

## Effect of counterions on the interactions in solid dispersions between polyethylene glycol, griseofulvin and alkali dodecyl sulphates

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### Abstract

Solid dispersions of polyethylene glycol (PEG) 3000 and 10% w/w griseofulvin with or without different surfactants incorporated were prepared by the melting method. The anionic surfactants lithium dodecyl sulphate (LiDS), sodium dodecyl sulphate (SDS) and potassium dodecyl sulphate (KDS) were added in equivalent amounts, ~ 2% w/w. Phase analysis was performed by X-ray powder diffraction and investigation of short-range structure by <sup>13</sup>C-CP/MAS solid-state NMR. In all samples with surfactant added, solid solutions (PEG/MDS)<sub>1-x</sub> griseofulvin<sub>x</sub> were formed. The properties of the solid solutions with Na<sup>+</sup> and K<sup>+</sup> ions were almost identical. The addition of LiDS created a structure of the solid solution that was more crystalline than that structure of the sodium- and potassium-containing compounds. The ion with the highest charge-to-radius ratio, Li<sup>+</sup>, formed chemical bonds that were different from those of the other ions. This was indicated by a changed influence on the hydrophilic parts of the griseofulvin molecules in the lithium compound. The melting behaviour of the solid solutions, investigated by DSC, showed a second transformation in the melt at 186–196°C, indicating a two-phase region in the liquid phase. For the lithium-containing compounds the transformation appeared at lower temperature than for the sodium- and potassium-containing compounds.

**Key words:** Structure; Griseofulvin; Polyethylene glycol; Lithium dodecyl sulfate; Sodium dodecyl sulfate; Potassium dodecyl sulfate; Solid solution; X-ray powder diffraction; Solid-state NMR; DSC

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### 1. Introduction

The long- and short-range order in solid-state systems containing a polymer, a drug and either

an anionic, cationic or nonionic surfactant has been examined in a recent study (Aldén et. al., 1993). The interaction between polymer and surfactant aggregates was found to be crucial for the formation of solid solutions of drug in the polymer phase. The negatively charged surfactants influence the binding of the griseofulvin molecules to the polymer forming a solid solution. The

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nonionic surfactant did not influence the particulate griseofulvin dispersion at all, while the cationic surfactant formed a solid solution only to a certain extent.

It was recently found for water solutions (Dubin et al., 1992; Xia et al., 1992) that the effect of counterions like  $\text{Li}^+$ ,  $\text{Na}^+$  and  $\text{NH}_4^+$  on the polymer (PEO)-surfactant interaction varies with the different ions. The binding process was assumed to start by the counterions coordinating to the polymer chain oxygen. The cations could then coordinate simultaneously with the polymer oxygens and with the aggregate/micelle. The charge-to-radius ratio of the ions proved to be an important factor for the binding strength of surfactant micelles to the polymer.

Also, in solid-state systems containing polyethylene glycol, griseofulvin and surfactants, the counterions might create a structure where the ions act as bridges between the polymer and the surfactant-griseofulvin aggregate. The observation that the binding between the polymer and cationic or nonionic aggregates is reduced or does not exist compared with the case involving the anionic aggregates could be explained by the counterions also acting as such bridges in the solid systems.

The aim of the present study was to investigate whether different counterions like  $\text{Li}^+$ ,  $\text{Na}^+$  or  $\text{K}^+$  influence in the same way the interaction between polymer, anionic surfactant and griseofulvin in the solid state. In the investigated systems the drug might appear in solid solution (one phase) or solid dispersions ( $\geq$  two phases). A comparison has, therefore, been made with the particulate dispersion received, when no surfactant was added.

## 2. Experimental

### 2.1. Material

Griseofulvin (GRIS) (Sigma, U.S.A.) with the formula  $\text{C}_{17}\text{H}_{17}\text{ClO}_6$  was used as hydrophobic model drug and polyethylene glycol (PEG) 3000 (Sigma, U.S.A.) as a carrier. The PEG melting

temperature interval is 56–58°C. Lithium dodecyl sulphate (LiDS), sodium dodecyl sulphate (SDS) and potassium dodecyl sulphate (KDS) (Sigma, U.S.A.) are all anionic surfactants with the formula  $\text{C}_{12}\text{H}_{25}\text{SO}_4\text{M}$  with  $\text{M} = \text{Li}^+$ ,  $\text{Na}^+$  or  $\text{K}^+$ .

