International Journal of Pharmaceutics, 79 (1992) 123–133

IJP 02615

Physicochemical aspects of drug release. XIV. The effects of some ionic and non-ionic surfactants on properties of a sparingly soluble drug in solid dispersions

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(Received 17 June 1991)
(Accepted 20 August 1991)

Key words: Solid dispersion; Solid solution; Griseofulvin; Polyethylene glycol; Polysorbate; Polyethylene dodecyl ether; Dodecyltrimethylammonium bromide; Sodium dodecyl sulfate; X-ray powder diffraction; Differential scanning calorimetry; Dissolution rate; Storage

Summary

The nonionic surfactants polysorbate 80 and polyethylene dodecyl ether (Brij 35), the anionic surfactant sodium dodecyl sulphate (SDS) and the cationic surfactant, dodecyltrimethylammonium bromide (DTAB) were incorporated in dispersions of 10% w/w griseofulvin with PEG 3000 as a carrier. An almost instant and complete dissolution was obtained for dispersions with 1 and 2% w/w SDS. X-ray diffraction revealed that a complete molecular dispersion, i.e. a solid solution, of griseofulvin in PEG/SDS was obtained when 2% w/w SDS was incorporated. A continuous increase in dissolution rate with increase in concentration was observed for dispersions containing the other surfactants but polysorbate 80, Brij 35 and DTAB were not as effective as SDS in increasing the dissolution rate. X-ray diffraction revealed a decrease in the amount of crystalline griseofulvin with increase in surfactant concentration except with polysorbate 80, for which no changes were observed. Differential scanning calorimetry studies supported the results obtained by X-ray diffraction. A relationship between the solubilizing efficiency of the surfactant in aqueous solutions and its ability to increase the solid solubility of a drug in PEG, and subsequently the dissolution rate, was observed. Measurements after 12 months of storage revealed that the dissolution rate was unchanged for the dispersions without surfactant or with polysorbate 80. However, at higher concentrations of Brij 35, DTAB and SDS, the dissolution rates were decreased upon storage.

Introduction

When a hydrophobic drug is dispersed in a readily soluble carrier, the dissolution rate is normally increased. If the drug is dispersed in molecular form, i.e. a solid solution, the rate limiting step in the dissolution process is the dissolution of the carrier (Chiou and Niazi, 1971). This is also valid for drugs dispersed in particular form, i.e. solid dispersions, up to a certain concentration, above which the dissolution may be decreased (Corrigan, 1985; Fernandez et al., 1989). This is because the pronounced hydrophobic

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character of the dispersion system affects the wettability, and the dissolution of the readily soluble carrier can be retarded by the incorporation of the hydrophobic drug (Corrigan, 1985; Sjökvist and Nyström, 1988). It appears, therefore, that there are two ways in which the dissolution of dispersions with a higher content of hydrophobic drug could be improved. Firstly, by increasing the solubility of the drug in the carrier and, secondly, by decreasing the hydrophobic nature of the solid dispersion system in order to improve the wettability.

Surfactants can be used to increase the dissolution rate of drugs in different dosage forms. In recent studies surfactants have been incorporated in solid dispersions to improve the dissolution rate. Sjökvist et al. (1991) found that the incorporation of the anionic surfactant sodium dodecyl sulphate (SDS) in dispersion systems of griseofulvin in PEG 3000 could transfer solid particulate dispersions into molecular dispersions, i.e. solid solutions. A solid dispersion of 20% w/w griseofulvin without the incorporation of surfactant has a low dissolution rate because of inadequate wetting, but the incorporation of 1% w/w SDS gives an almost instant drug dissolution. The possible mechanism is considered to involve the formation of polymer-surfactant complexes or micelles through the formation of bonds between the surfactant ions and the polymer. This was first reported by Jones (1967), who investigated the interaction between SDS and polyethylene oxide in solutions, and has been further investigated, for example, by Cabane (1977). Aldén et al. (1991) showed that in solid dispersions incorporating SDS, the drug molecule is dissolved in the polymer structure via the surfactant molecules, to form a solid solution.

Najib et al. (1986) suggested that the observed increase in dissolution with the incorporation of surfactant could be attributed to the ability of the surfactants to reduce the interfacial tension between the solid and the dissolution medium and hence improve the wettability of the drug particles. The same explanation was used by Fernandez et al. (1989). Pittaluga et al. (1988) suggested that the observed increase in dissolution was due to the formation of a molecular solution.

In the present study, different concentrations of the nonionic surfactants polysorbate 80 and Brij 35, the cationic surfactant DTAB and the anionic surfactant SDS were incorporated in dispersion systems of 10% w/w griseofulvin in PEG 3000. The aim of this study was, firstly, to investigate the effects of the incorporation of different concentrations of the surfactants on the dissolution rate and the incorporated state of the drug and, secondly, to investigate whether these effects could be attributed to increased solubility and/or improved wettability. It was also of interest to study the effect of ageing on these dispersions.

