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A comparison of alternative polymer excipients and processing methods for making solid dispersions of a poorly water soluble drug

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Abstract

Solid dispersions were prepared with the extremely poorly water soluble drug, probucol and the water soluble polymers, polyvinyl pyrrolidone (PVP), polyacrylic acid (PAA) or polyethylene oxide (PEO) and blends of these polymers. The solid dispersions were prepared either by the solvent evaporation method, or by compression moulding into films. The materials were characterised by a combination of thermal analysis and FT-Raman spectroscopy. The physical state of the drug was observed to be dependent on the carrier, thus the PVP solid dispersions contained amorphous probucol, whilst the PAA and PEO systems contained the crystalline polymorph II. The method of production was not found to greatly influence the state of the drug in the solid dispersion. The greatest extent of release into solution was observed for the binary blend of drug and PEO, and the blending of polymers was not found to have any advantageous effects in this study. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Probucol; Solid dispersion; Polymer; Crystalline; Amorphous

1. Introduction

Solid dispersions are an attractive method of enhancing the dissolution behaviour of poorly water soluble drugs. The term solid dispersion covers a wide range of systems as reviewed by Chiou and Reigelman (1971) and Ford (1986). The enhanced dissolution rate characteristic of solid dispersions can generally be accounted for by one of the following mechanisms; eutectic formation, increased surface area of the drug due to precipitation in the carrier, solid solution formation, improved wettability due to intimate contact with a hydrophilic carrier, precipitation as a metastable crystalline form or a decrease in substance crystallinity. Both the properties of the carrier-drug combination and the method of manufacture will influence the type of solid dispersion

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formed, and thus the subsequent behaviour of the solid dispersion (Serajuddin, 1999).

Solid dispersions are generally prepared by one of two methods, co-melting of drug carrier mixtures or dissolving drug and carrier in a mutual solvent followed by solvent removal. Neither method, as traditionally used, is ideal from the perspective of scale up. However, well-known processing techniques from the polymer industry, such as melt extrusion, compression moulding, transfer moulding and injection moulding (Brydson, 1995; Tadmoor & Gogos, 1979), could be imported and tailored for highly efficient and controlled production of pharmaceutical products. For example, direct extrusion of melts into hard gelatin capsules, or the compression moulding of transdermal patches, could be possibilities for large scale manufacturing.

Hydrophilic synthetic polymers have been widely investigated as carrier substances for solid dispersions. Polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG) are amongst the most frequently investigated polymeric carriers. One of the aims of this study was to characterise the behaviour of solid dispersions of the extremely poorly water soluble drug, probucol, with the following polymers; PVP, polyethylene oxide (PEO, a higher molecular weight polymer composed of the same monomeric unit as PEG) and polyacrylic acid (PAA). Another was to explore the additional influence of blending some of these polymers. Finally, the alternative manufacturing method of co-melting the components using compression moulding was evaluated by comparing the properties of the solid dispersions made by this method with those made using the more standard solvent evaporation method.

2. Materials and methods

Polyacrylic acid (MW 450 000) and polyethylene oxide (MW 100 000) were obtained from Aldrich Fine Chemical Ltd, USA. Polyvinyl pyrrolidone K30 (linear, MW 40 000) was purchased from BASF and probucol came from Sigma. The ethanol used in the study was 99.5% (Kemetyl, Sweden). Polysorbate 80 (Tween 80V) was supplied by ICI surfactants.

2.1. Fourier transform Raman spectroscopy

FT-Raman spectra were collected on a Perkin-Elmer System 2000 instrument with a near infrared Nd:YAG laser operating at 1064 nm. The laser power was typically 800 mW at the sample and a InGaAs detector was used. Back-scattered radiation at an angle of 180 °C was collected and the Stokes radiation reported. Indene was used as a reference standard to monitor wavenumber accuracy and variations of less than 1 cm^{-1} from the literature values were observed. All solid dispersions were analysed in duplicate (ie two different batches of a solid dispersion) in NMR tubes after drying under vacuum at 45 °C for 24 h. The NMR tubes were rotated during the analysis to minimise heating of the sample by the laser.

2.2. Differential scanning calorimetry

Differential scanning calorimetric measurements were carried out using a Mettler Toledo 820 DSC. Approximately 5 mg of sample was analysed at a heating rate of 10 °C min^{-1} (for crystalline materials) or 20 °C min^{-1} (for amorphous samples and solid dispersions), in vented aluminium pans, under a nitrogen purge. In general duplicate samples (ie two different batches of a solid dispersion) were run. Indium was used to calibrate for enthalpy and temperature.

2.3. Sample preparation

2.3.1. Compression moulding

A compression mould, of type J. Wickert & Söhne Maschinenbau, Landay-Pfalz, Germany, located at the Institute of Fibre and Polymer Technology (IFP), Mölndal, was used. The drug and excipient powders were preheated for 2 min, then pressed at a pressure of 25 tons for 2 min at 135 °C for the probucol/PAA and probucol/PEO samples and at 165 °C for the other samples (both pre-heating and pressing). The samples were then cooled in cold water, which possessed a temperature of about 15 °C. The samples generated had the same compositions as the solvent method samples (Table 1). The samples were subsequently stored at 4–8 °C.

2.3.2. Solvent method

Physical mixtures of drug and polymer at a 50:50 drug:polymer weight ratio for binary systems or 50:25:25 drug:polymer:polymer for ternary systems were dissolved in ethanol. The ethanol was removed using a rotary evaporator at 45 °C. Samples were subsequently dried in a vacuum oven at 45 °C for 24 h and stored desiccated at 4–8 °C. Ternary mixtures of PEO, probucol and PVP were prepared by dissolving the PEO in a minimum quantity of water and adding this to an ethanolic solution of PVP and probucol. However, it should be noted that precipitation was observed on addition of the aqueous solution.

