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Amorphous spray-dried hydroflumethiazide-polyvinylpyrrolidone systems: physicochemical properties

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Hydroflumethiazide was spray-dried with polyvinylpyrrolidone (PVP) to produce products containing 0–30% PVP. These systems were amorphous and differed from previously prepared coprecipitates of similar composition. Differential scanning calorimetry (DSC) suggested that at low PVP weight fractions both amorphous drug and an amorphous drug-PVP complex can be present in spray-dried systems. The apparent solubility of hydroflumethiazide in spray-dried products increased with increasing PVP content reaching a plateau value approximately four times that of the pure crystalline drug. The estimated free energy and entropy of the spray-dried drug were greater than that of crystalline drug and also increased with increasing PVP content. Dissolution studies with compressed discs supported the apparent solubility data. The results suggest that amorphous phases having different orders of organization are formed in spray-dried systems with increasing PVP content.

Numerous reports have shown that coprecipitation with polyvinylpyrrolidone (PVP) can markedly enhance the dissolution of drugs (Tachibana & Nakamura 1965; Simonelli et al 1969; Corrigan & Timoney 1975). The mechanism responsible for this enhanced dissolution has been the subject of debate. Some authors have proposed that the increased drug dissolution rate results from the formation of a high energy amorphous drug phase (Simonelli et al 1969, 1976; Corrigan et al 1980). Others have attributed the effect to drug being molecularly dispersed (Chiou & Riegelman 1971) or complexed in PVP (Shefter & Cheng 1980) while coacervate formation was implicated by Sekikawa et al (1979) and Badawi & El Sayed (1980).

Previous studies of hydroflumethiazide-PVP coprecipitates supported the existence of a high energy amorphous drug phase in systems containing more than 40% PVP. Dissolution data suggested that the solubility of this phase was four times that of the crystalline drug (Corrigan & Timoney 1975). Recently, spray drying yielded an amorphous form of pure hydroflumethiazide. However the apparent solubility of this form was only 1·6 times that of crystalline hydroflumethiazide (Corrigan et al 1983). In this report the physicochemical properties of spray-dried hydroflumethiazide-PVP systems were investigated with a view to clarifying the amorphous nature of these systems.

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MATERIALS AND METHODS

Materials

Spray-dried materials were prepared by dissolving PVP (Plasdone C-15 mol. wt 10 000, GAF (Great Britain Ltd)) and/or hydroflumethiazide BP in ethanol (Ceimici Teoranta, Dublin) and drying in a Buchi Minispray 190 drier as described by Corrigan et al (1983). The % symbol indicates % w/w. Mechanical mixes were prepared by shaking sub 85 mesh sieve samples in jars and these were checked by uv assay for mixing.

Methods

X-ray diffraction patterns were obtained on powder samples using a powder diffractometer (Philips PW 1050/26) employing nickel filtered copper radiation. Differential scanning calorimetry (DSC) (Perkin Elmer Model DSC—1B at a scanning speed of 16° min^{-1}) was used to examine samples, normally in the range 2–4 mg. Heats of fusion were measured from the peak areas of known weights of material as outlined by Summers (1978).

Apparent solubilities were determined in 0·1 M HCl at 37 °C as decribed by Shefter & Higuchi (1963) and Chiou & Kyle (1979). One per cent PVP was included in the medium to retard phase transformation (Corrigan & Timoney 1974).

Dissolution rates per unit surface area were determined using compressed discs mounted in paraffin wax (see Levy & Procknal 1964; Corrigan & Timoney 1975).

