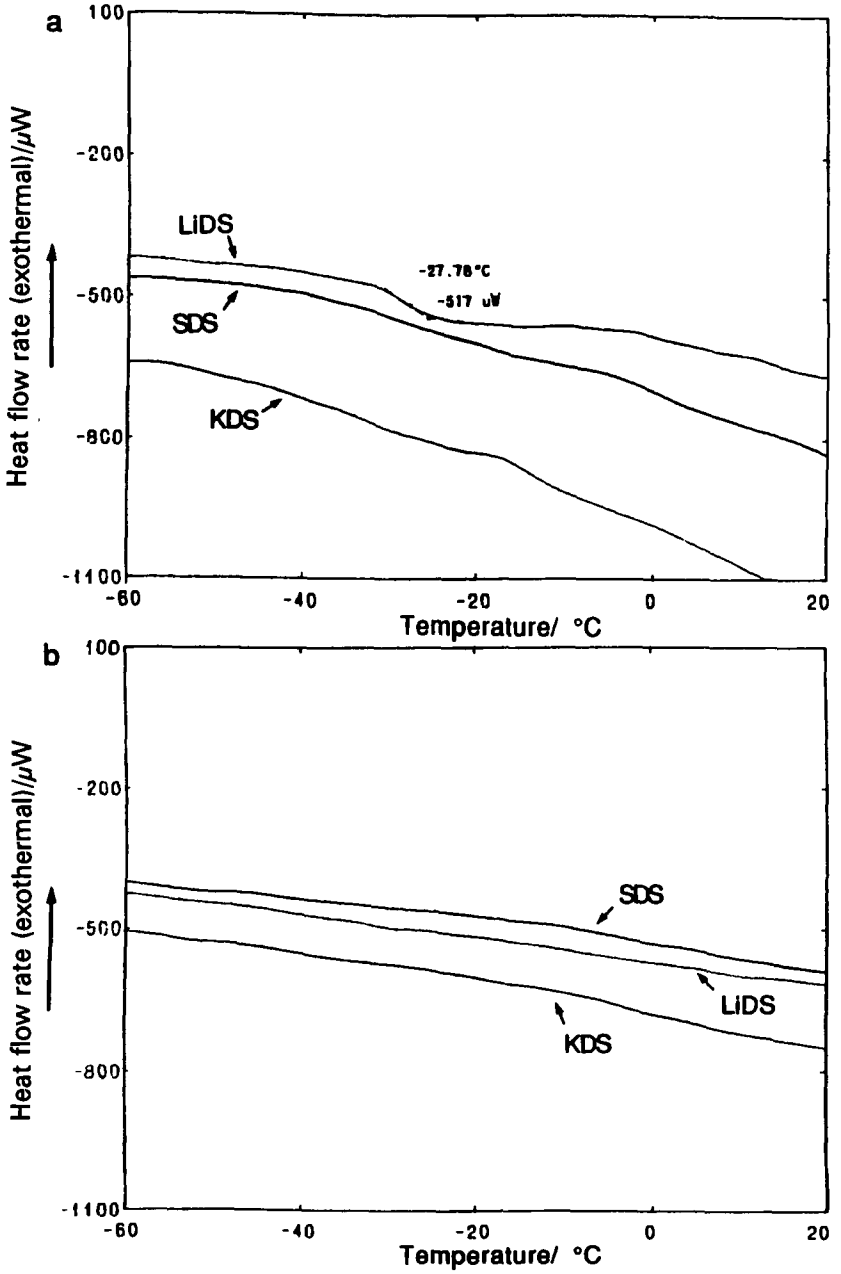

Fig. 4. (continued on next page).