2.3.3. Co-melting

Due to the difficulty in finding a mutual solvent for probucol and PEO, binary mixtures were prepared by co-melting the two components at 150 °C with stirring.

2.4. Dissolution

For dissolution studies, 13 mm tablets of the solid dispersions (samples from both solvent and compression moulding methods) were prepared using a hydraulic press, applying a load of 10 tons for 1 min.

Each tablet contained 100 mg of probucol. The rationale for preparing tablets of the solid dispersions was firstly so that the initial surface area would be similar and secondly to investigate the potential dissolution behaviour of the polymer e.g. gelling. Dissolution of the tablets was performed in 900 ml of dissolution medium consisting of 3% polysorbate 80 and 10% ethanol in a phosphate buffer, pH 6.8. Both surfactant and ethanol had to be included because of the extremely low solubility of probucol.

Table 1
Composition of the samples generated by the compression moulding and the solvent method

Components	Composition (by weight)
Probucol and PAA	50%:50%
Probucol and PVP K30	50%:50%
Probucol, PAA MW 450 000 and PVP K30	50%:25%:25%
PEO and probucol	50%:50%
PEO, PVP and probucol	25%:25%:50%

While the use of these additives makes the dissolution experiments not physiologically representative, it does enable a comparison of the different solid dispersions to be made.

The measurements were carried out at 37.1 °C using dissolution apparatus of JPXII paddle method. The paddle speed was 100 rpm. All samples were run in duplicate and mean values are reported. The repeat samples showed good agreement where the variation was less than the mean value $\pm$ 2% drug released Aliquots were withdrawn after 1, 2, 4, 6, 24 and 29 h. The solution was immediately filtered through a membrane filter (cellulose nitrate, pore size 0.45 μm) and analysed by HPLC. HPLC analysis was performed using a Waters 717 system with autosampler on a C8 column, d_p 5 μm, 3.9 × 150 mm from Waters symmetry with a Waters 600 controller gradient pump. Absorbance was measured at 242 nm with a Spectra 100 uv spectrometer from Spectra Physics.

3. Results

3.1. Characterisation of probucol

Probucol has been reported as having at least two polymorphs with onset melting points of 116 °C (Form II) and 125 °C (Form I), where the Form I polymorph is the thermodynamically stable form (Gerber et al., 1993). The material as received was found to have melting point of 125 °C as measured by DSC and is thus Form I. Form II was prepared by rapid crystallisation from a concentrated solution in ethanol as previously described and had a melting point of 116 °C (Gerber et al., 1993). Amorphous probucol could be prepared by melting the crystalline material, followed by quench cooling. The glass transition temperature (Tg) of amorphous probucol as measured by DSC was around 26°C. Raman spectroscopy was used as the primary method of

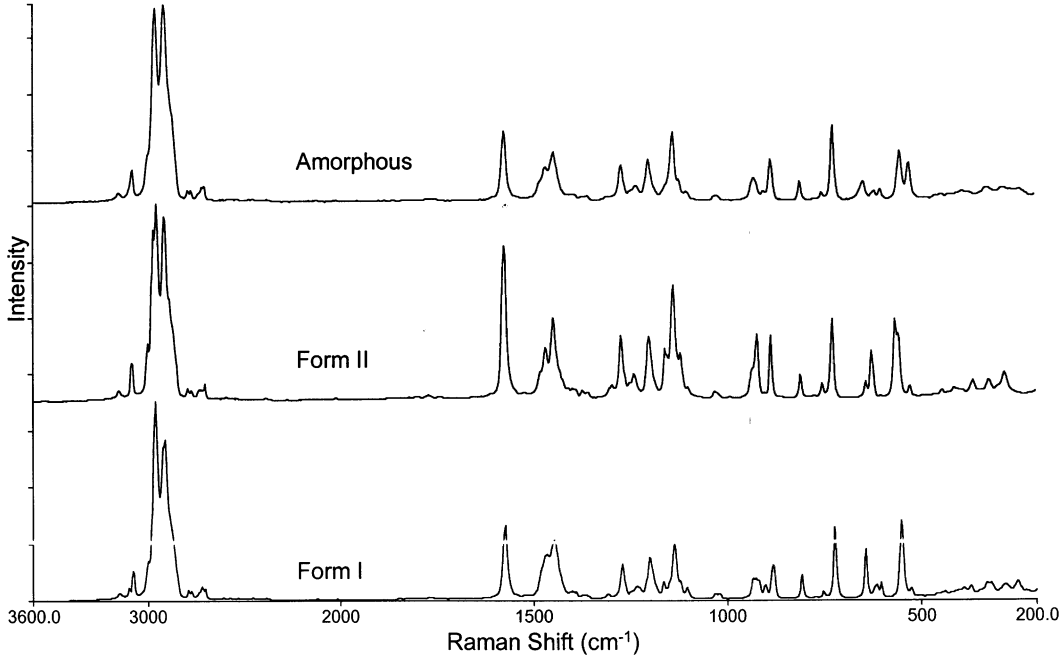

Fig. 1. FT-Raman spectra of the two polymorphs of probucol and the amorphous form.