## 2.2. Methods

### 2.2.1. Preparation of solid dispersions

Solid dispersions (3.0–5.0 g) were prepared by the melting method. Equivalent amounts of the anionic lithium dodecyl sulphate (LiDS), sodium dodecyl sulphate (SDS) and potassium dodecyl sulphate (KDS) ( $\sim 2\% \text{ w/w}$ ) were added to dispersions of 10% griseofulvin in PEG. The ratio between the number of PEG monomers and GRIS molecules was in all cases approx. 65. The ratio between the number of GRIS molecules and alkali dodecyl sulphate molecules was approx. 4. The preparations were made in a Carbolite furnace with a Eurotherm 818 P programmer. All samples were heated at a rate of  $10^\circ\text{C min}^{-1}$  from room temperature to  $170 \pm 1^\circ\text{C}$ , where they were kept for 30 min. The samples were brought to room temperature by rapid cooling ( $50\text{--}100 \text{ K s}^{-1}$ ).

After storing for 24 h, the samples were pulverized in a mortar. In all experiments the 300–500  $\mu\text{m}$  sieve fraction was used.

### 2.2.2. X-ray diffraction

The X-ray powder diffraction investigations were performed using a STOE position sensitive detector (PSD) system with Ge monochromatized  $\text{CuK}\alpha_1$  radiation. A linear detector was used covering  $7^\circ$  at 155 mm distance and was operated in a scanning mode. The minimum attainable full-width at half-height (FWHH) was approx.  $0.15^\circ$ . Room temperature runs were performed by rotating the powder sample attached to a cellulose membrane about the normal to the plane of the membrane. Exposure time was about 15 min.

The unit cell dimensions were evaluated using an indexing program belonging to the diffractometer system and a local program, CELL, that included a least-squares refinement of the cell dimensions (Ersson, N.-O., unpublished).

### 2.2.3. Solid state NMR

Carbon-13 CPMAS NMR spectra were recorded on a Bruker MSL 300 spectrometer at 75 MHz using 4 mm o.d. zirconium oxide rotors and spinning at about 5–7 kHz. The proton and carbon radio frequency fields used during cross-polarisation and decoupling correspond to 4  $\mu$ s 90° pulses. The cross-polarisation contact time was 1–2 ms.

### 2.2.4. Differential scanning calorimetry.

Samples (3.8–4.5 mg) were examined using a DSC 20 differential scanning calorimeter (Mettler, Switzerland) and a DSC 220C differential scanning calorimeter (Seiko, Japan). A heating rate of 10°C min<sup>-1</sup> was used from 25 to 240°C in an atmosphere of nitrogen with the samples kept in aluminium pans. The values of heat of fusion (from the DSC 20) were derived from integration in the temperature ranges 35–80 and 80–240°C. The results presented are mean values of three determinations.

## 3. Results and discussion

### 3.1. X-ray powder diffraction

The long-range order as reflected in the X-ray powder diffractograms of the dispersions with and without surfactants added is shown in Fig. 1 and the phase analysis is presented in Table 1. In the following the notations (PEG)<sub>1-y</sub>MDS<sub>y</sub> and PEG/MDS, where M is Li<sup>+</sup>, Na<sup>+</sup> or K<sup>+</sup>, represent a solid solution of MDS in PEG or a mixture of the solid solution and pure PEG.

### 3.2. PEG / griseofulvin / MDS in diffractograms

In the PEG-griseofulvin dispersion griseofulvin and PEG were both present as pure phases. The detection limit of griseofulvin in the PEG phase is 2% w/w (Sjökvist et al., 1991). In the samples of PEG with the anionic surfactants incorporated only one phase was observed. The diffractograms of PEG 3000 with MDS added were identical

with those of pure PEG. It is reasonable to assume that for all surfactants a solid solution (PEG)<sub>1-y</sub>MDS<sub>y</sub> of MDS in the PEG phase was formed, as reported earlier for the sample with 10% SDS (Aldén et al., 1992). In the PEG + griseofulvin dispersions with surfactants incorporated only one phase was observed. The diffraction pattern corresponded to that from pure PEG or from the solid solution (PEG)<sub>1-y</sub>MDS<sub>y</sub>. Griseofulvin dissolves in the PEG<sub>1-y</sub>(MDS)<sub>y</sub> phase to become the solid solution (PEG/MDS)<sub>1-x</sub>griseofulvin<sub>x</sub>.

### 3.3. Line intensities

Line intensities for some of the characteristic diffraction lines in the PEG pattern for the different samples are presented in Table 2. In all dispersions with surfactant incorporated there was some change of line intensities compared with pure PEG phase.