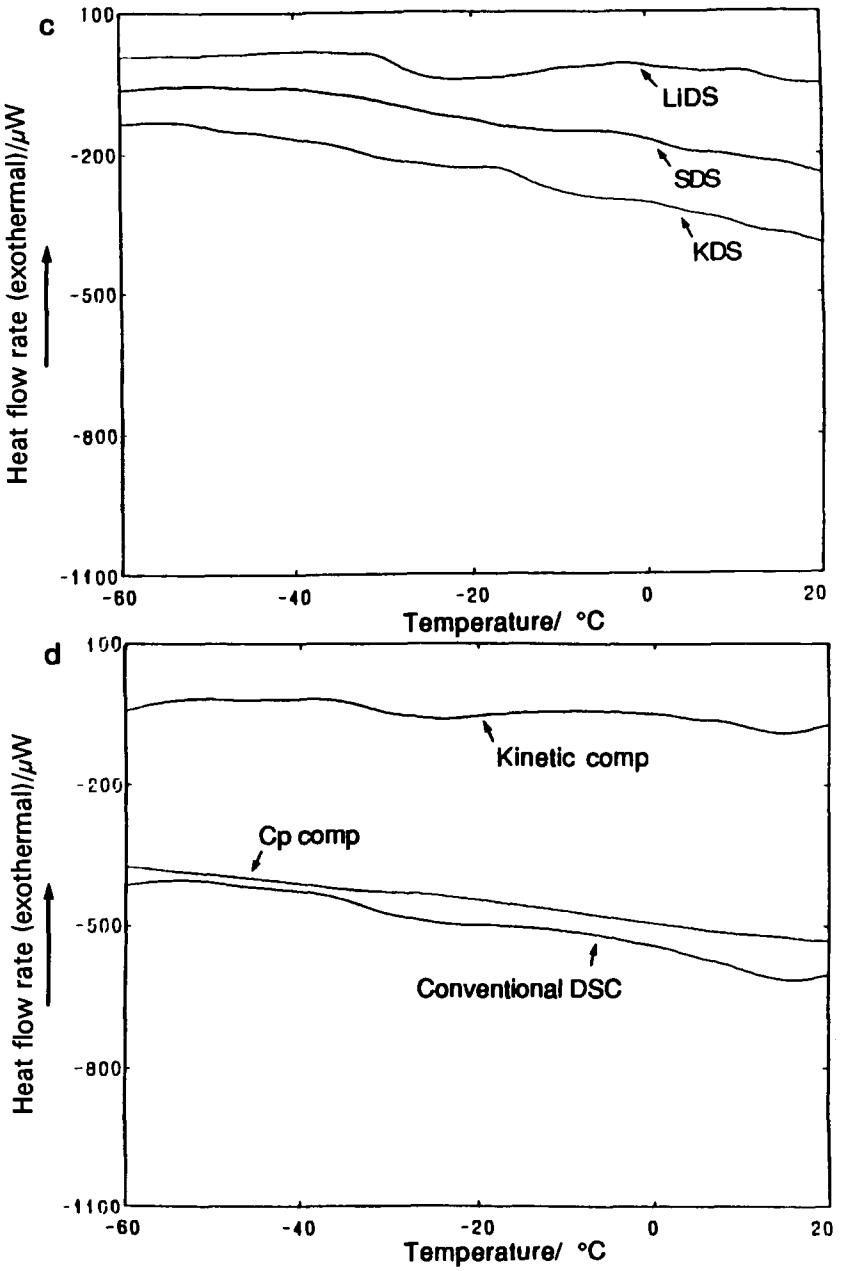

Fig. 4. Results obtained by oscillating DSC of samples in the griseofulvin (GRIS)–polyethylene glycol (PEG) 3000–alkali dodecyl sulphates (MDS) system in the interval −60–20°C. (a)–(c) PEG 3000 + 10% GRIS + 2% MDS: (a) conventional DSC; (b) C_p component; (c) kinetic component; (d) PEG 3000 + 10% GRIS.

