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Structures formed by interactions in solid dispersions of the system polyethylene glycol-griseofulvin with charged and non charged surfactants added

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Summary

Solid dispersions of polyethylene glycol (PEG) 3000 and 10% w/w griseofulvin with incorporation of different types of surfactants were prepared by the melting method. The anionic surfactant sodium dodecyl sulphate (SDS), the cationic surfactant dodecyltrimethylammonium bromide (DTAB) and the nonionic surfactant polyoxyethylene dodecyl ether (Brij) were added in equivalent amounts. Phase analysis was made by X-ray powder diffraction and investigation of the short-range structure by ¹³C-CP/MAS solid-state NMR. The addition of the different types of surfactants influences the structure of the dispersions in a varying manner. The anionic surfactant SDS forms a solid solution, the nonionic Brij does not influence the particulate dispersion and the cationic DTAB creates a dispersion, that only to a certain extent is a solid solution. The extent of interaction between polymer and surfactant aggregates (micelles) seems to be crucial for the formation of solid solutions of griseofulvin in the polymer phase. The charged surfactants can interact with the polymer forming aggregates, while the nonionic ones show no interaction. When a solid solution is formed, the hydrophilic parts of the griseofulvin molecule are significantly influenced. The surfactant aggregates bind griseofulvin in a molecular form at the surface or, more probably, in the interior of the aggregate.

Introduction

Interactions between ionic surfactants and neutral polymers have been investigated extensively because of their importance in industrial processes and in biological systems. These investi-

gations concern liquid solutions in particular water solutions, as do also the investigations on solubilization in micellar systems.

Several investigators (Jones, 1967; Cabane and Duplessix, 1982) have demonstrated, using the surface tension and NMR methods, that the surfactant concentration at which the interaction between a surfactant and a polymer first occurs, T_1 , is only weakly dependent on the amount of polymer in solution. On the other hand the value of T_2 , which represents saturation of the polymer

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sites, is directly proportional to the concentration of polymer.

The driving force for association of surfactant molecules is a reduction of the contact area between PEG and the alkyl chains of the dissolved surfactant in addition to steric and electrostatic interactions between polymer and surfactant micelles. In the presence of a polymer, clusters are formed with a size of 15–20 surfactant molecules (Smith and Muller, 1975; Gilanyi and Wolfram, 1981). Several authors have reported that interaction between uncharged water soluble polymers with anionic surfactants is much more facile than with cationic surfactants. Also, there is little indication of reactivity of polyoxyethylated nonionic surfactants with this kind of polymer (Saito, 1958; Nagarajan and Kalpakci, 1982).

The solid systems containing polymer and surfactant are just as important as those in water solutions. Additions of surfactants are used, for example, to increase the dissolution rate of water-insoluble drugs from a polymer carrier. The solid dispersions created can be considered as an extreme case of concentrated polymer solutions. In water solutions the enhanced solubility is accomplished by solubilization of the drug in the hydrophobic part of the surfactant micelles. A similar model was proposed for the solid state in a previous study (Aldén et al., 1992). The long- and short-range order of solid dispersions containing the neutral polymer PEG as carrier, the anionic surfactant, SDS, and the poorly water soluble, lipophilic model drug (griseofulvin) was investigated. The interactions and bonds between the PEG, SDS and griseofulvin molecules forming a solid solution were identified.

In a recent study (Sjökvist et al., 1992), a varying influence on dissolution rate by additions of different types of surfactants was observed. Anionic SDS, cationic DTAB, nonionic polysorbate, Tween, and polyoxyethylene dodecyl ether, Brij, surfactants were added to solid dispersions of griseofulvin and PEG. The anionic surfactant had a pronounced enhancement effect on the dissolution rate, while the cationic surfactant showed a limited influence and the nonionic surfactant only a minor influence on the dissolution process.