Experimental

Materials

Griseofulvin microsized (Glaxo, U.K.) was used as model substance for a drug of low aqueous solubility. The quality used in this study has been characterized earlier (Nyström et al., 1985; Sjökvist and Nyström, 1988).

Polyethylene glycol (PEG) 3000 (Apoteksbolaget, Sweden) was used as a readily soluble carrier.

Four surfactants were used:

Nonionic Polyethylene dodecyl ether, Brij 35 (Merck-Schuchardt, Germany), is a solid with a melting point of 33°C and a critical micelle concentration of 0.013% w/v (Handbook of Pharmaceutical Excipients, 1986).

Polyoxyethylene 20 sorbitan mono-oleate, polysorbate 80 (Apoteksbolaget, Sweden), is a liquid which is soluble in water (Handbook of Pharmaceutical Excipients, 1986). The critical micelle concentration has been stated to be 0.0014% w/v (Wan and Lee, 1974) or 0.0025% w/v (Bielsa et al., 1979).

Anionic Sodium dodecyl sulphate, SDS (Apoteksbolaget, Sweden), is a solid, with a melting point for the pure substance of 204–207°C, which is freely soluble in water (Handbook of Pharmaceutical Excipients, 1986). The critical micelle concentration is approx. 8 mmol/l, corresponding to 0.2% w/v (Mukerjee and Mysels, 1971; Sjökvist et al., 1991).

Cationic Dodecyltrimethylammonium bro-

mide, DTAB (Sigma, U.S.A.) has a critical micelle concentration of 14 mmol/l (0.43% w/v) (Mukerjee and Mysels, 1971; Brito and Vaz, 1986).

Methods

Preparation of solid dispersions Solid dispersions (100 g) of 10% w/w griseofulvin with polysorbate 80 (1, 6 and 12% w/w), Brij 35 (1, 3, 6 and 12% w/w), DTAB (1, 2 and 3% w/w) or SDS (1 and 2% w/w), and with PEG 3000 as a carrier, were prepared by the melting method at a temperature of 160°C. Dispersions of surfactant in PEG, at the concentrations listed above, were also made without the addition of griseofulvin. A dispersion of 10% w/w griseofulvin without surfactant was prepared as a reference.

The mixtures were heated under constant stirring until no particles could be observed. In dispersions incorporating surfactant, the surfactant was dispersed in the melted carrier prior to the addition of griseofulvin. After cooling at room temperature for at least 24 h the dispersions were pulverized and sieved to obtain the fraction 300–500 μm.

Polysorbate 80, Brij 35 and SDS were easy to dissolve in the melted carrier at all concentrations. However, it was more difficult to dissolve DTAB in the carrier as concentrations increased.

The dispersions with no surfactant, and those containing Brij 35 and the lowest concentrations of SDS and polysorbate 80, were easy to pulverize. However, difficulties were encountered with 2% w/w SDS, 12% w/w polysorbate 80 and all the dispersions with DTAB, because these dispersions are sticky and less brittle.

Characterization of drug dissolution Dissolution tests on dispersion particles in pure distilled water were performed as decribed earlier (Sjökvist et al., 1991). The dissolution studies were carried out under 'sink conditions' by adding 6 mg of each dispersion, corresponding to 0.6 mg griseofulvin, to 1000 ml of pure distilled water.

Characterization of drug solubility and surface tension in media with surfactant Solubility: The solubility of griseofulvin in pure distilled water and in distilled water with different concentrations of surfactant was determined as described earlier (Sjökvist et al., 1991).

Surface tension: The surface tension of distilled water on the addition of different concentrations of the surfactants was measured as described earlier (Sjökvist et al., 1991).

Characterization of structure in solid dispersion X-ray diffraction: Phase analyses were made by X-ray powder diffraction using a STOE Position Sensitive Detector (PSD), with Ge mono chromatized Cu$K\alpha_1$ radiation. A curve-wire detector ($r = 130$ mm) with an angular range of 45° in 2θ was used, operated in a stationary mode. The phases were identified by means of characteristic non-overlapping lines, for all samples except PEG 3000 and Brij 35. As these two substances consist of polyethylene units, the diffraction lines for PEG 3000 and Brij 35 are at the same positions. However, as the content of Brij 35 is not more than 12% w/w in the dispersions, the contribution is considered not to influence the results to any large extent.

Differential scanning calorimetry: Heat of fusion determinations were made using a DSC 20 differential scanning calorimeter (Mettler, Switzerland). A heating rate of 10°C/min was used in the temperature range 22–260°C for systems containing polysorbate 80, Brij 35 and SDS and 22–350°C for dispersions containing DTAB, all in an atmosphere of nitrogen. The values of heat of fusion were derived from integration in the temperature range 30–160°C, if not stated otherwise. The results presented are mean values of four determinations.