#### 3.3.1. SDS and KDS additions

The relative intensities of the lines in the PEG pattern were the same in the solid solutions and in the solid particulate dispersion of griseofulvin in PEG. This indicates that the griseofulvin molecules were randomly distributed over available sites. If the griseofulvin molecules had been dissolved in a periodic arrangement, differing from that of PEG, a change in the diffraction pattern would have resulted. Furthermore, the griseofulvin cannot exist as isolated crystallites without being observed by the X-ray diffraction method and thus griseofulvin was present in molecular form (Cullity, 1978). No evidence of an amorphous form of griseofulvin was obtained in the previous studies, where varying cooling rates were also used during sample preparation (Sjökvist Saers et al., 1993.).

#### 3.3.2. LiDS addition

The relative intensities of the lines of the PEG pattern of (PEG/LiDS)<sub>1-x</sub>griseofulvin<sub>x</sub> differ from those of the PEG pattern of the particulate dispersion and of the solid solution (PEG)<sub>1-y</sub>LiDS<sub>y</sub>. Both stronger lines and a changed inten-

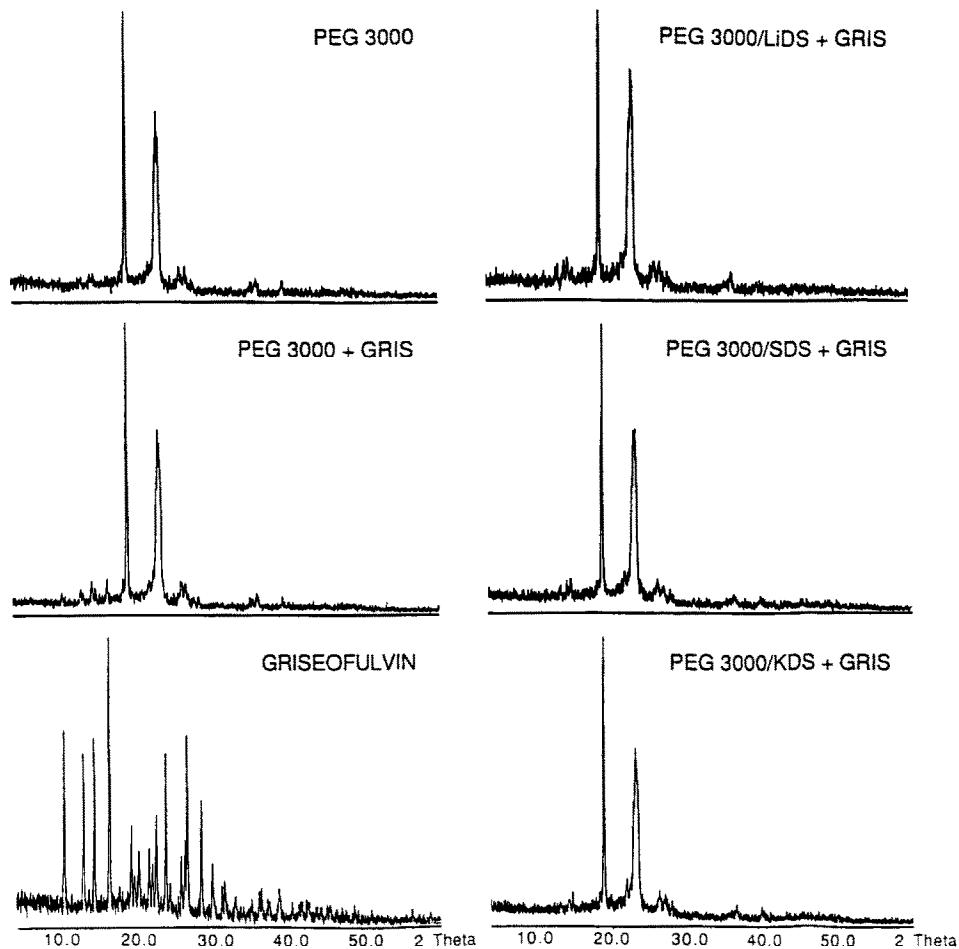


Fig. 1. X-ray powder diffractograms.

sity ratio between the lines were observed. This fact implies that, on certain diffraction planes in the crystal structure of PEG, the amount of scatter-

tering material has changed (Cullity, 1978). Since the molar ratios of PEG, griseofulvin and surfactant are the same in all the samples, the in-

