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International Journal of Pharmaceutics 245 (2002) 75–82

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Comparative physicochemical properties of hydrocortisone–PVP composites prepared using supercritical carbon dioxide by the GAS anti-solvent recrystallization process, by coprecipitation and by spray drying

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Received 7 May 2002; received in revised form 14 June 2002; accepted 18 June 2002

Abstract

Hydrocortisone–PVP composites were successfully prepared using the supercritical fluid gas anti-solvent method (GAS). Analysis by differential scanning calorimetry DSC and powder X-ray diffraction (XRD) indicated that these systems were more crystalline than corresponding systems prepared by spray drying. These systems, prepared by the GAS method were more similar in physicochemical properties to coprecipitates prepared by conventional solvent evaporation. Compressed composites of hydrocortisone–PVP systems, prepared by the GAS method, had dissolution rates lower than those of corresponding systems prepared by the other processing methods but equivalent to those of corresponding physical mixtures.

Keywords: Coprecipitation; Hydrocortisone; Polyvinylpyrrolidone; Supercritical CO2; Gas antisolvent recrystallization; Spray drying

1. Introduction

Drug–PVP composites, with enhanced biopharmaceutical properties such as solubility, dissolution rate and membrane transport, are traditionally produced by the solvent evaporation/coprecipitation method (Chiou and Riegelman, 1971; Corrigan, 1995; Ford, 1986; Serajuddin, 1999; Craig, 2002). The process employed may influence the properties of the resulting product and previously we obtained higher energy products, having enhanced drug dissolution and solubility characteristics, using the spray drying process (Corrigan and Holohan, 1984). These differences are particularly evident in composites rich in drug, where the drug characteristics control the release properties of the composite (Craig, 2002; Corrigan, 1985).

Recently increased attention has focused on the possible use of supercritical fluids (SF), primarily supercritical carbon dioxide ($scCO_2$), as a processing method in the production of pharmaceuticals. Of particular interest is the potential ability of the method to produce reproducible micro particu-

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0378-5173/02/$ - see front matter
PII: S0378-5173(02)00326-5

lates having a narrow size distribution. The non-toxic, non-inflammable and low cost nature of CO_2 as a solvent, together with its absence from the final product, in contrast to many organic solvents, makes the method particularly attractive. The original method is based on solution in $scCO_2$ followed by rapid expansion of the supercritical solution (RESS) to yield a microparticulate product (Matson et al., 1986; Debenedetti et al., 1993a; York and Hanna, 1996). However since the solubility of many drugs in $scCO_2$ is limited modifications to the basic method have been developed. For example the solvent power of the SF may be improved by the addition of small amounts of co-solvent, the SF effectively acting as an anti-solvent to the dissolved substance (Gallagher et al., 1989). The various anti-solvent techniques have been recently reviewed by Reverchon (1999).

In this work we examine the feasibility of producing drug-PVP high energy solid dispersions using the supercritical carbon dioxide gas anti-solvent recrystallization process (GAS) and compare the characteristics of these systems to corresponding systems prepared by spray drying and conventional coprecipitation. Hydrocortisone was used as the drug and ethanol as the solvent.

2. Experimental

Hydrocortisone–PVP solid dispersions (0–60% PVP (Plasdone C-15, GAF, Great Britain Ltd., UK)) were prepared by coprecipitation, spray drying (Buchi Mini 190) as previously described (Corrigan and Holohan, 1984) and by the GAS method using ethanol as co-solvent.

2.1. Preparation of coprecipitates

The required proportions of steroid and PVP were dissolved in sufficient ethanol. When both components were in solution, the ethanol was evaporated using a rotary evaporator (Rotavapor RE11, Buchi, Switzerland) at 40 °C. The resultant precipitate was collected and stored in a dessicator under vacuum for at least 12 h before characterization.

2.2. Preparation of spray dried samples

The required proportions of steroid and PVP were dissolved in sufficient ethanol. The solution was spray dried (Buchi Mini 190 Spray Drier, Buchi, Switzerland) at a rate of 5 ml/min^{-1} and inlet and outlet temperatures of 80 and 60 °C, respectively. The precipitated solute was removed from the collecting vessel using a plastic spatula.