differentiating between the different forms of probucol. The Raman spectra of Form I, Form II and amorphous probucol are shown in Fig. 1. The spectra resemble one another, since the molecular species are identical. However, the differences in intermolecular interactions between the different forms result in sufficient changes in the vibrational spectra to identify the particular solid state modification. The aromatic C-H region, shown in Fig. 2, was subsequently used to identify the form of probucol present in the solid dispersions since there are clear differences between the various solid state modifications in this spectral region and none of the polymers investigated contain aromatic groups (and therefore have no peaks in this region, see Fig. 3). Form I has a doublet with peaks at 3077 and 3082 cm^{-1} and a further peak at 3102 cm^{-1}. Form II has doublet at with peaks at 3083 and 3089 cm^{-1} whilst amorphous probucol has a broad peak at 3083 cm^{-1}. All three forms have a broad peak at around 3150 cm^{-1}. Raman spectroscopy has been used previously to investigate drugs in polymer matrices (Davies et al., 1990). Furthermore, the advantages of Raman spectroscopy for such studies have been pointed out, since drugs containing aromatic moieties are frequently much better Raman scatterers than polymers, facilitating their detection in mixed systems (Hendra, 1996).

3.2. Characterisation of the polymers

PAA, an amorphous polymer, was found to have a Tg of 132 °C. PVP K30, also an amorphous polymer, had a Tg of 163 °C. PEO is a semi-crystalline polymer and the crystalline regions melt at 62 °C (onset). The Tg of the amorphous region of PEO is expected to lie around −60 °C; as such, this value was not detected by DSC over the temperature range investigated. The Raman spectra of the polymers in the CH stretching region is shown in Fig. 3 and are compared with the spectra of the different forms of the drug. The peaks are broad and can be assigned to the various aliphatic CH stretching vibrations. PVP has peaks at 2975 and 2923 cm^{-1}, PAA at 2936 cm^{-1} and PEO at 2940, 2887 and 2840 cm^{-1}. It can be clearly seen from Fig. 3

that there are no polymer peaks above 3050 cm^{-1} and therefore no spectral overlap with the aromatic CH stretching modes of probucol.

3.3. Characterisation of binary mixtures

In order to study the miscibility of the various components, binary mixtures of probucol and each of the three polymers, PVP, PAA and PEO, were prepared at the 50% level using the solvent evaporation method and analysed. No mutual solvent could be found for probucol and PEO, so these two components were melted together. Solid dispersions prepared by compression moulding were analysed and the results compared with those obtained from the solvent methods. The mixtures were analysed by a combination of DSC and Raman spectroscopy in order to try and characterise the physical form of the drug in the polymer and to investigate for intermolecular interactions. Results are summarised in Table 2. Results from the DSC measurements should be interpreted with caution since changes in the physical state of solid dispersions may occur during heating, and the presence of the polymer may influence the melting behaviour of the drug e.g. through melting point depression. Thus the Raman results are considered to be a more reliable indicator of the solid state modification of the drug present in the solid dispersions since they were obtained at room temperature and involved minimal sample handling.

3.3.1. Probucol-PVP

Probucol seemed to form a single phase amorphous system with PVP for the solvent method. No melting peak for probucol could be detected by DSC, however, the solid dispersion of PVP and probucol displayed a glass transition at 95 °C which is intermediate to that of the individual components and this can often be used as an indication of miscibility (Bosma et al., 1988).

The Raman experiments confirmed that probucol was present as the amorphous phase (data not shown) and both a broadening of and a shift to lower wavenumbers was observed for the car-

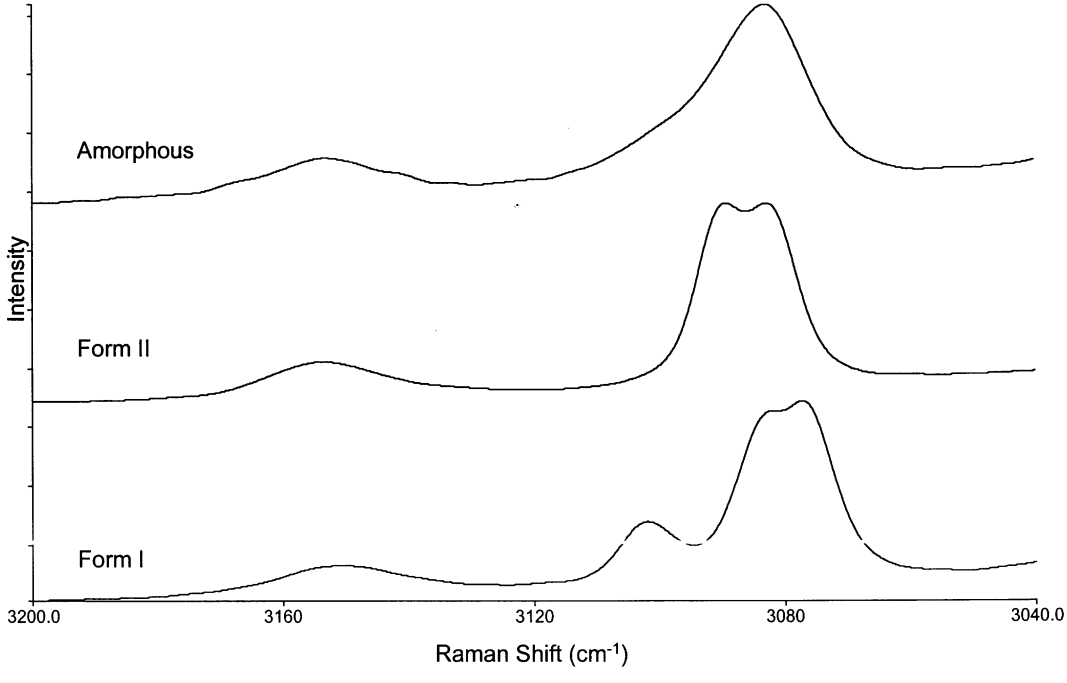

Fig. 2. FT-Raman spectra showing the aromatic CH stretching region of the different forms of probucol, illustrating that this spectral region can be used to differentiate the different forms.