Table 1  
X-ray powder diffraction analysis of solid dispersions of 10% griseofulvin in PEG 3000 with 2% surfactant added

Sample	$n_{\text{PEG}}/n_{\text{griseofulvin}}$	$n_{\text{surfactant}}/n_{\text{griseofulvin}}$	Phases observed <sup>a</sup>
PEG 3000			
+ griseofulvin + LiDS	65	0.246	(PEG/LiDS) <sub>1-x</sub> griseofulvin <sub>x</sub>
+ griseofulvin + SDS	65	0.244	(PEG/SDS) <sub>1-x</sub> griseofulvin <sub>x</sub>
+ griseofulvin + KDS	65	0.243	(PEG/KDS) <sub>1-x</sub> griseofulvin <sub>x</sub>
+ LiDS	—	—	(PEG) <sub>1-y</sub> LiDS <sub>y</sub>
+ SDS	—	—	(PEG) <sub>1-y</sub> SDS <sub>y</sub>
+ KDS	—	—	(PEG) <sub>1-y</sub> KDS <sub>y</sub>
+ GRIS	66	—	PEG + griseofulvin

<sup>a</sup> (PEG/MDS)<sub>1-x</sub>griseofulvin<sub>x</sub> is the solid solution of SDS and griseofulvin in the PEG structure. (PEG)<sub>1-y</sub>(MDS)<sub>y</sub> is the solid solution of MDS in the PEG structure.

Table 2

Intensities at characteristic diffraction angles  $2\theta$  ( $^{\circ}$ ) for PEG in pure phase or in solid solution

Dispersion	$2\theta$	$I$	$2\theta$	$I$	$2\theta$	$I$	$2\theta$	$I$	$2\theta$	$I$	$2\theta$	$I$
PEG 3000	14.752	5.5	not observed	not observed	18.888	100.0	22.994	60.0	23.239	51.5	26.682	7.3
+ LiDS	14.921	5.8	18.355	6.4	18.929	100.0	23.062	64.8	23.264	55.9	26.776	6.8
+ SDS	14.912	6.5	18.438	6.7	18.912	100.0	23.081	54.7	23.365	40.4	26.672	7.0
+ KDS	14.829	6.0	18.374	5.8	18.906	100.0	23.079	55.2	23.358	38.3	26.656	6.6
+ GRIS	14.813	6.2	18.364	7.6	18.910	100.0	23.008	57.5	23.228	52.2	26.870	4.9
+ LiDS + GRIS	14.855	10.1	18.353	9.9	18.878	100.0	23.070	70.6	23.338	54.9	26.692	8.7
+ SDS + GRIS	14.867	8.7	18.357	5.2	18.938	100.0	23.088	59.7	23.370	46.8	26.735	6.3
+ KDS + GRIS	14.806	6.4	18.298	6.3	18.911	100.0	23.007	54.1	23.245	47.8	26.757	6.3

creased relative intensity values for certain diffraction angles in this compound must reflect a more crystalline material.

It is interesting to compare the structure formed in the present case with the  $\text{NaSCNPEO}_3$  structure. The  $\text{Na}^+$  ions in the latter compound coordinate four oxygens from the PEG chain and two nitrogens from the  $\text{SCN}^-$  ion (Chatani et al., 1990). In this way, they stabilize the PEG chains and increase the crystalline character of the compound. In the dispersions with LiDS, the changed diffraction pattern might indicate a similar stabilization of the chain structure, in this case by the  $\text{Li}^+$  ions.

#### 3.4. Cell dimensions

In Table 3 the cell dimensions for the PEG phase in the pure PEG sample and in the PEG + griseofulvin dispersions with and without addition of LiDS are listed. The unit cell is monoclinic.

The cell parameters showed rather high standard deviations, reflecting the poor crystallinity of the PEG structure. Most of the cell parameters for the different systems were equal within the standard deviations. However, a clear difference was observed with the two compounds containing LiDS. Here, additional diffraction peaks at low  $2\theta$  values were observed, whereas the corresponding peaks were below the background noise in the samples with SDS and KDS addition. These low  $2\theta$  peaks reflected an increased long-range periodicity for the compounds with LiDS.