2.3. Supercritical processing method

A schematic diagram of the SF apparatus (modified SFE 400, Supelco, UK) employed is shown in Fig. 1. A flow diagram for the latter method is illustrated in Fig. 2. A $scCO_2$ phase was used as previously employed for steroids (Stahl and Quirin, 1983), operating at 2,000 psi and 40 °C (Bleich et al., 1993). Ethanol was selected as the organic solvent because of its good solubilizing power for both PVP and hydrocortisone and its known expansively with CO_2 under supercritical conditions (Debenedetti et al., 1993b). Samples of ethanolic solution (300 μl) were injected into the SCF flow via the rheodyne valve (Fig. 1). When all the solution had been injected the $SCCO_2$ flow was stopped by closing the fluid delivery valve. The extraction vessel was depressurised, removed and the precipitate in the extraction vessel collected.

2.4. Physicochemical characterisation

Materials, processed and unprocessed, were examined by differential scanning calorimitry, hot stage microscopy, powder X-ray diffraction and SEM as previously described (Corrigan et al., 2002). Powder X-ray diffraction patterns were obtained using Nickel filtered copper radiation in the range 5–35° (Siemens, Germany).

DSC (Mettler DSC 20) analysis was performed on ~5 mg samples, under dry nitrogen at a heating rate of 10 °C/min^{-1} in aluminium pans having pierced lids using GraphWare TA70 software (Mettler, Switzerland).

Apparent solubilities were determined at 37 °C by the dynamic solubility method as previously described (Corrigan and Holohan, 1984). Dissolution studies were carried out on compressed discs,

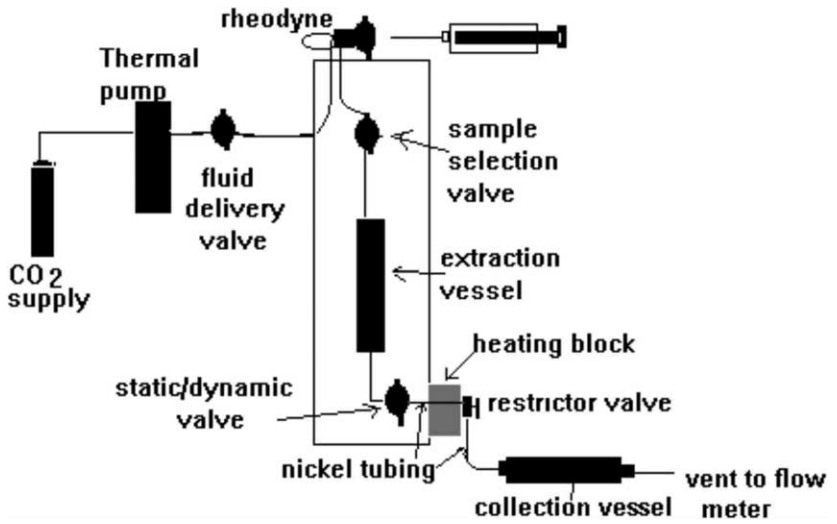

Fig. 1. Schematic diagram of supercritical fluid apparatus.

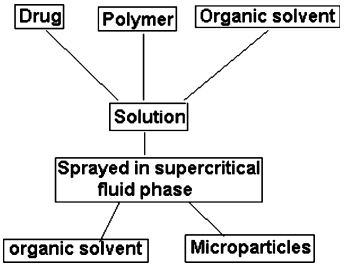

Fig. 2. Flow diagram of the gas anti-solvent (GAS) process.

50 mg at 7,000 kg for 10 min using the rotating disc (9 mm) method at 60 rpm in phosphate buffer pH 7.4 at 37 °C. Hydrocortisone in solution was assayed by UV from the linear absorbance versus concentration relationship.

