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Physicochemical characterization of ibuprofen–polyvinylpyrrolidone dispersions

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Summary

The nature of the interaction between ibuprofen and polyvinylpyrrolidone was studied in solution and the solid state; pH titration, conductivity measurements, solution infrared (IR) spectroscopy and solubility determination techniques were used to elucidate the mechanism of interaction in the solution state. X-Ray powder diffraction and differential scanning calorimetry (DSC), were used to study the nature of the interaction in the solid state. The pH titration and conductivity measurement studies reflected a weak acid–weak base type of interaction between the carboxylic group of the drug and the basic centre of the pyrrolidone moiety of the polymer. Solution IR studies confirmed this type of interaction. The X-ray diffraction pattern indicated that the dispersion had an amorphous nature as compared to the crystalline drug. The DSC studies indicated that the melting point and the heat of fusion (ΔH_f) values change with the dispersion composition. The solubility studies showed that the highest solubility was obtained for dispersion of drug-to-polymer ratio of 1 : 1. This ratio was also found to have the lowest melting point and ΔH_f values.

Introduction

This paper is the third in a series of papers on the characterization of the ibuprofen–polyvinylpyrrolidone (PVP) solid dispersion system. It was previously shown (Najib et al., 1986) that the dispersion of ibuprofen in PVP resulted in an increase in the in vitro release of the drug. This effect was attributed to the formation of a weak acid–weak base salt-like complex. Further evidence to the formation of such a complex was obtained from infrared (IR) spectroscopy and proton nuclear magnetic resonance (^{1}H-NMR) studies (El-Hinnawi and Najib, 1987). Other workers have attributed the enhancement in the release of drugs when dispersed in PVP to various mechanisms. Simonelli et al. (1969, 1976) and Corrigan et al. (1980) have suggested that the formation of a high energy complex between sulphathiazole and PVP was responsible for the observed increase in solubility. Chiou and Riegelman (1971) have sug-

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gested that the molecular dispersion of the drug in the polymer matrix resulted in an increase in drug release. Shefter and Cheng (1980) have studied the interaction of a number of drugs with PVP and suggested that the increase in release is related to the ability of the drug to form hydrogen bonding with the pyrrolidone moiety of the polymer. Sekikawa et al. (1979) attributed the increase in release to coacervate formation with the polymer.

In view of the above variation in the proposed mechanisms for the interaction of drugs with PVP, this work was undertaken in order to provide further evidence for the mechanism of interaction between ibuprofen and PVP. This was done by studying the nature of the interaction in the solution state by means of pH titration, conductivity measurements, solution IR studies and solubility determinations and by studying the nature of the interaction in the solid state using X-ray powder diffraction and differential scanning calorimetry (DSC) studies.

Materials and Methods

Materials

Aluminium oxide, anhydrous citric acid, chloroform-d, indium and phosphorous pentoxide were purchased from Aldrich Chemical Co., U.S.A. Disodium phosphate and ethanol AnalaR grade were obtained from BDH Chemicals, U.K. Chloroform, ibuprofen, PVP 40,000 were obtained from Sigma Chemical Co., U.S.A. The water used was double-distilled with a surface tension of 71–72 $mN \cdot m^{-1}$ at 25 °C.

Methods

Preparation of the solid dispersions. PVP–drug dispersions were prepared by dissolving the required amounts of the drug and the polymer which was dried under vacuum in a minimum volume of chloroform previously dried under P_2O_5. The solvent was then removed under vacuum. The resulting mass was left under vacuum for 3 days and then removed, size reduced and kept under nitrogen for further studies.

pH titration. 15 ml of 0.016 M solution of ibuprofen in ethanol were placed in a beaker and its pH was determined at 25 °C. PVP 0.016 M ethanolic solution was added in small volumes to the drug solution, the solution was then thoroughly mixed and the pH was measured; this was repeated until no change in pH was obtained as a result of PVP addition.

Conductivity measurements. 15 ml of 0.016 M solution of ibuprofen in ethanol were placed in a beaker and the conductivity was measured at 25 °C using a Karl Kolb model 6072, conductivity meter. 0.016 M PVP ethanolic solution was added in small increments from a burette to the drug solution and the conductivity of the resulting solution was determined after the solution was stirred for 5 min. This was continued until no change in conductivity was obtained. The obtained values of the conductivity were not corrected for dilution factor.

Infrared spectra measurements. The spectra were recorded on Pye-Unicam SP3-100 spectrometer using KBr 0.1 mm solution cell. All solution samples were prepared in chloroform.

