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Physicochemical aspects of drug release. XIII. The effect of sodium dodecyl sulphate additions on the structure and dissolution of a drug in solid dispersions

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Summary

Solid dispersions of the sparingly soluble drug griseofulvin were prepared by the melting method with polyethylene glycol (PEG) 3000 as a carrier. The anionic surfactant sodium dodecyl sulphate (SDS) was incorporated during the preparation, in order to study the effect on incorporated state and dissolution of the drug. Dissolution rate measurements were performed according to USP XXI (paddle method) on dispersion particles in media of pure distilled water or distilled water with different concentrations of SDS, all below the critical micelle concentration. For solid dispersions without SDS incorporated, the dissolution rate was reduced with an increase in griseofulvin content. When SDS was added to the medium the dissolution rate increased in proportion to the concentration of SDS. These results support the assumption that wetting the dispersion particles is important in the dissolution process of these systems. The fastest drug dissolution was obtained for dispersions incorporating SDS. In dispersions containing 1% w/w SDS, 90% of the griseofulvin was dissolved within 2 min, independent of drug concentration and dissolution medium. It was possible to determine the relative amounts of each phase using the X-ray diffraction method. It was observed that in solid dispersions without SDS incorporated, both the pure griseofulvin phase and the pure PEG phase were present. In samples with SDS incorporated the phase composition changed. A large amount of griseofulvin was dissolved in the PEG/SDS structure forming a solid solution. In solid dispersions of 3 and 10% w/w griseofulvin with 1 and 2% w/w SDS incorporated, respectively. no pure griseofulvin phase was seen and the solid solution of griseofulvin in the PEG/SDS structure was the only phase appearing. The heat of fusion values, obtained by DSC, supported the idea of a change in the phase composition in the systems with the incorporation of SDS.

Introduction

Solid dispersions of drugs in easily soluble carriers can be used to increase the dissolution rate of sparingly soluble drugs. However, with an increase in drug content the dissolution rate is normally retarded (Sjökvist and Nyström, 1988; Sjökvist et al., 1989). In a previous study (Sjökvist and Nyström, 1988) it was observed that in solid dispersions prepared by a solvent method, the drug is present mainly in particulate form. For these dispersions containing relatively coarse drug particles, increased drug content is associated with

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increased particle size and decreased dissolution rate. In the same study it was found that the drug particles within solid dispersions prepared by a melting method, were fine and remained so for the range of drug concentrations tested. The explanation for the observed retarded dissolution rate at higher drug concentrations could be that higher concentrations of a hydrophobic drug in fine particulate form provide increased dissolution surface areas of a pronouncedly hydrophobic nature. The wetting of these surfaces and the subsequent drug release may then be a rate-limiting step in the drug dissolution process.

The aim of the study was to examine the effect of the incorporation of a surfactant into the dispersions and also to add different concentrations of surfactant to the dissolution medium and to characterize the subsequent effects on the dissolution rate and incorporated state of the drug.

Experimental

Materials

Griseofulvin microsized (Glaxo, U.K.) is a sparingly soluble drug with an aqueous solubility of approximately 8 mg/l. The primary characteristics have been characterized and described earlier (Nyström et al., 1985; Sjökvist and Nyström, 1988).

Polyethylene glycol (PEG) 3000 (Apoteksbolaget, Sweden) was used as an easily water-soluble carrier. The melting temperature is 56–58°C as measured with a DSC 20.

Sodium dodecyl sulphate (SDS) (Apoteksbolaget, Sweden) is an anionic surfactant used as a wetting and solubilizing agent, which is freely soluble in water. The critical micelle concentration in water is approx. $7–8 \times 10^{-3}$ mol/l, corresponding to approx. 0.2% (Williams et al., 1955; Handbook of Pharmaceutical Excipients, 1986; De Smidt et al., 1987; Carlsson et al., 1988).

Methods

Preparation of solid dispersions

Solid dispersions of three concentrations of griseofulvin (3, 10 and 20% w/w) were prepared by the melting method at a temperature of 145°C as described earlier (Sjökvist et al., 1989). In dispersions with SDS included, the surfactant was dispersed in the melted carrier prior to the addition of griseofulvin. The dissolution of griseofulvin in the carrier system was faster in the presence of SDS.

Dissolution studies

Drug dissolution rate. Dissolution tests according to USP XXI (paddle method, 100 rpm) were carried out under 'sink conditions' at room temperature (21°C) on dispersion particles (300–500 μm). The media used were pure distilled water or distilled water with different concentrations of SDS, all below the critical micelle concentration. Dissolution rate studies were also performed in media with 0.001 and 0.01% polysorbate 80 with and without 0.9% sodium chloride.

