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An investigation into the critical surfactant concentration for solid solubility of hydrophobic drug in different polyethylene glycols

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Abstract

Solid dispersions of 10% w/w griseofulvin in different polyethylene glycols (PEGs) with or without incorporation of alkali dodecyl sulphates (MDS) were prepared by the melting method. The investigations concerned the solid state (X-ray powder diffraction), the transition from solid to liquid state (Oscillating DSC) and the liquid state (low frequency dielectric spectroscopy). The critical concentrations of SDS for the formation of solid solutions in varying PEGs were evaluated. In PEG 3000 this formation occurs at 1.4% w/w SDS, whereas PEG 6000 and PEG 20 000 require solely 1.0% w/w SDS to transfer a dispersion into a solid solution. PEG 3000 was also investigated with the addition of MDS. The critical surfactant concentrations for the formation of solid solutions with the counterions Li^+, Na^+ and K^+ were 1.0%, 1.4% and 2.1% w/w, respectively. The investigated systems had varying degrees of crystallinity. With the addition of SDS to PEGs with a range of molecular weights, the highest crystallinity was seen in the PEG 3000 sample. The different polymers contained different amounts of folded and extended chains which influences the amount of amorphous material within the polymer structure. When surfactants with different counterions were added to PEG 3000, the lithium sample showed the highest crystallinity. In the melt the Li^+ sample showed the lowest dielectric mobility. The results show that concentration and structure of surfactant together with the presence of folded and extended chains form the conditions for the formation of solid solutions.

Keywords: Crystallinity; Solid solution; Alkali dodecyl sulphates; Griseofulvin; X-ray powder diffraction; ODSC; MTDSC; Dielectric spectroscopy

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1. Introduction

The interactions between neutral polymers and ionic surfactants in aqueous solutions and polymer solubilisation in micellar systems have been investigated extensively over the years (Jones, 1967; Cabane, 1977). In the solid state, as in aqueous solutions, the addition of surfactants can be used to improve the dissolution rate of water-insoluble drugs. The solid dispersions can be considered as an extreme case of concentrated polymer solutions and some similarities between the liquid and the solid state have been found. Sjökvist et al. (1991) showed that the addition of the anionic surfactant sodium dodecyl sulphate (SDS) to dispersions of griseofulvin in PEG 3000 creates solid solutions of the drug in the polymer phase. In liquid solutions of polymers the enhanced solubility is due to solubilisation of the drug in the hydrophobic part of the surfactant micelles. A similar model for the solid state was proposed by Aldén et al. (1992).

Crucial for the formation of solid solutions is the interaction between the polymer and surfactant-drug aggregates. The counterion with the highest charge-to-radius ratio, Li^+, has the greatest impact on the binding between polymer and surfactant-drug aggregates, forming a more crystalline structure with a different melting behaviour. The properties of the solid solutions with Na^+ and K^+ as counterions are almost identical (Aldén et al., 1993, 1994).

The molecular weight of polyethylene glycol is an additional factor that greatly influences the formation of solid solutions. Wulff and Aldén (1995) found that PEG 6000 with SDS incorporated dissolves a higher amount of griseofulvin in the solid state compared to PEG 3000 and PEG 20 000 with SDS added. The solubility of griseofulvin in solely PEG did not vary with molecular weight of PEG (Wulff and Aldén, 1995). In the crystal lattice, the PEGs are arranged as lamellae and the hydroxyl end groups are rejected onto the outside of the lamellae (Kovacs et al., 1975). The folded parts of the polymer and the ends of the chains form the amorphous part of the structure (Arlie et al., 1967). The melting behaviour of low molecular weight poly(ethylene-oxide) (PEO) fractions was investigated by Buckley and Kovacs (1976). They found that n-times folded chain PEO crystals are metastable with respect to $(n\text{-}1)$-times folded ones and so on to extended chain crystals.

The aim of the present study was to determine the surfactant concentrations where solid solutions are formed between polymer, anionic surfactant and drug, when the polymer molecular weight is varied and when the counterion of the surfactant is varied. The interactions in the system were investigated in the solid state, in the transition from solid to liquid state and in the liquid state where the conditions for the structure of the solid state are formed.

