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The effect of water-soluble polymers, PEG and PVP, on the solubilisation of griseofulvin in aqueous micellar solutions of Pluronic F127

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ABSTRACT

The purpose of this study was to investigate the possibility of enhancing the solubilisation capacity of micellar solutions of Pluronic F127 for the poorly water-soluble drug griseofulvin by co-formulating with a water-soluble polymer. The effect of the addition of the polyethylene glycols PEG6000 and 35000, and the poly(vinylpyrrolidone)s PVP K30 and K90, on the solubilisation capacity of 1 wt% solutions of Pluronic F127 was related to the effect of these additives on particle size as determined by dynamic light scattering measurements. The addition of PEG35000 to 1 wt% F127 solutions significantly increased the solubility capacity expressed in terms of unit weight of F127; PVP K90 had a smaller effect but no enhancement was noted following the addition of PEG6000 or PVP K30. Solubilisation enhancement was thought to be a consequence of the association of the polymers with the E-blocks of the micelle corona so providing an expanded region of reduced polarity for drug solubilisation.

1. Introduction

Pluronic copolymers of ethylene oxide and propylene oxide, type $E_mP_nE_m$, are available over a wide range of compositions and block lengths: we use the notation $E = OCH_2CH_2$, $P = OCH_2CH(CH_3)$, and subscripts m and n to indicate number-average block lengths in repeat units. Among their many applications is the solubilisation of poorly-soluble drugs in dilute aqueous micellar solutions (see, e.g., Chiappetta and Sosnik, 2007). As we have noted in recent reviews (Attwood et al., 2007; Attwood and Booth, 2007), the solubility of hydrophobic drugs in dilute solutions of these copolymers is lower than in micellar solutions of copolymers with more hydrophobic core-forming blocks, e.g. cores formed from 1,2-butylene oxide or styrene oxide. However, such copolymers are not readily available and a simple means of improving the performance of Pluronic copolymers would be useful. Recently (Oliveira et al., 2011) we reported a significant increase in the solubilisation capacity of 1 wt% micellar solutions of copolymer F127 ($E_{98}P_{67}E_{98}$) for the aromatic drug griseofulvin (see Scheme 1) on addition of a small quantity (0.5 wt%) of polyethylene glycol PEG35000. In a parallel experiment replacing PEG35000 with 0.5 wt% poly(vinylpyrrolidone) PVP K30 the solubilisation capacity for griseofulvin was not increased significantly. We define the solubilisation capacity as $(S - S_o)/w_t$ expressed in mg g^{-1}, where S is the solubility of the drug in the solution, S_o the solubility in water, and w_t the total weight of copolymer plus polymer. We focus on the solubilisation of griseofulvin as it has poor water solubility and has long been used (Elworthy and Patel, 1982; Rekatas et al., 2001) as a standard for testing micellar hosts.

In this paper, we report the results of a broader investigation of these effects, maintaining our interest in copolymer F127 as the source of micelles and griseofulvin as the solubilised drug, but with PVP and PEG samples with different molar masses studied over a wider range of concentrations. Also included is an investigation of the effect of addition of the polymers on the micelles as determined by dynamic light scattering measurements.

2. Experimental

2.1. Materials

Griseofulvin was obtained from Sigma–Aldrich, Poole, Dorset, UK) and was used in the form of finely ground (1 mm^2 mesh) powder. Differential scanning calorimetry indicated one crystalline

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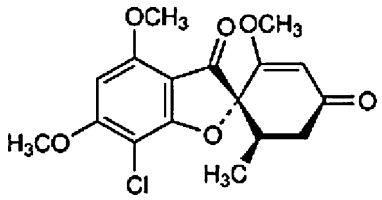

Scheme 1. Griseofulvin.