Effect of ageing Samples of all prepared dispersions were stored in amber glass jars with lids, at room temperature (20–23°C), for 12 months. Dissolution rate studies and phase analyses were then performed as described above.

Results and Discussion

Drug solubility as a function of surfactant concentration

The critical micelle concentrations of nonionic surfactants in aqueous solutions are generally extremely low (Handbook of Pharmaceutical Excipients, 1986). The critical micelle concentration in distilled water was approx. 0.001% w/v for

polysorbate 80 and Brij 35, 0.4% w/v for DTAB and 0.2% w/v for SDS (Fig. 1).

Above the critical micelle concentration, the solubility of griseofulvin increased linearly. Such a relationship between equilibrium solubility of drug and concentration of surfactant has been reported earlier (e.g. Kakemi et al., 1965; Taylor and Wurster, 1965; Barry and El Eini, 1976; Watari and Kaneniwa, 1976; Nyström and Bisrat, 1986). The solubility of griseofulvin was considerably increased in solutions containing the cationic surfactant DTAB or the anionic surfactant SDS in concentrations exceeding the critical micelle concentration (Fig. 1). For the nonionic surfactants polysorbate 80 and Brij 35 the solubility of griseofulvin was increased at concentrations above the critical micelle concentration, but not to the same extent. The solubility of griseofulvin in media with 1.0% w/v polysorbate 80, Brij 35, DTAB or SDS was 49.6, 63.3, 203 and 941 mg/l, respectively. The slope values from the graphs of solubility vs concentration of surfactant, above the critical micelle concentration, can be used as an indication of the solubilizing efficiency (Barry and El Eini, 1976). The calculated slope values were 40.5, 54.3, 351 and 1150 for polysorbate 80, Brij 35, DTAB and SDS, respectively. The solubilizing efficiency was thus higher for the ionic than for the non-ionic surfactants.

The effect of surfactant incorporation on drug dissolution rate

For the dispersions incorporating surfactant the final concentration of surfactant in the dissolution media after complete dissolution was not high enough to affect the solubility or surface tension to any large extent. At the highest concentration of the non-ionic surfactants (12% w/w) the final concentration in the media was approximately 7×10^{-5}% w/v. The lowest concentration

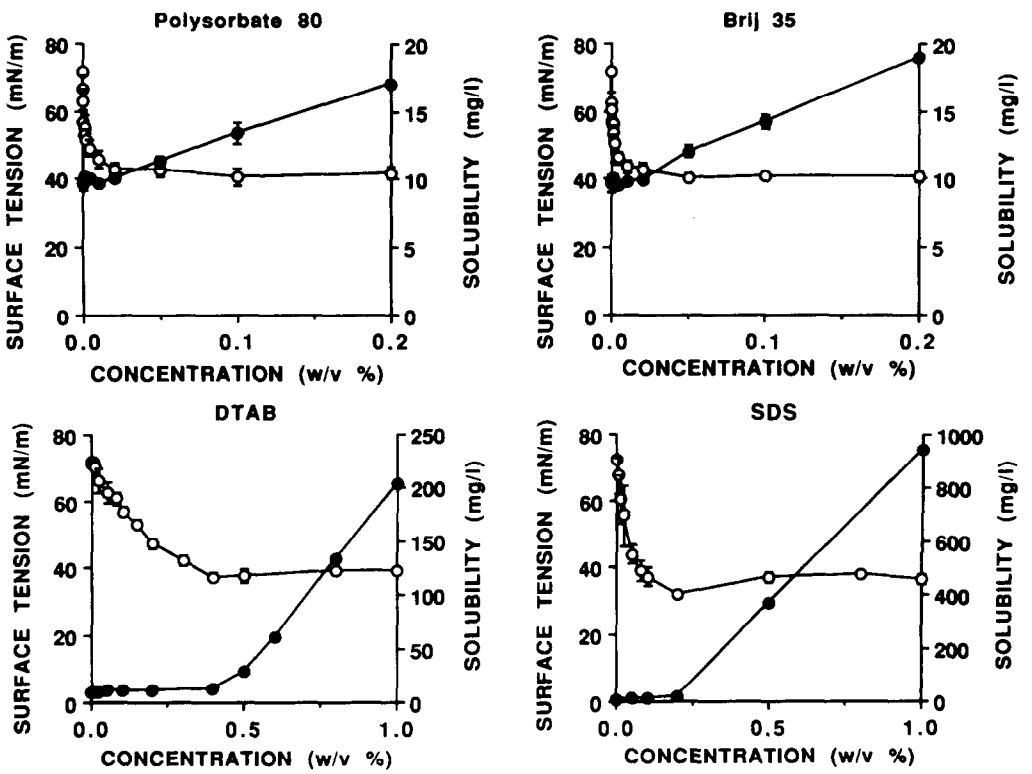

Fig. 1. Surface tension and the solubility of griseofulvin as a function of surfactant concentration in distilled water. (○) Surface tension (mN/m); (●) solubility of griseofulvin (mg/l). The data for SDS are from Sjökvist et al. (1991).