2. Experimental

2.1. Materials

Polyethylene glycols (PEGs) with the general formula $HO(C_2H_4\text{-}O)_nH$: PEG 3000 (Sigma, USA) with $n = 70$ and average M_W 3350. PEG 6000 (Janssen, Belgium) with $n = 140$ and average M_W 5600–7000. PEG 20 000 (Janssen, Belgium) with $n = 450$ and $M_r > 17000$.

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

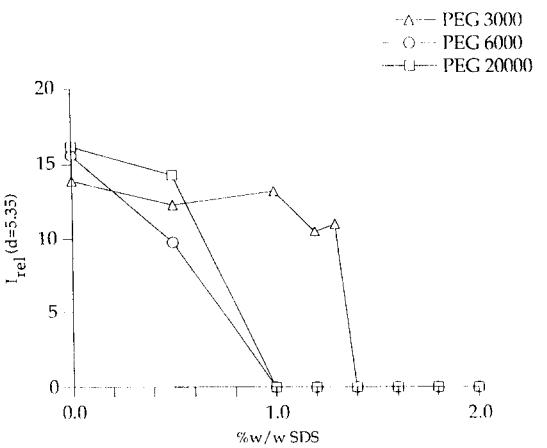

Fig. 1. Intensity of strongest griseofulvin peak vs. % w/w sodium dodecyl sulphate (SDS) in dispersions of different PEGs.

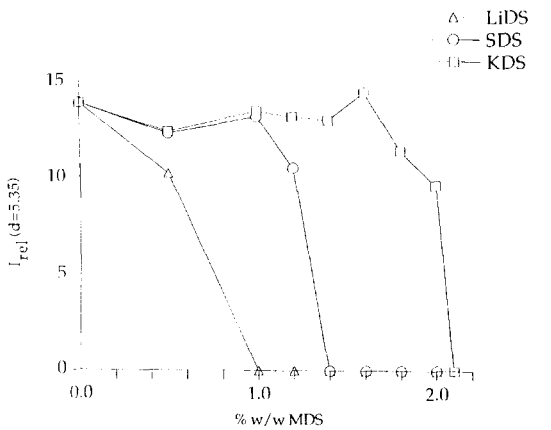

Fig. 2. Intensity of strongest griseofulvin peak vs. % w/w alkali dodecyl sulphate (MDS) in PEG 3000 dispersions.

Alkali dodecyl sulphates (Sigma, USA) denoted by MDS, anionic surfactants with the general formula $C_{12}H_{25}SO_4M$: LiDS where $M = Li^+$, purity approximately 99%. SDS where $M = Na^+$, purity approximately 99%. KDS where $M = K^+$, purity minimum 95%.

2.2. Methods

2.2.1. Preparation of solid dispersions

Various solid dispersions of 10% w/w griseofulvin in the three carriers with and without the addition of 0–2.0% w/w MDS were prepared by the melting method in a CARBOLITE furnace HRF 7/22 with an Eurotherm 818P Programmer at a temperature of 170°C for PEG 3000 and 190°C for PEG 6000 and PEG 20 000. The 10% w/w dispersion was chosen as a model system for the investigations since this dispersion is easy to prepare by the melting method and the drug content is well above the detection limit of 2% w/w griseofulvin for X-ray diffraction (XRD). The samples were brought to room temperature by fast cooling (50–100°C/s) and after at least 24 h the dispersions were pulverised in a mortar and sieved to obtain the fraction 300–500 μm. Grinding is an inevitable step in the preparation of solid dispersions when using the melting method. It does not seem however to effect the crystallinity of the samples significantly. Three different fractions of the samples, ≤ 100, 100–300 and 300–500 μm were investigated by XRD and no significant differences between them could be found. The large size fraction was originally chosen for the dissolution studies performed by Sjökvist et al. (1989, 1991). Since the original idea was to investigate the coupling between the dissolution rates and the structure of the material, we chose in our more mechanistic studies to continue with this fraction thereby changing as few parameters as possible. Since a small amount of water may be absorbed by these samples all possible measures were taken to minimize water absorption. Using the larger size fraction was thus also a way to minimize the water absorption of the samples.