form with a melting point of 220.4 °C and an enthalpy of fusion of 115.6 J g^{-1}. There was no detectable transition consistent with a glassy component. Triblock copolymer F127, a product of BASF Corp. and purchased from Sigma–Aldrich, was used as received. The value of the number-average molar mass supplied with the sample was 12,500 g mol^{-1}. A value of the ratio of weight- to number-average molar mass, $Mw/Mn = 1.20$, was determined by gel permeation chromatography (GPC) using *N*,*N*-dimethylacetamide (DMA) at 70 °C as solvent and poly(ethylene oxide) calibrants, as described previously (Chaibundit et al., 2000). The polymers were also obtained via Sigma–Aldrich, PEG6000 and PEG35000 from Sigma, PVP K30 and PVP K90 from Fluka. Our check of the polyethylene glycols by GPC, using DMA solvent at 70 °C and poly(ethylene oxide) calibrants, yielded distribution widths (M_w/M_n) of 1.07 (PEG6000) and 1.16 (PEG35000). The molecular characteristics reported for PVP, both in the technical literature and in publications (Haaf et al., 1985; Segre et al., 1998; Xu et al., 1999; Zeng et al., 2001) vary considerably. Values of the ratio M_w/M_n determined for our samples using GPC with DMA/$LiNO_3$ at 70 °C as solvent and poly(ethylene oxide) calibrants were 2.8 for PVP K30 and 3.6 for PVP K90, much as expected for samples known to have broad chain length distributions. Adopting the

