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Structure of solid dispersions in the system polyethylene glycol-griseofulvin with additions of sodium dodecyl sulphate

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Summary

Solid dispersions of polyethylene glycol (PEG) 3000 and 10% w/w griseofulvin were prepared by the melting method. Samples were also prepared with 10% w/w of the anionic surfactant sodium dodecyl sulphate (SDS) added to the melt. Phase analysis was performed by X-ray powder diffraction and investigation of the short-range structure by ^{13}C-CP/MAS solid-state NMR. In the samples without the added surfactant, a solid particulate dispersion of griseofulvin in PEG is obtained. The periodic structure of the pure phases is retained and so is the local structure as seen by NMR. When a surfactant is added to the dispersion a solid molecular dispersion, i.e., a solid solution, is formed. The interaction between the environment and certain carbons in griseofulvin and SDS is evident. Both hydrophilic and hydrophobic parts of the molecules are influenced in a significant way. The solid solution of griseofulvin in PEG obtained on addition of SDS seems to depend on an interaction between the polymer and SDS in aggregates (micelles). These aggregates can bind griseofulvin in a molecular form at the surface or in the interior of the aggregate.

Introduction

The properties of the polymer carriers used in solid dispersions are of major importance for the dissolution and stability of the formulation product (Chiou and Riegelman, 1971; Chatham, 1987). The structure of the polymers themselves and the systems and phases that emerge when a drug in combination with some additive is dispersed in the carrier are of particular interest. Knowledge of the interactions on a molecular level between a polymer, drug and additive is of definite interest for the prediction of the physical and chemical properties of the formulation product.

In a previous paper (Sjökvist et al., 1991), the effect of the addition of SDS on the dissolution rate and structure of solid dispersions was investigated. The clearly enhanced dissolution rate introduced by the additive could be explained by the formation of solid solutions. The long-range and short-range structure introduced in the melt

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during the preparation was assumed to be retained in the solid state by the fast cooling process.

Most of the structural information for solid dispersion systems available today concerns the long-range structure of crystalline materials. The periodic three-dimensional arrangements are mainly investigated by X-ray powder diffraction, which gives a time and space average of the molecular distribution in the systems. However, there is very little information concerning the deviation from periodic order, i.e., the short-range (local) structure for these potentially disordered systems. Most investigations on such short-range interactions are made in dilute or concentrated liquid solutions (Cabane and Deplussix, 1982; Carlsson et al., 1988). For investigation of the short-range order in the solid state, ^{13}C-NMR is a sensitive tool and can give information concerning specific interactions in powder samples. High-resolution ^{13}C solid-state NMR spectra are obtained by proton decoupling and magic angle spinning (MAS) and sensitivity enhancement is achieved by cross-polarization (CP).

The aim of this work is to investigate both the long-range and short-range (local) order of the phases in polyethylene glycol-griseofulvin dispersions when the anionic surfactant SDS is added. A high SDS content was chosen in order to ensure that the occasional existence of a pure SDS phase would be detected by the X-ray method. Valuable information is obtained about the interactions on a molecular level between polymer, drug and surfactant.

Experimental

Materials

The hydrophobic drug, griseofulvin, microsized was obtained from Glaxo, U.K. (formula: $C_{17}H_{17}ClO_6$). Polyethylene glycol (PEG) 3000, used as a carrier (melting temperature interval: 56–58°C; formula: $HO(C_2H_4\text{-}O)_n$ with $n = 70$), and the anionic surfactant, SDS (formula: $C_{12}H_{25}SO_4Na$), were both supplied by Apoteksbolaget, Sweden.

Methods

Preparation of the solid dispersions

Solid dispersions of 10% griseofulvin and PEG with and without the addition of 10% SDS were prepared by the melting method at a temperature of 145°C. In dispersions with SDS included the surfactant was dissolved in the melted carrier prior to the addition of griseofulvin. The samples were brought to room temperature by fast cooling.