3. Results and discussion

3.1. Hydrocortisone processed systems

Powder XRD and DSC of pure hydrocortisone samples prepared by the coprecipitation and GAS methods gave crystalline products of equivalent crystal structure as the starting material and having powder XRD patterns similar to that reported by Florey (1983). In contrast spray drying yielded an amorphous solid as was evident from the absence of peaks in the powder XRD scan and the presence, by DSC, of an exothermic event at 130 °C, preceding the melting endotherm (216 °C). SEM of the spray dried drug showed smooth spherical microparticles, in contrast to the crystalline morphology evident in samples prepared by the precipitation and GAS methods (Figs. 3 and 4). Velaga et al. (2002) have prepared hydrocortisone by a supercritical fluid extraction process using acetone, methanol and chloroform as solvents. The morphology of crystalline hydrocortisone samples obtained in the current work was similar to that obtained by Velaga et al. (2002) using conventional crystallisation from methanol, but were much smaller in size ($\sim$2 μm) and were unlike the needle shaped products obtained by these authors using their SEDS processing with acetone and methanol.

3.2. Hydrocortisone–PVP processed systems

SEM images of hydrocortisone samples subjected to the GAS process in the presence of PVP indicated that these materials were microcrystalline in nature (Fig. 3). In contrast SEM's of spray dried materials indicated spherical amorphous like particles (Fig. 4). X-ray diffraction patterns of hydrocortisone–PVP coprecipitate composites showed crystallinity at the lower PVP loadings

Fig. 3. SEM of hydrocortisone–PVP (9:1) powder prepared by the GAS process.

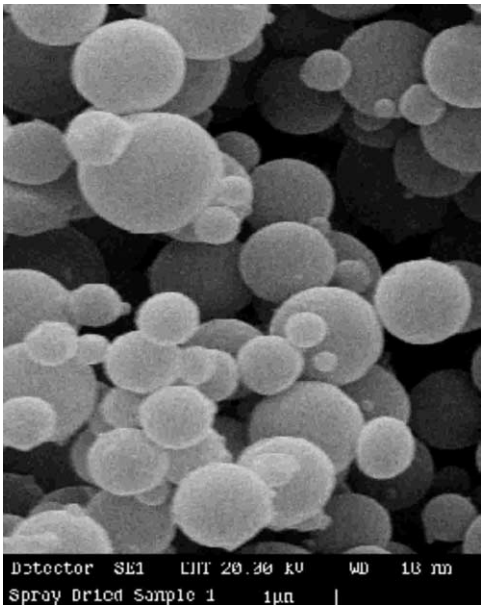

Fig. 4. SEM of spray dried hydrocortisone powder.

(0–40% PVP). At and above 60% PVP, systems were amorphous. XRD patterns of the corresponding GAS processed systems (Fig. 5) also

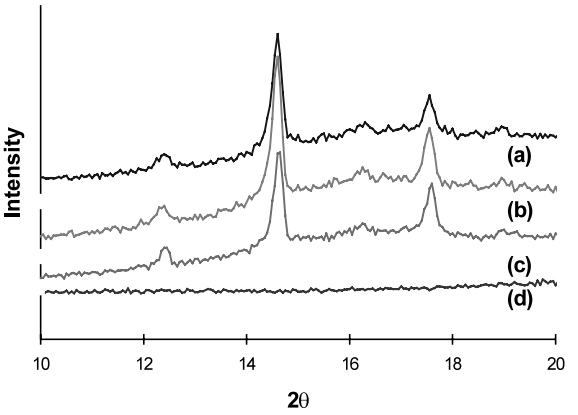

Fig. 5. XRD patterns of hydrocortisone:PVP GAS systems (a) 0; (b) 20; (c) 40 and (d) 60% w/w PVP.

showed crystallinity at and below 40% PVP. In contrast XRD patterns indicate the absence of crystallinity in all the spray dried hydrocortisone samples, with or without PVP (Fig. 6).