The aim of the present work is to investigate and compare the long-range and short-range order resulting, when equivalent amounts of the anionic SDS, the cationic DTAB and the non-ionic Brij surfactants are added to dispersions of griseofulvin and PEG. Samples with 2% w/w SDS, 3% w/w DTAB and 6% w/w Brij, respectively, were chosen. The length of the carbon chains influences the aggregate formation between polymer and surfactant (Arai et al., 1971). Therefore, in our study the surfactants all contain a dodecyl chain.

Experimental

Materials

Griseofulvin (GRIS) microsized (Glaxo, U.K.) is a hydrophobic drug with the formula $C_{17}H_{17}ClO_6$.

Polyethylene glycol (PEG) 3000 (Apoteksbolaget, Sweden) is used as a carrier. The melting temperature interval is 56–58°C. The formula is $HO(C_2H_4-O)_nH$ with $n = 70$.

Sodium dodecyl sulphate (SDS) (Apoteksbolaget, Sweden) is an anionic surfactant with the formula $C_{12}H_{25}SO_4Na$.

Polyoxyethylene dodecyl ether (Brij 35), (Merck-Schuchardt, Germany) is a nonionic surfactant with the formula $CH_3(CH_2)_{11}(O-CH_2-CH_2)_yOH$ and with $y = 23$.

Dodecyltrimethylammonium bromide (DTAB) (Sigma, U.S.A.) is a cationic surfactant with the formula $(CH_3)_3N-(CH_2)_{11}CH_3Br$.

Methods

Preparation of solid dispersions Solid dispersions of 10% w/w griseofulvin with Brij (6% w/w), DTAB (3% w/w) or SDS (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. In dispersions incorporating a surfactant, the latter was dispersed in the melted carrier prior to the addition of griseofulvin. The

samples were brought to room temperature by fast cooling ($50\text{--}100\text{ K s}^{-1}$).

X-ray diffraction The X-ray powder diffraction investigations were performed using a STOE position sensitive detector (PSD) system with Ge monochromatized $\text{CuK}\alpha_1$ radiation. A curved-wire detector ($r = 130\text{ mm}$) 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 -CP/MAS NMR spectra were recorded on a Bruker MSL 300 spectrometer at 75 MHz using 4 mm o.d. zirconium oxide rotors and spinning at about 6.5 kHz. The proton and carbon r.f. fields used during cross-polarization and decoupling correspond to $4\ \mu\text{s}$ 90° pulses.

Results and Discussion

X-ray powder diffraction

The long-range order as reflected in the X-ray powder diffractograms of some of the dispersions is shown in Fig 1. In the PEG-griseofulvin dispersion griseofulvin and PEG are both present as pure phases. In the following the notation PEG/SDS, PEG/DTAB and PEG/Brij represents a phase composition where the phases are pure PEG and pure SDS, DTAB or Brij or a partial solid solution of the surfactants in the PEG phase combined with pure PEG and pure

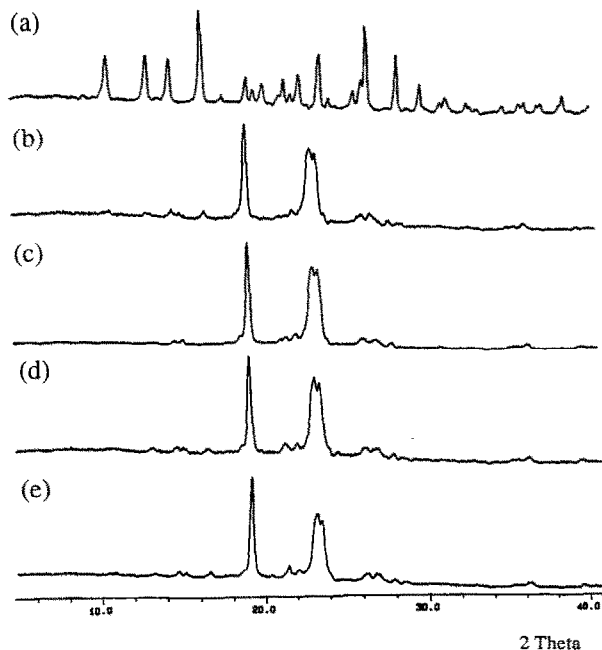


Fig. 1. X-ray powder diffractograms (a) Griseofulvin, (b) PEG + 10% griseofulvin, (c) PEG + 10% griseofulvin + 2% SDS, (d) PEG + 10% griseofulvin + 3% DTAB, (e) PEG + 10% griseofulvin + 6% Brij.