Solubility studies. Equilibrium solubility studies were performed by adding 50 mg of the drug or an amount of the drug–polymer solid dispersion, of the required drug-to-polymer ratio containing this weight of the drug to each of a series of Erlenmeyr flasks containing 10 ml of McIlvain buffer solution adjusted to pH 2.20 The flasks were then placed in a water bath at 37 ± 0.1 °C with continuous shaking for 24 h. 5 ml samples were then transferred to a syringe and rapidly filtered through a 0.3 μm Millipore filter unit (Millipore, London, U.K.). The concentration of ibuprofen was then determined spectrophotometrically at 263 nm. The absorbance values were then converted to the corresponding concentrations by reference to a suitable calibration curve.

X-Ray diffraction measurements. X-Ray diffraction measurements were recorded using Philips PW 1729 X-ray generator with Cuk_x radiation ($\lambda = 0.15405$ nm) for dispersions of different drug: PVP ratios.

Differential scanning studies. The thermograms of ibuprofen, PVP and ibuprofen–PVP solid dispersions of different ratios were recorded on a Stanton Redcroft STA 785 thermal analyzer equipped with Data Acquisition and Processing

System 2. The instrument was calibrated with pure indium (99.99%, m.p. 156.6 °C). Samples ranging in weight between 6.0 and 8.0 mg were placed into aluminium pans. About 10 mg of activated aluminium oxide in an aluminium pan was used as a reference. The thermal behaviour was studied under dynamic conditions using nitrogen gas at a flow rate of 50 ml/min. All thermal runs were carried out at a heating rate of 10 °C/min. Heats of fusion were determined from the manufacturer software package. Averages of duplicate thermograms were used for all calculations.

Results and Discussion

Fig. 1 shows the pH titration curve obtained when 15 ml of 0.016 M ethanolic solution of the drug were titrated against 0.016 M ethanolic solution of the polymer at 25 °C. The pH of the drug solution was 5.7, on addition of PVP solution, the pH increases until it reaches the value of 6.1 when approximately 30 ml of PVP solution were added, then the pH remains constant on further addition. Since the amide nitrogen in the pyrrolidone ring of the polymer is a very weak base in ethanol – the measured pH was 8.3 – and the drug is a weak acid, the titration curve obtained reflects the previously proposed weak acid–weak base type of interaction between the drug and the polymer (Najib et al., 1986).

The conductivity results are shown in Fig. 2. The conductivity of the drug as a weak electrolyte in ethanolic solution increases significantly when the PVP solution was added which indicates that the solution of the mixture is a stronger electrolyte than either of the pure substances. This would be due to the formation of ions as a result of the

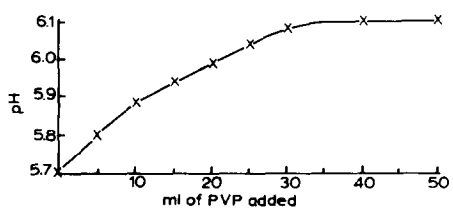

Fig. 1. pH titration of ibuprofen with PVP.

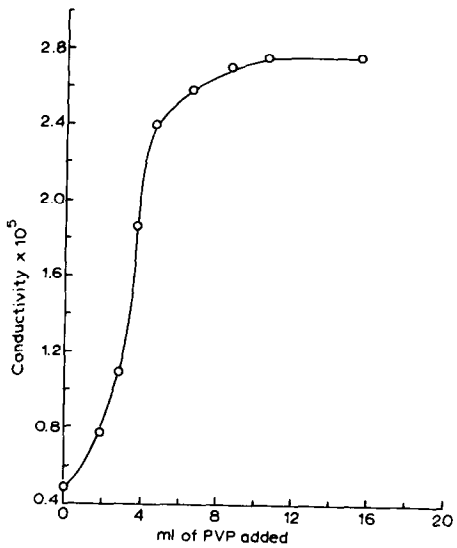

Fig. 2. Conductivity measurements of ibuprofen PVP solutions.

weak acid – weak base interaction between the drug and the polymer.

In an attempt to further study the nature of the interaction between ibuprofen and PVP in solution, the IR spectra of solutions for the drug, PVP and drug–PVP 1 : 1 solution were determined. Fig. 3 shows the spectra obtained. In the region 4000–2000 cm^{-1} (Fig. 3a) the drug shows the aliphatic stretching frequency at 2960 cm^{-1}. This

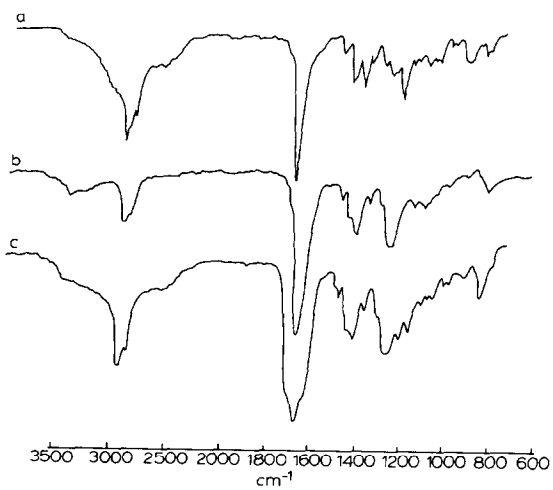

Fig. 3. Solution (CH_2Cl_2) IR spectra of (a) ibuprofen, (b) PVP, and (c) 1 : 1 drug : PVP dispersion.