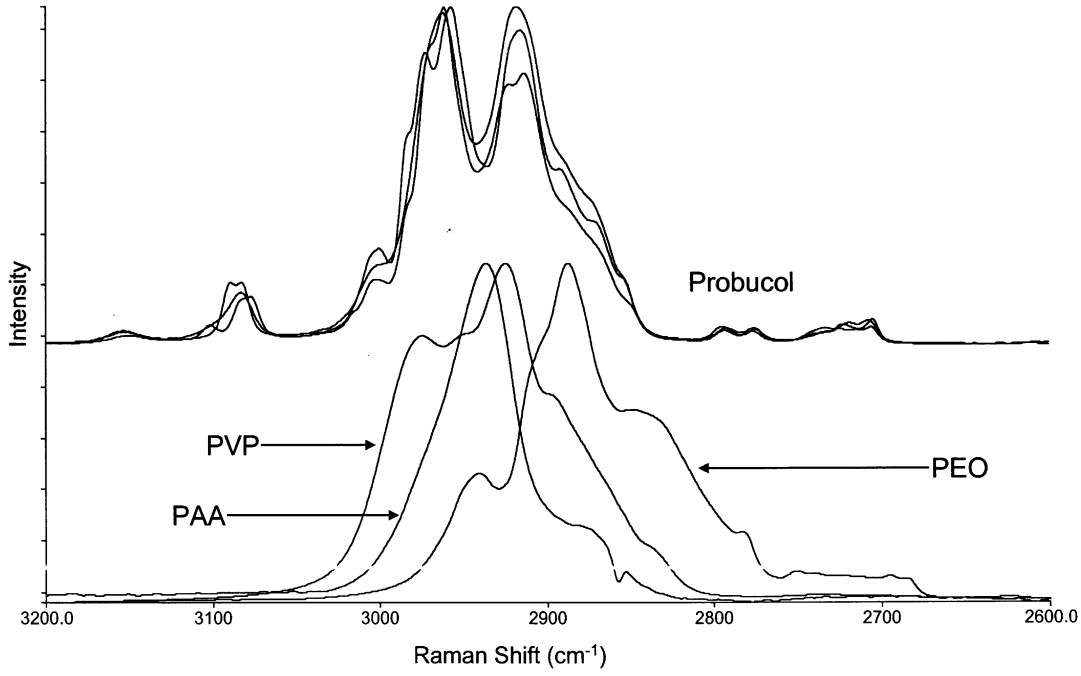

Fig. 3. CH stretching region of the polymers used in the solid dispersions. The spectra of the different forms of probucol are also shown and it can be seen that there is no spectral interference from the polymers in the drug aromatic CH stretching region.

bonyl peak of the PVP molecule (Fig. 4). This shift is consistent with the formation of a hydrogen bonding interaction between the drug hydroxyl group and carbonyl function of PVP (Taylor and Zografi, 1998) and supports the conclusion from the DSC experiments that a one phase amorphous system has been produced. For the compression moulded sample, a single broad glass transition was observed by DSC at 129 °C (as shown in Fig. 5), somewhat higher than for the solvent solid dispersion. This suggests that the probucol and PVP have not been able to fully mix during the melt, perhaps due to the short moulding time allowed, and the Tg value represents a PVP rich phase, but with the presence of an interphase corresponding to some intimate interaction between the two components. This assumption is supported by the Raman results, which show that whilst the probucol is present as the amorphous form (data not shown), the shift of the PVP carbonyl, as displayed in Fig. 4, is less than for the solvent dispersion, indicating that the interaction between the two components is less.

3.3.2. Probucol-PAA

In contrast, with PAA, crystalline probucol was detected with both Raman spectroscopy and DSC for both the solvent solid dispersion and the compression moulded sample. For the solvent solid dispersion, an endothermic peak was observed in the DSC thermogram at 110 °C. This is thought to represent the melting of polymorph II of probucol, reported to lie at about 116 °C. The lower temperature can be explained by melting point depression in the presence of a second component, the PAA. The Raman spectrum of the probucol-PAA solid dispersion is shown in Fig. 6. It can clearly be seen from the spectrum, that probucol is mainly present as polymorph II in the solid dispersion. The peak is however, somewhat broadened relative to pure form II peak, suggesting the presence of some amorphous material. Similar results were obtained for the compression moulded samples as summarised in Table 2 and a typical DSC scan is shown in Fig. 4.

3.3.3. Probucol-PEO

For probucol and PEO, no solvent solid dispersions could be made, since a mutual solvent could not be found, thus solid dispersions were made by co-melting and compression moulding. Both of these samples, unsurprisingly, gave similar results. For the sample prepared by co-melting at 150 °C, two endotherms are present, at 65 and 118 °C, which can be assigned to the melting of PEO and probucol respectively. The results from the Raman spectroscopy indicate that the probucol was present mainly as the form II polymorph, with a small amorphous component. A typical DSC thermogram for the solid dispersion of probucol and PEO prepared by compression moulding is shown in Fig. 4. The results indicate that the melting point of probucol was lowered to 101 °C, however the Raman spectra (Fig. 7) do not reveal any further polymorphs, but indicate the presence of the form II polymorph, with a small fraction of amorphous material (indicated by the broadening of the peak towards the higher wavenumber side). We therefore suggest that the DSC results may be due to melting point depression. It is interesting to note that the melting temperature of the PEO is also depressed in the melt compression sample, which may suggest that some interaction can occur between the two components in the molten state, when pressure is applied.