RESULTS

In contrast to mechanical mixtures of crystalline hydroflumethiazide and PVP, corresponding spray dried systems proved amorphous on X-ray diffraction analysis. Typical DSC scans of crystalline and spray-dried hydroflumethiazide, together with those of spray-dried hydroflumethiazide-PVP systems are shown in Fig. 1. An exothermic peak, not present in crystalline hydroflumethiazide or in mechanical mixtures of crystalline hydroflumethiazide and PVP, was observed in spray-dried systems containing up to 15% PVP. The size of this exotherm decreased with increasing PVP content. Furthermore, the temperature at which the exotherm occurred increased with increasing PVP content. The exothermic peak defines the temperature (T_D) at which spontaneous crystallization of the amorphous phase occurs, i.e. the temperature at which molecular mobility permits nuclear growth and the resultant evolution of heat (de Nordwall & Staveley 1956). The observation that T_D increases with increased PVP concentration suggests a stabilizing effect on the transformation.

The rate of conversion of amorphous hydroflumethiazide to the crystalline form at room temperature (20 °C), detected by X-ray diffraction and by the absence of the DSC exotherm, was also retarded by co-spray drying with PVP. The hydroflumethiazide-PVP system containing 1% PVP took six months to convert, whereas pure amorphous spray-dried hydroflumethiazide (see Corrigan et al 1983) converted to crystalline drug in approximately 10 days. Systems spray-dried with higher PVP contents have remained physically stable for over a year.

DSC scans of hydroflumethiazide-PVP mechanical mixtures had a single endothermic peak, corresponding to melting of the drug, the area of which decreased with increasing PVP content. From a plot of the change in heat of fusion (H_f) vs drug content in the sample (%) (Fig. 2), the apparent solubility of hydroflumethiazide at its melting point can be obtained from the intercept (Theeuwes et al 1974; Shefter & Cheng 1980). This occurs when 69% hydroflumethiazide is present, which represents a 1 : 1·3 molar ratio of drug to each PVP sub-unit. Heat of fusion estimates for the spray-dried systems are also included in Fig. 2. These were more variable but are distributed about the same trend line, consistent with the conversion of amorphous drug to the crystalline phase at T_D. The DSC results suggest that in spray-dried systems of low PVP weight fraction, hydroflumethiazide can be present as an amorphous drug phase and also complexed (dissolved) in PVP.

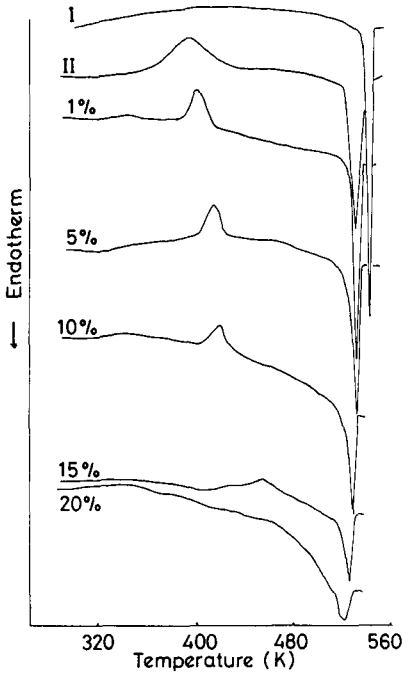

FIG. 1. DSC scans of hydroflumethiazide spray-dried with PVP. I crystalline drug, II spray-dried drug. % values represent the per cent of PVP present in the final spray-dried material.

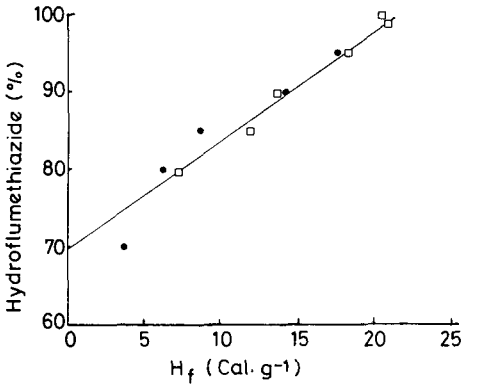

FIG. 2. Change in heat of fusion (H_f) of hydroflumethiazide-PVP systems with PVP content. Key: □ Physical mixtures, ● spray-dried systems.