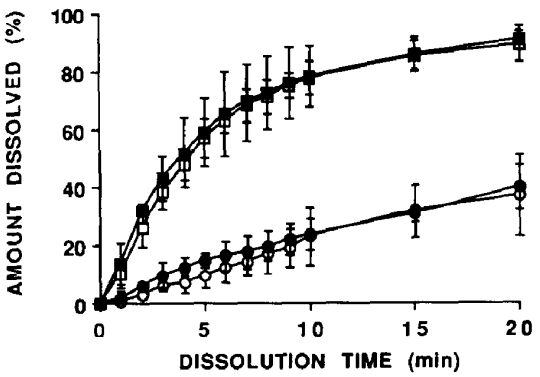

Fig. 2. Dissolution rate profiles for solid dispersions of 10% griseofulvin incorporating different concentrations of polysorbate 80. Amount of polysorbate 80 incorporated: (○) no polysorbate 80; (●) 1% w/w; (□) 6% w/w; (■) 12% w/w. Error bars represent the 95% confidence interval for the mean.

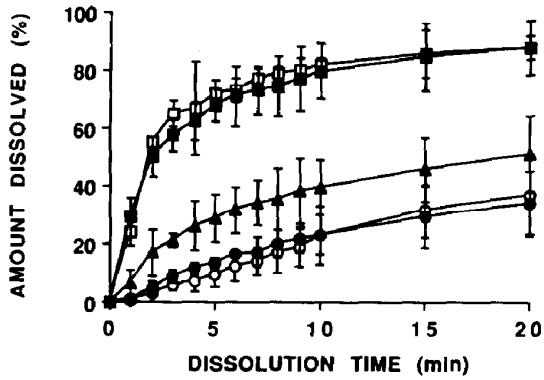

Fig. 3. Dissolution rate profiles for solid dispersions of 10% griseofulvin incorporating different concentrations of Brij 35. Amount of Brij 35 incorporated: (○) no Brij 35; (●) 1% w/w; (▲) 3% w/w; (□) 6% w/w; (■) 12% w/w. Error bars as in Fig. 2.

for which the surface tension was measured was 1×10^{-4}% w/v, which decreased the surface tension from approx. 71 mN/m to 67 and 62 mN/m for polysorbate 80 and Brij 35, respectively. At these concentrations the solubility of griseofulvin was unchanged.

Dissolution rate data for dispersions incorporating 1, 6 and 12% w/w polysorbate 80 are presented in Fig. 2. The dissolution with 1% w/w was similar to that seen with no incorporated surfactant. When the surfactant concentration was increased to 6 and 12% w/w the dissolution was increased, producing similar but not complete dissolution profiles for the two concentrations.

The dissolution rate profiles for dispersions containing Brij 35 (Fig. 3) were quite similar to those for dispersions containing polysorbate 80. The profiles for dispersions with no surfactant and with 1% w/w were similar and the dissolution of dispersions containing 6 and 12% w/w was increased to give approximately the same profile. The dispersion with 3% w/w showed an intermediate dissolution rate profile. Dispersions containing the two highest concentrations of Brij 35 had faster initial dissolution rates than those containing the two highest concentrations of polysorbate 80. However, after 20 min the amount dissolved was the same for the two surfactants.

There was a continuous increase in dissolution rate with increase in concentration of DTAB (Fig. 4). The fastest rate, obtained for the dispersion with 3% w/w, was initially quite fast but a decrease in rate was then observed.

As reported earlier (Sjökvist et al., 1991), dispersions with SDS dissolved almost instantaneously, especially the dispersion containing 2% w/w (Fig. 5).

Characterization of structure in solid dispersions

Phase analysis The relative amounts of each phase in the solid dispersion can be determined by X-ray powder diffraction. The ratio of the

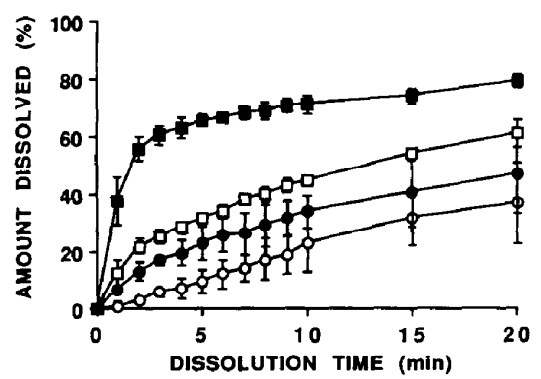

Fig. 4. Dissolution rate profiles for solid dispersions of 10% griseofulvin incorporating different concentrations of DTAB. Amount of DTAB incorporated: (○) no DTAB; (●) 1% w/w; (□) 2% w/w; (■) 3% w/w. Error bars as in Fig. 2.

