Interpolymer complexation. I. Preparation and characterization of a polyvinyl acetate phthalate-polyvinylpyrrolidone (PVAP-PVP) complex

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Abstract

Polyvinyl acetate phthalate (PVAP) and polyvinylpyrrolidone (PVP) readily reacted in ethanol and acidic aqueous solutions to produce an insoluble PVAP-PVP complex. The complex has a pK_a of 3.8. It is practically insoluble in common organic solvents, but dissolves in dimethylsulfoxide, an alkali or ammonical solution, and a 4:1 (v/v) mixture of methylene chloride and methanol. The powder X-ray diffraction analysis revealed the complex to be an amorphous material. The Fourier-transform infrared spectrum of the complex exhibited characteristics carbonyl stretching vibrations at 1724 and 1657 cm^{-1} due to phthalate and acetate moieties in PVAP and cyclic amide groups in PVP, respectively, and at 1632 cm^{-1} (appeared as a shoulder) due to cyclic amide groups of PVP bound to PVAP. The proton and carbon-13 (solution and solid-state) nuclear magnetic resonance spectra of the complex showed peak profiles that were linear combinations of those of PVAP and PVP. No new peaks appeared and no change in chemical shifts was observed due to complexation. The spectral data suggest that the interaction between PVAP and PVP probably initially involves the formation of hydrogen bonds between carbonyl groups of PVP and carboxylic groups of PVAP at some point of the polymer chains, causing the hydrophilic parts of the two flexible polymer chains strongly hydrophobic. As a result, the two polymer chains coil up into a compact structure and, consequently, precipitate out from the solution as an insoluble complex. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Polymers are commonly and widely used as excipients in the design and development of a controlled- and/or sustained-release product. Depending on the physicochemical properties, they may serve as a coating material, film-forming agent, drug carrier, granulating agent, tabletting excipient (binder, disintegrant, or filler), and/or solubilizing agent. Often, it is not uncommon to use two or more polymers in a formulation to develop pharmaceutically acceptable product. The

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varied structure and chemistry of various polymers that are available for use in pharmaceutical preparations, however, may render ample opportunity for them to undergo physical and/or chemical interaction in-situ. Such interactions may greatly influence product stability, modify drug release kinetics, and alter drug bioavailability, and/or may pose safety concerns. Satoh et al. (1989) reported that the use of a 3:2 weight ratio of hydroxylpropylcellulose (HPC) and carboxylvinyl polymer (CP) as excipients in tablets significantly decreased the bioadhesion force and greatly affected the drug release. Similar effects were noted by Takayama et al. (1990) with compressed tablets prepared using chitosan and sodium hyaluronate. Tablets prepared using chitosan alone exhibited weak bioadhesive strength, whereas sodium hyaluronate alone and a physical mixture of sodium hyaluronate and chitosan produced tablets with strong adhesive forces. The release of brilliant blue varied with the weight ratios of the two polymers, suggesting the occurrence of an interaction between sodium hyaluronate and chitosan. Recently, the interaction of CP with HPC and sodium carboxymethylcellulose (NaCMC) and its effects on the bioadhesive strength and the release of verapamil have been reported (Gupta et al., 1994). CP reportedly formed a stronger complex with HPC than with NaCMC.

Polyvinylpyrrolidone (PVP, Fig. 1B) is a water soluble, physiologically inert polyamide polymer (Blecher et al., 1980; BASF, 1986; Aldeyeye and Barabas, 1993). It exhibits unusual colloidal and complexing properties, and has been extensively used in pharmacy as a protective colloid, viscosity-enhancing agent, solubility promoter, granulating/tabletting agent, and film-forming material. It has been used to retard/inhibit crystallization of drugs, and is known to forms complexes with many substances, including drugs, polybasic acids such as polyacrylic acid, and phenolic materials. Elgindy and Elegakey (1981), Elegakey and Elgindy (1981) prepared PVP-polyacrylic acid (Carbopol 934, 940, and 941) complexes and demonstrated their use in the development of sustained-release drug products. Studies suggest that hydrogen bonding between carbonyl groups of PVP and the carboxyl groups of polyacrylic acid may be the driving force for the complexation between PVP and polyacrylic acid (Tsutsui et al., 1978; Tsuchida et al., 1980; Saski and Yokoyama 1984). Takayama and Nagai (1987) reported that PVP forms a 1:1 complex with carboxyvinyl polymer. Recently, Gupta et al. (1994) reinvestigated the interaction between Carbopol 934 and PVP. The degree of complexation was found to be higher at low acidic conditions, and decreased with increasing pH of the solution. Compared to the parent polymers, the complex exhibited increased bioadhesive strength and decreased drug release rates. More recently, Bell and Peppas (1996) studied the interaction of poly(methacrylic acid) (PMMA) with polyethylene glycol. They reported that complexation occurred at pH low enough to protonate the acid of PMMA. At high pH, the acid group becomes neutralized and consequently, no complexation occurs.