Profiles of apparent solubility obtained for hydroflumethiazide-PVP spray-dried systems determined at 37 °C in 0·1 M HCl containing 1% PVP are shown in Fig. 3. Also included are the data for crystalline and amorphous pure hydroflumethiazide. The apparent solubility of systems spray-dried with

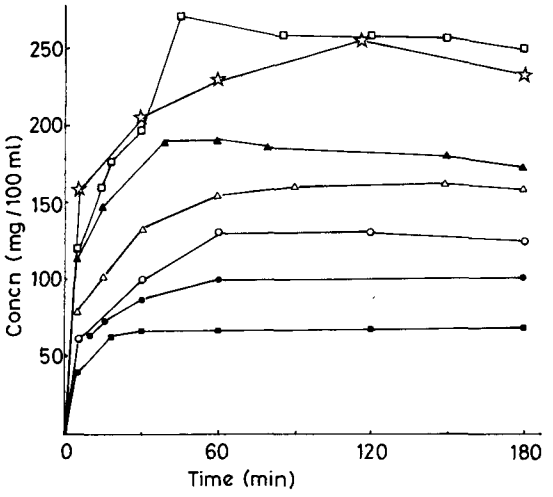

FIG. 3. Solubility profiles of hydroflumethiazide-PVP systems at 37 °C in media containing 1% PVP. Key: ■ Crystalline drug, ● spray-dried drug, spray-dried hydroflumethiazide-PVP systems containing ○ 5%, △ 10%, ▲ 15%, ☆ 20% and □ 30% PVP in the solid.

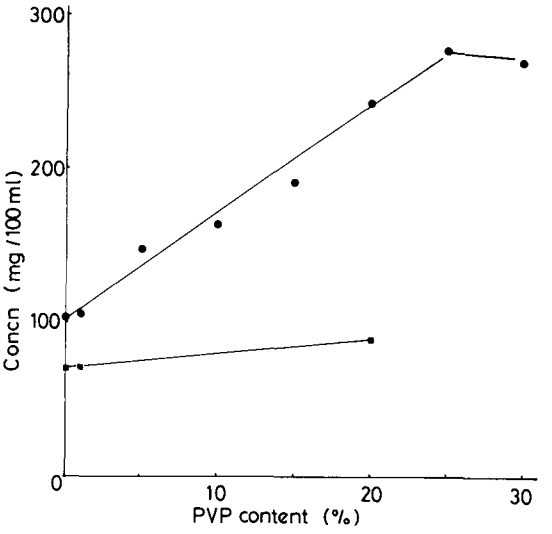

FIG. 4. Effect of solid phase PVP content on the apparent solubility of hydroflumethiazide from drug-PVP spray dried systems. Key: ● Spray-dried systems, ■ physical mixtures of crystalline drug and PVP.

more than 10% PVP tended to be metastable, the apparent solubility declining with time. To ensure that the apparent solubility estimates for these systems were maximal, successive additions of the spray-dried material were made to the solution medium. In some systems, slightly higher plateaux were initially observed and subsequent additions gave no further increase. The final plateau was taken as the apparent solubility of the sample. The change in maximum apparent solubility with increasing PVP content of the spray-dried sample is shown in Fig. 4. The apparent solubility increased to a plateau approximately four times the solubility of the crystalline hydroflumethiazide. Solubility runs were carried out on the spray-dried systems containing 10 and 15% PVP, during which PVP was added to the solution medium to bring the PVP content up to 15 and 20% respectively. These slightly higher levels of PVP in solution made no significant contribution to the apparent solubility. Solubility profiles of mechanical mixtures of PVP and crystalline hydroflumethiazide were obtained to determine the contribution, if any, of PVP alone to the enhanced apparent solubilities. These data are also included in Fig. 4 and show that PVP in solution could only make a minor contribution to the solubility enhancements observed in spray-dried systems. Thus, the possibility that the enhanced solubilities are solely due to the formation of a soluble drug-PVP complex in solution may be ruled out. Furthermore the results suggest that the increases in the apparent solubility of hydroflumethiazide-PVP spray-dried systems are due to the presence of a less ordered amorphous state of the drug, the degree of disorder increasing with increasing PVP content. The influence of temperature on the apparent solubility of the crystalline, spray-dried amorphous, 1% PVP and 20% PVP systems was determined. The Van't Hoff plots obtained are shown in Fig. 5. These are lines of best fit based on statistical assessment. The decreasing slope with increasing PVP content in the solid suggests the presence of a less ordered form of drug. Assuming the contribution of PVP in solution to the overall solubility is negligible, apparent heats of solution may be calculated from the slopes of the curves in Fig. 5. The values obtained, together with the estimated heats of transition are summarized in Table 1.