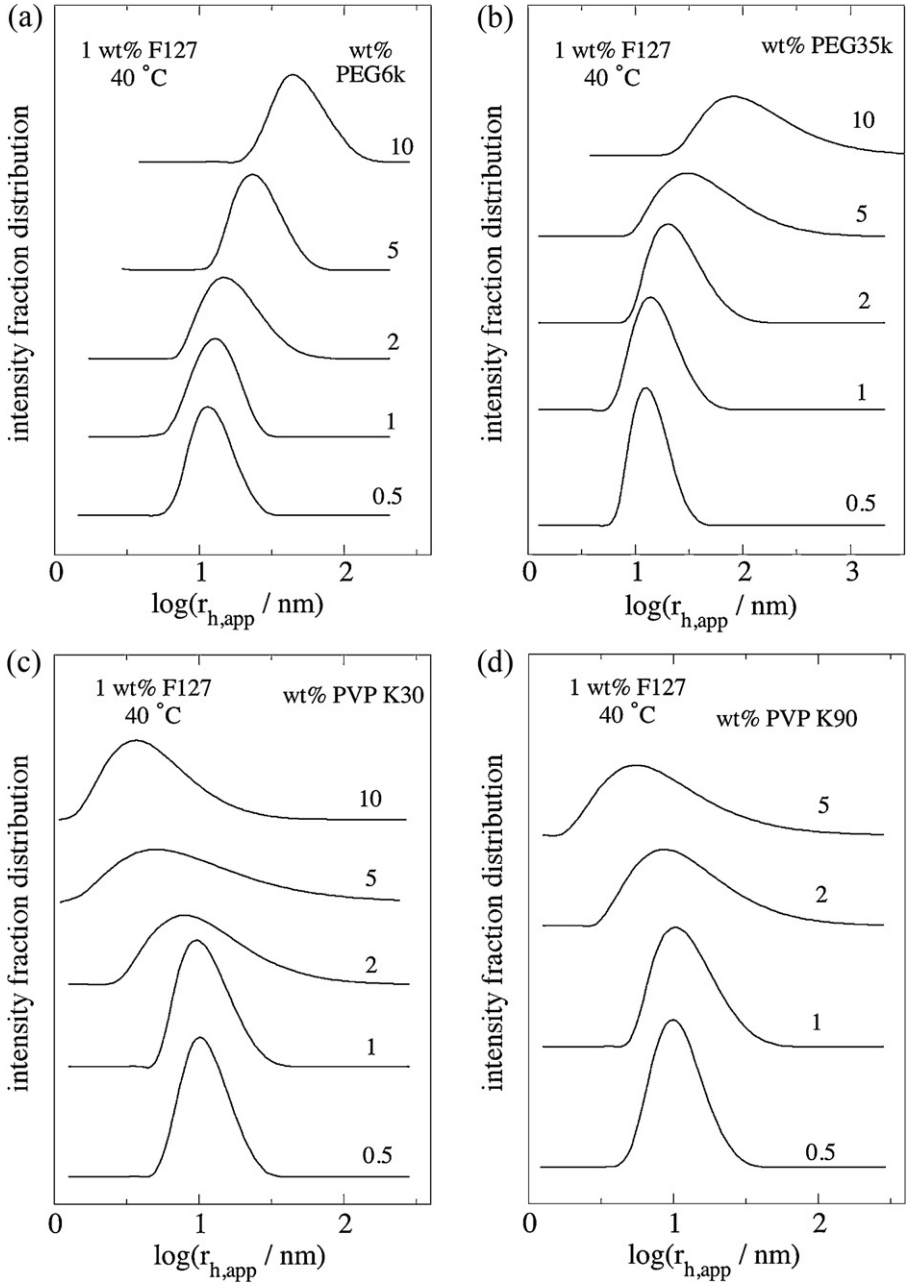

Fig. 1. Intensity distributions from DLS: intensity-fraction versus the logarithm of apparent hydrodynamic radius for aqueous solutions containing 1 wt% F127 and 0.5–10 wt% PEG6000, PEG35000, PVP K30 and PVP K90, as indicated. $T = 40$ °C.

manufacturers' values of $M_w \approx 40{,}000$ and $360{,}000\ g\ mol^{-1}$ for PVP K30 and PVP K90 respectively, our values of M_w/M_n lead to $M_n \approx 14{,}000$ and $100{,}000\ g\ mol^{-1}$ for the two polymers.

2.2. Solubilisation of griseofulvin

A stock solution of 1 wt% F127 in water was used to prepare further stock solutions containing amounts of PEG6000, PEG35000 and PVP K30 in the range 0–10 wt%, and of PVP K90 in the range 0.5–5 wt% to avoid the very viscous solutions of this polymer at higher concentrations. Corresponding solutions were prepared without F127. Powdered griseofulvin (10 mg) was mixed with stock solution (10 ml), and the mixture was stirred at constant temperature (37 °C) for 48 h before being filtered (0.45 μm Millipore filters) to remove unsolubilised drug. The procedure is equivalent to the standard Shake-Flask method. The extent of solubilisation at 37 °C was determined by UV spectroscopy, a method which has been checked against other procedures, e.g. ^{1}H NMR spectroscopy (Crothers et al., 2005) and liquid chromatography (Zhou et al., 2008). The drug-loaded solutions were diluted quantitatively with sufficient methanol to enable determination of the absorbance at optimum wavelength (griseofulvin 292 nm), and this absorbance was compared with the Beer's Law plot for griseofulvin in methanol. The water content after dilution was low enough to allow the calibration with methanol solutions to be used without correction. Blank experiments (no F127) gave the solubility of the drug in water or in polymer solution. The uncertainty in an individual measurement was ca. $\pm 1.5\ g\ dl^{-1}$, hence measurements were carried out in triplicate and the results were averaged.

2.3. Dynamic light scattering

Solutions containing 1 wt% F127 and the polymers at concentrations in the range 0–10 wt% (PVP K90 0–5 wt%) were clarified for light scattering by filtering through Millipore Millex filters (Triton free, 0.22 μm) directly into the cleaned scattering cell. In certain experiments, the most concentrated solution was filtered and subsequently diluted with filtered water. Dynamic light scattering (DLS) measurements were made at 40 °C with incident light of wavelength 488 nm (Coherent Innova Argon ion laser) using a Brookhaven BI-HV goniometer combined with a Brookhaven BI9000AT digital correlator to acquire data. The duration of the experiment was 10 min, and each experiment was repeated two or more times. Scattered light intensity was measured at an angle $\theta = 90°$ to the incident beam.