We have found that PVP also readily interacts with poly vinyl acetate phthalate (PVAP, Fig.

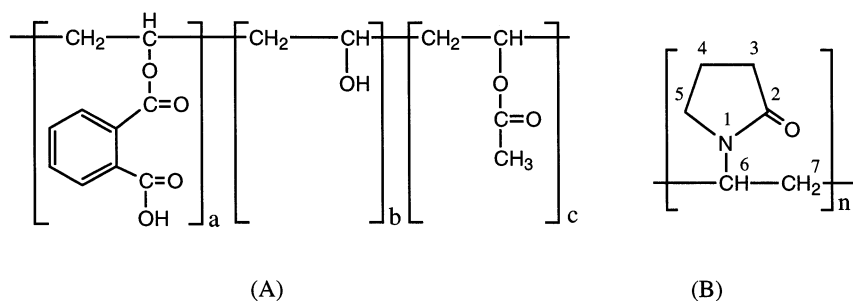(A)   (B)

Fig. 1. Chemical structures of (A) PVAP and (B) PVP.

1A), a commonly and widely used enteric polymer. In this paper, the preparation and characterization of a complex prepared using a 2:1 weight ratio of PVAP and PVP in ethanol and aqueous acidic medium are presented. Unlike PVP, PVAP shows a pH-dependent solubility. It is soluble in methanol, ethanol (95%), and mixed solvent systems such as methanol or ethanol:acetone (1:1), methanol:methylene chloride (1:1), etc. PVAP films have been shown to be much less permeable to water vapor and simulated gastric fluid than those prepared from other enteric polymers such as cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP) (Porter, 1980), and hence, serves as a superior enteric polymer from a stability standpoint.

2. Experimental

2.1. Materials

PVAP, containing 56.6–61.2% phthalyl content (Lot # 3665-B), and PVP K-90 (Lot # 63) were received from Colorcon (West Point, PA, USA) and International Specialty Products (Wayne, NJ, USA), respectively. All other chemicals were reagent grade and used as received.

2.2. Preparation of PVAP-PVP adduct

The following two methods were used:

1. PVAP and PVP were separately dissolved in minimum volumes of ethanol and then mixed in different ratios, corresponding to 4:1, 2:1, 1:1, 1:2, and 1:4 weight ratios of PVAP and PVP. An immediate precipitation of a white gummy solid occurred. The reaction mixture was heated for one hour at boiling temperature and then filtered hot. The gummy solid obtained was extracted with ethanol using a soxhlet extractor and then dried in a vacuum oven.

2. Stock solutions of PVP and PVAP were prepared in minimum volumes of water and a 28% aqueous ammonium hydroxide solution, respectively. Appropriate volumes of the two solutions, corresponding to a 2:1 weight ratio of PVAP and PVP, were then mixed. The pH of the resulting solution was then adjusted to 1.0 with 0.1 N HCl. The white solid precipitated was filtered, washed extensively first with water and then with ethanol, and finally dried under vacuum.

To ensure that the product isolated was not co-precipitate but a complex, the pH of the stock solutions of PVAP and PVP was also adjusted to 1.0. PVAP, being an enteric polymer, precipitated, whereas PVP remained in solution at this pH.

2.3. Characterization methods

2.3.1. Infrared spectroscopy

The Fourier-transform infrared (FT-IR) spectra of products were obtained as KBr pellets on a Nicolet 5DXB infrared spectrophotometer.

2.3.2. Nuclear magnetic resonance (NMR) spectroscopy

The pulse Fourier-transform ^1H and ^{13}C solution NMR spectra of PVAP, PVP and PVAP-PVP complex in deuteriated dimethylsulfoxide (DMSO-d_6) were recorded at 25 or 50°C on a Bruker MSL-300 spectrometer. The identification of methine, methyl, methylene, and quaternary carbon signals in the ^{13}C nmr spectra of the three materials was achieved using the APT (Attached Proton Test) pulse sequence, which afforded methine and methyl carbon signals opposite to that of methylene and quaternary carbons. The spectral width, acquisition time, first pulse, pulse width, relaxation delay time, and spin rate used were 10 000 Hz, 0.496 s (or 0.973 s), 180°, 90°, 5.0 s, and 25 Hz (or 50 Hz), respectively.