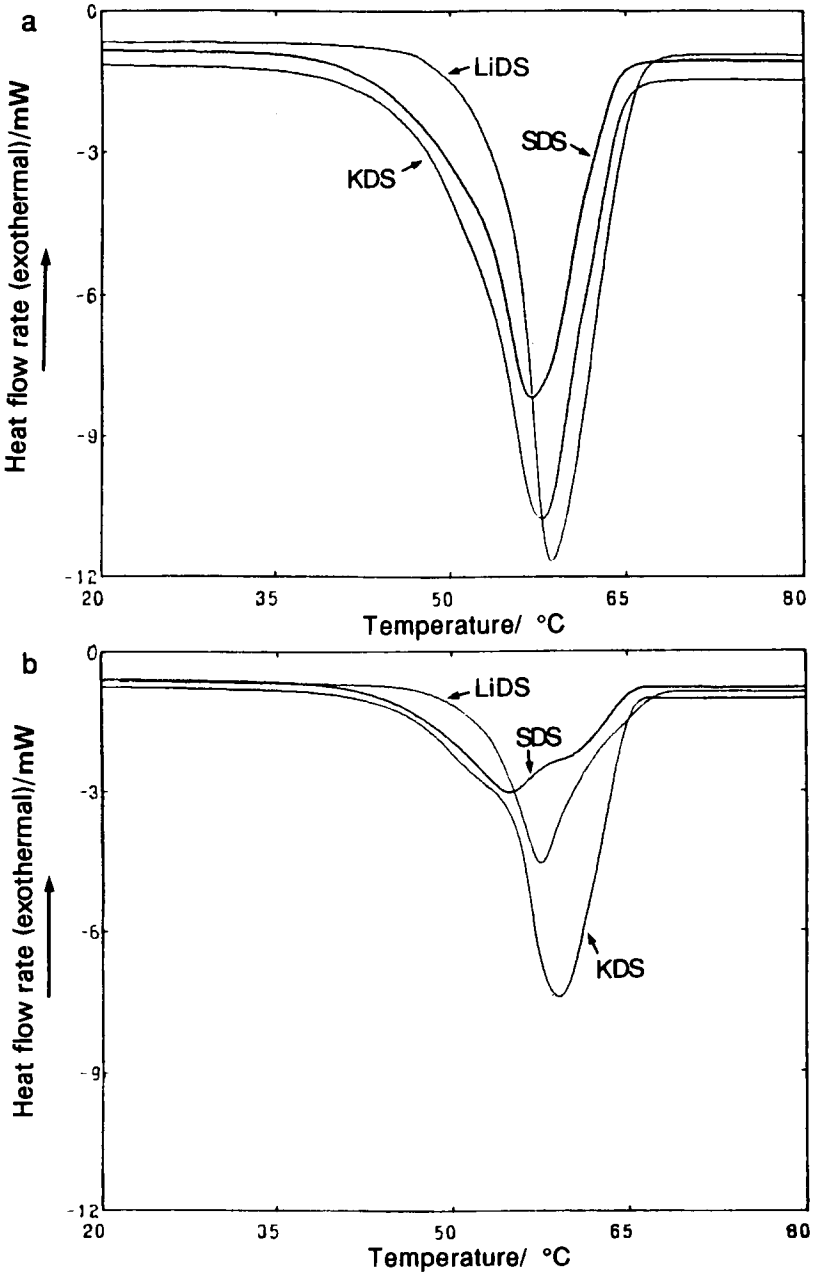

Fig. 5. (continued on next page).

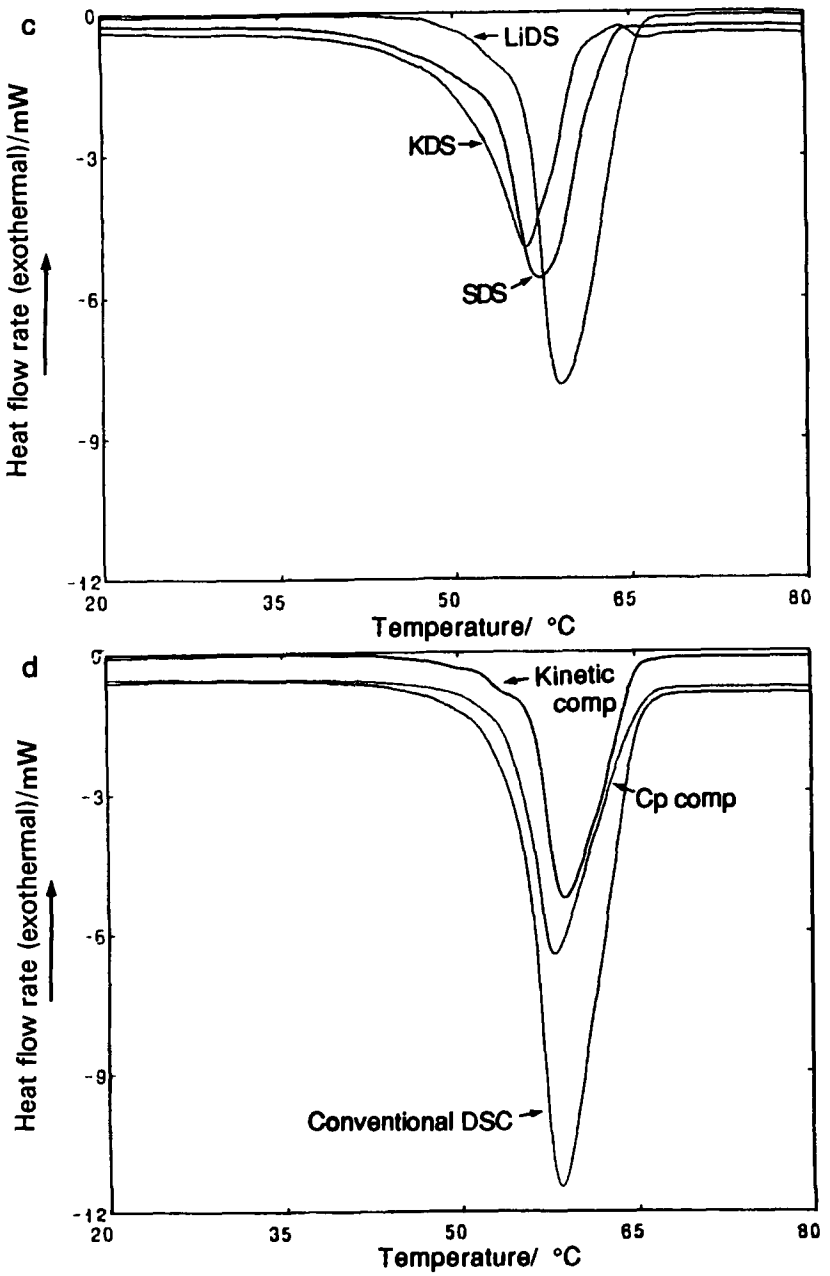

Fig. 5. Results obtained by oscillating DSC of samples in the griseofulvin (GRIS)–polyethylene glycol (PEG) 3000–alkali dodecyl sulphates (MDS) system in the interval 20–80°C. (a)–(c) PEG 3000 + 10% GRIS + 2% MDS: (a) conventional DSC; (b) C_p component; (c) kinetic component; (d) PEG 3000 + 10% GRIS.