X-ray diffraction

The X-ray powder diffraction investigations were performed using an STOE position-sensitive detector (PSD) system with Ge monochromatized CuKα_1 radiation. A curved-wire detector ($r = 130$ mm) was used with an angular range of 45° in 2θ and was operated in a stationary mode. Room temperature runs were performed by rotating the powder attached to a cellulose membrane about the normal to the film plane in an $\omega = 0$ transmission mode.

Solid-state NMR

^{13}C CPMAS NMR spectra were recorded on a Bruker MSL 300 spectrometer at 75 MHz using 4 mm o.d. zirconium oxide rotors and spinning at 4–8 kHz depending on the sample. The proton and carbon radiofrequency fields used during cross-polarization and decoupling correspond to 4.5 μs 90° pulses. The cross-polarization contact time was 1–2 ms.

Results and Discussion

X-ray powder diffraction

The long-range order, as reflected in the X-ray powder diffractograms of the dispersions, is shown in Fig. 1. The peaks represent the reflections from the crystalline phase.

PEG / SDS samples

The relative amounts of the phases in the solid dispersions can be determined by the X-ray powder diffraction method. For an ideal crystalline

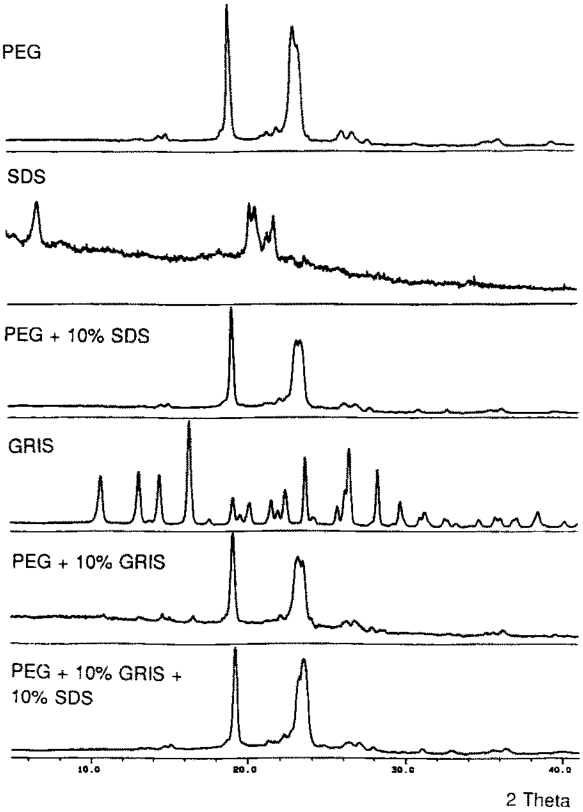

Fig. 1. X-ray powder diffractograms.

system, the relationship between the intensities of characteristic diffraction lines reflects these relative amounts. The rather high SDS content of 10% w/w should give characteristic peaks in the pattern, if SDS is present as a pure phase. However, in the PEG/SDS sample the diffraction pattern was essentially identical with that of the pure PEG phase. This suggests that SDS in a molecular form is periodically distributed in the original PEG structure and PEG/SDS is thus a solid solution.

PEG / SDS / griseofulvin samples

In a previous paper (Sjökvist et al., 1991), it was shown that the griseofulvin phase is detectable by the X-ray method in dispersions where the concentration of drug is greater than 2% w/w in the PEG phase.

In the dispersions investigated here, different phase compositions were observed depending on the SDS content in the samples. In the PEG/griseofulvin dispersion, griseofulvin and PEG are both present as pure phases. However, in the dispersion with 10% SDS incorporated, the diffraction pattern corresponds closely to that from pure PEG; no peaks are observed at the positions corresponding to pure griseofulvin or pure SDS. This suggests that griseofulvin is incorporated in a molecular form in the PEG/SDS structure. A solid solution has been formed, in this case a solid solution of griseofulvin in the PEG/SDS structure, here denoted by $(\text{PEG/SDS})_{1-x}$griseofulvin$_x$ (Table 1).