2.2.2. Preparation of pure polymer specimen

The supplied polymers were pulverised in a mortar and sieved to obtain the fraction 300–500 μm. Samples of supplied PEG, ground supplied PEG and PEG treated by the melting method showed no significant differences in their X-ray patterns.

2.2.3. X-ray diffraction

Phase analysis was made by X-ray powder diffraction using a STOE position sensitive detector (PSD) system (Germany) with Ge monochromatised Cu$K\alpha_1$ radiation. A linear detector covering 7° at 155 mm distance was operated in a scanning mode. Room temperature runs were performed by rotating the powder attached to a cellulose membrane about the normal to the membrane plane. Exposure time was about 15 min ensuring statistical reability in the measurements. The detection limit for the XRD equipment is 2% w/w or more for griseofulvin in the investigated systems (Sjökvist et al., 1991). All phases present could be identified by means of characteristic non-overlapping lines (Cullity, 1978).

2.2.4. Oscillating differential scanning calorimetry (ODSC)

The dispersions were analysed using an oscillating Seiko DSC 220 differential scanning calorimeter (Japan). The samples (4.0–5.0 mg) were kept in aluminium pans in an atmosphere of nitrogen. An amplitude of 6°C and a frequency of 0.02 Hz

Table 1
Comparison of critical surfactant concentration for solid solution formation and ratio of charge-to-radius ratios for Li^+, Na^+ and K^+.

Ion	Critical concentration (% w/w)	Radius (pm) (Ahrens, 1952)	Charge-to-radius ratio Li^+/M^+
Li^+	1.0	68	1.0
Na^+	1.4	97	1.4
K^+	2.1	133	2.0

were selected in the oscillating mode together with a heating rate of 5°C/min in the temperature range 10–260°C. The degree of oscillation according to Aldén et al. (1995) is 1.4 with the selected values. The pure polymers were analysed in the range 20–100°C using a heating rate of 1°C/min with an amplitude of 2°C at frequency 0.02 Hz giving a degree of oscillation of 2.4. The calorimeter was calibrated with indium, tin and gallium as standards. The three heat of fusion values determined are the reversible c_p-component ΔH_c, the irreversible kinetic component ΔH_k, and the conventional component ΔH. The results are presented as mean values with the standard deviations based on three to five determinations.

2.2.5. Low frequency dielectric spectroscopy

The dielectric responses of the samples were measured at 70°C using a low-frequency dielectric spectrometer (Dielectric Instrumentation Ltd, UK). The samples were placed in a PTFE pot and two stainless steel electrodes (area 0.5 cm^2, separation distance 1 mm) inserted into the melt. A voltage of 0.1 V r.m.s. was applied to the sample in the frequency range 10^5–10^{-2} Hz. The returning signal was subsequently analysed to allow calculation of the capacitance, C, and loss, G/ω. All reported data represent the average of at least three measurements taken by the instrument.

3. Results and discussion

3.1. The solid state investigated by X-ray diffraction

The long-range order, as reflected in the X-ray powder diffractograms, was used for phase analysis of the samples. The X-ray diffractogram of griseofulvin can be found in a previous paper (Aldén et al., 1994). The peaks represent the reflections from the crystalline phase.