Samples were transferred to a UV spectrophotometer (Ultrospec II, LKB, Sweden) flow cell where the absorbance was measured at 295 nm. The results presented are mean values of three determinations.

Carrier dissolution rate. The USP XXI disintegration test, basket rack assembly (Pharmatest, Germany), was used as a simplified dissolution rate test, as described earlier (Sjökvist et al., 1989). Tablets of pure carrier and of solid dispersions were made and tested for disintegration times in 900 ml of pure distilled water and in distilled water with 0.1% SDS at 23°C. The presented results are mean values of six tablets.

Characterization of drug solubility and surface tension in dissolution media

Drug solubility. The solubility of griseofulvin in pure distilled water and in distilled water with different concentrations of SDS (0.05–1.0% w/v) was determined spectrophotometrically. 100 mg of griseofulvin was added to 100 ml medium. The samples were exposed to sound waves (Bransonic, U.S.A.) for 20 min and agitated for 24 h at room temperature. After temperature equilibration to 21°C, samples were withdrawn and passed through a 0.6 μm filter (Nuclepore, U.S.A.). The results presented are mean values of five determinations.

The media of different concentrations of SDS were used as blanks.

Surface tension. The surface tension was measured with a du Nuoy ring tensiometer (Tensiometer 8551, Krüss, Germany) in media of distilled water with different concentrations of SDS (0.005–1.00% w/v) at 22°C.

Characterization of structure in solid dispersions

X-ray diffraction. Phase analysis and determination of unit cell dimensions were made by X-ray powder diffraction using a Guinier-Hägg type focusing camera with CuK_α radiation, as described earlier (Sjökvist et al., 1989).

Differential scanning calorimetry. Heat of fusion determinations were made by a DSC 20 (Mettler, Switzerland) as described earlier (Sjökvist et al., 1989). The sample weight was 3.5–4.5 mg for all samples. A heating rate of 10°C/min was used and the results presented are mean values of at least four determinations.

Results and Discussion

Drug solubility as a function of surfactant concentration

The critical micelle concentration for SDS in distilled water is between 0.1 and 0.2% (Fig. 1). The solubility of griseofulvin was considerably increased when the surfactant concentration in the medium exceeded this concentration range (Fig. 1). To avoid the formation of micellar solutions, dissolution rate studies were carried out at concentrations of 0.1% SDS or below.

Drug dissolution rate as a function of surfactant concentration in the dissolution media

In earlier studies (Sjökvist and Nyström, 1988; Sjökvist et al., 1989) a dissolution medium of water containing 0.9% sodium chloride and 0.01% polysorbate 80 has been used. In this study different dissolution media were tested and it was observed that the choice of medium was of substantial importance.

Polysorbate 80. Dissolution rate studies were performed on particles of solid dispersions of 10% w/w griseofulvin in pure water and water with

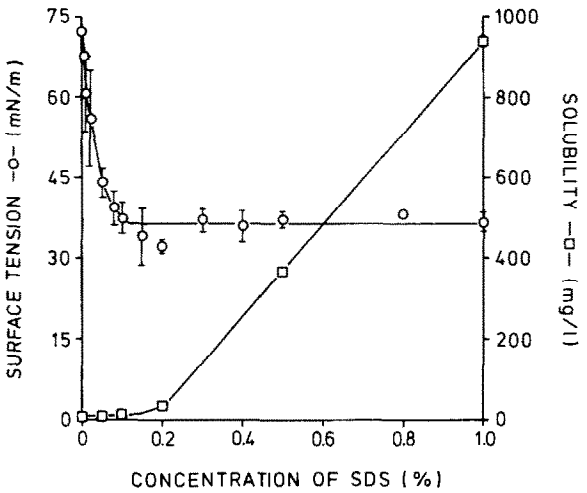

Fig. 1. Surface tension and the solubility of griseofulvin as a function of SDS concentration in distilled water. (○) Surface tension (mN/m), (□) a solubility of griseofulvin (mg/l). Error bars represent the 95% confidence interval for the mean. For some of the surface tension and solubility values the confidence intervals are covered by the symbols.

0.001 and 0.01% polysorbate 80, with and without 0.9% sodium chloride added (Fig. 2). Sodium chloride itself had a favourable effect on the dissolution rate and an increase in polysorbate concentration increased the dissolution rate further.