surfactant. $(\text{PEG})_{1-y}\text{SDS}_y$ represents one phase, a solid solution of SDS in PEG.

PEG / SDS / griseofulvin samples

In the dispersions containing 2% SDS it is reasonable to assume that a solid solution of SDS in PEG, $\text{PEG}_{1-y}\text{SDS}_y$, is formed, as reported

TABLE 1

X-ray powder diffraction phase analysis

Sample	Phases observed
PEG 3000	PEG
Griseofulvin	griseofulvin
PEG 3000 + 10% griseofulvin	PEG + griseofulvin
PEG 3000 + 10% griseofulvin + 2% SDS	$(\text{PEG}/\text{SDS})_{1-x}\text{griseofulvin}_x$
PEG 3000 + 10% griseofulvin + 3% DTAB	PEG/DTAB + griseofulvin + $(\text{PEG}/\text{DTAB})_{1-x}\text{griseofulvin}_x$
PEG 3000 + 10% griseofulvin + 6% Brij	PEG/Brij + griseofulvin

PEG/DTAB and PEG/Brij represent pure PEG and pure DTAB or Brij or a solid solution of the surfactants in PEG combined with the pure phases. $(\text{PEG}/\text{SDS})_{1-x}\text{griseofulvin}_x$ and $(\text{PEG}/\text{DTAB})_{1-x}\text{griseofulvin}_x$ are the solid solutions of griseofulvin and SDS or DTAB in the PEG structure.

earlier for dispersions with 10% SDS (Alden et al., 1992). Griseofulvin dissolves in the matrix to become a solid solution $(\text{PEG}/\text{SDS})_{1-x}\text{griseofulvin}_x$. The diffraction pattern corresponds to that from $(\text{PEG})_{1-y}\text{SDS}_y$. No peak corresponding to pure griseofulvin phase is observed. The dissolution of griseofulvin in the complex would introduce a change into the diffraction pattern, if the molecules were bound on the same crystallographic sites as the PEG molecules, but in a periodic arrangement, which differs from that of PEG. No indication of this is found. The relative intensities of the PEG pattern are the same in the solid solution and in the solid dispersion, which shows that the griseofulvin molecules are randomly distributed over available sites.

PEG / DTAB / griseofulvin samples

In a dispersion with 3% DTAB both pure griseofulvin and PEG/DTAB phase were present. The relative amounts, as reflected in the intensity of the diffraction lines of PEG and griseofulvin, were somewhat lower than from those obtained in the PEG/griseofulvin dispersion without a surfactant. This fact implies a partial solid solution of griseofulvin in the PEG/DTAB phase, here denoted by $(\text{PEG}/\text{DTAB})_{1-x}\text{griseofulvin}_x$. A certain amount of the added DTAB is observed as a pure phase in the diffraction pattern at $2\theta = 21.1$ and 24.3° .

PEG / Brij / griseofulvin samples

Both the PEG/Brij and the griseofulvin phase were also present in the dispersions with 6% Brij. No Brij phase could be observed in spite of the relatively high content. It cannot be determined here whether this implies that a solid solution is formed between PEG and Brij. The similarity between the chemical composition of Brij and PEG creates structures of the same type and thus gives similar diffraction patterns. The relative amount of the phases griseofulvin and PEG did not differ significantly from the ratio in samples without a surfactant. This implies that there is no dissolution of griseofulvin in the PEG structure, when the non-ionic surfactant is added.