3.1.1. PEGs/griseofulvin/SDS samples

In Fig. 1 the intensity of the strongest peak from griseofulvin is plotted against % w/w SDS added to different PEGs. The disappearance of pure griseofulvin phase and thus the formation of solid solution occur at approximately 1.4% w/w SDS for PEG 3000, whereas for PEG 6000 and PEG 20 000 an amount approximately equal to 1.0% w/w SDS is necessary to transfer the dispersion into a solid solution. The different critical surfactant concentrations for formation of the solid solution might be correlated to the structure of PEGs. Low molecular weight fractions of poly(ethylene-oxide) crystallise with molecules either fully extended or folded an integer number, n, of times, where n increases with molecular weight (Buckley and Kovacs, 1976). The folding and the ends of the chains form the amorphous part of the structure (Arlie et al., 1967). The surfactant-drug aggregates are likely to dissolve in the amorphous part and a certain amount of folded chains may therefore be a prerequisite of the formation of surfactant-drug aggregates in the PEG structure. If 2% w/w SDS is added to a sample, the solid solubility of griseofulvin in PEG 6000 is much higher than in PEG 3000 or PEG 20 000 (Wulff and Aldén, 1995). Thus a high molecular weight of PEG with large amount of folded chains does not necessarily imply an increased solubility of the surfactant-drug aggregates. A possible explanation to this is that the intramolecular interaction within the folded parts of the polymer chains intensifies in relation to the

Table 2
Number of weak PEG lines in the series of samples with 0–2% w/w surfactant added

d-value	PEG 3000+GRIS+ LiDS[a]	PEG 3000+GRIS+ SDS[a]	PEG 3000+GRIS+ KDS[a]	PEG 6000+GRIS+ SDS[b]	PEG 20000+GRIS+ SDS[b]
20.25	1 sample	—	—	—	—
19.77	—	1 sample	—	—	—
18.76	1 sample	—	—	—	1 sample
18.29	—	1 sample	—	—	—
18.03	—	—	—	1 sample	—
15.40	1 sample	—	1 sample	—	—
14.90	1 sample	—	—	—	—
14.64	—	1 sample	—	—	—
14.51	—	—	2 samples	—	—
14.26	—	—	—	1 sample	1 sample
8.84	9 samples	1 sample	—	—	—
7.39	10 samples	3 samples	—	—	—
6.54	10 samples	6 samples	1 sample	6 samples	4 samples
5.65	7 samples	1 sample	—	—	—
5.18	10 samples	3 samples	—	—	—
4.08	1 sample	—	—	—	—

[a] Serie of ten samples with a concentration of 0–2% w/w MDS.
[b] Serie of eight samples with a concentration of 0–2% w/w SDS.

interaction between the PEG chain and the aggregates. Our results suggest that a certain balance between amount of folded chains and surfactant concentration might be important for the creation of the solid solution.

3.1.2. PEG 3000/griseofulvin/MDS samples

PEG 3000 was investigated with the addition of three different alkali dodecyl sulphates, here denoted by MDS, where $M = Li^+$, Na^+ and K^+ respectively. In Fig. 2 the intensity of the strongest peak from griseofulvin is plotted versus the amount of MDS in PEG 3000. Significant differences are seen between the critical surfactant concentrations. It is evident that the counterions influence the formation of the surfactant-drug aggregates in the polymer phase. In Table 1 the critical surfactant concentrations for solid solution formation are listed as are the radii of the ions. The ratios of the critical concentrations are related to the size or charge-to-radius ratio of the counterions. If the counterions act as bridges between the polymer chain and the surfactant-drug aggregate (Aldén et al., 1993) the distance between the counterion and the electronegative part of the polymer chain must be important. The lithium ion can create the shortest bridge which might give the strongest chemical bond between polymer and surfactant-drug aggregates.

3.1.3. Crystallinity

The number of diffraction lines and their intensity in the PEG diffraction pattern reflect the crystallinity of the sample. Table 2 presents the number of weak PEG lines that appears in the series of samples with 0–2% w/w surfactant added. In the dispersions of griseofulvin in solely PEG these weak PEG lines are not seen with the exposure time used. The crystallinity varies with the molecular weight of the polymer and with the counterion of the surfactant. Addition of surfactant with Li^+ as counterion has a great impact on the crystallinity of PEG 3000, while Na^+ effects the crystallinity moderately and K^+ hardly at all. A possible explanation might be that the surfactant-drug aggregates to a large extent effect the hydroxyl end groups in the amorphous fraction. It suggests that the affinity for the hydroxyl end groups decreases in the order $Li^+ > Na^+ > K^+$. The crystallinity of PEG 6000 and PEG 20 000 is not much influenced by the additives which can be explained by the fact that the relative proportion