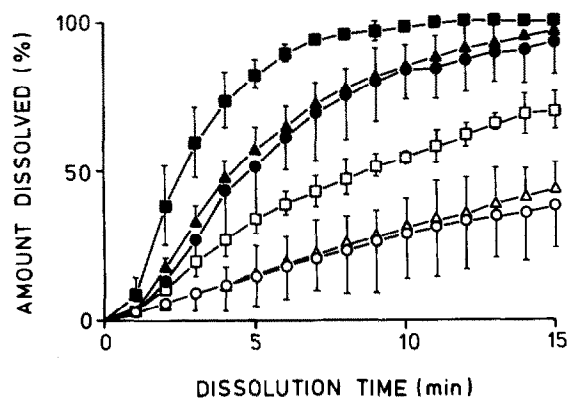

Fig. 2. Dissolution rate profiles for solid dispersions (sieve fraction 300–500 μm) of 10% w/w griseofulvin in PEG 3000, in media of different concentrations of polysorbate 80 with and without 0.9% sodium chloride. (○, ●) No polysorbate 80; (△, ▲) 0.001% polysorbate 80; (□, ■) 0.01% polysorbate 80. Open symbols: no sodium chloride; closed symbols: with 0.9% sodium chloride. Error bars represent the 95% confidence interval for the mean.

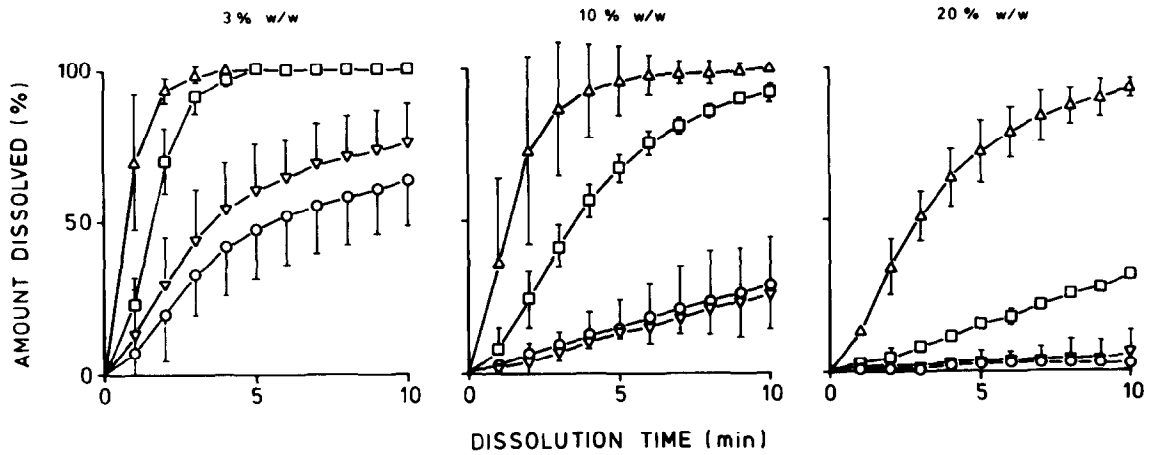

Fig. 3. Dissolution rate profiles for solid dispersions of 3, 10 and 20% w/w griseofulvin in PEG 3000 in media with different concentrations of SDS. (○) No SDS, (▽) 0.001% SDS, (□) 0.01% SDS, (△) 0.1% SDS. Error bars represent the 95% confidence interval for the mean.

The dissolution enhancing effects of sodium chloride and polysorbate seemed to be additive.

A possible explanation for the increased dissolution rate could be that as polysorbate 80 lowers the surface tension, the wettability is improved and subsequently the dissolution rate is increased (Chiou and Niazi, 1971). The addition of sodium chloride may increase the solubility of PEG and thereby enhance the release of griseofulvin particles to the dissolution medium.

The addition of sodium chloride does not influence the solubility of griseofulvin. In media with 0.01% polysorbate 80 with and without 0.9% sodium chloride, the solubilities were 8.2 ($\pm$0.4) and 8.4 ($\pm$0.2) mg/l, respectively (with standard deviation given in parentheses).

Sodium dodecyl sulphate (SDS). Dissolution rate studies were performed on solid dispersion particles of the three drug concentrations in media of distilled water and water containing different concentrations of SDS (Fig. 3). As reported earlier (Sjökvist and Nyström, 1988) the fastest drug dissolution was obtained with the lowest content of drug, for all the tested concentrations of SDS in the media.

With increasing content of SDS in the media, the dissolution rate increased. A fraction of the solid dispersion particles floated on the surface of distilled water, especially for the dispersion with highest drug content, while they were rapidly wetted and dissolved when the concentration of SDS in the medium was high. This supports the idea that wetting is important in the dissolution process of these systems.