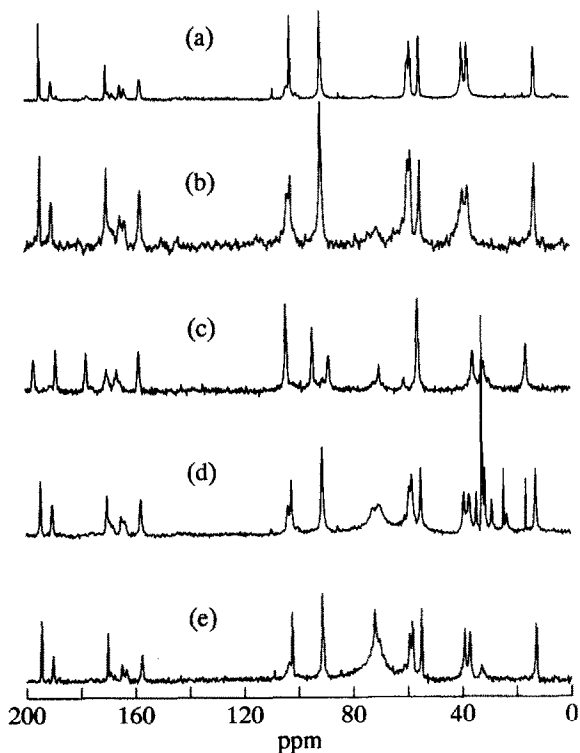
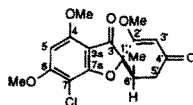


Fig. 2. ^{13}C -CPMAS NMR spectra. (a) Griseofulvin, (b) PEG + 10% griseofulvin, (c) PEG + 10% griseofulvin + 2% SDS, (d) PEG + 10% griseofulvin + 3% DTAB, (e) PEG + 10% griseofulvin + 6% Brij.

NMR spectra

To obtain more information on the short-range interaction in the samples a NMR study was performed. The ^{13}C -NMR spectra of PEG-SDS, PEG-DTAB and PEG-Brij systems with 10% griseofulvin added and the PEG-griseofulvin dispersion without surfactant are given in Fig. 2.

PEG / griseofulvin

The spectrum of PEG with 10% griseofulvin 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.

PEG / SDS / griseofulvin

The main pattern for the sample with 10% SDS (Aldén et al., 1992) is also observable in the samples with 2% SDS. All the peaks in the griseofulvin spectra are sharp and well defined. This indicates that all griseofulvin molecules experience the same environment. The most prominent differences between samples with and without SDS were:

In the SDS spectrum the C12 peak, i.e., the carbon most distant from the sulphate head group, has disappeared in the solid solution most probably as a result of peak broadening. The SDS molecules or a micelle-like aggregation of SDS is

likely to have several distinct sites available, provided by the original PEG structure. The CH₃ groups sample varying environments and may thus give a broad range of peaks.

In the griseofulvin spectrum the observation of three CH₃ peaks implies three different surroundings. The most hydrophilic part of the molecule, the OMe and the C-O carbons, C3 and C4' are strongly influenced by the solid solution formation. The 4-, 2'- and 6-OMe carbon peaks are reduced to one in the solid solution, probably because of the 4- and 2'-peaks being hidden by the PEG peak.