#### 3.5. NMR spectra

More information on the short-range interaction in the samples was obtained by an NMR study. The  $^{13}\text{C}$ -NMR spectra of pure LiDS, pure griseofulvin, PEG and griseofulvin dispersions together with spectra of solid solutions  $(\text{PEG})_{1-y}$   $\text{LiDS}_y$  and  $(\text{PEG}/\text{MDS})_{1-x}$  griseofulvin<sub>x</sub> are

Table 3

Unit cell dimensions ( $\text{\AA}$ ) for PEG 3000 in solid dispersion systems with 10 w/w% griseofulvin and 2% lithium dodecyl sulphate

	Cell dimensions				Number of indexed peaks <sup>a</sup>	$2\theta$ range ( $^{\circ}$ )
	$a$	$b$	$c$	$\beta$		
PEG 3000	8.229 (41)	13.036 (85)	19.061 (73)	125.91 (37)	10	14.1–35.9
PEG 3000 + griseofulvin	8.163 (95)	13.057 (133)	18.920 (175)	125.12 (63)	9	14.4–36.1
PEG 3000 + LiDS	8.140 (71)	13.055 (160)	19.052 (136)	125.72 (67)	14	13.3–36.1
PEG 3000 + griseofulvin + LiDS	8.301 (81)	12.907 (62)	18.895 (199)	124.21 (77)	12	13.3–26.7

<sup>a</sup> Over a certain background level and used in the calculation of the unit cell parameters.

demonstrated in Fig. 2. The spectra of pure SDS and pure KDS were almost identical with that of LiDS and the  $(\text{PEG})_{1-y}\text{SDS}_y$  and  $(\text{PEG})_{1-y}\text{KDS}_y$  spectra were identical with the  $(\text{PEG})_{1-y}\text{LiDS}_y$  spectrum.

### 3.6. PEG / griseofulvin

The spectrum of PEG with 10% griseofulvin is essentially a superposition of the spectra from the two components. There is no apparent interaction between polymer and griseofulvin changing the short-range order.

### 3.7. MDS and PEG / MDS spectra

In all samples of pure MDS, LiDS being the example here, the C1, central part peaks and C12 peak appear well defined. In the PEG/LiDS solid solution the peaks had disappeared probably because of the small amount of MDS compared with PEG. The intensities of the peaks of LiDS in PEG/LiDS were below the noise level.

### 3.8. PEG / MDS / griseofulvin spectra

The main pattern for the sample with 10% SDS (Aldén et al., 1992) was also observable for the samples with 2% LiDS, SDS or KDS. All the peaks in the griseofulvin spectra are sharp and well defined. This indicates that all griseofulvin molecules experience the same environment. The most prominent differences in the griseofulvin spectra between samples with and without MDS are: the most hydrophilic part of the molecule, the OMe and C = O carbons C3 and C4' at 180–200 ppm are strongly influenced by the solid solution formation. The OMe carbons 4, 2' and 6 at 60 ppm are not resolved in the solid solution, probably because of the 4 and 2' peaks being hidden by the PEG peak. The two carbon peaks at 90–110 ppm gave three distinct peaks (probably C3, C7 and C5) in the solid solution. The changes in the pattern from pure griseofulvin to solid solution were identical in the SDS- and KDS-containing compounds. For the LiDS-containing compound, however, a differing intensity distribution was observed in the spectrum for the

C = O carbons, C3 and C4', and the C2' carbon. These carbons are thus influenced differently by the formation of a solid solution. This could be a result of differences in the dynamics for the three compounds either in the griseofulvin molecules themselves or in their surroundings. The observations indicate that at least part of the griseofulvin molecule experiences a somewhat different surrounding in the  $\text{Li}^+$  compound from that in the SDS and KDS compounds.

### 3.9. Heat of fusion determinations

Thermograms of pure MDS and of the particulate dispersion of griseofulvin in PEG together with thermograms of the solid solutions  $(\text{PEG})_{1-y}\text{MDS}_y$  and  $(\text{PEG}/\text{MDS})_{1-x}\text{griseofulvin}_x$  are presented in Fig. 3a–d.

The MDS thermograms show different characteristic peaks. In the LiDS thermogram two dis-