Table 1. Thermodynamic parameters of hydroflumethiazide samples. I Apparent heat of solution. II Heat of transition. III Free energy (25 °C).

	kCal mol^{-1} (kJ mol^{-1})			Entropy
Solid form	I	II	III	(25 °C)
Crystalline drug	10·271 (43·02)	—	—	—
Spray-dried sample	8·360 (35·04)	1·911 (8·00)	0·3052 (1·27)	5·39
Spray-dried with 1% PVP	8·130 (34·01)	2·141 (8·36)	0·3864 (1·62)	5·88
Spray-dried with 20% PVP	0·906 (3·82)	9·365 (39·20)	1·1151 (4·66)	27·67

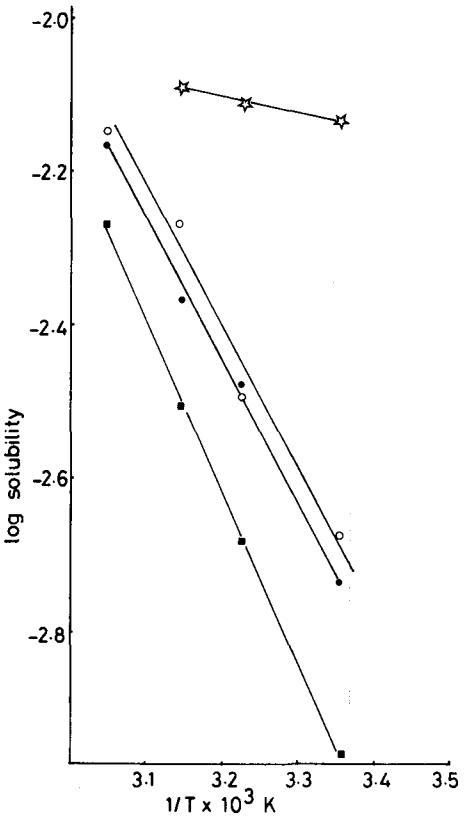

FIG. 5 Change in hydroflumethiazide apparent solubility with temperature. Key: ■ Crystalline drug, ● spray-dried drug, ○ spray-dried with 1% PVP, ☆ spray-dried with 20% PVP.

The free energy of hydroflumethiazide in each system, relative to crystalline drug ($\Delta F^T_{i,x}$) (assuming that the activity coefficients in solution remain constant), can be calculated from

$$\Delta F^T_{i,x} = RT \ln \frac{S^o_x}{S^o_i} \qquad (1)$$

where S^o_x and S^o_i, are the solubilities of the spray-dried and crystalline phase respectively (Shefter & Higuchi 1963: Simonelli et al 1976). The estimated values at 25 °C are also listed in Table 1. The free energy of spray-dried hydroflumethiazide was greater than that of the crystalline drug and increased the more PVP was present in the spray-dried system. The free energy of the hydroflumethiazide present in the spray-dried 20% PVP system was over three times higher than that of spray-dried amorphous pure drug. A quantitative measure of the more random, less ordered, state of drug in the spray-dried systems can be obtained from the change in entropy relative to crystalline drug calculated using equation 2.