Table 3
Enthalpy changes partitioned into reversible (ΔH_{C_p}) and irreversible (ΔH_K) components determined by ODSC in the range 20–80°C for the griseofulvin–polyethylene glycol (PEG) 3000–alkali dodecyl sulphates systems. Enthalpy changes and peak temperatures with standard deviations are given

Sample	T_p in °C	ΔH in J g^{-1}	T_p (C_p) in °C	ΔH_{C_p} in J g^{-1}	T_p (kin) in °C	ΔH_K in J g^{-1}
PEG 3000 + griseofulvin	58.9 ± 0.1	169.0 ± 1.4	58.3 ± 0.5	93.1 ± 16.9	59.1 ± 0.5	75.9 ± 17.9
PEG 3000/LiDS + griseofulvin	58.9 ± 0.1	168.0 ± 3.3	58.3 ± 1.9	66.7 ± 8.9	58.9 ± 0.1	101.2 ± 6.4
PEG 3000/SDS + griseofulvin	57.7 ± 0.7	162.2 ± 0.6	57.0 ± 1.9	95.3 ± 27.6	56.1 ± 0.9	67.0 ± 28.2
PEG 3000/KDS + griseofulvin	57.5 ± 0.6	162.3 ± 1.5	56.9 ± 2.1	79.8 ± 13.6	57.1 ± 0.9	82.4 ± 13.0

3.2.2. The interval 20–80°C

From the conventional DSC curve in Fig. 5(a), it is found that the melting peak of the LiDS solid solution is narrower than the other solid solution peaks and similar to the peak of the solid dispersion without surfactant. This fact confirms the results by X-ray diffraction demonstrated in a previous work [4]. A higher crystallinity in the LiDS compound than in the other solid solutions was reflected in the melting behaviour. The SDS and KDS compound peaks are broader and show a more complex melting behaviour in the range 50–55°C. From the kinetic and C_p curves (see Fig. 5(c) and 5(b), respectively), it is observed that the melting might include reversible processes where two transformations are superimposed. Domains with a diversified crystallinity of the polymer could induce such a melting process. It has earlier been reported that the amount of folded or extended polymer chains in low-weight polymer crystals influences the melting behaviour of the polymer [6].

The enthalpy changes (ΔH values) for the samples calculated from the conventional curves and presented in Table 3, confirm the similarity between the LiDS solid solution and the solid dispersion, and also between the SDS- and KDS-containing compounds. The enthalpy changes calculated from the C_p and kinetic component, ΔH_{C_p} and ΔH_K values, are extremely sample-dependent. The shapes of the curves are, however, similar in all samples. The kinetics of the investigated processes might greatly influence the response to the oscillating temperature.

4. Conclusions

PEGs with molecular weights 3000, 6000 and 20 000, respectively, dissolve less than 3% w/w griseofulvin. When SDS is incorporated in the dispersion, the solid solubility increases to 40% w/w in PEG 6000 and to 25% w/w in PEG 3000 and PEG 20 000. Solid solutions of griseofulvin in PEG with SDS incorporated are formed. The solid solutions melt close to the melting temperature of the pure PEG phases. Their heat of fusion values differed significantly from those of the solid dispersions. There is a similarity between the thermal behaviour of the LiDS solid solution and the solid dispersion without surfactant as well as between the SDS- and KDS-containing solid solution in the range −60–80°C. The transformations at low tempera-

tures are mainly irreversible. In the 20–80°C range, the reversible contribution to the melting process creates a more complex melting pattern for the SDS- and KDS-containing compounds than for the LiDS compound. The structure of the compounds could be composed of domains with a diversified crystallinity of the polymer, depending on the polymer chain type. This could explain the complex melting process and the extreme sample dependence of the ΔH_{C_p} and ΔH_K contributions.

Acknowledgements

The authors are very grateful to Professor Josh Thomas, Institute of Chemistry, Uppsala University for providing the X-ray diffractometer equipment and to Professor Christer Nyström, Department of Pharmacy, Division of Pharmaceutics, for providing the Mettler DSC equipment. We also thank Procordia AB for grants.

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