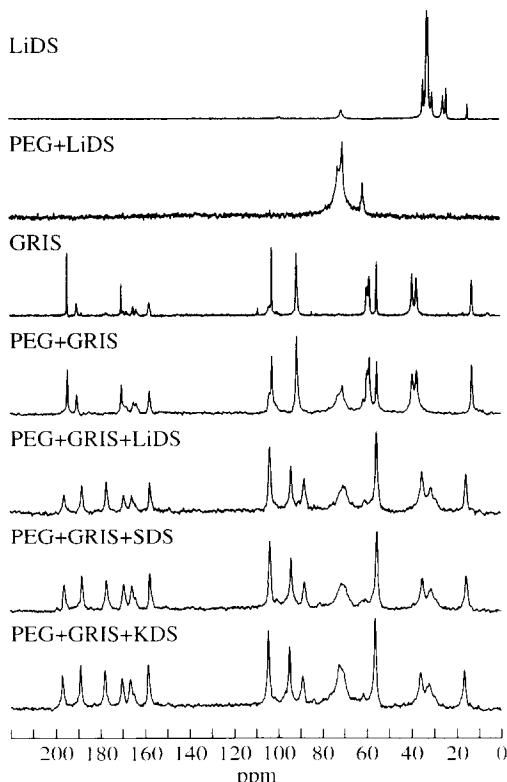


Fig. 2.  $^{13}\text{C}$ -CPMAS NMR spectra.

tinct peaks at 140 and 213°C appear and in the KDS thermogram three peaks at 58, 140 and 222°C, respectively. None of them showed a decomposition in the temperature range investigated. The SDS thermogram exhibits two defined peaks at 106 and at 198°C. This compound started to decompose at about 210°C.

All the thermograms of PEG-containing samples show the characteristic melting peak at about 50°C, where the solid solutions or the solid dispersion start to melt. For the  $(\text{PEG}/\text{LiDS})_{1-x}$

griseofulvin<sub>x</sub> sample the melting peak is narrower than for the corresponding  $\text{Na}^+$ - and  $\text{K}^+$ -containing compounds (Fig. 3d). The increased crystallinity of the  $\text{Li}^+$  compound demonstrated by the X-ray diffraction investigation was thus also reflected in the thermal behaviour. An additional small endothermic peak was found in the solid solutions  $(\text{PEG})_{1-y}\text{MDS}_y$ , there was a transfor-

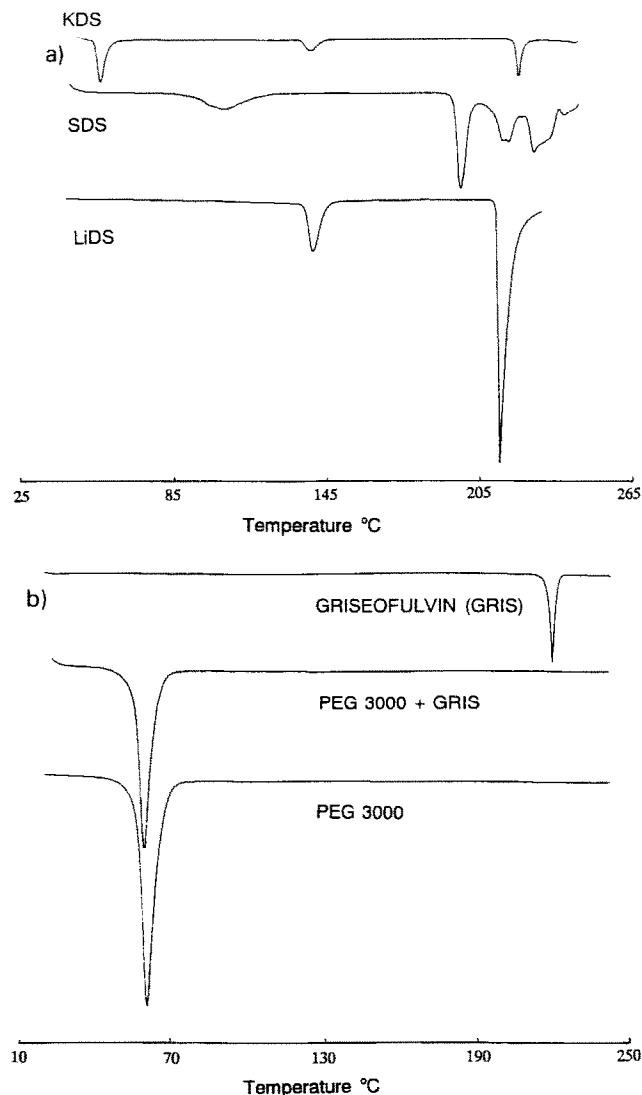


Fig. 3. (a-d) DSC thermograms.