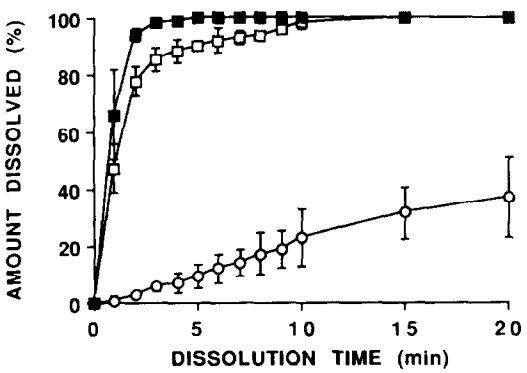

Fig. 5. Dissolution rate profiles for solid dispersions of 10% griseofulvin incorporating different concentrations of SDS. Amount of SDS incorporated: (○) no SDS; (□) 1% w/w; (■) 2% w/w. Error bars as in Fig. 2.

intensities of the characteristic non-overlapped diffraction lines of each phase can be calculated to describe such a relationship (Sjökvist et al., 1991). In Table 1 this relationship between dispersion systems is presented as the quotient of the intensity of a characteristic diffraction line of the griseofulvin phase divided by the intensity of a characteristic diffraction line of the PEG-containing phase.

TABLE 1

X-ray powder diffraction analysis of solid dispersions of 10% griseofulvin in PEG 3000

Sample	Ratio [a]	
	Before storage	After storage
No surfactant	0.8	0.7
Polysorbate 80		
1%	0.8	0.8
6%	0.6	0.7
12%	0.8	0.9
Brij 35		
1%	0.7	0.7
3%	0.6	0.6
6%	0.6	0.8
12%	0.5	0.8
DTAB		
1%	0.7	0.6
2%	0.8	0.8
3%	0.5	0.7
SDS		
1%	0.7	0.7
2%	0	0

[a] The ratio of the intensity of a characteristic line of the griseofulvin phase to the intensity of a characteristic line of the PEG-containing phase.

As observed earlier, the ratio was decreased with an increase in SDS concentration, so that with 2% w/w SDS there was no griseofulvin phase registered and the solid solution of griseofulvin in PEG/SDS was the only phase present.

For dispersions containing polysorbate 80, the ratio was unchanged for the concentrations tested, indicating that the solubility of griseofulvin in this carrier/surfactant system was unchanged. In dispersions containing Brij 35 the ratio was somewhat decreased with an increase in surfactant concentration, which indicates that the solubility of griseofulvin in the carrier is slightly increased with an increase in Brij 35 content.

For dispersions containing 1 and 2% w/w DTAB the ratio was unchanged. However, the ratio decreased when 3% w/w was incorporated, indicating a loss of griseofulvin to the other phase.

These data can explain the observations from the dissolution rate studies. As presented in Fig. 5, griseofulvin was instantly dissolved on the formation of a complete solid solution in PEG/2% w/w SDS. For Brij 35 and DTAB the solid solubility of griseofulvin seemed to be somewhat increased with an increase in surfactant concentration. As part of the griseofulvin is in molecular form, there was a fast initial dissolution followed by a slower dissolution as the particles of griseofulvin were dissolved. In solid dispersions containing polysorbate 80, the solubility of griseofulvin in the carrier system was unchanged. The faster dissolution rates obtained at higher polysorbate 80 concentrations were probably due to increased wettability.

Heat of fusion determinations Thermograms of the pure materials and the solid dispersions were obtained by the DSC method. Thermograms for PEG 3000, griseofulvin and SDS have been presented earlier (Sjökvist et al., 1991). As polysorbate 80 is a liquid there was no distinct peak in its thermogram. Brij 35 is a solid waxy substance that starts to melt when the heating programme of the DSC method starts to register

TABLE 2

Heat of fusion of raw materials

Sample	Heat of fusion ($J\ g^{-1}$)
PEG 3000	209 ± 3 [a]
Griseofulvin	122 ± 2 [b]
Polysorbate 80	- [c]
Brij 35	130 ± 5 [d]
DTAB	132 ± 6 [a]
SDS	250 ± 3 [e]

[a] The value of heat of fusion is derived from integration in the temperature range 30–160°C.
[b] The value of heat of fusion is derived from integration in the temperature range 200–240°C.
[c] Polysorbate 80 is a liquid at room temperature and a heat of fusion value cannot be obtained in the studied temperature range.
[d] The value of heat of fusion is derived from integration in the temperature range 29–54°C.
[e] From Sjökvist et al. (1991).

(at approx. 30°C), giving a peak temperature of 47°C.

DTAB has a very small endothermic peak (heat of fusion 0.9 J/g) at 76°C. This small peak disappears if DTAB is dried prior to the measurement, indicating that it was caused by a small amount of impurity. DTAB also has a sharp peak at approx. 100.6°C and a broader peak between 200 and 300°C, with a maximum at 272°C.