Table 2
Summary of solid dispersion characteristics. (1) samples prepared by the solvent method and (2) samples prepared by compression moulding.

System		Thermal analysis (°C)	Raman spectroscopy
Probucol as received		Melt onset 126	
Amorphous probucol		Glass transition 26	
Probucol form II		Melt onset 116	
PVP K30		Tg 163	
PAA		Tg 131	
PEO		Melt 68	
Probucol-PVP	1)	Tg 95	Amorphous
	2)	Tg 129	Amorphous
Probucol-PAA	1)	Melt 110	Mainly form II
	2)	Melt 116	Mainly form II
Probucol-PEO	1)	Melt 65 (PEO) Melt 118	Mainly form II
	2)	Melt 58 Melt 101	Mainly form II
Probucol-PVP-PAA	1)	Melt 116 (minor peak)	Mainly amorphous
	2)	Melt 114 (minor peak)	Mainly amorphous
Probucol-PVP-PEO	1)	Melt 57 (PEO) Melt 106	Mainly form II
	2)	Melt 58 (PEO)	Mainly amorphous

3.4. Characterisation of tertiary mixtures

Two different three-component mixtures were prepared by both the solvent and melt compression methods and results are summarised in Table 2.

3.4.1. Probucol-PVP-PAA

Both solid dispersions of probucol with PVP and PAA made by the solvent and compression moulding methods were found to result in mainly amorphous probucol, according to the Raman spectra. The DSC thermograms did show a small endothermic event in the probucol melting point region, but this was very diminished relative to the other samples, supporting the Raman results that most of the drug is present in a non-crystalline form.

3.4.2. Probucol-PVP-PEO

For the PVP-PEO-probucol system, the compression moulding method produced probucol which was predominantly amorphous, whilst the solvent method resulted in probucol as the Form II polymorph. However it should be noted that not all three components could be dissolved in the same solvent in this instance (see Methods section), which may account for the observed crystallinity of the probucol.

3.5. Dissolution results

The results of the dissolution studies are shown in Fig. 8 which shows the percentage released after 29 h. Owing to the extremely low solubility

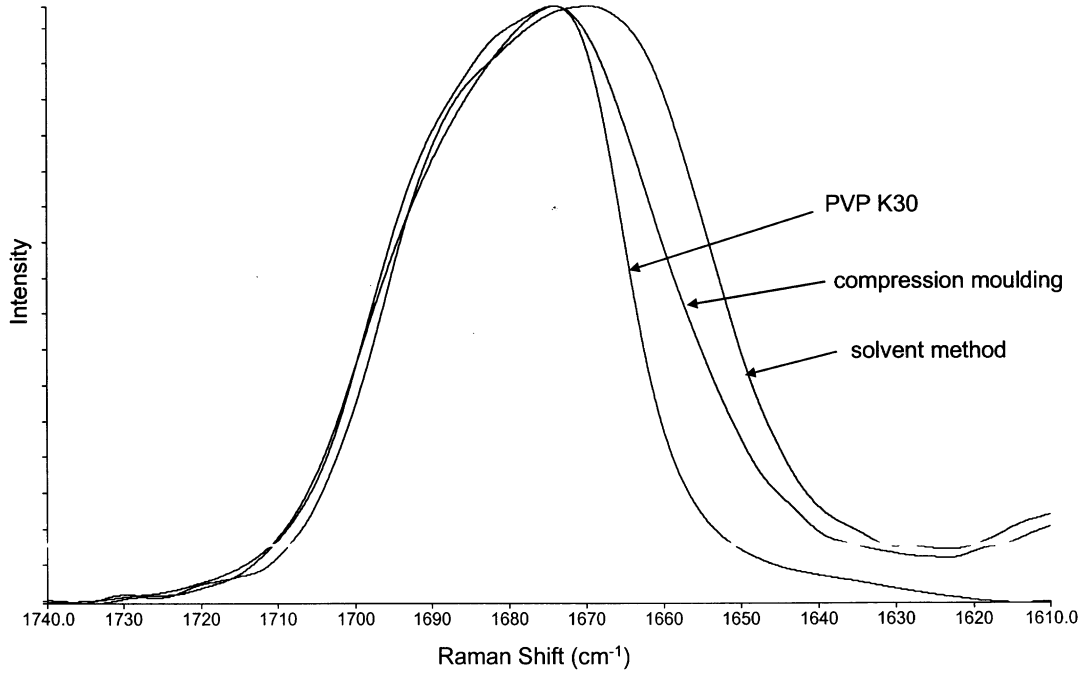

Fig. 4. Carbonyl peak of PVP in pure PVP as compared to in PVP-probucol solid dispersions made by either the solvent method or by compression moulding. The shift and broadening on the peak in the solid dispersions suggests hydrogen bond interactions between drug and polymer.

and dissolution rate of the drug, no probucol could be detected at even this time period for the reference crystalline and amorphous samples. Whilst the 29 h time period is not physiologically significant, it does enable a comparison of the different solid dispersions to be made, since shorter time periods did not allow detection of drug from all the solid dispersions. This argument also holds for the need in this work to include a surfactant and ethanol in the solutions used for the dissolution experiments. Fig. 8 shows most clearly that, when comparing polymer carriers alone, the highest drug release is obtained with the binary and ternary blends made with PEO. This is followed by PAA-probucol, PVP-probucol and lastly, the ternary blend PAA-PVP-Probucol.