The cross-polarization/magic angle spinning (CP/MAS) solid-state ^{13}C nmr spectra of the samples were obtained on a Bruker MSL-300 spectrometer using the true 90° pulse calibration time of 6 μs, the proton transmitter dead time of 2 μs, and the contact time for polarization transfer with Hartmann-Hahn match of 3 μs. The data acquisition time was 29 μs. A spectrum width of about 510 ppm was acquired, but only the region between 0 and 200 ppm was plotted. The number of scans for all spectra was 1200. To discern the spinning side bands, each sample was run at two different spinning rates, 4500 and 5000.
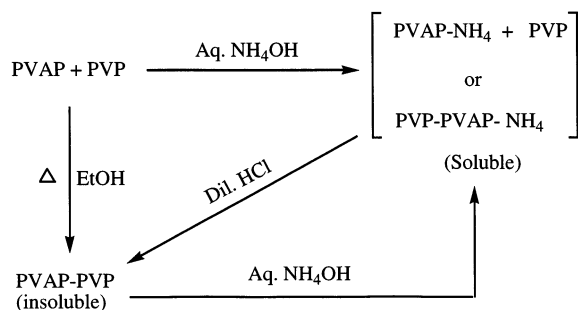
PVAP + PVP →(Aq. NH₄OH)→ [PVAP-NH₄ + PVP or PVP-PVAP- NH₄] (Soluble)

PVAP + PVP →(Δ EtOH)→ PVAP-PVP (insoluble)

Dil. HCl / Aq. NH₄OH

Fig. 2. Preparation of PVAP-PVP complex.

Table 1
Amounts of PVAP and PVP used and the yield of PVAP-PVP complex isolated

PVAP (g)	PVP (g)	PVAP-PVP complex (g)
8.0	2.0	7.0
6.7	3.3	8.7
5.0	5.0	6.5
3.3	6.7	5.5
2.0	8.0	2.9

2.3.3. Thermal analysis

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) were performed using a Perkin Elmer 7 Series Thermal Analysis System under a constant purge of nitrogen over a temperature range of 40–300°C. The heating rate was 5 or 35°C min^{-1}. Prior to running DSC analysis, the system was calibrated using indium (melting temperature 156°C), a reference standard.

2.3.4. Powder X-ray diffraction measurements

The powder X-ray diffraction measurements on PVAP, PVP, and PVAP-PVP complex were conducted on a Philips PW 1710 powder X-ray diffractometer using a monochromatic CuK$_\alpha$ radiation and a scanning rate of 3° 2θ min^{-1} over a 2θ range of 10–35°.

2.3.5. Measurement of apparent pK_a

An accurately weighed amount (about 100 mg) of the PVAP-PVP complex, previously dried at 105°C for 2 h and cooled in a desiccator over calcium chloride desiccant, was suspended in 14

ml of deionized water, and subsequently dissolved by adding drop wise a 0.01 N NaOH solution. The resulting solution was titrated with 0.1 N HCl until a pH of 3 was reached and then back titrated using a 0.1 N NaOH until the solid that precipitated during the base-to-acid titration completely dissolved. The apparent pK_a of the product was determined using the Gran's method (Gran, 1952). The plot of $G^*[H]$ versus G was constructed, where G is given by:

$$G = V_t + \frac{(V_0 + V_t)(\{H\} - \{OH\})_t}{N}$$

where V_t is the titrant volume, V_0 is the original volume, and N is the titrant normality. K_a was obtained from the slope of the plot.

3. Results and discussion

A schematic presentation of the preparation of the PVAP-PVP complex is shown in Fig. 2. PVAP and PVP readily reacted in ethanol to produce an insoluble complex. The yield of the complex was the highest when a 2:1 weight ratio of PVAP and PVP was employed (Table 1). The complex is insoluble in aqueous acidic solutions, but readily dissolves in alkaline media. Acidification of the alkali solution yields the same complex again. The PVAP-PVP complex can also be prepared directly from PVAP and PVP by mixing an ammonical solution of PVAP with an aqueous solution of PVP and subsequently adjusting the pH to 1.0 with a dilute hydrochloric acid solution. Unlike the parent polymers, the complex is practically insoluble in common organic solvents (e.g. ethanol and acetone) but dissolves in dimethylformamide, dimethylsulfoxide, and a 4:1 (v/v) mixture of methylene chloride and methanol. The apparent pK_a of the complex, as determined by the Gran's method (Gran, 1952), is 3.85. It completely dissolves at a pH about 5.8.

The SEM photographs of PVAP, PVP, and PVAP-PVP complex are shown in Fig. 3. PVP particles appear as flakes, whereas PVAP particles were small aggregates. The complex, on the contrary, consisted of large (of 300 μm or greater) agglomerated particles formed during processing

as a result of coalescence of the primary particles' boundaries.