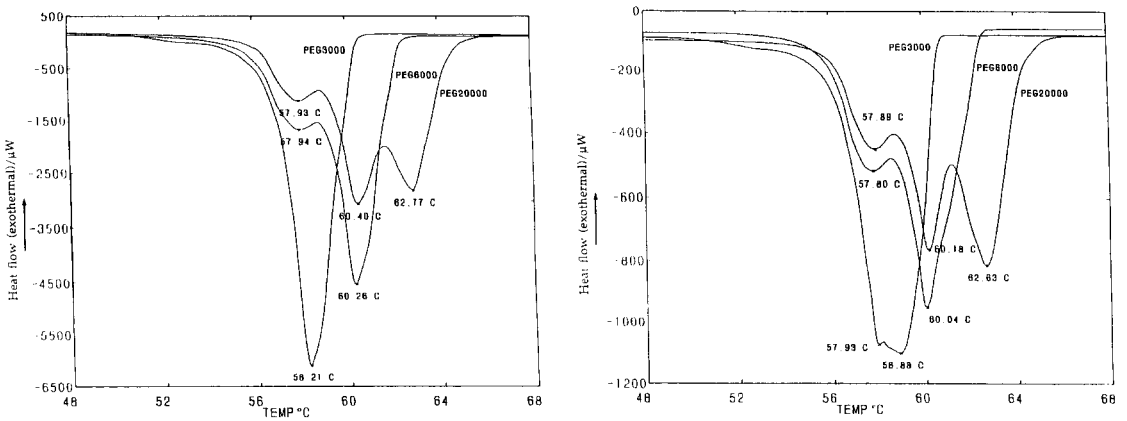

Fig. 3. Thermograms for PEG 3000, PEG 6000 and PEG 20 000 obtained by ODSC. (a) Conventional component; (b) c_p (reversible) component.

of hydroxyl end groups decreases with molecular weight. This might indicate that the surfactant-drug aggregate is dissolved in, and influences especially, the amorphous part of the structure where both the folding of chains and the hydroxyl end groups are found.

3.2. The melting process investigated by ODSC

3.2.1. Pure PEG samples

The melting process of the pure polymers was investigated with a low heating rate by ODSC. Thermograms for PEG 3000, PEG 6000 and PEG 20 000 are presented in Fig. 3(a, b). According to the study by Buckley and Kovacs (1976) on melting endotherms of PEGs, the lower melting peak could be assigned to the melting of the folded chains and the higher melting peak to the fully extended chain crystals. Buckley and Kovacs found some evidence of once folded chain crystals in PEG 3000, but the thermograms showed only one endothermic peak and the folded chain crystals were supposed to unfold too rapidly to be observed by conventional DSC. The melting endotherms here suggests that PEG 3000 contains only fully extended chain crystals ($n = 0$), PEG 6000 partly once folded chain crystals ($n = 0$ and 1) and PEG 20 000 also twice folded chain crystals ($n = 0$, 1 and 2). The reversible component of the melting endotherms, however, reveals two peaks, very close in temperature, in the melting endotherm of PEG 3000. The lower melting peak might represent the melting of once folded chain crystals. The fact that the polymers have different amounts of folded and extended chains and thereby different amounts of amorphous parts in the crystals supports the differences in solid solution formation found by X-ray for the investigated systems.