In the further dissolution rate studies, media with SDS was used. Due to precipitation, sodium chloride was not added to the media.

Drug dissolution rate as a function of surfactant incorporation into solid dispersions

To investigate if the incorporation of SDS could improve the dissolution, different concentrations of SDS were incorporated in the solid dispersions during the preparation. In Fig. 4 the dissolution rate profiles, in distilled water as dissolution medium, for solid dispersions of 10% w/w griseofulvin containing different concentrations of SDS are presented. The dissolution rates increased significantly, giving an almost instant dissolution, when 1 and 2% w/w of SDS was incorporated. The same was observed for dispersions of 3 and 20% w/w griseofulvin incorporating 1% w/w SDS (Fig. 5).

The dispersion of 10% w/w griseofulvin incorporating 1% w/w SDS was also dissolved in media containing increasing amounts of SDS (Fig. 6). It was observed that, independent of the medium used, 90% of drug was dissolved within 2 min.

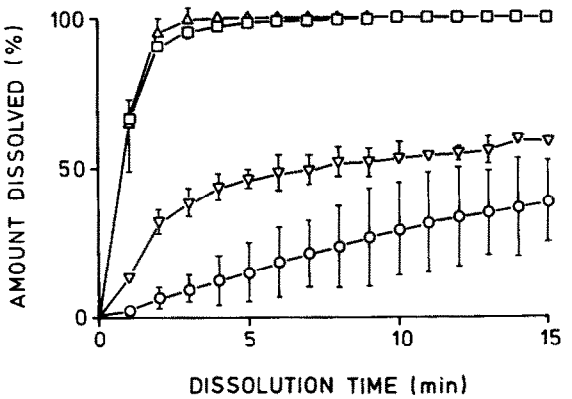

Fig. 4. Dissolution rate profiles in pure distilled water for solid dispersions of 10% w/w griseofulvin with different concentrations of SDS incorporated in the solid dispersions. Amount of SDS incorporated: (○) no SDS, (▽) 0.5% SDS, (□) 1% SDS, (△) 2% SDS. Error bars represent the 95% confidence interval for the mean.

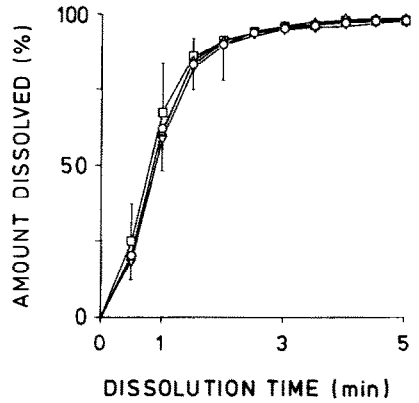

Fig. 6. Dissolution rate profiles in media with different concentrations of SDS, for dispersions of 10% w/w griseofulvin in PEG 3000 with 1% SDS incorporated. Amount of SDS in distilled water: (○) no SDS, (▽) 0.001% SDS, (△) 0.01% SDS, (□) 0.1% SDS. Error bars represent the 95% confidence interval for the mean.

The extremely high dissolution rates obtained, which are faster than those obtained for dispersions with only griseofulvin in dissolution medium containing SDS (Fig. 3), show that the incorporation of SDS during preparation of the dispersions not only improves the wetting of the dispersion particles at the release stage, but also promotes some other change.

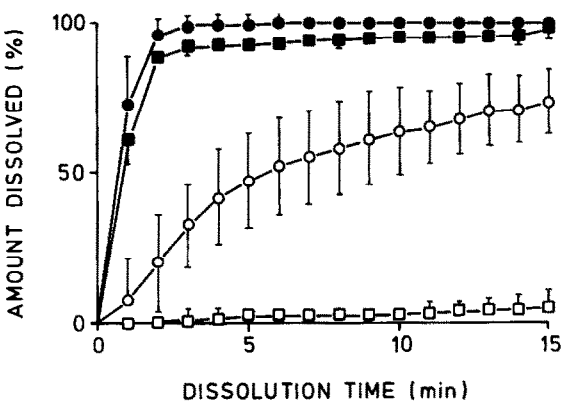

Fig. 5. Dissolution rate profiles in pure distilled water for dispersions of 3 and 20% w/w griseofulvin with and without 1% SDS incorporated. (○, ●) 3% w/w griseofulvin; (□, ■) 20% w/w griseofulvin. Open symbols: no SDS; closed symbols: 1% SDS incorporated. Error bars represent the 95% confidence interval for the mean.