PEG / DTAB / griseofulvin

The main patterns from pure DTAB and pure PEG are retained in the polymer dispersions

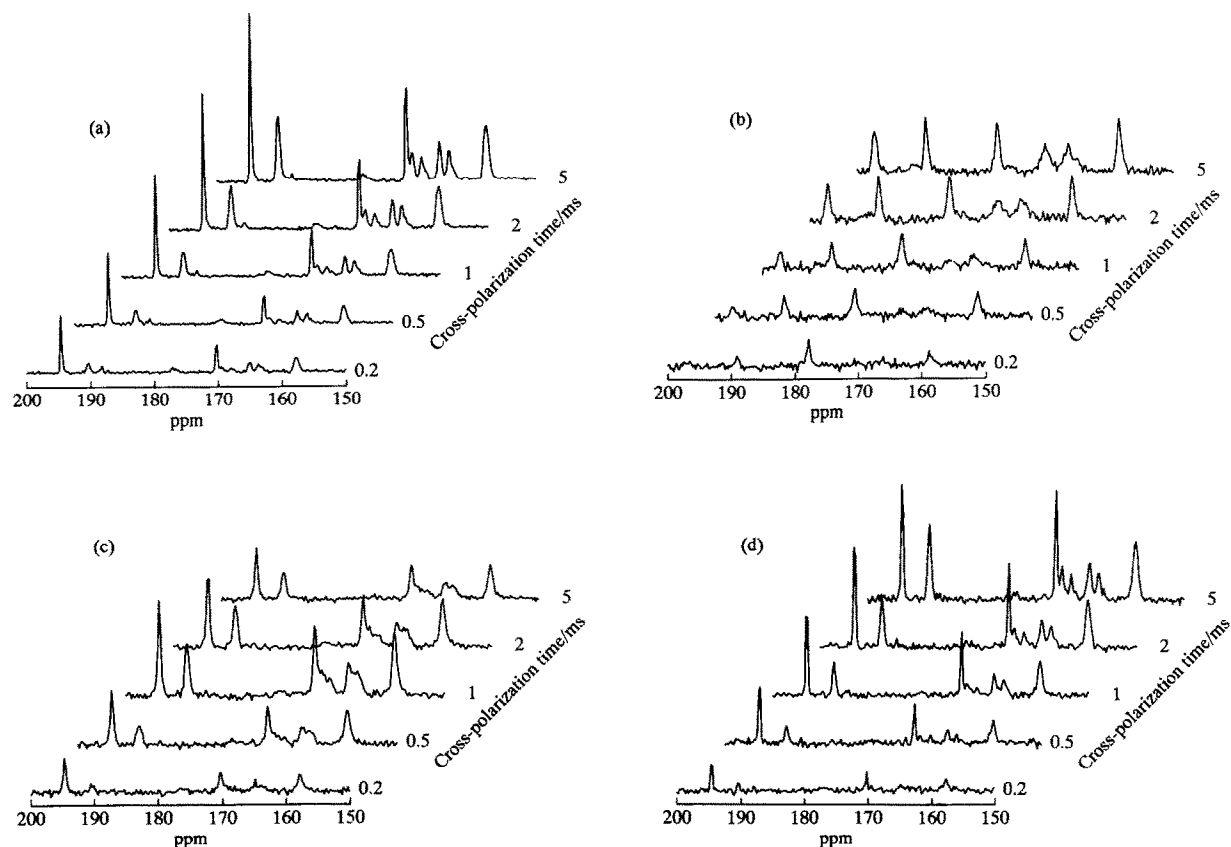


Fig. 3. Dependence of part of the ¹³C-CPMAS NMR spectrum on the cross-polarization time. (a) Griseofulvin, (b) PEG + 10% griseofulvin + 2% SDS, (c) PEG + 10% griseofulvin + 3% DTAB, (d) PEG + 10% griseofulvin + 6% Brij.

without griseofulvin added. The spectrum of the PEG-DTAB sample is essentially a superposition of the DTAB and PEG spectra.

In the PEG-DTAB-griseofulvin dispersion the griseofulvin spectrum differs somewhat compared to that spectrum of griseofulvin in the pure phase or in the dispersion of PEG and griseofulvin. An overall broadening is found indicating different surroundings.