The correlation functions from DLS were analyzed by the constrained regularized CONTIN method (Provencher, 1979) to obtain distributions of decay rates (Γ), from which distributions of apparent mutual diffusion coefficient [$D_{app} = \Gamma/q^2$, $q = (4\pi n/\lambda)\sin(\theta/2)$, n = refractive index of the solvent, λ = wavelength] were determined. The apparent hydrodynamic radius ($r_{h,app}$, radius of the hydrodynamically equivalent hard sphere corresponding to D_{app}) was then calculated via the Stokes–Einstein equation.

$$r_{h,app} = \frac{kT}{(6\pi\eta D_{app})} \quad (1)$$

where k is the Boltzmann constant and η is the viscosity of the medium at temperature T. Anticipating association of the polyethylene glycols with the micelles, similar to that reported for C_nE_m (Feitosa et al., 2002) and the related Triton X-100 copolymer (Ge et al., 2007), we assumed that the solvent was water and used the viscosity of water in our analysis. In practice intensities $I(\Gamma)$ delivered by the CONTIN program at logarithmically spaced values of the decay rate were transformed to $I(\log\Gamma) = I(\Gamma)\Gamma$ to obtain intensity distributions of $\log(\Gamma)$ and hence of $\log(r_{h,app})$. Normalization of $I(\log r_{h,app})$ gave the intensity fraction distributions presented in Section 3.1. Average values of $r_{h,app}$ were delivered by the program.

3. Results and discussion

3.1. Apparent hydrodynamic radius

The intensity fraction distributions of $\log(r_{h,app})$ obtained for aqueous solutions containing 1 wt% of F127 and 0.5–10 wt% of each of the four polymers are illustrated in Fig. 1. Temperatures were held at 40 °C, approximating the temperature of 37 °C used for the solubilisation experiments. Small peaks at low values of $\log(r_{h,app})$ in the distributions of the samples with the highest concentrations of PEG were not reliably reproduced and were not included.

As illustrated in Fig. 1, the intensity distributions shifted to higher values of $\log(r_{h,app})$ as the concentration of PEG was increased, and to lower values of $\log(r_{h,app})$ as the concentration of PVP was increased. This effect is reproduced in the intensity-average values of $r_{h,app}$ obtained from the CONTIN output for the four copolymer and plotted in Fig. 2. The intensity-average delivered by the CONTIN program includes the full range of particle sizes – polymers, micelles and clusters. The intensity weighting (essentially z-weighting) means that the contribution to the DLS signal from micelles, and particularly that from micelle clusters, greatly outweighs that from any residual polymer chains.

The increase in $r_{h,app}$ resulting from the presence of PEG6000 and PEG35000 in micellar solutions of F127 is consistent with related results from DLS for micellar solutions of $C_{12}E_8$ with 0–5 wt% PEG12000 (Feitosa et al., 2002) and for solutions of Triton X-100 (C_8PhE_{10}) with 5 wt% PEG (range 400–20,000) (Ge et al., 2007). It is also consistent, with results from DLS for a range of polyethylene glycols and a diblock copolymer formed by coupling ibuprofen ($C_{12}CO$ overall) to PEG800 (E_{18}) (Wei et al., 2010). Polyethylene glycols are compatible with the E-blocks of the micelle corona, and the implication is that in dilute PEG solutions micelle coronae are favoured as an environment for the PEG chains and in more concentrated solutions this leads to the PEG chains bridging between micelles to form clusters. It should be noted that values of $r_{h,app}$ include contributions from particle interaction, and are also affected by any increase in viscosity caused by