Carrier dissolution rate

Compacts of PEG and of solid dispersions were also made and tested for disintegration times. This test is designed to give an approximate measure of the dissolution rate of the carrier system. The disintegration media used were pure distilled water and distilled water with 0.1% SDS. The compact erodes rather than disintegrates. The disintegration of pure PEG is approx. 12 min independent of the medium used (Table 1). The incorporation of SDS in the pure carrier does not affect the dissolution, as PEG itself is easily wetted and dissolved in pure water.

The disintegration times in distilled water were prolonged to approx. 30 min with dispersions of 10 and 20% w/w griseofulvin and to 20–25 min in a dissolution medium of 0.1% SDS. The disintegration is faster in the medium of 0.1% SDS for dispersions without SDS and for the dispersion with 0.5% SDS incorporated compared to in pure water. However, in dispersions with 1 or 2% w/w SDS incorporated, the disintegration times decreased to approx. 14–16 min independent of drug concentration in dispersions or media used.

The results from the disintegration studies support the interpretations presented above, that solid dispersions without SDS become more hydrophobic when the content of griseofulvin is in-

TABLE 1

Characterization of carrier dissolution from disintegration measurements of compacts [a]

Sample	Tablet weight (mg)	Tablet height (mm)	Disintegration time in (min ± SD)	
			Water	0.1% SDS
PEG 3000				
No SDS	500	4.36	12.0 ± 1.2	11.7 ± 1.1
1% SDS	500	4.30	11.5 ± 0.5	12.4 ± 1.1
3% griseofulvin/PEG 3000				
No SDS	502	4.34	18.0 ± 5.2	14.3 ± 1.3
1% SDS	502	4.36	14.7 ± 2.5	14.6 ± 2.6
10% griseofulvin/PEG 3000				
No SDS	508	4.33	35.3 ± 6.3	21.4 ± 4.6
0.5% SDS	508	4.35	33.7 ± 7.4	21.8 ± 2.6
1% SDS	506	4.30	14.0 ± 0.4	14.6 ± 1.2
2% SDS	506	4.28	14.4 ± 1.9	15.6 ± 2.2
20% griseofulvin/PEG 3000				
No SDS	517	4.28	29.6 ± 2.3	25.6 ± 2.4
1% SDS	511	4.26	15.6 ± 3.2	16.3 ± 2.7

[a] Maximum upper punch pressure constant at 100 MPa.

creased. If SDS is added to the medium, the systems become more easily wetted and thus a faster dissolution of the carrier can be obtained. For dispersions incorporating SDS the dissolution is further improved, indicating that SDS influences the carrier and drug combination in some other way than just by increasing the wettability.

Characterization of structure in solid dispersions

Phase analysis. The relative amounts of each phase can be determined by the X-ray powder diffraction method. For an ideal crystalline system, this information is obtained from the relationship between the intensities of the characteristic diffraction lines of each phase (Cullity, 1978). This relationship in dispersion systems (Table 2) is calculated as the quotient of the intensity of the griseofulvin phase divided by the intensity of the PEG-containing phase.

In all the dispersions, without SDS incorporated, both the pure griseofulvin and the pure carrier phases could be identified. The griseofulvin phase is detectable by the X-ray method in dispersions where the concentration of drug is greater than 2% in the PEG phase.

For the 10% w/w drug dispersion the intensity quotient between the phases was 0.6. Both phases were also present in the dispersion with 0.5% w/w SDS incorporated, but the relationship had decreased to 0.4. In the dispersions with more SDS incorporated, the phase composition was further changed. In the dispersion containing 1% w/w SDS there were still two phases appearing, but the relationship had significantly decreased to approx. 0.06.

The intensity quotient is not expected to follow a linear relationship in the dispersion system, because of the pronounced amorphous character of the carrier obtained by the fast cooling method during the preparation of the dispersions. However, the decrease from 0.6 to 0.06 in the SDS-con-

TABLE 2

X-ray powder diffraction analysis

Sample	Phases observed [a]	Relationship [b]
PEG 3000		
No SDS	PEG	–
1% SDS	PEG/SDS	–
3% griseofulvin/PEG 3000		
No SDS	PEG + griseofulvin	0.08
1% SDS	$(PEG/SDS)_{1-x}(griseofulvin)_x$	0
10% griseofulvin/PEG 3000		
No SDS	PEG + griseofulvin	0.6
0.5% SDS	PEG/SDS + griseofulvin	0.4
1% SDS	$(PEG/SDS)_{1-x}(griseofulvin)_x$ + griseofulvin	0.06
2% SDS	$(PEG/SDS)_{1-x}(griseofulvin)_x$	0
20% griseofulvin/PEG 3000		
No SDS	PEG + griseofulvin	0.4
1% SDS	$(PEG/SDS)_{1-x}(griseofulvin)_x$ + griseofulvin	0.05
Griseofulvin		
Raw material	griseofulvin	–

[a] $(PEG/SDS)_{1-x}(griseofulvin)_x$ is the solid solution of griseofulvin in the PEG/SDS structure.