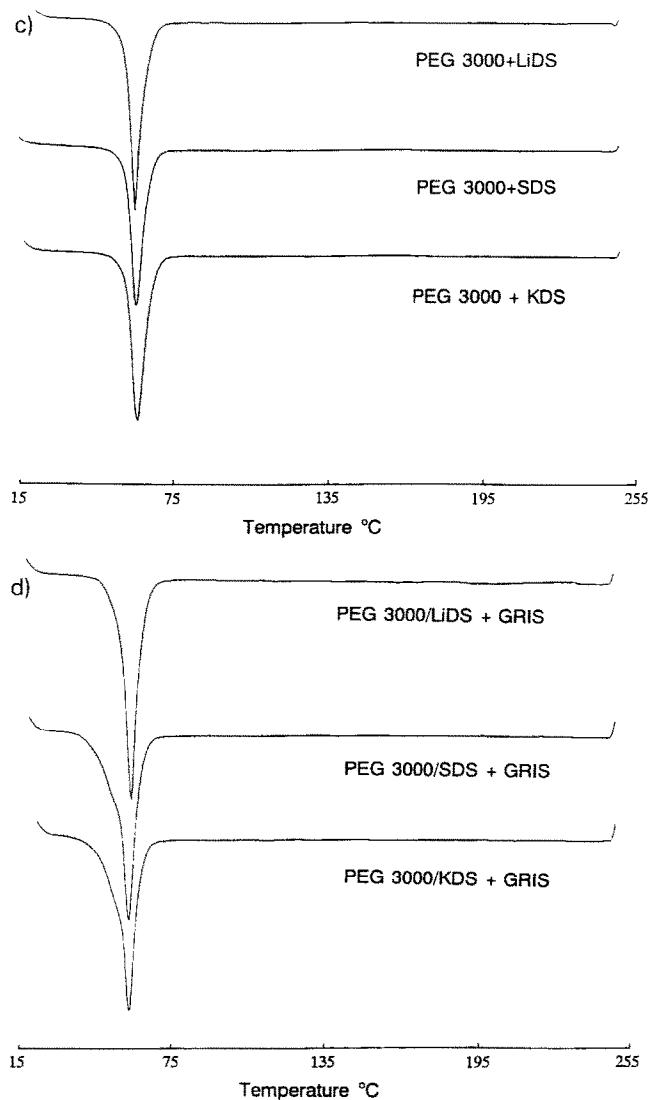


Fig. 3. (continued).

mation at higher temperature, 116°C, only in the  $\text{Li}^+$  compound and the transformation was exothermic.

The peak temperatures differ from those in pure MDS for the LiDS- and KDS-containing compounds. For the SDS-containing compound the peak at 197°C might represent the same transformation as that found in pure SDS.

Recently, it has been shown (Aldén et al., unpublished) by dielectric spectroscopy that at 70°C the solid solutions are all in a liquid phase.

The transformations at higher temperatures observed in the solid solutions thus indicate that a monotectic mixture of two liquid phases were formed above the melting temperature of the sample.

The heat of fusion values (Table 4) were derived from integration in the 35–80 and 80–240°C intervals. The solid solutions  $(\text{PEG}/\text{MDS})_{1-x}$  griseofulvin<sub>x</sub> all show a heat of fusion value of approx. 160 J g<sup>-1</sup>. This value is consistent with the heat of fusion reported in a previous paper

on solid solutions with SDS added (Sjökvist et al., 1991). The heat of fusion of  $(\text{PEG})_{1-y}\text{MDS}_y$  solid solutions is approx.  $180 \text{ J g}^{-1}$ . The second transformation is associated with small but significant heat of fusion values lower than  $10 \text{ J g}^{-1}$ .

If a monotectic mixture of two liquid phases forms when the solid solution melts, a transformation from a two-phase to a single-phase region can occur at a temperature well above the melting point. The  $\text{Li}^+$ ,  $\text{Na}^+$  and  $\text{K}^+$  ions might interact with the polymer, griseofulvin and surfactant aggregates in the melt, creating remaining short-range structures. To destroy these short range structures energy will be needed. In a study (Robitaille et al., 1987) on the thermal properties of polyethylene oxide with additions of  $\text{NaSCN}$  and  $\text{KSCN}$ , liquid-liquid miscibility gaps were found. The miscibility gaps result from changing

complexation between the polymer and the salt in the melt.

#### 4. Conclusions

The addition of equivalent amounts of the anionic surfactants LiDS, SDS and KDS (MDS) to the PEG-griseofulvin system created solid solutions  $(\text{PEG})_{1-y}/\text{MDS}_y$  and  $(\text{PEG}/\text{MDS})_{1-x}$  griseofulvin<sub>x</sub>, where MDS and griseofulvin are dissolved in a molecular form. The lithium compound forms a more crystalline structure than the sodium- or potassium-containing compounds.