3.2.2. Crystallinity

Table 3 presents the ΔH_c, ΔH_k, ΔH and $\Delta H_c/\Delta H$ values for the dispersions and solid solutions formed when griseofulvin is dispersed in different PEGs with or without the critical concentration of surfactant for solid solution formation. It was found in a recent study (Aldén et al., 1995) that the ratio $\Delta H_c/\Delta H$ might be a possible measure of the degree of crystallinity in a system at certain degrees of oscillation. Here the lithium sample has the highest ratio of the solid solutions, implying a more crystalline structure, consistent with the results found by Aldén et al., 1994. For the PEG 3000 samples with Na^+ and K^+ the ratios remain almost the same as for the dispersion considering the relatively high standard deviation for the sodium sample. The change in the ratio $\Delta H_c/\Delta H$ between systems with and without surfactant added is presented as a percentage value in Table 3. For all systems with SDS added a decrease in

Table 3
Heat of fusion and $\Delta H_c/\Delta H$ values for dispersions and solid solutions of griseofulvin in PEGs with and without the critical surfactant concentration

Sample	ΔH_c (J/g)[a]	ΔH_k (J/g)[a]	ΔH (J/g)[a]	$\Delta H_c/\Delta H$	($\Delta H_c/\Delta H$ dispersion)/($\Delta H_c/\Delta H$ solution)
PEG 3000+10% GRIS	76.9 ± 4.1	93.7 ± 3.5	170.6 ± 0.9	0.451	—
PEG 3000+10% GRIS+1.0% LiDS	78.8 ± 0.46	78.4 ± 2.4	157.2 ± 2.1	0.501	+10%
PEG 3000+10% GRIS+1.4% SDS	73.5 ± 5.9	94.2 ± 5.3	167.7 ± 0.55	0.438	−3.0%
PEG 3000+10% GRIS+2.1% KDS	72.8 ± 2.1	86.4 ± 2.2	159.2 ± 1.4	0.457	+1.3%
PEG 6000+10% GRIS	62.5 ± 3.4	96.0 ± 3.4	158.4 ± 0.8	0.395	—
PEG 6000+10% GRIS+1.0% SDS	69.3 ± 2.2	91.7 ± 1.4	161.4 ± 0.95	0.429	−7.9%
PEG 20000+10% GRIS	66.9 ± 2.5	86.9 ± 3.5	153.9 ± 2.6	0.435	—
PEG 20000+10% GRIS+1.0% SDS	58.0 ± 2.3	100.3 ± 2.0	158.3 ± 0.35	0.366	−19%

[a] Integration interval: 20–80°C+80–150°C

the ratio is seen when going from a dispersion, a two-phase system, to a solid solution. The change in the ratio increases with molecular weight suggesting a higher crystallinity in the solid solutions with PEG 3000 than in solutions with PEG 20 000. This is in accordance with the results on crystallinity found by XRD.

3.2.3. PEGs/griseofulvin/SDS samples

In Fig. 4(a–c) the ΔH_c, ΔH_k and ΔH values for dispersions of griseofulvin in PEG 3000/SDS (a), PEG 6000/SDS (b) and PEG 20 000/SDS (c) are plotted against the concentration of SDS. The phase areas determined by XRD are marked in the diagrams. The diagrams for PEG 6000/SDS and PEG 20 000/SDS are quite similar with values of the kinetic component fairly large compared to the c_p component. The c_p component also tend to decrease for both polymers as the concentration of SDS increases. The behaviour of PEG 3000/SDS is more complex, especially in the two-phase area. The c_p component is closer to the kinetic component in size revealing a higher crystallinity. The c_p values might be considered to be fairly constant through the concentration range.

3.2.4. PEG 3000/griseofulvin/MDS samples

The corresponding plots for dispersions of griseofulvin in PEG 3000 with addition of LiDS and KDS have shapes similar to the plot of PEG 3000/SDS (Fig. 4(a)). For LiDS and SDS the values of the kinetic and c_p component vary in the two-phase area, while the values become more constant when entering the one-phase (solid solution) area. Also the KDS-containing dispersions, which represent two-phase systems in the concentration range examined, show the same variation.

3.3. The melt investigated by LFDS

The dielectric response of the pure polymers was measured at 70°C to investigate a complete melt. The shape of the curves were similar to those reported by Craig et al. (1993). No significant differences between the three polymers could be observed.