The spectral changes for individual carbon atoms concern the most hydrophilic parts of the griseofulvin molecule. For the C=O carbons, C4' and C3, a broadening of the peaks is observed. The integrals shown in Fig. 4 indicate that the relative areas under the peaks are different from those in pure griseofulvin. The OMe carbons and the 2', 4- and 6-carbons are influenced in the same way but to a lesser extent. At least part of the griseofulvin molecule seems to experience different surroundings than in the pure phase.

The dependence of the C=O peak intensities for the PEG-DTAB-griseofulvin dispersion as a function of the cross-polarization time differs considerably from those of pure griseofulvin. This could be a result of a difference in the mobility of the molecules in the two systems. In Fig. 3 the variation in CP behaviour for dispersions with different surfactants is shown. In the DTAB-sample the size of the C3 and C4' peaks shows a maximum at 1 ms, whereas in pure griseofulvin the corresponding peak intensities increase monotonically when the cross-polarization time increases from 200 μ s to 5 ms.

PEG / Brij / griseofulvin

Both the PEG-Brij and the PEG-Brij-griseofulvin dispersions give spectra which are superpositions of the spectra from the pure phases. No interaction between griseofulvin and the other components is detected.

Interactions

The reason for the changing spectrum in the dispersion with DTAB and SDS is that the surfactant addition influences the polymer-griseofulvin interaction. The observations in the X-ray

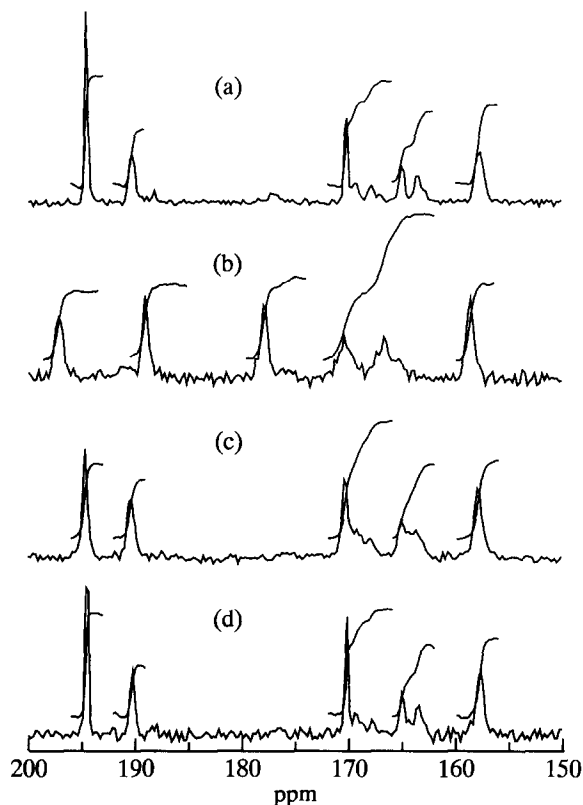


Fig. 4. Integrated peak areas in part of the ^{13}C -CPMAS NMR spectrum. (a) Griseofulvin, (b) PEG + 10% griseofulvin + 2% SDS, (c) PEG + 10% griseofulvin + 3% DTAB, (d) PEG + 10% griseofulvin + 6% Brij.

pattern indicate that a certain amount of griseofulvin is dissolved in the PEG phase on addition of DTAB and all the griseofulvin with the addition of SDS. In both samples the hydrophilic parts of the griseofulvin molecule are bound to the surfactant and the complex formed is subsequently dissolved in PEG.

The results indicate an interaction between polymer and surfactant aggregate, varying with the charge of the surfactant. In the melt as well as in the solid state the interaction seems to be most facile with the anionic surfactant and least with the non-ionic one. The largest amount of griseofulvin in solid solution should therefore be observed in the PEG-SDS system and the lowest amount in the PEG-Brij system. This is in agreement with the dissolution rate data from Sjökvist et al. (1992).