[b] The relationship between the intensity of a characteristic line of the griseofulvin phase and the intensity of a characteristic line of the PEG-containing phase.

taining dispersion definitely indicates a loss of griseofulvin to the other phase. This phase has a diffraction pattern which is quite similar to that of the pure PEG phase, with a monoclinic unit cell. The griseofulvin appears thus to be dissolved in the PEG/SDS structure, forming a solid solution. The solid solution is here denoted by $(PEG/SDS)_{1-x}(griseofulvin)_x$.

In the 10% w/w drug dispersion containing 2% w/w SDS, no pure griseofulvin phase was present and the solid solution of griseofulvin in PEG/SDS was the only phase appearing. The increased amount of SDS, from 1 to 2% w/w, seemed to be enough to dissolve the last part of the griseofulvin.

In the 3% w/w dispersion with 1% w/w SDS incorporated, no pure griseofulvin phase was present. For the 20% w/w drug dispersion the amount of pure griseofulvin decreased in the dispersion when 1% w/w SDS was incorporated.

From the phase analysis it can be concluded that in dispersions incorporating 1% w/w SDS the solubility of griseofulvin in the PEG/SDS structure can be estimated to be approx. 6–8 % w/w, as all of the griseofulvin in the 3% w/w drug dispersion is dissolved while some pure griseofulvin phase is remaining in the 10% drug dispersion. In dispersions incorporating 2% SDS the solubility of griseofulvin is at least 8%, as no pure griseofulvin phase is detected.

Heat of fusion determinations. Thermograms for the pure materials and for the solid dispersions were obtained by the DSC method. PEG and griseofulvin have characteristic single-peak thermograms with melting peaks at approx. 59 and 219°C, respectively (Fig. 7). SDS has, in the temperature interval 30–240°C, one short broad peak at around 98°C, one sharper peak at around 196°C and a broad peak with a maximum at around 216°C.

The thermograms of the solid dispersions without SDS show the characteristic melting peak of PEG and an additional small endothermic deviation from the baseline at approx. 130, 140 and 170°C for the dispersions of 3, 10 and 20% w/w griseofulvin, respectively. These temperatures represent values on the liquidus curve in a phase diagram of PEG and griseofulvin, where the eutectic point is close to the melting temperature

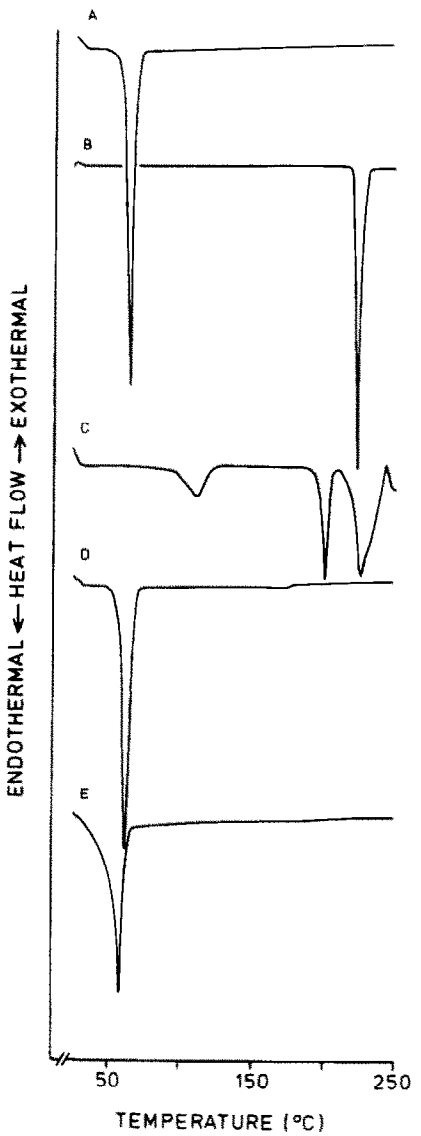

Fig. 7. DSC thermograms of (A) PEG 3000, (B) griseofulvin, (C) SDS, (D) solid dispersion of 20% w/w griseofulvin, (E) solid dispersion of 20% w/w griseofulvin incorporating 1% w/w SDS.

of PEG (Kaur et al., 1980). These deviations in the thermograms disappear or decrease in size in dispersions with SDS incorporated. This indicates that the melting range of the dispersions decreases, and that a lower temperature is required to melt all the griseofulvin.