3.3.1. PEG 3000/MDS samples

Firstly the molten solid solutions of solely surfactants (MDS) in PEG 3000 were investigated. The spectra of log capacitance (a) and loss (b) against log frequency are presented in Fig. 5(a, b). It can be seen that the addition alters the curve of PEG 3000 by shifting it to higher values of capacitance and loss respectively. The small differences between the samples are probably due to different mobility of the counterions, Li^+, Na^+ and K^+, in an electric field.

3.3.2. PEG 3000/griseofulvin/MDS samples

Secondly the molten solid solutions of griseofulvin in PEG 3000 with MDS incorporated

were examined. The dielectric responses of the samples are presented in Fig. 6(a, b). The shapes of the curves are similar to molten PEG 3000

Figure 4a

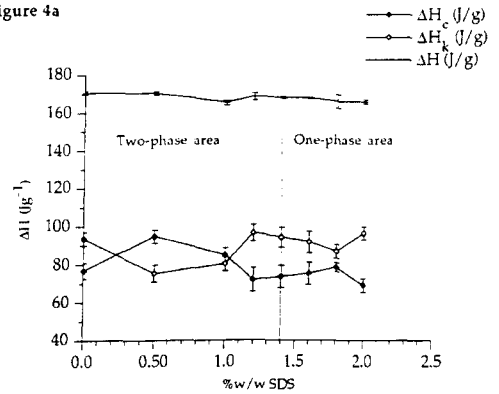

Figure 4b

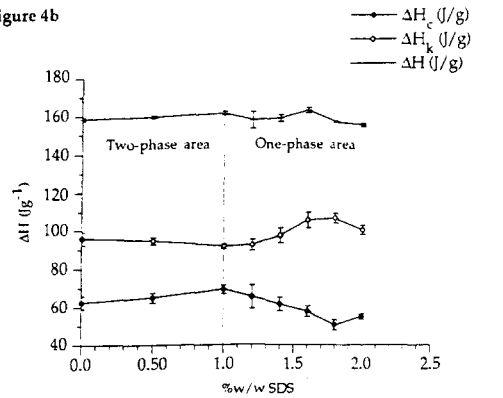

Figure 4c

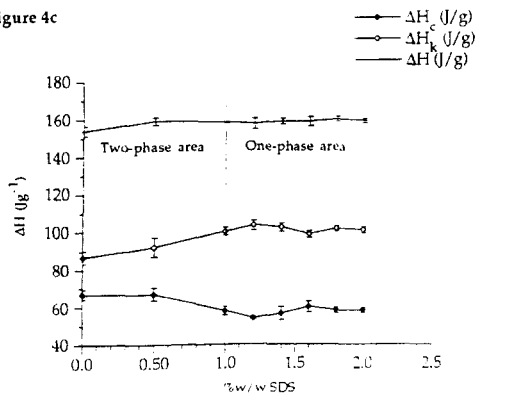

Fig. 4. Heat of fusion values for dispersions of griseofulvin in: (a) PEG 3000/SDS; (b) PEG 6000/SDS; (c) PEG 20000/SDS vs. % w/w SDS.

Figure 5a

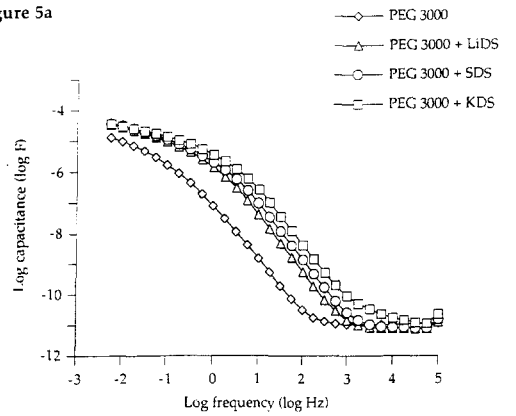

Figure 5b

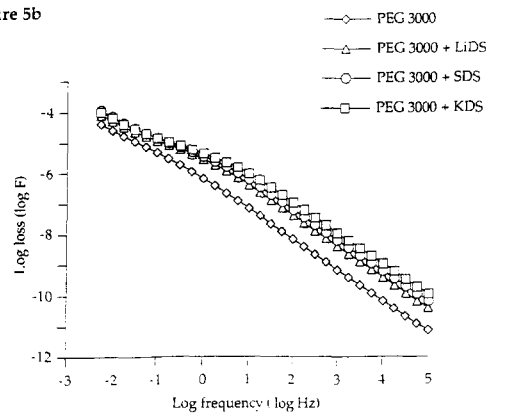

Fig. 5. Dielectric response of PEG 3000 and solid solutions of alkali dodecyl sulphates (MDS) in PEG 3000. (a) Capacitance; (b) loss.