The most hydrophilic parts of the griseofulvin molecules were influenced by surfactant addition in the same way for SDS as for KDS. With LiDS addition, at least part of the griseofulvin

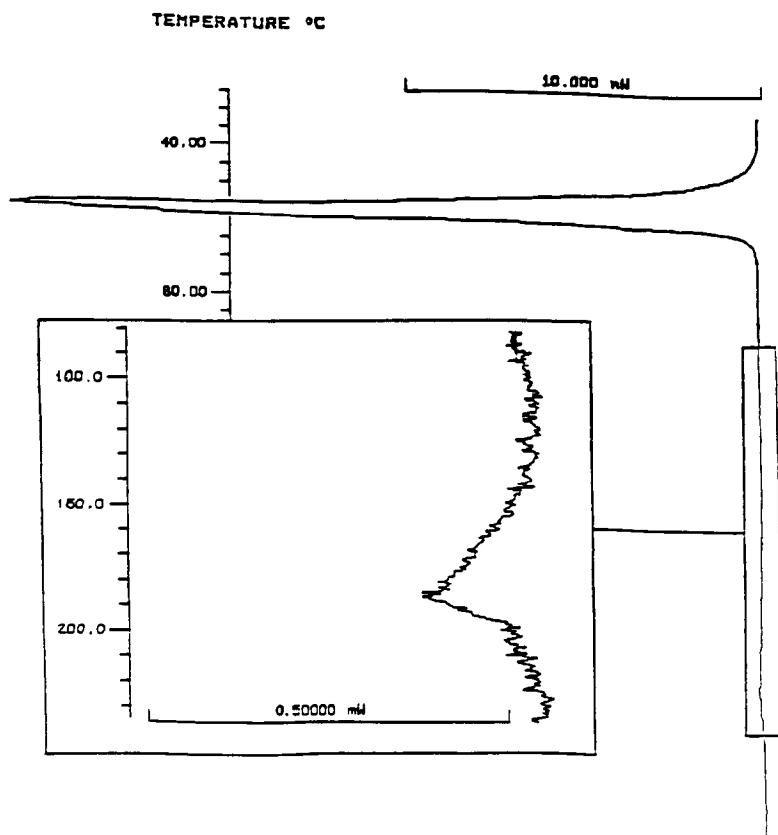


Fig. 4. Thermogram of the solid solution  $(\text{PEG}/\text{LiDS})_{1-x}$  griseofulvin<sub>x</sub> and magnification of the temperature interval 80–240°C.

Table 4  
Heat of fusion of solid solutions

Sample	Heat of fusion (J g <sup>-1</sup> ) <sup>a</sup>		Peak temperatures	
	35–80°C	80–240°C	35–80°C	80–240°C
PEG 3000 + 10% griseofulvin +				
2% LiDS	164 ± 6	4 ± 1	49.1 ± 0.4	186.3 ± 1.7
2% SDS	160 ± 3	6 ± 1	48.9 ± 0.2	196.9 ± 1.0
2% KDS	155 ± 7	10 ± 7	49.9 ± 0.9	196.9 ± 2.6
PEG 3000 +				
2% LiDS	178 ± 1	-3 ± 1	48.5 ± 0.1	115.8 ± 1.9
2% SDS	181 ± 3	-	48.7 ± 0.1	-
2% KDS	175 ± 4	-	48.7 ± 0.2	-

<sup>a</sup> The values of heat of fusion are derived from integration in the temperature range 35–80°C and 80–240°C, respectively.

molecules experience somewhat different surroundings.

The thermal properties of the compounds showed that the solid solutions (PEG/MDS)<sub>1-x</sub> griseofulvin<sub>x</sub> and the solid solution (PEG)<sub>1-y</sub> LiDS<sub>y</sub> undergo a second transformation at high temperature, that can be associated with a transition in the melt.

When a bond is formed between the polymer and the griseofulvin-surfactant aggregate (Aldén et al., 1992) the counterions of the surfactants may act as the bridges between them. The ion with the highest charge-to-radius ratio, Li<sup>+</sup>, forms bonds that are different from those formed with the Na<sup>+</sup> and K<sup>+</sup> ions. This could explain the observed increased crystallinity in the Li<sup>+</sup>-containing solid solution and the deviation in thermal behaviour of the melted Li<sup>+</sup>-containing compounds from that demonstrated by the Na<sup>+</sup>- and K<sup>+</sup>-containing compounds.

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