All the thermograms for dispersions without griseofulvin incorporated show the characteristic melting peak of PEG. This is the only peak appearing in dispersions containing SDS or polysorbate 80, and dispersions containing 1% w/w Brij 35. However, in dispersions containing 3, 6 and 12% w/w Brij 35, a small peak can be observed at approx. 46°C. This peak increases in size with increase in Brij 35 concentration.

The thermograms of dispersions containing

TABLE 3

Heat of fusion of PEG and solid dispersion systems

	Heat of fusion ($J\ g^{-1}$) [a]		Deviation from theoretical value (%)	Heat of fusion ($J\ g^{-1}$) [a]		Deviation from theoretical value (%)
	Experimental	Theoretical [b]		Experimental	Theoretical [c]	
	(Without griseofulvin)			(Solid dispersion with 10% griseofulvin)		
No surfactant	208.6 ± 3.0	–	–	185.5 ± 3.7	200.0	−7.2
Polysorbate 80						
1%	197.5 ± 6.6	206.5	−4.4	192.5 ± 4.0	190.0	+1.3
6%	189.6 ± 3.0	196.1	−3.3	174.1 ± 8.1	182.9	−4.8
12%	177.8 ± 2.6	183.6	−3.2	158.9 ± 5.4	172.2	−7.7
Brij 35						
1%	206.6 ± 2.3	207.8	−0.6	187.8 ± 6.9	198.2	−5.2
3%	202.9 ± 3.2	206.2	−1.6	186.2 ± 6.1	194.8	−4.4
6%	202.8 ± 3.5	203.9	−0.5	178.9 + 5.6	194.7	−8.1
12%	190.3 ± 8.9	199.1	−4.4	175.8 ± 11.0	183.5	−4.2
DTAB						
1%	204.5 ± 4.2	207.8	−1.6	178.2 ± 5.7	196.3	−9.2
2%	197.3 ± 6.2	207.1	−4.7	171.1 ± 4.0	189.8	−9.9
3%	191.1 ± 4.1	206.3	−7.4	169.9 ± 2.2	184.2	−7.8
SDS						
1%	208.0 ± 7.4	209.0	−0.5	186.8 ± 5.2	199.4	−6.3
2%	201.3 ± 14.0	209.4	−3.9	165.9 ± 11.0	193.4	−14.2

The values of heat of fusion are derived from integration in the temperature range 30–160°C.
[a] Mean ± SD.
[b] Calculated from experimental values, assuming a physical mixture of PEG and surfactant.
[c] Calculated from experimental values, assuming a physical mixture of PEG/surfactant and griseofulvin.

DTAB also show a small additional endothermic deviation from the baseline at approx. 210°C, which corresponds to the larger peak in the thermogram for pure DTAB. In the dispersion containing the highest concentration of DTAB, 3% w/w, a smaller peak can also be observed at 100°C, where the first melting peak can be seen in the thermogram for pure DTAB.

The additional peaks in thermograms of dispersions without griseofulvin at the highest concentrations of Brij 35 and DTAB indicate that these surfactants are in crystalline form and not dissolved in the PEG phase at these concentrations.

For dispersions with griseofulvin the same observations are made, except that the deviation from the baseline in thermograms for dispersions containing DTAB is displaced to approx. 221°C.

There is also a small deviation from the baseline at approx. 140°C, for the dispersion with 10% w/w griseofulvin, without surfactant. This represents the liquidus curve in a phase diagramme of PEG and griseofulvin (Sjökvist et al., 1991). This deviation disappears or decreases in size in dispersions incorporating surfactant.

The heat of fusion values for the raw materials and the solid dispersions are presented in Tables 2 and 3, respectively. In Table 3 the theoretical values for dispersions without griseofulvin have been calculated from the experimental values for a physical mixture of PEG (heat of fusion 208.6 J/g) and surfactants (heats of fusion 0, 129.6, 132.2 and 250.5 J/g for polysorbate 80, Brij 35, DTAB and SDS, respectively). The theoretical values for dispersions with griseofulvin have been calculated from experimental values for a physical mixture of griseofulvin (heat of fusion 122.2 J/g) and PEG/x% surfactant.