TABLE 3

Heat of fusion of PEG 3000 and solid dispersion systems

Sample	Heat of fusion ($J\ g^{-1}$) [a]		Deviation from theoretical value (%)
	Experimental	Theoretical	
PEG 3000			
No SDS	210.2 ± 4.0	–	–
1% SDS	206.0 ± 3.6	–	–
Griseofulvin [b]			
Raw material	116.4 ± 2.6	–	–
SDS [c]			
Raw material	250.5 ± 3.4	–	–
3% griseofulvin/PEG 3000			
No SDS	201.5 ± 1.8	207.4 [d]	−2.8
1% SDS	191.3 ± 5.7	203.3 [e]	−5.9
10% griseofulvin/PEG 3000			
No SDS	183.1 ± 3.8	200.8 [d]	−8.8
0.5% SDS	187.3 ± 4.6	–	–
1% SDS	164.4 ± 5.8	197.0 [e]	−16.5
2% SDS	165.7 ± 2.2	–	–
20% griseofulvin/PEG 3000			
No SDS	174.7 ± 2.4	191.4 [d]	−8.7
1% SDS	149.1 ± 5.2	188.1 [e]	−20.7

The values of heat of fusion are derived from integration in the temperature range 30–200°C.

[a] Mean ± SD.

[b] The value of heat of fusion is derived from integration in the temperature range 200–240°C.

[c] The value of heat of fusion is derived from integration in the temperature range 30°C to approx. 232°C.

[d] Calculated from experimental values, assuming a physical mixture PEG and griseofulvin.

[e] Calculated from experimental values, assuming a physical mixture PEG/1% w/w SDS and griseofulvin.

The heat of fusion values support the idea of the formation of a solid solution with the incorporation of SDS (Table 3). The theoretical values are calculated from the experimental values for a physical mixture of griseofulvin and PEG (heat of fusion 116.4 and 210.2 J/g, respectively) or a physical mixture of griseofulvin and the carrier system PEG/1% SDS (heat of fusion 116.4 and 206.0 J/g, respectively).

The experimental values are all lower than the theoretical values, and the largest deviations are obtained for the dispersions with SDS incorporated. This indicates that there is a change in phase composition. If it is assumed that the dispersion of 10% w/w griseofulvin incorporating 1 and 2% w/w SDS, represent systems where most or all of the griseofulvin is in the solid solution state, then the heat of fusion value of approx. 165 J/g is the value of the $(PEG/SDS)_{1-x}(griseofulvin)_x$ phase.

In the dispersion of 20% w/w griseofulvin incorporating SDS, the pure components give a theoretical heat of fusion value of approximately 188 J/g. If a solid solubility of 8% griseofulvin in the PEG/SDS structure can be assumed, and the experimental value for the solid solution is 165 J/g, the theoretical heat of fusion value would be approx. 158 J/g. The heat of fusion value obtained experimentally is 149 ± 5 J/g, which is not so far from the theoretical value.

Lattice parameters. The lattice parameters for the monoclinic PEG phase and the solid solution phase were determined (Table 4). The values of the cell dimensions did not show any systematic change and the values were all similar within the standard deviation. However, in the 10% w/w dispersion incorporating 2% w/w SDS there seems to be some influence on the cell parameters, as the enlarged standard deviations indicate.

A structural model developed from neutron scattering results and NMR could be used to explain the formation of a solid solution, where griseofulvin is in a molecular form. The model presented by Cabane (1977) and Cabane and Duplessix (1982, 1985) describes the interaction between a polymer and SDS in concentrated liquid solutions.

Surfactant molecules form small spherical aggregates which are uniformly distributed throughout the polymer. The polymer is adsorbed to these aggregates in such a way that the more hydrophobic parts of the structure are in contact with the aggregate surfaces while the more hydrophilic parts form loops or strands which join the aggregates.

