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Communication

Comparison of surface modification and solid dispersion techniques for drug dissolution☆

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Abstract

Surface modification and solid dispersion formulations using hydrophilic excipients can significantly alter the dissolution behaviour of hydrophobic drug materials. The effect of these techniques used individually and in combination on the dissolution properties of the hydrophobic drug, phenylbutazone (PB), are compared. PB was treated with a poloxamer, Synperonic® F127 by an adsorption method. Solid dispersions (10 and 20% w/w) were prepared with untreated PB or PB previously modified with Synperonic® F127 (PBT) in molten F127. Dissolution tests of capsule formulations of PB, PBT and solid dispersion formulations, in pH 6.4 buffer at 37 ± 0.5°C demonstrated that after 140 min, release of PB was 16.7%, but 71.4% from the solid dispersion, whereas from the PBT formulation 85.6% was released. The Synperonic® F127 content of PBT was only 0.05% of that in the solid dispersion formulation which suggests that it is the nature of the drug polymer contact rather than the amount of polymer which is more critical in influencing dissolution behaviour. Comparison of PBT and the 10% w/w solid dispersion of PBT in F127 showed similar amounts of drug in solution after 140 min. However there was a significantly higher release rate for PBT. Both formulation techniques offer significant improvements in drug release over untreated PB, and a combination of techniques changes the rate but not the extent of release in comparison with the surface modification technique alone.

Keywords: Surface modification; Solid dispersions; Poloxamer; Hydrophobic drugs, Dissolution

1. Introduction

Many formulation techniques have been investigated in order to overcome the dissolution difficulties associated with hydrophobic drugs. These include interactive powder mixes (Ibrahim et al., 1988), addition of surfactants (Watts et al.,

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1991), the use of solid dispersions (Hawley and Rowley, 1998) and surface modification by the adsorption of hydrophilic polymers (Cassidy et al., 1998a). Previous work in these laboratories has indicated that the surface modification technique can significantly improve the dissolution of the hydrophobic drug, phenylbutazone, by the adsorption of very small amounts of poloxamer at the drug particle surface (Nguyen et al., 1997; Cassidy et al., 1998a).

The aim of this study is to compare solid dispersion formulation and surface modification techniques, individually and in combination using the model hydrophobic drug, phenylbutazone (PB) in order to improve drug release characteristics. A nonionic surfactant, the ABA block copolymer of polyoxyethylene-polyoxypropylene-polyoxyethylene (PEO-PPO-PEO), or commonly known as a poloxamer, trade name Synperonic® F127, was chosen as a surface modifier and as a solid dispersion carrier as it possessed the appropriate physicochemical characteristics for both formulation techniques. The ability of Synperonic® F127 to adsorb on to hydrophobic surfaces and the extent and mechanism of adsorption has been extensively investigated by modifying the surface of polystyrene particles. Data on the adsorbed layer thickness together with qualitative information on the conformation of polymer at the particle surface has been established (Cassidy et al., 1997, 1998b, 1999a,b). Surface analysis techniques, X-ray photon spectroscopy and time of flight secondary ion mass spectrometry provided evidence to show that it is the PPO portion of the poloxamer which anchors to the hydrophobic surface of particles, leaving the PEO chains to protrude into the surrounding aqueous media. Additionally, previous surface modification work on phenylbutazone, employing different poloxamers, Synperonic® F68, F88 and F108, has demonstrated that there is a progressive decrease in contact angle for modified samples with increases in poloxamer treatment concentration which indicated improved wetting of the treated drug surface and suggesting subsequent improvements in drug release extent and rate. However, it was the drug sample treated with the lowest concentration of poloxamer by the surface modification technique which produced the highest rate and amount of drug release. The results from these studies demonstrated that although the surface modification improved wetting of the hydrophobic surface and increased dissolution rate when compared with untreated material, there is a more complex drug release mechanism than would be predicted by improved wetting alone. It was suggested that it may be the orientation and layer thickness of the polymer which has more influence on the dissolution behaviour of treated drugs (Nguyen et al., 1999). Synperonic® F127 has a melting point of 56°C and is therefore suitable for the preparation of solid dispersion formulations by the fusion method and by virtue of its polyoxyethylene content (70%), the polymer also possesses a relatively high degree of hydrophilicity which should improve dissolution rate and extent of PB when dispersed throughout the matrix.