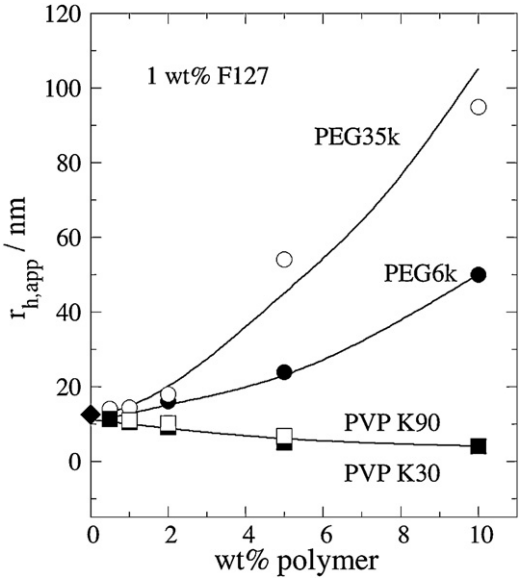

Fig. 2. The effect of addition of (●) PEG6000, (○) PEG35000, (■) PVP K30 and (□) PVP K90 on the apparent hydrodynamic radii of particles in aqueous solutions of 1 wt% F127: (♦) indicates 1 wt% F127 alone. $T = 40$ °C.