The same effect, the disappearance of pure griseofulvin phase and thus formation of solid solution, was observed at the low SDS concentration of 2% in the previous work mentioned above.

NMR spectra

To obtain more information on the short-range interaction in the solid solution, an NMR study was performed on the samples. The ^{13}C-NMR spectra of pure PEG, SDS and griseofulvin together with spectra of the solid solutions (dispersions) PEG/SDS and $(\text{PEG/SDS})_{1-x}$griseofulvin$_x$ are demonstrated in Fig. 2. The structural

TABLE 1

X-ray powder diffraction phase analysis

Sample	Phases observed
PEG 3000	PEG
PEG 3000 + 10% SDS	PEG/SDS
griseofulvin	griseofulvin
PEG 3000 + 10% griseofulvin + 10% SDS	$(\text{PEG/SDS})_{1-x}$griseofulvin$_x$
PEG 3000 + 10% griseofulvin + 2% SDS [a]	$(\text{PEG/SDS})_{1-x}$griseofulvin$_x$ [a]
PEG 3000 + 10% griseofulvin + 1% SDS [a]	$(\text{PEG/SDS})_{1-x}$griseofulvin$_x$ + griseofulvin [a]

PEG/SDS is the solid solution of SDS in the PEG structure. $(\text{PEG/SDS})_{1-x}$griseofulvin$_x$ is the solid solution of griseofulvin and SDS in the PEG structure.

[a] From Sjökvist et al. (1991).

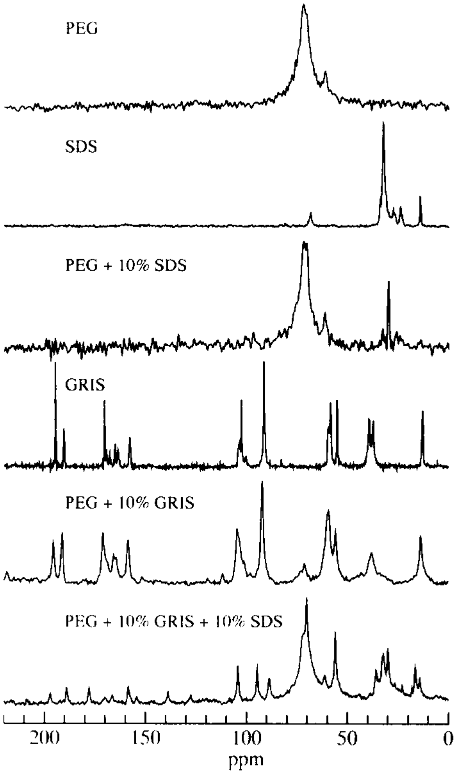

Fig. 2. ^{13}C CPMAS NMR spectra.

formulae of SDS and griseofulvin are depicted in Fig. 3 with the different carbon atoms denoted by appropriate numbers.

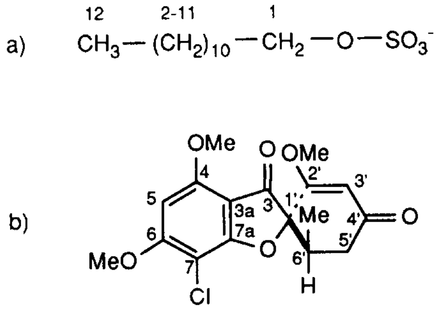

Fig. 3. Structural formula of: (a) dodecyl sulphate ion and (b) griseofulvin.

SDS in the spectra

^{13}C-NMR chemical shifts have earlier been measured on the surfactant SDS in aqueous solutions and have been used successfully to investigate the amphiphile aggregation state in micelles. Significant downfield shifts of 0.3–1.3 ppm at the central part of the chain and upfield shifts of 0.5 ppm at the C1 carbon atom have been observed when micelles are formed in such systems (Okabayashi et al., 1982).