2. Materials and methods

The materials employed were the poloxamer, Synperonic® F127, obtained from ICI (Wilton, UK) as waxy flakes and micronized phenylbutazone (Sigma). The contact angle of phenylbutazone (PB) has been determined as 110° in these laboratories using dynamic contact angle analysis, which confirms its hydrophobic nature. The poor aqueous solubility of drug in distilled water and aqueous poloxamer solution (100 mg l^{-1}) was established (≈ 55 and 60 mg l^{-1} in water and poloxamer, respectively) so that the amount dissolved during the adsorption procedure was known in order to accurately quantify the amount of Synperonic® F127 adsorbed onto PB. Known quantities of PB powder were agitated in a shaking incubator with solutions of poloxamer of 100-mg l^{-1} concentration for 22 h at 25 ± 0.5°C, when equilibrium was attained. Investigations of equilibration conditions of different concentration poloxamer/PB systems undertaken in these laboratories, have indicated that equilibrium is achieved within 2 h and maintained for > 50 h. The powder was separated from the liquid by filtration and the supernatants were further cen-

trifuged at 3600 rpm (MSE Mistral 1000) for 25 min. The polymer concentration in the supernatant was determined by UV spectrophotometric analysis at λ_{max} of 495 nm, by using a method similar to that of Baleaux et al. (1972). The amount of poloxamer adsorbed per gram of PB was calculated by solution depletion based on the difference between initial and final (equilibrium) concentrations.

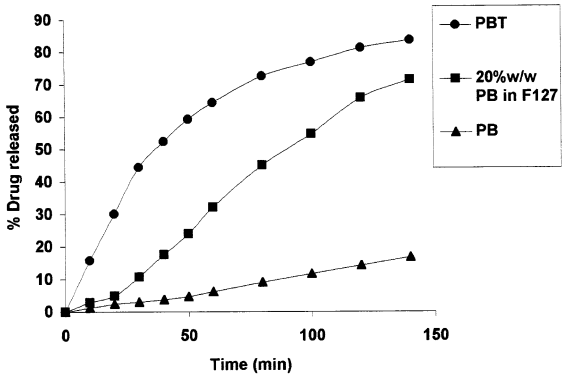

Fig. 1. Dissolution profiles of PB, PBT and 20% w/w solid dispersions of PB in Synperonic® F127, at 37°C.

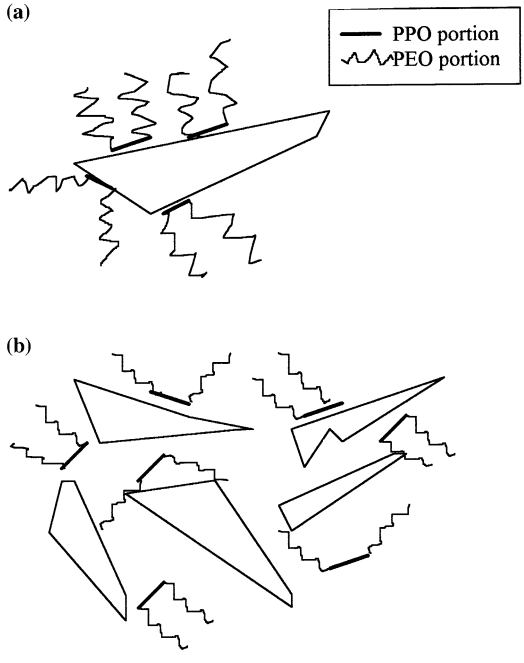

Fig. 2. (a) Conformation of Synperonic® F127 at the surface of PB crystal in PBT. (b) Conformation of Synperonic® F127 in 20% w/w solid dispersion formulation of PB.

The 10 and 20% w/w solid dispersions were prepared with untreated PB or PB previously surface modified with Synperonic® F127 (PBT) in molten F127 and filled into either size 1 or size 0 hard gelatin capsules (Capsugel).

Dissolution tests of capsule formulations containing 50 mg of PB, PBT and solid dispersions with 50 mg drug content were carried out in phosphate buffer pH 6.4 at 37 ± 0.5°C for 140 min using BP (1993) dissolution apparatus I at 100 rpm. Drug solubility in phosphate buffer pH 6.4 at 37°C was established as 639 mg l^{-1} and as only 50 mg of drug was contained in each capsule, sink conditions were maintained throughout dissolution testing. Drug concentration was determined at 264.5 nm and the mean percent release was calculated for six capsules of each formulation.