However, when comparing methods, the compression moulding method appears to have worked significantly well for PEO-containing samples, but for none of the others. The PEO-probucol system prepared by co-melting but not compression moulded (see Methods section) also shows a comparatively high release, but less than that induced by compression moulding. In this context it should be remembered that PEO is the only semi-crystalline polymer used as a carrier; melting methods appear to suit these systems better.

The other notable observation from the dissolution results is that, in all of the systems containing PEO as a carrier, the tablets were observed to form a gel. Of the three carriers, PEO is again the only polymer showing strongly gelling properties. For the PVP and PAA containing tablets, the polymer was observed to erode away relatively rapidly resulting in a cloudy dispersion, presumably composed of probucol particles. Gel behaviour is also a factor to be considered when interpreting the dissolution results, and especially how this affects wetting and/or interactions in solid dispersions. This will be discussed further in the next section.

4. Discussion

4.1. Solid state form of the drug

The term solid dispersions is broad and covers a range of physical states of drug in carrier. The results from this study suggest that the physical state of the drug is very dependent upon the properties of the carrier, even for identical manufacturing processes. Thus, melting probucol with PVP, resulted in an amorphous form of the drug, whilst melting with either PAA or PEO did not. Since it is possible to produce amorphous probucol by melting the crystalline drug and cooling, we must assume that in both systems, the drug was initially amorphous following melting, and that PVP is able to inhibit crystallisation, presumably by interacting with the drug on a molecular level to some extent, whilst PEO is not. The ability of PVP to inhibit crystallisation from the amorphous state is well documented and it has been suggested that it is related to the ability of PVP to both increase the glass transition temperature and to form hydrogen bonded complexes (Yoshioka et al., 1995; Taylor & Zografi, 1997). In order for PVP to inhibit crystallisation, mixing must have occurred on a molecular level and the experimental results support that this has occurred to some extent. Results from the Raman spectroscopy indicate that some hydrogen bonding is indeed occurring between PVP and probucol, and the DSC results indicate that the Tg of the solid dispersion lies between that of probucol (26 °C) and PVP (163 °C, Table 2). Although probucol alone can be rendered amorphous by melting, crystallisation at room temperature was observed to occur relatively rapidly (hours to days, depending on sample handling). In contrast, neither PAA nor PEO were able to stabilise amorphous probucol against crystallisation, either following melting (compression moulding method), or on evaporation of the solvent. Presumably neither polymer is able to

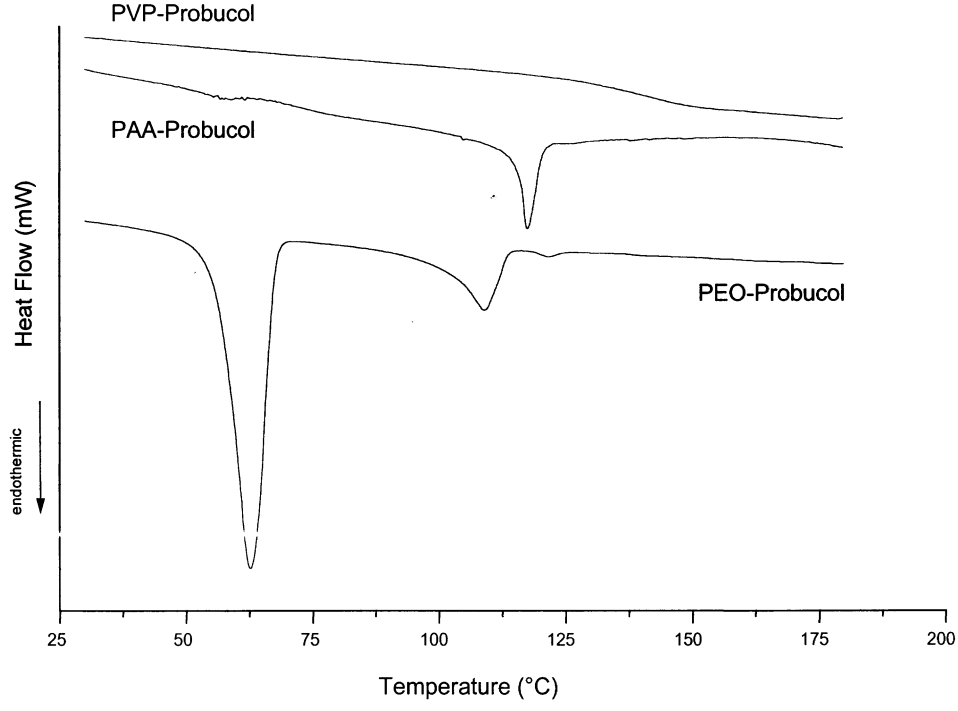

Fig. 5. DSC traces showing the thermal behaviour of different drug-polymer solid dispersions. All of the examples shown here were made by compression moulding.