DSC data of the spray dried and GAS processed systems are shown in Figs. 7 and 8, respectively. Scans of spray dried samples indicate the presence of exotherms reflecting the presence of amorphous drug which converts to the crystalline form during heating. In contrast no such exotherms were evident in either the GAS processed or coprecipitate systems. The spray drying process produced

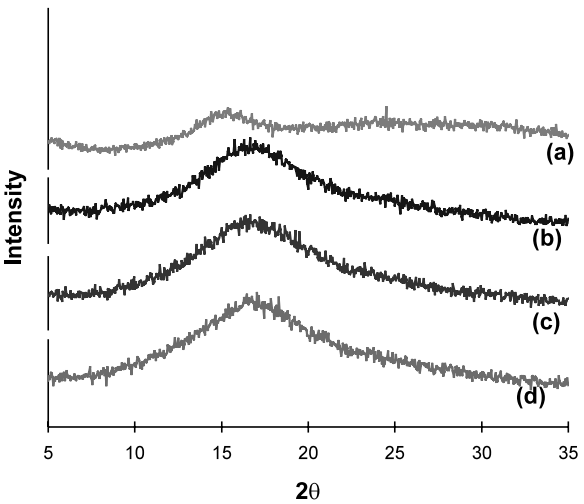

Fig. 6. XRD patterns of hydrocortisone:PVP spray dried systems (a) 0; (b) 20; (c) 40 and (d) 60% w/w PVP.

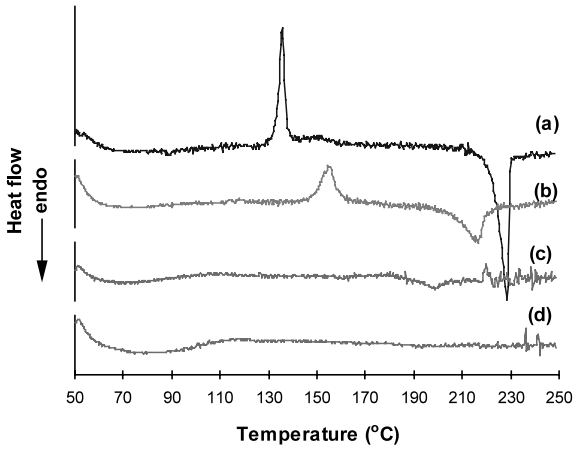

Fig. 7. DSC scans of hydrocortisone:PVP spray dried systems (a) 0; (b) 20; (c) 40 and (d) 50% w/w PVP.

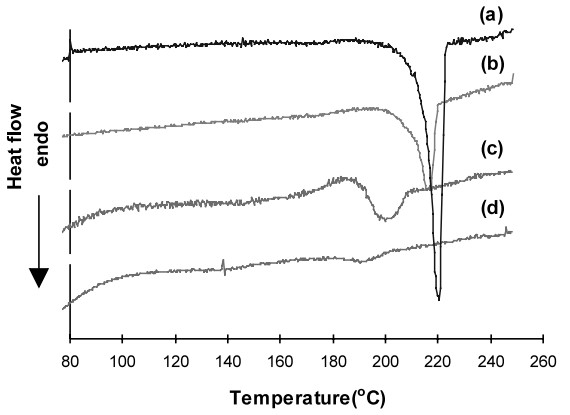

Fig. 8. DSC scans of hydrocortisone:PVP GAS processed dispersions (a) 0; (b) 20; (c) 30 and (d) 40% w/w PVP.

the highest energy products. Plots of ΔH_f, the enthalpy of the hydrocortisone melting event, versus PVP mass fraction (Fig. 9) declined linearly with increasing PVP content. The intercepts on the x-axis indicate the threshold level or apparent solubility of the drug in the polymer. The processed systems give greater slopes than that of the physical mixes and the results (Fig. 9 and Table 1) indicated that spray drying was the most effective process for eliminating hydrocortisone crystallinity, followed by the composites prepared by the GAS and coprecipitate processes. Threshold values based on the XRD results are also included