In pure solid SDS the peaks have moved compared to aqueous solutions. The C1 peak has moved approx. 1 ppm upfield while the C12 and central part peaks have moved approx. 5 ppm downfield. On formation of the PEG/SDS solid solution, the central part peaks have moved upfield approx. 1 ppm. These small changes might depend on packing effects. The C12 peak from SDS has disappeared in the PEG/SDS dispersion (solid solution) probably because of peak broadening. This might be an effect caused by a decrease in mobility of CH_3.

A dynamically disordered SDS molecule that rapidly switches between its various conformations and environments should give a sharp C12 peak with a distinct shift resulting from the average surroundings around the CH_3 group. If the phase is statically disordered, or only slowly changing between environments, the CH_3 groups should sample varying environments and thus give a broad range of peaks. In the solid solution of SDS in PEG, the SDS molecules or a micelle-like aggregation of SDS is likely to have several distinct sites available, given by the original PEG structure, and thus a broad peak range would appear.

In the PEG/SDS and $(PEG/SDS)_{1-x}$griseofulvin$_x$ dispersions, the C1 peak from SDS is not resolved; it is possibly located in the PEG peak at 84 ppm.

Griseofulvin and PEG in the spectra

In the solid solution $(PEG/SDS)_{1-x}$griseofulvin$_x$ all the peaks emanating from griseofulvin are sharp and well defined. This indicates that all griseofulvin molecules 'see' closely the same environment, at least on the average, either because there is only one environment available for the griseofulvin molecules or because the molecules are moving rapidly between the different available environments (as in a liquid). The average surroundings, however, are different from those in pure griseofulvin. Most of the peaks in the spectrum have moved to a greater or lesser extent from the positions in the pure phase. The different peaks could be identified by the spectrum presented by Levine et al. (1975) for griseofulvin in liquid solution.

The C4′ and C3 in griseofulvin are strongly influenced by the solid solution formation. Thus, two of the OMe carbon atoms and the C=O carbons representing the most hydrophilic parts of the molecule are heavily perturbed.

Below about 20 ppm where CH_3 peaks are observed in pure griseofulvin and in pure SDS, there are three peaks in the solid solution. This implies, as mentioned earlier, the existence of CH_3 with three different surroundings, e.g., in solid solutions, in free griseofulvin molecules or in different aggregate with SDS.

At the location of the 4-, 2′- and 6-OMe peaks in pure griseofulvin only one peak is observed in the solid solution. This might be a result of the 4- and 2′-OMe peaks having moved to the location in the PEG peak at 84 ppm; this peak actually shows a sharp and distinct feature in the solid solution with griseofulvin, that is not visible in pure PEG or in the PEG/SDS dispersion. The griseofulvin peak from 6-OMe remains at the same position in the solid solution as in pure griseofulvin. The rest of the PEG spectrum is unchanged in comparison to that of pure PEG.

The C1′, C5 and C7 peaks have shifted compared to pure griseofulvin as have the C2′ and C6 peaks.

The PEG + 10% griseofulvin spectrum is essentially a superposition of the spectra from the two components. This indicates that there is no interaction between polymer and griseofulvin, changing the short-range order. The reason for the changing griseofulvin spectrum in the solid solution must be that the addition of SDS influences the polymer-griseofulvin interaction. It is interesting to note that such changes in the griseofulvin spectrum in the solid solutions already occur at the low SDS concentration of 1%.