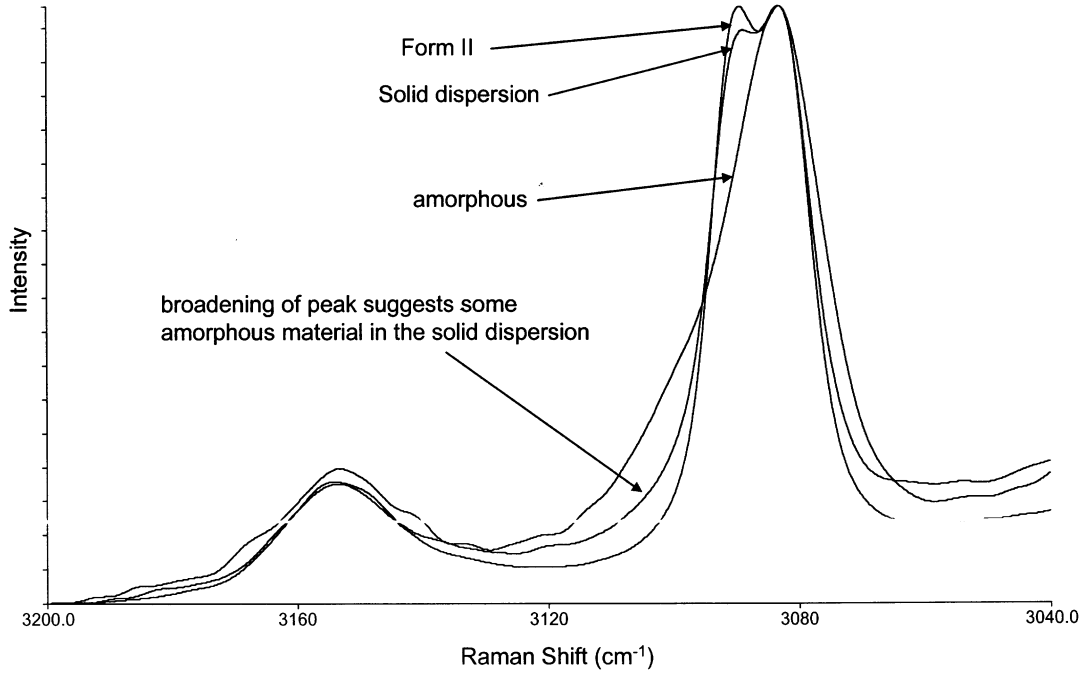

Fig. 6. FT-Raman spectrum of a probucol-PAA solid dispersion prepared by the solvent method, showing that the sample contains probucol mainly as the form II polymorph, with a small contribution from amorphous probucol. The spectra of pure amorphous and form II probucol are shown for comparison.

form a single phase system with probucol at room temperature.

The influence of the solid state modification of the drug versus the carrier system on the dissolution results is extremely interesting though perhaps counter intuitive. It is well known that the amorphous form of a drug generally has a higher apparent solubility than the crystalline counterpart, and in many cases also has a faster dissolution rate (Hancock & Zograf, 1997). It is therefore somewhat surprising that the amorphous probucol-PVP solid dispersion shows less release than the crystalline probucol-PEO system. It can be speculated that the highly water soluble PVP erodes rapidly from the solid dispersion, leaving behind the hydrophobic drug, which most likely crystallises upon the loss of the crystallisation inhibiting PVP. The erosion behaviour for PVP was expected, considering that the grade used was a linear polymer possessing a very low MW (ca. 40 000), showing low gelling and fast erosion properties.

For the PAA system, although the drug was also present as the crystalline Form II polymorph, as in the PEO system, the release was poor. Some other reason must therefore exist to explain this difference of behaviour in PAA and PEO.

4.2. Gelling properties of the polymer carrier

PEO is a rather special polymer with unique properties in the solid, gel and solution states (Graham, 1987). The highly gelling properties of linear PEO are well known within the pharmaceutical industry, and the swelling and erosion properties have been shown to vary consistently with MW. The high MW grades are often used to provide delayed drug release through the hydrophilic matrix approach. A high MW PEO, for example, with MW 5 million, may swell up to 700% of its initial weight, and continue swelling even after 20 h. Only about 50% of the gel will have eroded after about 22 h. Low MW PEO (MW 100 000), which is what was used in this

work, swells only to about 30% its initial weight, and starts eroding noticeably after about 15 min. However, even here, the erosion process goes on for a relatively long time, over several hours (Khoo & Nygren, unpublished).

It has been suggested that, for drugs with a low solubility, the release of the drug is primarily controlled by the relative magnitude of the rate of swelling/erosion of the polymer (Kim, 1998). The enhanced contact time of PEO with the drug due to gel formation, compared to the other polymers, may thus enhance the wetting of the drug, providing access of the dissolution medium to the drug surface and prevent aggregation of particles and subsequent decrease in surface area. In addition to wetting, some degree of interaction between the PEO and the drug may occur.

Ozeki et al. (Ozeki et al., 1997) reported that PEO functioned very well as a solubiliser for the slightly water-soluble drug, flurbiprofen, and observed a linear relationship between the release rate of the drug and the amount of PEO used in the solid dispersions prepared. They explained this by proposing hydrogen bonding interaction between PEO and the drug, which increases in degree with PEO concentration. They also suggested that the mobility of PEO was enhanced by precedent melting of PEO during sample preparation, increasing probability of contact and interaction with the drug at a later stage. Although we found no evidence of hydrogen bond interactions between drug and polymer, we observe the same trends for improvement in drug release and believe the melting of both drug and polymer to be important factors as discussed later.

4.3. Effect of compression moulding

Compression moulding of probucol with PEO alone, or together with PEO and PVP, appeared to give a significant advantage in dissolution results, compared to the simple melting or solvent methods. It is suspected that the additional presence of the controlled high pressure factor in