If a similar model is also valid for a polymer melt with added surfactant, which is fast cooled to the solid state, the original PEG structure should remain. The griseofulvin molecules may attach to the hydrophobic parts of the SDS aggregates and thus become periodically distributed in the

TABLE 4

Unit cell dimensions (A) and volumes ($Å^3$) for PEG and $(PEG/SDS)_{1-x}(griseofulvin)_x$

Sample (–)	Cell dimensions				
	a [a] (Å)	b [a] (Å)	c [a] (Å)	β [b] (°)	V [c] ($Å^3$)
PEG 3000 [d]					
No SDS [e]	8.081 (8)	13.083(14)	19.077 (35)	125.63(12)	1639 (5)
1% SDS	8.092 (5)	13.078(10)	19.049 (30)	125.72(10)	1637 (4)
3% griseofulvin/PEG 3000					
No SDS [e]	8.081 (3)	13.091 (8)	19.086 (18)	125.61 (6)	1641 (2)
1% SDS	8.084 (6)	13.087(11)	19.093 (25)	125.63(10)	1642 (4)
10% griseofulvin/PEG 3000					
No SDS [e]	8.073(10)	13.090(13)	19.095 (30)	125.67(16)	1639 (5)
0.5% SDS	8.067 (6)	13.149(18)	19.051 (28)	125.64(10)	1642 (4)
1% SDS	8.077(11)	13.082(18)	19.075 (47)	125.46(17)	1642 (6)
2% SDS	8.072(33)	13.137(50)	19.039(184)	125.91(69)	1638(11)
20% griseofulvin/PEG 3000					
No SDS [e]	8.065(15)	13.076(23)	19.030 (50)	125.48(22)	1634 (8)
1% SDS	8.076 (8)	13.079(13)	19.087 (31)	125.65(12)	1638 (4)
Griseofulvin [f]					
Raw material [e]	8.969 (2)	–	19.916 (10)	–	1601 (1)

[a] Standard deviation in thousandths is given in parentheses.
[b] Standard deviation in hundredths is given in parentheses.
[c] Standard deviation in units is given in parentheses.
[d] PEG 3000 has a unit cell which is monoclinic.
[e] According to Sjökvist et al. (1989).
[f] Griseofulvin has a unit cell which is tetragonal.

PEG/SDS structure forming a solid solution. The diffraction pattern of the solid solution found here coincides with the original PEG/SDS pattern showing a monoclinic unit cell. In contact with the dissolution media, the PEG/SDS structure is rapidly dissolved and griseofulvin is released directly in a molecular form.

If the negatively charged aggregates of the anionic surfactant are distributed throughout the polymer, the electrostatic repulsion will expand the polymer strands. However, this expansion is counteracted by the solubilization of the more hydrophobic parts of the polymer in the aggregates. The system becomes more dense as loops are formed among the aggregates and the volume is decreased. The two effects, electrostatic repulsion and volume reduction caused by loop formation, counteract each other. This can explain the fact that the cell dimensions are not changed when a solid solution is formed.

In a current work using solid-state NMR, the actual short range structures are being investigated in more detail (Aldén et al.).

Conclusions

Fast cooling of a polymer melt, saturated with a drug, yields small drug particles. With an increase in concentration of a hydrophobic drug, the dissolution surface areas of the dispersion particles become more hydrophobic and wetting can thus be of importance in the dissolution process. The lower the surface tension of the dissolution medium, the easier it becomes to wet the particles with a subsequent increase in the dissolution. This

effect is most pronounced for dispersions with a high content of drug, but is also observed for dispersions of lower drug content.

The incorporation of the anionic surfactant sodium dodecyl sulphate into the dispersion systems can transfer the solid particulate dispersions into molecular dispersions, that is solid solutions. As the drug is in molecular form, the release and dissolution of drug is instantaneous. When a hydrophobic drug is dispersed in molecular form the dissolution is only affected by the dissolution of the carrier system (Chiou and Niazi, 1971).

The dissolution of PEG does not seem to be affected to any large extent by the incorporation of SDS, as compacts of pure PEG and of PEG/1% w/w SDS have the same dissolution times.

The solubility of griseofulvin in PEG with 1% w/w SDS incorporated was estimated by the results from the phase analysis to be between 6 and 8% w/w, as all of the drug was dissolved in the carrier/surfactant system in the 3% w/w drug dispersion, but not all of the drug in the 10% w/w drug dispersion.

In the 20% w/w drug dispersion with 1% w/w SDS incorporated the dissolution was almost instant (Fig. 5) even though the drug was not completely dissolved in the PEG/SDS system. This may be due to a combination of two effects, partial solubility of the drug in the carrier system and increased wettability of the system. During the dissolution process the concentration of SDS is high around the dispersion particles affecting the microenvironment (diffusion layer) surrounding the drug particles (Chiou and Niazi, 1971). Thus the solubility of griseofulvin is improved and subsequently the dissolution is increased.

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