3. Results and discussion

The results in Fig. 1 after 140 min show that release of untreated PB was 16.7%, the release of PB from capsules containing the 20% w/w solid dispersion formulation was 71.4% and that from capsules containing surface modified PB was 85.6%. Both formulation techniques offer significant improvements in dissolution of PB over untreated drug. However 50 mg of PBT contained only 0.099 mg adsorbed Synperonic® F127, whereas the solid dispersion formulation contained 200 mg of Synperonic® F127 with 50 mg of drug. This would indicate that it is the nature of the drug/ polymer contact and possibly the orientation of the polymer in the adsorbed layer(s) at the drug surface which is more critical in influencing dissolution behaviour than the amount of polymer in the formulation. A possible conformation of poloxamer adsorbed at the surface of the drug crystal using the surface modification technique (PBT) is presented in Fig. 2a. Evidence for this polymer orientation at the drug surface was obtained from time of flight secondary ion mass spectrometry studies of another poloxamer, Synperonic® F108 adsorbed onto PB. This evidence

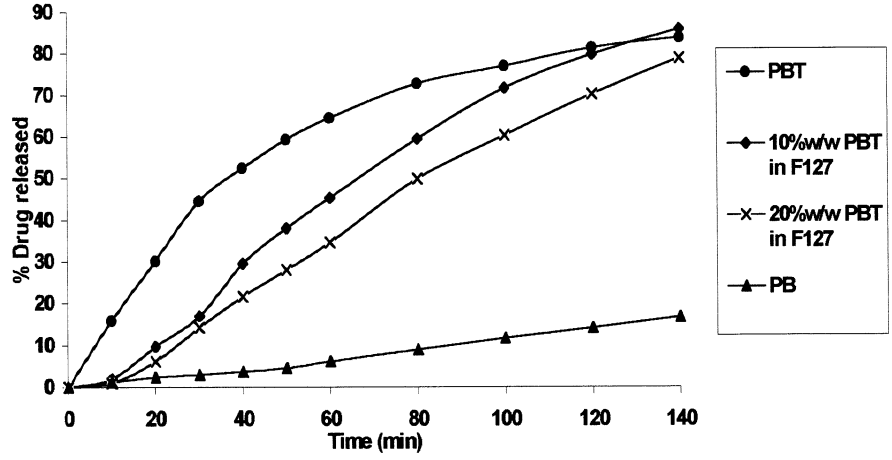

Fig. 3. Dissolution profiles of PB, PBT and 10 and 20% w/w solid dispersions of PBT in Synperonic® F127, at 37°C.

for the attachment of the PPO portion of the poloxamer to the hydrophobic surface of the drug particle (Cassidy et al., 1999b) suggests that it is in this conformation that the poloxamer contributes to improvements in dissolution, although the mechanism by which it does this has yet to be fully established. Furthermore, X-ray photon spectroscopy (XPS) analysis has demonstrated that the adsorbed layer of poloxamer is not homogenous. XPS of polystyrene spheres treated with Synperonic® F127 has shown that the adsorbed poloxamer layer(s) are extremely thin with evidence of multiple layers in localised areas and completely bare patches of exposed particle surface (Cassidy et al., 1999a). It would seem from the studies reported here, the minute amount of poloxamer (0.099 mg/50 mg drug) if orientated appropriately but not necessarily uniformly distributed in a monolayer across the PB surface, is sufficient to allow the ingress of aqueous media and to alter significantly the dissolution characteristics of PB. Also illustrated, in Fig. 2b, is a representation of the 20% w/w solid dispersion formulation of PB containing substantially more poloxamer than in the case of PB with adsorbed poloxamer, and where the PEO chains of Synperonic® F127 are not necessarily oriented with the PEO portions protruding towards the dissolution medium. Therefore, although the hydrophilicity of the poloxamer will contribute to an overall improvement in dissolution over PB alone, the conformation and greater amount of the polymer in the solid dispersion can affect not only the ingress of dissolution fluids into the dosage form, but drug release by erosion and/or diffusion (Hawley and Rowley, 1998).

Results in Fig. 3 for PBT and the 10% w/w solid dispersion of PBT in Synperonic® F127 show similar amounts in solution after 140 min ($\approx 86\%$). Comparison of mean drug release values by t-test for unpaired values, have shown no statistically significant difference at 120 min for these formulations. However there were significant differences in drug release at 30 min ($P < 8.0 \times 10^{-7}$) and at 60 min ($P < 9.0 \times 10^{-5}$). These results indicate that while there is no difference in final extent of release between these formulations, there is a significant difference in the release rate with an increase in rate for the adsorption technique.

Comparison of PBT and the 20% w/w solid dispersion formulation profiles indicate that the adsorption technique offers significantly improved drug dissolution over this solid dispersion formulation with release values at 140 min of 86 and 79%, respectively. Again a significant increase in release rate is observed for the adsorption technique. Statistical differences between values for mean drug release at 30 and 60 min were demonstrated ($P < 6.0 \times 10^{-7}$ and $P < 0.003$, respectively).