band has a broad baseline due to the presence of carboxylic OH group which is subjected to an intermolecular hydrogen bonding which was more extensively observed in solid spectra (El-Hinnawi and Najib, 1987). In the same region, Fig. 3b, the polymer exhibits the aliphatic C–H stretching frequency at 2940 cm^{-1} and a broad weak band around 3500 cm^{-1} which could be attributed to the presence of traces of moisture in the polymer. The spectrum of the drug–PVP solution (Fig. 3c) showed the same bands of C–H stretches for the drug and polymer at 2940–2960 cm^{-1} with a very broad baseline covering the range 2400–3500 cm^{-1} indicating the presence of pronounced hydrogen bonding between the drug and the polymer in solution. In the carbonyl frequency region the drug shows a strong band at 1700 cm^{-1} due to the C=O stretch in carboxylic group. The polymer gives a strong band at 1670 cm^{-1} due to the C=O stretch in the cyclic amide. The spectrum of the mixture showed a broad strong band centered at 1670 cm^{-1} with two shoulders at 1700 and 1630 cm^{-1}. In a previous IR study (El-Hinnawi and Najib, 1987) for solid PVP–drug dispersion it was shown that for physical mixture in which there is no hydrogen bonding interaction the carbonyl frequency of the drug appeared as a narrow and separated band from broad C=O stretching band of the polymer, while in the solid dispersion both C=O stretches appeared as a broad strong band due to the possible complex formation most likely through hydrogen bonding. The observation of a broad band with the shoulders in the carbonyl region for PVP–drug mixture might also indicate the PVP–drug interaction through hydrogen bonding in solution. In the low frequency region, 1600–600 cm^{-1} the bands observed in the mixture are almost the same for both the drug and the polymer. This might indicate that the drug molecule, even though it is hydrogen bonded with the polymer through the carboxylic OH group but the total symmetry of the molecule has not been significantly affected.

The nature of the interaction between the drug and the polymer in the solid state was also investigated by X-ray diffraction studies, DSC studies, heat of fusion (ΔH_f) and melting point (m.p.) determination.

The X-ray diffractograms for the drug, PVP, drug–PVP physical mix and drug–PVP dispersion is shown in Fig. 4. Fig. 4a shows the diffraction pattern of the crystalline drug. Very strong reflection peaks are observed at 2θ equal to 16.6, 20.0 and 22.2. Fig. 4b shows the amorphous nature of the polymer. Fig. 4c and d show the diffraction results for the drug–polymer physical mixture and drug–polymer dispersion, respectively. These results indicate that the crystalline nature of the free drug is maintained in the physical mixture, while the dispersion exhibits a totally amorphous glassy nature. Similar results were reported for the nature of the solid dispersion of other drug–PVP

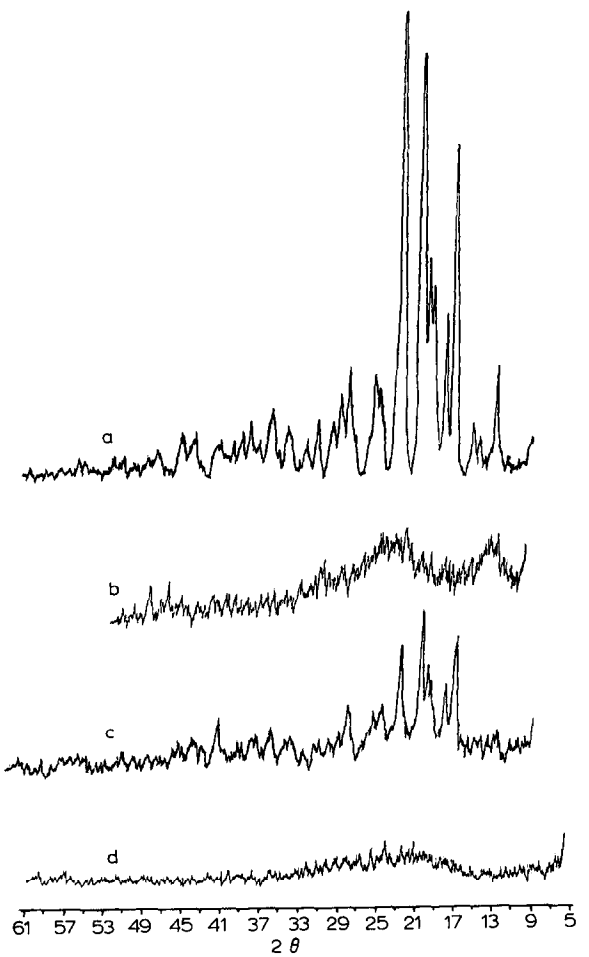

Fig. 4. X-Ray diffration patterns of (a) ibuprofen, (b) PVP, (c) 1:3 drug:PVP physical mixture, and (d) 1:3 drug:PVP dispersion.