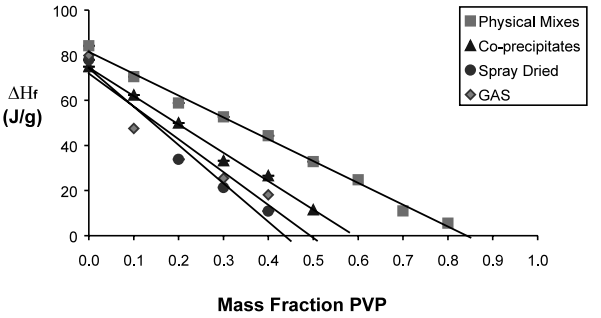

Fig. 9. Plot of ΔH_f (J/g of dispersion) of hydrocortisone/PVP dispersions against the mass fraction of PVP present.

Table 1
Threshold levels of PVP (w/w), indicating fraction of polymer required to eliminate drug crystallinity, for hydrocortisone–PVP dispersions determined from DSC scans and powder XRD patterns

Method of processing	DSC data	XRD data
	Mass fraction PVP	Mass fraction PVP
Physical mix	0.83	$>0.80^a$
Co-precipitation	0.58	0.60
Spray drying	0.44	0.0
GAS processing	0.56	0.60

[a] 80% w/w PVP was the highest level of PVP examined.

in Table 1 for comparison. The DSC and XRD results obtained for hydrocortisone–PVP spray drying and coprecipitate systems are qualitatively similar to those obtained for hydroflumethiazide–PVP systems (Corrigan and Holohan, 1984; Corrigan and Timoney, 1975) in that only on spray drying were all systems amorphous and showed an exothermic event prior to the drug melt endotherm.

3.3. Solubility and dissolution

Preliminary solubility studies, at 37 °C in phosphate buffer pH 7.4, containing 1% PVP to retard recrystallization of higher energy drug forms, using the dynamic solubility method indicated that spray dried hydrocortisone had a higher solubility (0.65 mg/ml) than that of the crystalline form (0.47 mg/ml).

Intrinsic dissolution rates were determined for hydrocortisone–PVP composites containing 20 and 60% PVP, i.e. at contents above and below the threshold levels (Table 1). Dissolution profiles of these system prepared by the three processing methods together with mechanical mixtures are compared to that of the compressed pure drug in Fig. 10.

Dissolution characteristics from these compressed discs were complex, due to possible recrystallization of amorphous drug, the proportion of PVP present and its impact on drug solubility and recrystallization during dissolution of both components. Dissolution tended to be higher at the higher PVP content, the effect being greater for processed systems compared to physi-