In a previous paper (Alden et al., 1992), the geometric conditions for the griseofulvin molecules to be bound to the SDS aggregates in a 10% SDS dispersion were discussed. Since the amount of SDS in the present study was 2% the number of griseofulvin molecules per aggregate would be 65, requiring a volume of $25\,000\text{ \AA}^3$ or an area of 1300 \AA^2 . If the SDS aggregates are assumed to be spherical with a radius of the order of 20 \AA , corresponding to a volume of $34\,000\text{ \AA}^3$ and a surface area of 5000 \AA^2 , there is no problem, as far as space is concerned, to contain 65 griseofulvin molecules in the interior hydrophobic part of a spherical aggregate, nor at the exterior surface.

The cationic and anionic surfactants, DTAB and Brij, are added in amounts that are equivalent to the 2% SDS addition. Why is it then, that the amount of griseofulvin dissolved in PEG/surfactant complex is much less or none at all in the dispersions with this type of surfactants?

The extent of interaction of the surfactant aggregate with the polymer seems to be crucial for the dissolution of griseofulvin in the solid phase. Since the polymer chain is rather hydrophilic with a negative charge on the ether oxygen, one would expect the cationic surfactant to be at least as favourable for bonding as the anionic surfactant. A possibility of explaining the differences emerges if it is assumed that the process starts by the counter ions binding towards the polymer chain oxygens. These ions can then interact simultaneously with the micelle/aggregate through electrostatic forces. Such a mechanism was recently proposed by Dubin et al. (1992) for an aqueous solution containing polymer and anionic surfactant.

In the solid state at least part of the sodium ions, that are counterions in the anionic surfactant salt, could be bound to the polymer chain. The hydrophilic parts of the SDS aggregates might then bind to the positively charged regions. It is most probable that the surfactants bind as aggregates (micelles). A $\text{Na}^+ \text{DS}^-$ ion pair, for example, would not change the hydrophilic character of the environment of PEG enough to give the distinct increase in the solubility of griseofulvin in

the polymer phase, that has been observed (Sjökqvist et al., 1992)

The counterion in the cationic surfactant, Br^- , has a lower charge density than Na^+ , $0.052 \times 10^{-19}\text{ C \AA}^{-3}$ and $0.42 \times 10^{-19}\text{ C \AA}^{-3}$, respectively. This might result in a lower affinity to the polymer chain for this ion. It might also mean that cationic micelles have a reduced tendency to bind to and form stable compounds with the polymer. Furthermore, the absence of counterions might explain why no interaction is observed when nonionic surfactants are added.

Conclusions

The addition of the anionic surfactant SDS to the PEG-griseofulvin system creates the solid solutions $(\text{PEG}/\text{SDS})_{1-x}\text{griseofulvin}_x$. The addition of an equivalent amount of cationic surfactant, on the other hand, creates a limited solid solubility of griseofulvin in the polymer-surfactant system. Most of the griseofulvin is in particulate form as a dispersion in the PEG surfactant matrix. Equivalent nonionic surfactant additions create no solid solution. All the griseofulvin appears as pure crystalline phase.

The most hydrophilic parts of the griseofulvin molecules are influenced by the anionic and cationic surfactant addition. The measurements on anionic samples indicate a greatly modified environment of the molecules, whereas in the cationic ones a similar but smaller modification is observed. The nonionic surfactant addition results in no change in the short-range interaction of the griseofulvin molecule compared to pure griseofulvin.

A possible model for the dissolution of griseofulvin in the PEG/surfactant system is the formation of small aggregates of the surfactant molecules to which the griseofulvin molecules are bound. This hydrophilic complex is then dissolved in the PEG structure (Alden et al., 1992).

For all types of surfactants investigated here the geometric conditions allow the amount of griseofulvin considered to dissolve in the surfactant aggregate. If there is a reduced strength of

the bond formed between the polymer and the cationic or nonionic surfactant aggregate compared with the anionic aggregate, a smaller tendency to create solid solutions would appear. Such a weaker bond might be introduced by a structure, where the possible counterions of the surfactants are the bridges between the polymer and the surfactant aggregates.

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