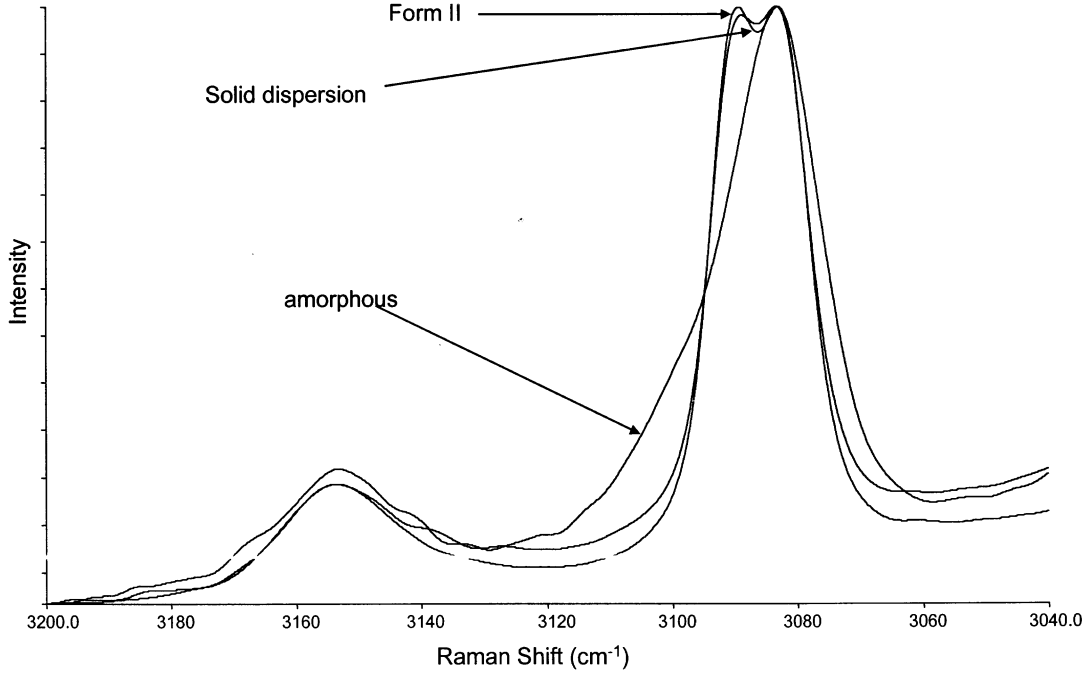

Fig. 7. FT-Raman spectrum of a probucol-PEO solid dispersion prepared by compression moulding, showing that the sample contains probucol mainly as the form II polymorph. The spectra of pure amorphous and form II probucol are shown for comparison.

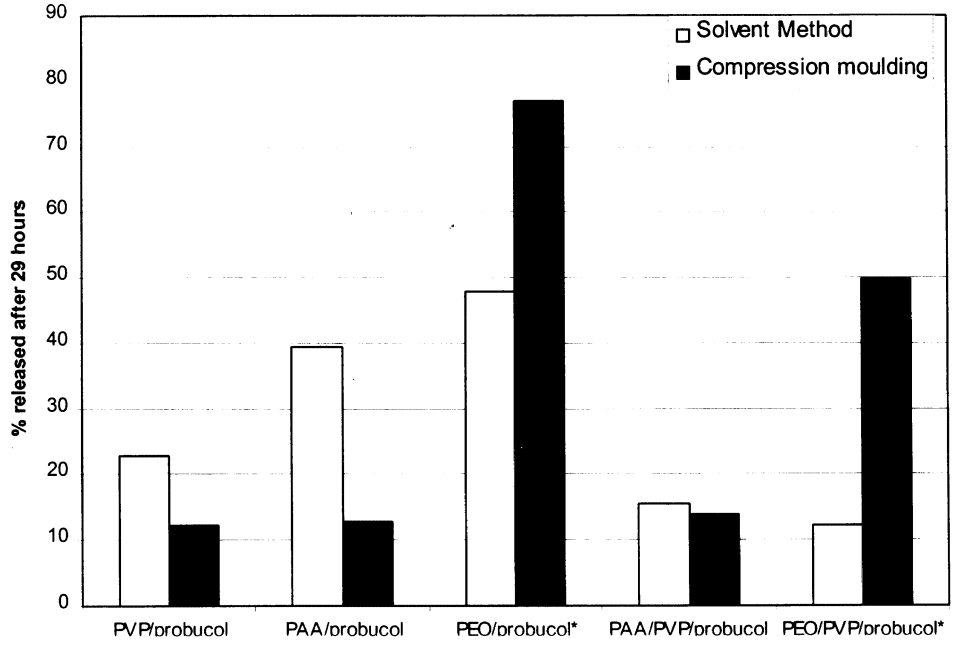

Fig. 8. A comparison of the percentage of drug released into solution after 29 h for the different solid dispersion systems prepared either by compression moulding or the solvent method. *The 'solvent' method sample was prepared by co-melting, see methods section.

compression moulding, together with high local temperature, produces this effect. We hypothesis that these factors result in intimate contact and mixing of the molten components. On cooling, although phase separation occurs (in the form of crystallisation), the drug is still in intimate contact with the polymer, possibly in the form of a fine precipitate dispersed in the polymer (Chiou and Reigelman, 1971). The observed melting point depression of both the PEO and the drug supports the suggestion of close contact between the two components and the ability to interact in the molten state. This method therefore appears to give an advantage over simple melt or solvent methods, at least for semi-crystalline polymer carriers like PEO.

5. Summary

Solid dispersions of probucol and various hydrophilic polymers and their blends were prepared by two methods; solvent evaporation or by compression moulding into films, and the resultant materials characterised. The final release properties of the solid dispersions appear to depend mainly on the properties of the polymer carrier, rather than on the solid state modification of the drug in the solid dispersion. It was found that probucol was amorphous in the presence of PVP, but mainly crystalline when blended with either PAA or PEO. At the same time, the most extensive release was seen for the PEO-probucol solid dispersion, made by compression moulding. Compression moulding appeared to have a positive effect on the properties of the solid dispersions, and simultaneously provides a viable and practical alternative to existing methods for the large-scale production of solid dispersions. Blending together two polymers was found to have little effect on the release behaviour in the systems studied here.

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