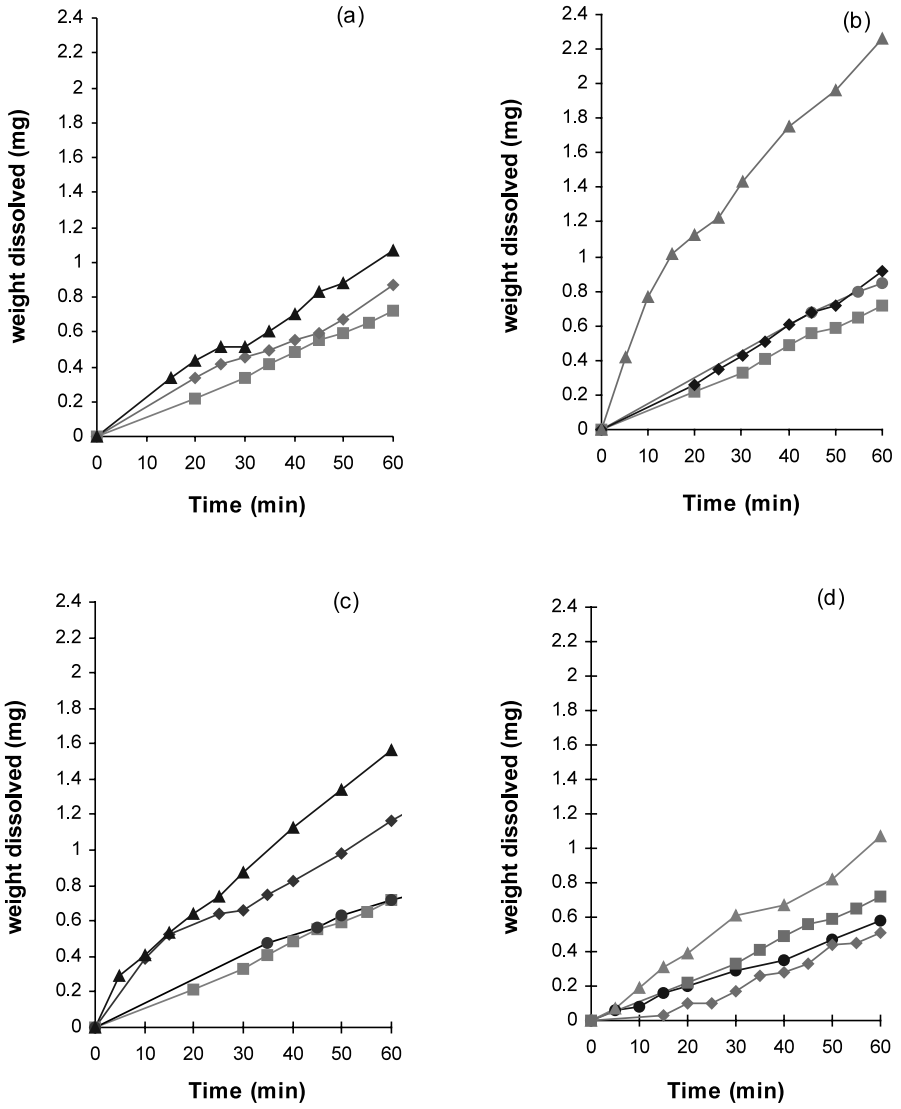

Fig. 10. Intrinsic dissolution profiles of hydrocortisone:PVP solid dispersions in phosphate buffer pH 7.4. (■) Starting material; (●) 0% w/w PVP; (◆) 10% w/w PVP and (▲) 60% w/w PVP, plot (a) physical mixes, (b) co-precipitates, (c) spray dried dispersions and (d) GAS processed dispersions.

cal mixes. PVP (60%) increased the initial and limiting intrinsic dissolution rates of hydrocortisone from compressed physical mixes by 2- and 1.3-fold, respectively, reflecting the solubility enhancing effect of PVP and its more rapid dissolution rate. In contrast coprecipitation with 60% PVP gave corresponding values of 7- and 2.3-fold, respectively, spray drying gave enhancements of 5.2- and 1.9-fold while products prepared by the GAS process gave values of 1.9-and 1.3-fold for initial and limiting dissolution rates. Thus the GAS process seems likely to produce the least amorphous systems. Factoring out the dissolution enhancing effect of PVP, the maximum relative enhancement due to processing was 3.5-fold. While this enhancement in activity is similar to that reported for sulphathiazole (Simonelli et al., 1969) and hydroflumethiazide (Corrigan and Timoney, 1975) it is much lower than the values of 18–19-fold (Corrigan et al., 1980) and sixfold (Merkle, 1983) previously reported in dissolution and/or membrane transport studies with hydrocortisone–PVP coprecipitates (Corrigan, 1995). However these maximum enhancements were obtained using systems containing 80–90% PVP and in the former report 5% PVP was also included in the medium to inhibit drug recrystallization and crystal growth. Both these reports established the propensity of hydrocortisone in hydrocortisone-PVP coprecipitates of lower PVP content to recrystallize from solution.

4. Conclusions

Drug–PVP solid dispersions, containing up to 60% PVP were prepared by the GAS method. The systems of lower PVP content contained crystalline drug and were more similar in physicochemical properties to coprecipitates prepared by conventional solvent evaporation rather than to the higher energy systems prepared by spray drying. Consequently systems prepared by the GAS method did not dissolve more rapidly from compressed compacts than the other processed systems.

Acknowledgements

The authors acknowledge the financial assistance of Elan Corporation, Ireland.

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