$$\Delta S_{i,x} = \frac{\Delta H_{i,x} - \Delta F_{i,x}}{T} \qquad (2)$$

where $\Delta H_{i,x}$ is the apparent heat of solution. The values obtained are summarized in Table 1 and confirm the increased randomness of the various spray dried-systems relative to crystalline drug. Dissolution profiles of crystalline and spray-dried hydroflumethiazide mixed with 20% PVP and of spray-dried systems containing 5% and 20% PVP are shown in Fig. 6. The initial dissolution rate of the spray-dried system containing 20% PVP was 4–5 times greater than that of the corresponding physical mixture. Furthermore the mixture of spray-dried hydroflumethiazide with PVP (20%) gave an initial dissolution rate only slightly higher than the corresponding mixture containing crystalline drug. This result substantiates the difference in activity of the form of hydroflumethiazide present in systems spray-dried with PVP. The spray-dried system containing 5% PVP had an intermediate dissolution rate.

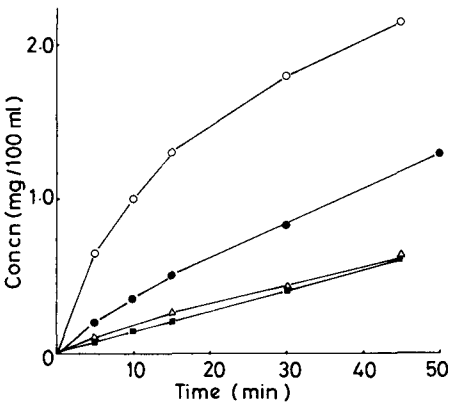

FIG. 6. Dissolution profiles of hydroflumethiazide from drug-PVP systems. Key: ○ Spray-dried with 20% PVP, ● spray-dried with 5% PVP, △ mixture containing 20% PVP and spray-dried drug, ■ mixture containing 20% PVP and crystalline drug.

DISCUSSION

The spray-dried hydroflumethiazide-PVP systems containing up to 30% PVP, prepared in this work, differ from the coprecipitate systems of similar composition previously reported (Corrigan & Timoney 1975). The systems were amorphous on X-ray diffraction and systems with up to 15% PVP displayed an exothermic peak on DSC analysis,

which is a feature of amorphous pure hydroflumethiazide. The apparent solubility of systems spray-dried with PVP increased with increasing PVP content and reached a plateau at a value approximately four times that for crystalline drug. Previous reports indicated the existence of two amorphous states of hydroflumethiazide i.e. the pure spray-dried form, having a solubility 1·6 times the crystalline drug, and the amorphous phase present in coprecipitates, which on the basis of dissolution data had a solubility 4 to 5 times that of crystalline hydroflumethiazide. If the spray-dried systems containing PVP contained solely mixtures of either, or both, of these two amorphous phases, then only discrete solubility plateaux corresponding to the solubilities of these phases should have been observed. However the gradual increase in solubility seen (Fig. 4), together with the differences in initial dissolution rates of the 20 and 5% PVP systems, suggest that the phase(s) of drug present in the spray-dried systems containing up to 20% PVP were different. The increased solubility reflects an increasing degree of molecular randomness and lack of structure as PVP content was increased. The shift of T_D to higher temperatures in the 0–20% PVP content range suggests that the polymer is acting as a barrier to the cohesive forces of crystallization. Ultimately, sufficient PVP is present to prevent reorientation and crystal growth.

Furthermore, with increasing PVP content, drug is also dissolving in the polymer as reflected by the decrease in endothermic peak area. Simonelli et al (1976) reported thermodynamic parameters for a number of sulphathiazole phases including a glassy supercooled melt and a PVP coprecipitate. The estimated free energies for these two phases, relative to crystalline form I sulphathiazole, were 431 and 1125 cal mol^{-1} (1·80 and 4·71 kJ mol^{-1}) respectively; values of similar magnitude to the hydroflumethiazide systems in the current work. Likewise, heats of solution and entropy differences for the glassy and coprecipitate sulphathiazole forms corresponded in magnitude to those estimated for pure amorphous spray-dried hydroflumethiazide and the 20% PVP spray-dried system. Thus, it seems that pure drug amorphous phases still have considerable structure despite the absence of crystallinity. The inclusion of PVP before drying leads to a solid phase with the drug in a more random solid state.

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