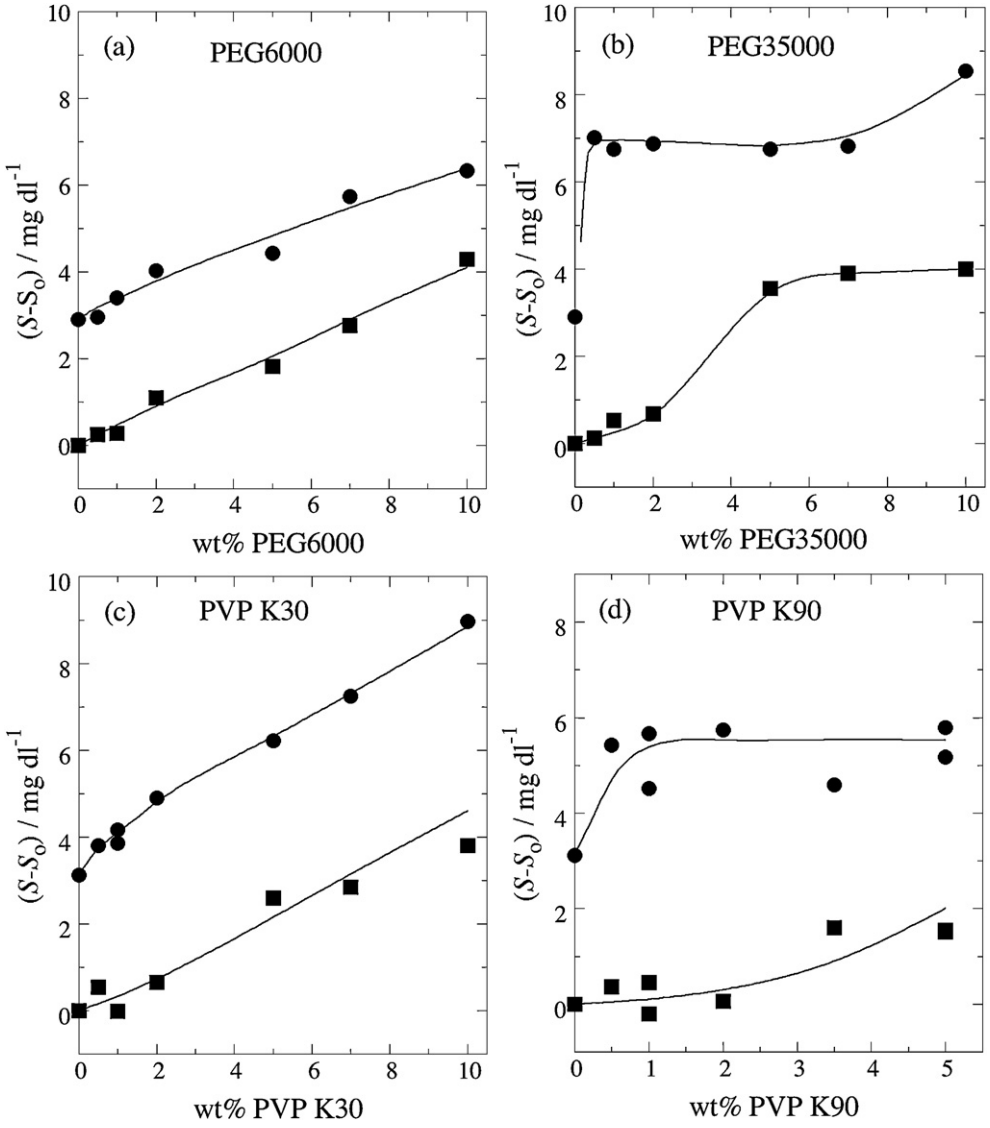

Fig. 3. The solubility (S) of griseofulvin in aqueous solutions of either (■) the polymers alone or (●) the polymers plus 1 wt% F127. $T = 37\,^{\circ}C$. The curves are included to lead the eye through the points.

unassociated PEG chains, but this complication does not preclude qualitative interpretation of the results.

To understand the driving force for association of PEG with the chains of the micelle corona it is necessary to bear in mind that the oxyethylene chain is predominantly hydrophobic yet it is readily soluble in dilute aqueous solution when the water is structured by hydrogen bonding, as it will be at 40 °C. As summarised some time ago (Marinov and Marsuura, 2002) the solubility of poly(oxyethylene) in dilute solution arises from the fact that the distance between the oxygen atoms of the oxyethylene chain in gauche conformation almost coincides with the distance between the oxygen atoms of neighbouring molecules in structured water, allowing the E-chains to participate in the H-bonded structure. However, the coincidence of distance is not perfect and not all oxyethylene groups are in the gauche conformation, hence the residual hydrophobic effect in dilute solution which causes association of PEG35000 with the micelle.

PVP is not compatible with the E-blocks of the micelle corona and association is restricted. Indeed coincidence of the enthalpy changes detected by isothermal titration calorimetry of micellar solutions of copolymer $C_{12}E_6$ with and without added PVP K90 (Li et al., 2000) indicates that interaction of PVP with the E-blocks in the micelle coronae is enthalpically neutral. In contrast, a negative enthalpic effect is well established when PVP binds to micelles carrying charges, such as those formed from sodium dodecyl sulphate (SDS) (Li et al., 2000). The shift of the intensity distribution to lower values of $\log(r_{h,app})$ (Fig. 1) can be assigned to the micelles maintaining their separate identity with the effect of the increase in viscosity of the solvent (see Eq. (1)) reinforced by an increase in the proportion of chains included within the main peak taking the intensity average to smaller values.

3.2. Solubilisation of griseofulvin

3.2.1. Solubility

Fig. 3 illustrates values obtained for the solubility of griseofulvin in 0.5–10 wt% aqueous solutions of the four polymers at $T = 37\,^{\circ}C$ and also in the same range of solutions but including 1 wt% F127. The quantity plotted ($S - S_o$, mg dl^{-1}) is the solubility in excess of that in water alone, where S is the solubility in solution and S_o is the solubility of griseofulvin in water. As noted in Section 2.2, measurements were carried out in triplicate giving an uncertainty in the resulting average of ca. ±0.5 mg dl^{-1} for PEG6000, PEG35000

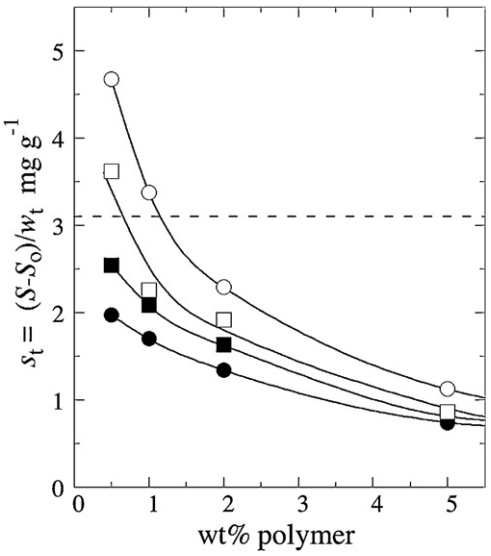

Fig. 4. Solubilisation capacities for solubilisation of griseofulvin of aqueous solutions of 1 wt% F127 and (●) PEG6000, (○) PEG35000, (■) PVP K30 or (□) PVP K90. The solubilisation capacity $s_t = (S - S_o)/w_t$ (mg g^{-1}), where S_o is the solubility of griseofulvin in water and w_t is the total concentration of polymer and copolymer in solution. $T = 37\,^{\circ}C$. The curves are included to lead the eye through the points. The dotted line indicates the solubilisation capacity of F127 alone in water.