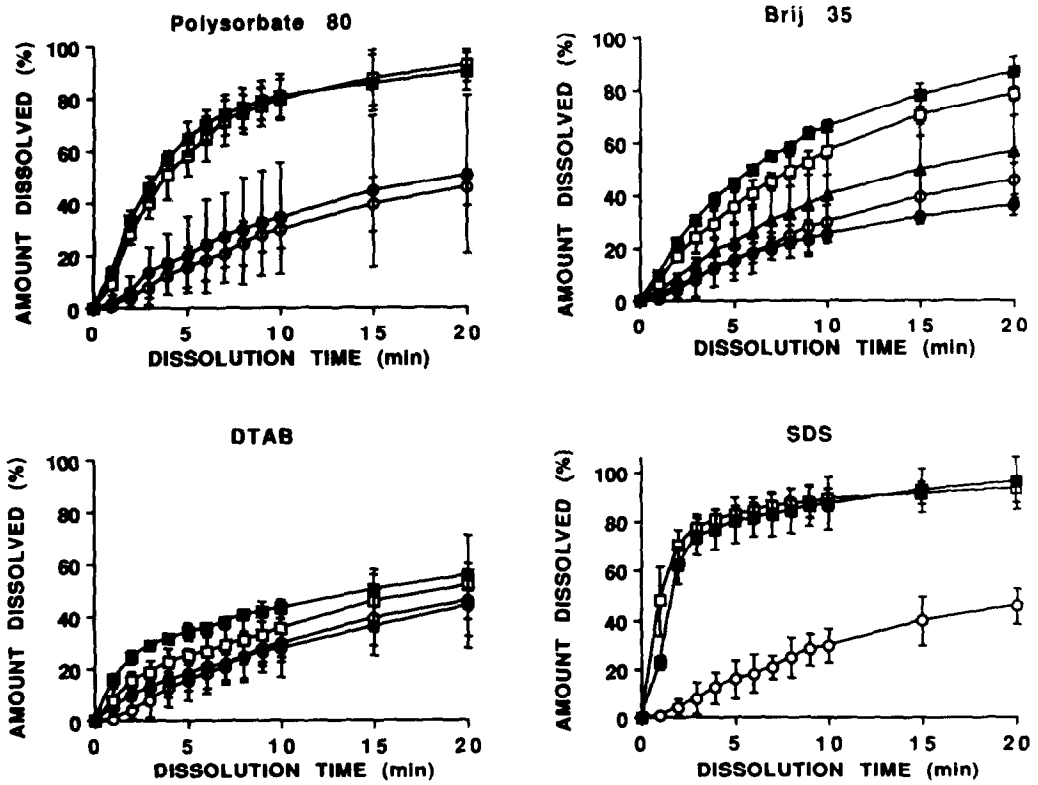

Fig. 6. Dissolution rate profiles for solid dispersions of 10% w/w griseofulvin incorporating surfactants, after storage for 12 months. Symbols as in Figs 2–5. Error bars as in Fig. 2.

A change in heat of fusion value for PEG with the incorporation of another substance can indicate a change in crystallinity (e.g. Ford et al., 1986; Sjökvist et al., 1991). For instance a large decrease in the heat of fusion value can be due to a decrease in the crystallinity of PEG, resulting in an increased dissolution rate.

In all samples, with one exception, the theoretical values were higher than the experimental. However, for dispersions without griseofulvin, the experimental values did not deviate considerably from the theoretical values, indicating that the incorporation of surfactant did not alter the crystallinity of PEG to any large extent.

The deviations from theoretical values were, with few exceptions, more pronounced for dispersions with griseofulvin than for those without. The largest deviations could be seen for the dispersions containing the ionic surfactants, DTAB and SDS, with the largest deviation for the dispersion with 2% w/w SDS, as reported earlier (Sjökvist et al., 1991). This supports the idea of a change in the phase composition, observed by X-ray diffraction.

Effect of ageing

Dissolution rate Dissolution rate studies were performed after storing the dispersions for 12 months (Fig. 6). The dissolution of the dispersion without surfactant was unchanged after storage, which is in accordance with results by Chiou and Riegelman (1969). This was also valid for the dispersions with polysorbate 80, irrespective of the concentration incorporated. It thus appears that dispersions containing polysorbate 80 are stable under these storage conditions.

A decrease in dissolution rate was observed for the other surfactants. The profiles of dispersions containing Brij 35 at the lowest concentrations, 1 and 3% w/w, were similar to the profiles of the freshly made dispersions. However, the dissolution rates were decreased for the dispersions containing 6 and 12% w/w.

Dispersions containing DTAB all showed a decrease in dissolution rate, with the most pronounced decrease for the dispersion containing 3% w/w. The dispersions containing SDS had similar dissolution profiles to those for the freshly made dispersions. The dissolution of the dispersion containing 1% w/w was not changed at all. However, dissolution of the dispersion with 2% w/w SDS was not instant after storage.