for all three solid solutions. This fact shows that at 70°C the samples are all in a liquid phase with no undissolved particles present. The lithium sample clearly shows a different dielectric behaviour, with less mobility at any frequency, than the others. This may indicate that the lithium ion is associated more tightly to the polymer chain or to the surfactant-drug aggregate, than the others. One prerequisite of the formation of solid solution is the interaction between the counterions of the surfactant and the polymer chain oxygens. Obviously this condition for the formation of a solid solution is created already in the melt. An increased diversity between the samples occurs when griseofulvin is present in the systems.

4. Conclusions

Different critical surfactant concentrations are required for solid solution formation depending on the molecular weight of the polymer and on the counterion of the surfactant. A higher concentration of SDS was required for PEG 3000, than for PEG 6000 and 20 000 to form a solid solution. The PEGs investigated have different amounts of folded chains and thereby varying degree of amorphous parts. Since the surfactant-drug aggregates are supposed to dissolve in the amorphous part of the polymer the results may show that both surfactant concentration and amount of folded and extended chains form the prerequisite for the formation of a solid solution. In PEG 3000, Li^+ as the counterion of the surfactant showed the lowest critical concentration for formation of solid solutions. Furthermore, the Li^+ compounds showed an increase in crystallinity at the solid solution formation. If the counterions act as a bridge between the polymer and the surfactant-drug aggregate, the strongest chemical bond and thereby the most stable system can be formed with Li^+ having the highest charge-to-radius ratio. Furthermore the prerequisites of the structure of the solid state are given in the melt. In the melt the mobility of the ions decreases in the order $K^+ > Na^+ > Li^+$, indicating that Li^+ is more tightly associated to the polymer chain or the surfactant-drug aggregate.

Figure 6a

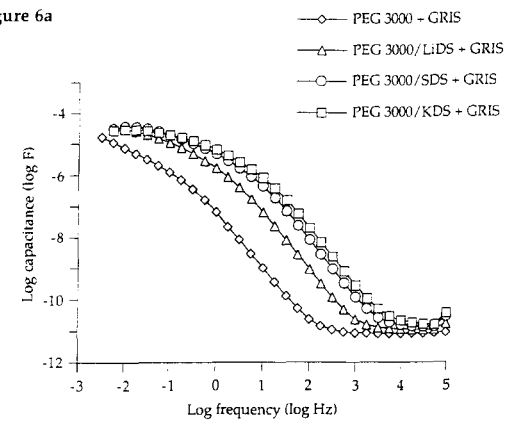

Figure 6b

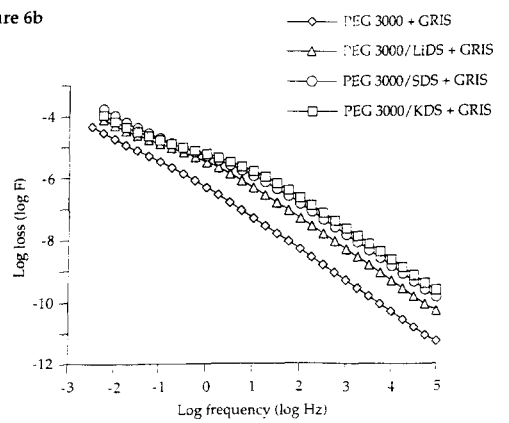

Fig. 6. Dielectric response of griseofulvin in PEG 3000 and of solid solutions of griseofulvin in PEG 3000/MDS. (a) Capacitance; (b) loss.

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