In addition, Fig. 3 illustrates that the 10% w/w formulation of PBT provides improved dissolution over the 20% w/w solid dispersion formulation of PBT. Drug release values are statistically significantly different at $t = 60$ min (45.3 and 34.6% release for the 10 and 20% w/w formulations of PBT, respectively) and $t = 120$ min (79.8 and 70.1% for 10 and 20% w/w PBT, respectively) although there was no statistical difference at $t = 30$ min (18 and 14.3% for the 10 and 20% w/w PBT, respectively). This increased release for the 10% w/w PBT formulation may be due to greater amount of total hydrophilic polymer in the capsule 450 mg in the 10% w/w formulation as opposed to 200 mg in the 20% w/w capsule and the increased surface area of the larger dosage form presenting to the dissolution medium. However, there may also be an influence on dissolution due to a combination of the aforementioned effects with the adsorbed polymer at the drug surface. This phenomenon can be more thoroughly compared by examination of all the solid dispersion formulation release profiles.

Fig. 4 shows the dissolution plots of all solid dispersion formulations. Both solid dispersions containing previously surface modified drug (PBT) demonstrate greater rate and extent of drug release than the formulations containing PB. In addition and as previously mentioned, there is a significant difference between the 10 and 20% w/w PBT formulations. In contrast, the profiles in Fig. 4 demonstrate that there is no difference between the 10 and 20% w/w formulations containing untreated PB. This would indicate that there appears to be a combination of effects contributing to the dissolution behaviour, as amount of polymer and the increased surface area of formulation exposed to the dissolution medium of the 10% w/w solid dispersions alone cannot account for the difference in extent or rate of release between formulations using previously modified PB.

Additionally, linear regression analysis of data for the 10 and 20% w/w PBT formulations between $t = 0$ and $t = 140$ min give correlation coefficients of 0.987 and 0.997, respectively, indicating an approximately zero order drug release process for these formulations and providing evidence for diffusion controlled dissolution. However, much further work is required to fully investigate whether these solid dispersion formulations could indeed be exploited for the purposes of controlled drug release and to ascertain release mechanisms. Characterisation of the solid dispersion systems using thermal analysis could provide information regarding the behaviour of the adsorbed polymer during the fusion process used

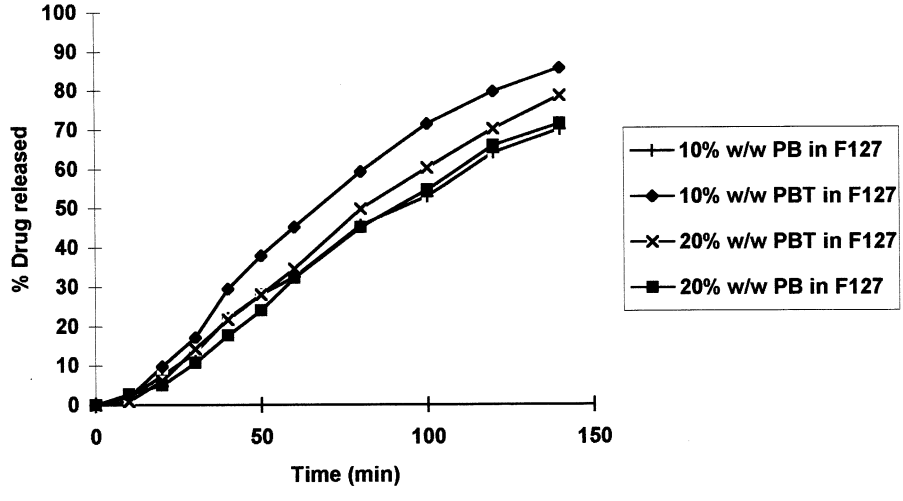

Fig. 4. Dissolution profiles 10 and 20% w/w solid dispersions of PB and 10 and 20% w/w solid dispersions of PBT in Synperonic® F127, at 37°C.

prior to capsule filling and may be used to explain the differences in drug release between previously treated PB and untreated PB in the solid dispersion formulations.

4. Conclusion

Both formulation techniques offer significant improvements in drug release over untreated drug. Using previously surface modified material in a solid dispersion formulation results in greater drug release than using untreated PB in the same carrier system. Additionally, combining the techniques offers the ability to change the rate but not the extent of release in comparison with the adsorption technique alone.

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