Phase analyses The relationship between phases for the dispersion without incorporated surfactant was unchanged after storage (Table 1). This was also true for the dispersions containing polysorbate 80 and 1% w/w SDS. For polysorbate 80 this is consistent with the results from the dissolution rate studies. However, for the dispersion incorporating 2% w/w SDS a decrease was observed in dissolution rate, although the solid solubility of griseofulvin seemed to be unchanged. The reason could be that the detection limit for the griseofulvin phase (approx. 3% w/w griseofulvin; Sjökvist et al., 1991) is not reached. Another explanation might be that the dissolution of PEG itself may be influenced by the incorporation of SDS during storage. Compacts of freshly made and stored solid dispersions were made and tested for disintegration time in distilled water to give an approximate measure of the dissolution rate of the carrier system (Sjökvist et al., 1991). The dispersion with 10% w/w griseofulvin incorporating 2% w/w SDS had a disintegration time of 10.7 ± 1.5 min before storage and 13.9 ± 1.3 min after storage for 12 months. This can indicate that the dissolution of PEG incorporating SDS is somewhat changed upon storage.

The relationship for dispersions containing Brij 35 and DTAB was somewhat changed compared to the relationship for the freshly made samples, especially for the higher concentrations. After storage, the amount of griseofulvin in solid solution was decreased, resulting in a decrease in dissolution rate.

Conclusions

The dissolution rate is generally increased with the incorporation of surfactants. Lower concentrations of ionic than of non-ionic surfactants are needed in order to obtain an increase in the dissolution. From X-ray powder diffraction analyses it was shown that, especially for the ionic surfactants, the amount of pure griseofulvin phase

is decreased with an increase in surfactant concentration. However, it was only in the dispersion incorporating 2% w/w SDS that all the griseofulvin was dissolved in the carrier. These results were supported by the results from the DSC measurements where the largest deviations from theoretical values of heat of fusion were obtained in solid dispersions incorporating SDS.

It appears that there are two ways to improve the dissolution of drugs in solid dispersions. Firstly, the wettability can be improved. Secondly, the drug solubility in the solid carrier can be increased. A combination of the two factors can also increase the dissolution rate. In dispersions with polysorbate 80 the solid solubility of griseofulvin is unchanged, but an increase in dissolution can still be obtained at higher concentrations. This ought then to be caused by an enhanced wettability of the dispersion particles. A limited increase in solid solubility of drug was found in dispersions containing Brij 35. However, the dissolution rates were similar for dispersions containing polysorbate 80 and Brij 35. For these two surfactants there seems to be a threshold in surfactant content below which an effect on the dissolution and the wettability cannot be observed.

The increase in solubility of the drug in the solid carrier, here obtained by the incorporation of DTAB and especially SDS has, beside improved wettability, a major effect on the dissolution.

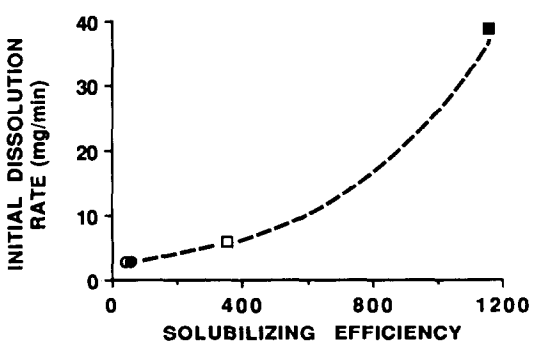

Fig. 7. Initial dissolution rate for solid dispersions of 10% w/w griseofulvin incorporating 1% w/w surfactant vs solubilizing efficiency of surfactants in aqueous solutions. Surfactant incorporated: (○) polysorbate 80; (●) Brij 35; (□) DTAB; (■) SDS.

The solubilizing efficiency, as represented by the slope value from the solubility graph above the critical micelle concentration, is higher for ionic surfactants than for nonionic surfactants, Fig. 1. In Fig. 7 the initial dissolution for dispersions of 10% w/w griseofulvin incorporating 1% w/w surfactant has been plotted against the solubilizing efficiency. The relationship indicates that the solubilizing efficiency of the surfactant is of importance for the dissolution properties of dispersions incorporating surfactant. For surfactants with low solubilizing efficiency, the effect on dissolution rate is limited and mainly due to improved wetting. Such a relationship could be used to select surfactants for incorporation in solid dispersions in order to increase the dissolution rates.

Studies after storage for 12 months showed that dispersions incorporating polysorbate 80, which does not increase the solid solubility of griseofulvin, had unchanged dissolution rates irrespective of the concentration incorporated. For the other surfactants, which increase the solubility of griseofulvin in PEG, especially DTAB and SDS, a decrease in dissolution rate was observed after storage. The observed decrease in dissolution rate could be explained by a change in the solid solubility of griseofulvin, probably in combination with a decrease in carrier dissolution obtained by the incorporation of surfactant.

Particulate dispersions, which generally give slower dissolution rates than solid solutions, have the advantage of giving unchanged dissolution rates after storage. The dissolution rates of solid solutions, obtained by incorporating surfactants in solid dispersions, are decreased after storage and the stability needs to be improved.

Acknowledgement

The authors are very grateful to Dr Claes Ahlneck for valuable discussions during the preparation of this manuscript and to Professor Josh Thomas for providing the X-ray diffraction facilities.

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