and PVP K30 but with values as high as ± 1 mg dl^{-1} for the more viscous solutions of PVP K90.

In water alone, the excess solubility increased almost linearly for PEG6000 and PVP K30 to reach ca. 3 or 5 mg dl^{-1} respectively at 10 wt% polymer. Values of $(S - S_o)$ increased slowly for PEG35000 and PVP K90 in the range 0–2 wt%, but more rapidly thereafter to reach 2 mg dl^{-1} for PVP K90 at 5 wt% and a little higher, 3–4 mg dl^{-1}, for PEG35000 in the range 5–10 wt%.

The effect of inclusion of 1 wt% F127 in water was an immediate increase in solubility to 3.1 mg dl^{-1}. The almost linear increase in solubility with polymer concentration recorded for PEG6000 over the whole concentration range was essentially reproduced in the mixed solvent, and following a more rapid increase to 4.5 g dl^{-1} at 1 wt% the linear increase in $(S - S_o)$ with concentration observed for PVP K30 also mirrored that of the polymer in water (see Fig. 3a and c). For PEG35000 and 1 wt% F127 (Fig. 3b) values of $(S - S_o)$ increased rapidly to ca.7 mg dl^{-1} at 0.5 wt% polymer and this value was maintained to 7 wt% PEG35000 until a further steady increase to $(S - S_o) \approx 8.5$ mg dl^{-1} at 10 wt%. For PVP K90 (Fig. 3d) a rapid increase to $(S - S_o) \approx 5.5$ mg dl^{-1} at 1 wt% polymer was maintained to 5 wt% polymer, which is the limit of the measurements for this system.

3.2.2. Solubilisation capacity

In pharmaceutical practice, the need is to minimise the amount of excipient needed to solubilise an effective amount of drug, and the important quantity is the solubilisation capacity of the copolymer/polymer mixture, defined here as $s_t = (S - S_o)/w_t$ (mg g^{-1}) where $S - S_o$ (mg dl^{-1}) is the increased solubility of griseofulvin over that in water and w_t is the total concentration of copolymer plus polymer in solution (mg dl^{-1}). Therefore we look for values of the solubilisation capacity exceeding that of a 1 wt% micellar solution of F127 alone, i.e. $s_t \approx 3.1$ mg g^{-1}. Values of s_t for the polymers alone in water are lower than 1 mg g^{-1} across the concentration range. Values of s_t for the polymers with 1 wt% F127 are illustrated in Fig. 4 for the concentration range 0–5 wt%; at higher concentrations values continue their steady decrease. The dotted line indicates the solubilisation capacity determined for F127 alone in water, and it is seen that solutions with 0.5 and 1 wt% PEG35000 and 0.5 wt% PVP K90 exceed that value.