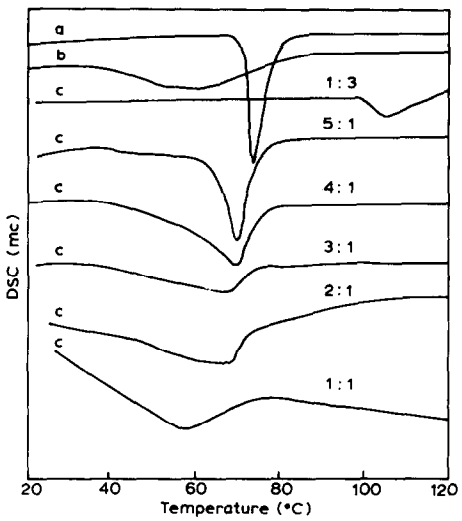

Fig. 5. DSC thermograms of (a) ibuprofen, (b) PVP, and (c) dispersions of different drug : PVP ratios.

systems (Corrigan and Holohan, 1984). X-Ray diffractograms were obtained for other ratios of drug–PVP dispersions, but no detectable difference in crystallinity or amorphousness of the dispersions was noticed. This made it difficult to explain the difference in appearance of the dispersions. The 2 : 1 and 1 : 1 drug : polymer dispersions were more glassy and transparent than the other combinations.

The DSC thermograms of ibuprofen, PVP and ibuprofen–PVP dispersion (1 : 3) were previously reported (Najib et al., 1986). Fig. 5 shows the thermograms obtained for dispersions of different drug : PVP ratios. The thermograms of pure drug and polymer are included in Fig. 5 for reference. It is evident from Fig. 5 that the temperature of the peaks varies with the composition of the dispersion. For the dispersions studied, as the ratio of the ibuprofen to PVP decreases, the melting point decreases (Table 1). ΔH_f was also calculated for these dispersions and found to follow similar pattern (Fig. 6). Fig. 6 shows the relationship between ΔH_f, equilibrium solubility and the composition of the dispersion. It is obvious from the figure that the ΔH_f value decreases as the percentage of the PVP increases until a minimum is reached corresponding to a drug : polymer ratio of approximately 1 : 1. Increasing the percentage of

TABLE 1

The melting points of ibuprofen and ibuprofen PVP solid dispersions of different compositions

Dispersion, drug : PVP	Melting point (°C)
1:0	74.5
5:1	70.4
4:1	69.3
3:1	67.3
2:1	66.6
1:1	59.0

PVP beyond this value results in an increase in ΔH_f.

The solubility plot is opposite in shape to the ΔH_f plot. This is to be expected since the aqueous solubility of a sparingly soluble organic compound is inversely related to its ΔH_f value. Therefore low ΔH_f values are indicative of a high potential energy and a high degree of thermodynamic activity, and hence high solubility. Therefore as shown in Fig. 6, the solubility increases as the percentage of PVP increases and as ΔH_f decreases until a maximum solubility is obtained for dispersions of approximately 1 : 1 drug : PVP, which corresponds to a minimum ΔH_f value. As the percentage of PVP increases beyond 50% the solubility begins to decrease and the ΔH_f value increases.

From the results discussed it can be concluded that a weak acid–weak base salt-like complex is formed from the dispersion of ibuprofen in PVP as indicated from the pH titration and conductivity studies. X-Ray diffraction, IR, and DSC studies were used to characterise such a complex. The

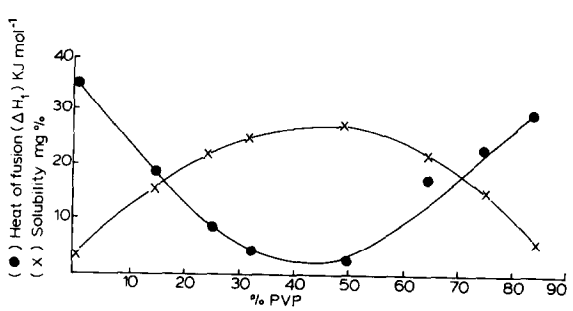

Fig. 6. The relationship between the heat of fusion (ΔH_f), solubility of the dispersions and the percentage of PVP present.

complex formed has the highest solubility in the region of 1 : 1 drug : polymer ratio. This composition also has lower ΔH_f and melting point values than any of the other compositions studied.

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