The observations in the X-ray patterns and the NMR spectra might be explained by the binding of the OMe and C=O parts of the griseofulvin molecules to SDS and the subsequent dissolution of this complex in PEG. An association of griseofulvin molecules to the SDS aggregates would result in a complex which is much more hydrophilic than the griseofulvin molecules themselves. This rather hydrophilic complex can then be dissolved in the PEG structure. The aggregates must be seated at the same crystallographic sites as the PEG molecules in pure PEG, otherwise the diffraction pattern from the solid solution would be different from that of the pure PEG phase. Furthermore, no large aggregates of griseofulvin can be present in the solid solution, otherwise the periodic griseofulvin structure would have been detected in the X-ray diffraction pattern.

Two main possibilities for the association of griseofulvin molecules with the SDS aggregates are available. Either griseofulvin molecules are dissolved in the interior of the SDS aggregates/micelles or they are bound to the hydrophilic exterior of these aggregates, where they have to compete with the sodium counterions from the surfactant.

Size of aggregates

In one unit cell of pure, crystalline griseofulvin there are four molecules sharing a volume of 1600 Å^3, i.e., 400 Å^3/molecule (Malmros et al., 1977). In a PEG sample with 10% griseofulvin and 10% SDS there are about twice as many SDS molecules as griseofulvin molecules. Assuming an aggregate (micelle) containing 20 SDS molecules, which is a reasonable number in polymer water solutions (Turro et al., 1984) the number of griseofulvin molecules per aggregate would be 13, requiring a volume of about 5000 Å^3 if the packing density is as high as in crystalline griseofulvin. The radius of a spherical micelle in liquid solutions is of the order of 20 Å (Cabane and Deplussix, 1982) corresponding to a volume of 34 000 Å^3 and a surface area of 5000 Å^2.

If one assumes a similar size aggregate to occur in the polymer melt, and thus also in the solid state obtained by the fast cooling of the melt, there is no problem as far as space is concerned in containing 13 griseofulvin molecules in the interior hydrophobic part of a spherical aggregate.

Another possibility is that the griseofulvin molecules are bound to the exterior surface of the SDS aggregate. Again there is enough room: even the most unfavourable bonding of the griseofulvin molecule at the surface will allow sufficient molecules to bind. Assuming a planar griseofulvin molecule with the same distance between different atoms as in the crystalline state, 13 griseofulvin molecules would cover approx. 300 $\mathring{A}^2$ of the spherical surface area. Still there will be space at the surface to bind the sodium ions, which are twice as numerous as the griseofulvin molecules.

It should be noted that the incorporation of 2% w/w SDS is also enough to allow the binding of 10% griseofulvin either in the interior of a similar aggregate or to the exterior surface. On the other hand, the addition of 1% SDS is too little to allow all griseofulvin molecules to bind in the interior of the aggregate. As reported before (Sjökvist et al., 1991), in a solid dispersion with 2% SDS incorporated, all griseofulvin was present in a solid solution within the PEG/SDS matrix, while in a solid dispersion with 1% SDS, griseofulvin was present both in a solid solution and as a pure phase (Table 1).

Conclusions

The addition of the anionic surfactant SDS to the PEG-griseofulvin system creates solid solutions PEG/SDS and $(\mathrm{PEG/SDS})_{1-x}$griseofulvin$_x$, where SDS and griseofulvin are dissolved in a molecular form. The SDS and griseofulvin molecules are distributed in the periodic PEG structure on the same crystallographic sites as the PEG molecules in the original PEG structure.

One possible model for the dissolution of SDS in PEG is the formation of small aggregates/micelles of the surfactant molecules which are attached to the polymer chains, similar to the model presented by Cabane and Deplussix (1982) for the interaction between a polymer and SDS in concentrated liquid solutions.

The griseofulvin molecules are bound via the SDS aggregates to PEG. The most hydrophilic parts of the molecules are greatly influenced by short-range interaction, which indicates a modified environment of the molecules. They are either dissolved in the hydrophobic interior of the SDS aggregates or bound to the hydrophilic exterior. In both cases, the geometric conditions allow the amount of griseofulvin considered to dissolve in the structure.

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