4. Discussion

Usually the solubilisation of hydrophobic drugs in aqueous solutions of block copolymers is related to the formation of micelles stabilised by a corona of E-blocks with the hydrophobic cores being the major site of a solubilised hydrophobic drug and the poly(oxyethylene) corona making only a minor contribution (see, e.g. Crothers et al., 2005). The large increase in solubility of hydrophobic griseofulvin in aqueous solutions of 1% F127 on addition of PEG35000 and PEG6000 may be a consequence of the association of the E-chains of PEG with the E-blocks of the micelle corona thus providing an expanded region of reduced polarity for drug solubilisation. As seen in Fig. 3b, for solutions containing PEG35000 and F127 the value of $S - S_o$ is almost constant at about 7 mg dl^{-1} across the range of PEG35000 concentration from 0.5 to 7 wt%, which is consistent with the swollen micelle coronae being fully saturated with griseofulvin when the PEG35000 concentration reaches 0.5 wt%, with further increase in particle size (see Fig. 2) attributable to the formation of micelle clusters. Further increase in S as the PEG35000 concentration is increased beyond 7 wt% can be related to the increase observed at high PEG35000 concentrations in the absence of F127 (see Fig. 3b), i.e. the polymer solution as a whole is taking up the drug. Indeed, judging by the parallel behaviour seen for solutions of PEG6000 with and without F127 in Fig. 3a, association of PEG6000 with the E-blocks of the micelle corona is not a major mechanism for the increase in solubilisation on addition of PEG6000.

The mechanism of solubilisation by F127 and PVP K30 or PVP K90 is less obvious. It is clear from the spectroscopic study of drug/PVP blends (Nair et al., 2001) that there is no strong interaction between griseofulvin and PVP K90, and our solubilisation measurements for griseofulvin in solutions of PVP alone bear this out. However, the inclusion of micellar F127 in a solution of PVP increases griseofulvin solubility, markedly so for solutions of PVP K90 (see Fig. 3d). Moreover, as noted in Section 3 there are striking similarities between the solubility curves for griseofulvin in solutions of F127 micelles and the two lower molecular weight polymers (PEG6000 and PVP K30, Fig. 3a and c) on the one hand and between corresponding curves for the two higher molecular weight polymers (PEG35000 and PVP K90, Fig. 3b and d) on the other, most notably in the sharp increase in solubility at polymer concentration 0.5 wt% recorded for both PEG35000 and PVP K90. Our DLS measurements provide no direct evidence for association of PVP with F127 micelles (see Fig. 2 and related discussion). However, if, as discussed in the previous paragraph, we assign the marked increase in $r_{h,app}$ observed for the F127/PEG system to the formation of micelle clusters then association of PVP with the corona of the micelles is not ruled out. Indeed, from a thermodynamic viewpoint transfer of PVP from dilute aqueous solution to the micelle corona is likely, because hydrophobically-bonded water around the largely-hydrophobic PVP chains, and also structured water around the E-blocks of the micelle corona, will be released with the consequent decrease in Gibbs energy of the whole system driving the association. The effect for the lengthy chains of PVP K90 will be much greater than for the shorter chains of PVP K30. Solubilisation of hydrophobic griseofulvin in micelle corona swollen with PVP K90 will then follow a parallel path to that described for PEG35000.

5. Conclusion

We note that the value of $S - S_o = 7.0$ mg dl^{-1} reported for a solution of 1 wt% F127 and 0.5 wt% PEG35000 is higher than the value

of 6.1 mg dl^{-1} found in related work for a 2.5 wt% solution of F127 alone, in fact similar to the value expected for a 3 wt% solution of F127 alone. In terms of the solubilisation capacity, $s_t = (S - S_o)/w_t$ (mg g^{-1}), that of 1 wt% F127 alone is $s_t \approx 3$ mg g^{-1} while that of 1 wt% F127 and 0.5 wt% PEG35000 is $s_t = 4.9$ mg g^{-1}. Of the other three polymers investigated, only the solubilisation capacity of 1 wt% F127 and 0.5 wt% PVP K90 exceeds that of 1 wt% F127. The use of high concentrations of surfactants for drug delivery is pharmaceutically undesirable as well as costly; it is therefore of interest to note from our study that the addition of a relatively small amount of PEG35000 (or to a lesser extent PVP K90), allows a smaller quantity of F127 to be used for solubilisation while still achieving a similar or enhanced solubilisation capacity.

Since the most significant solubilisation enhancement noted in this study derives essentially from interaction of the high molecular weight PEG with the oxyethylene chains of the corona of the F127 micelles, it would be expected that other micelle forming EPE copolymers should behave in a similar manner.

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