The powder X-ray diffraction patterns of PVAP, PVP, and PVAP-PVP complex, reproduced in Fig. 4, showed diffuse halos, suggesting that the materials are amorphous. The amorphous
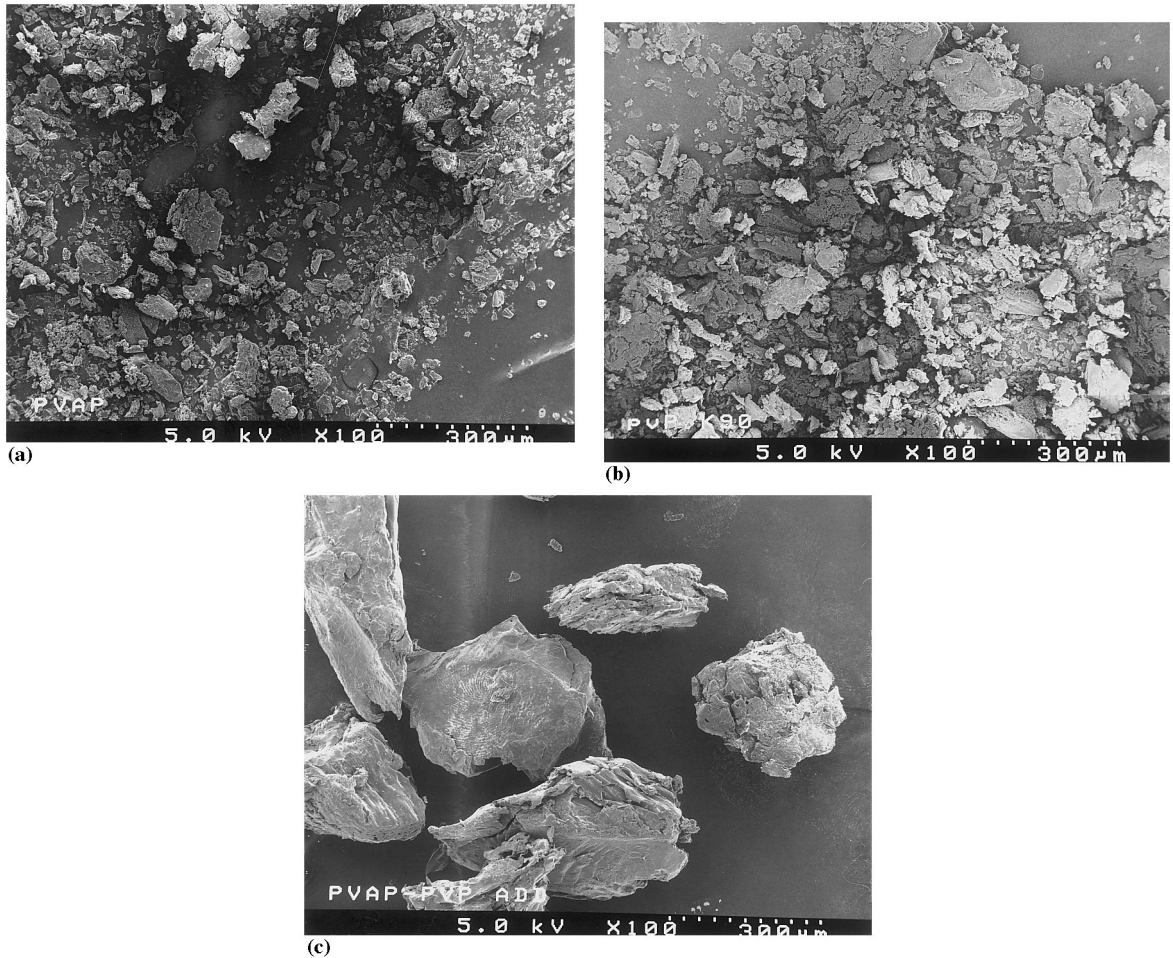

Fig. 3. SEM photographs (A) PVAP; (B) PVP and (C) PVAP-PVP complex (taken on a Hitachi S-4000 scanning electron microscope).
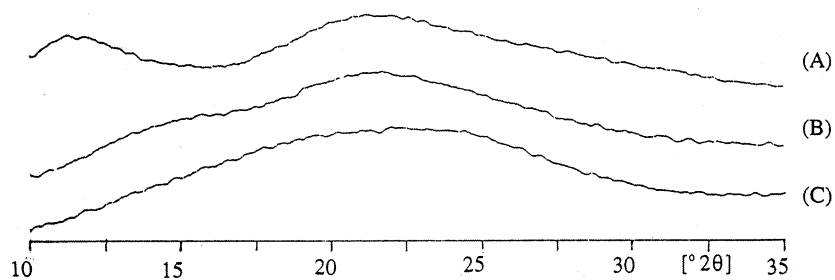

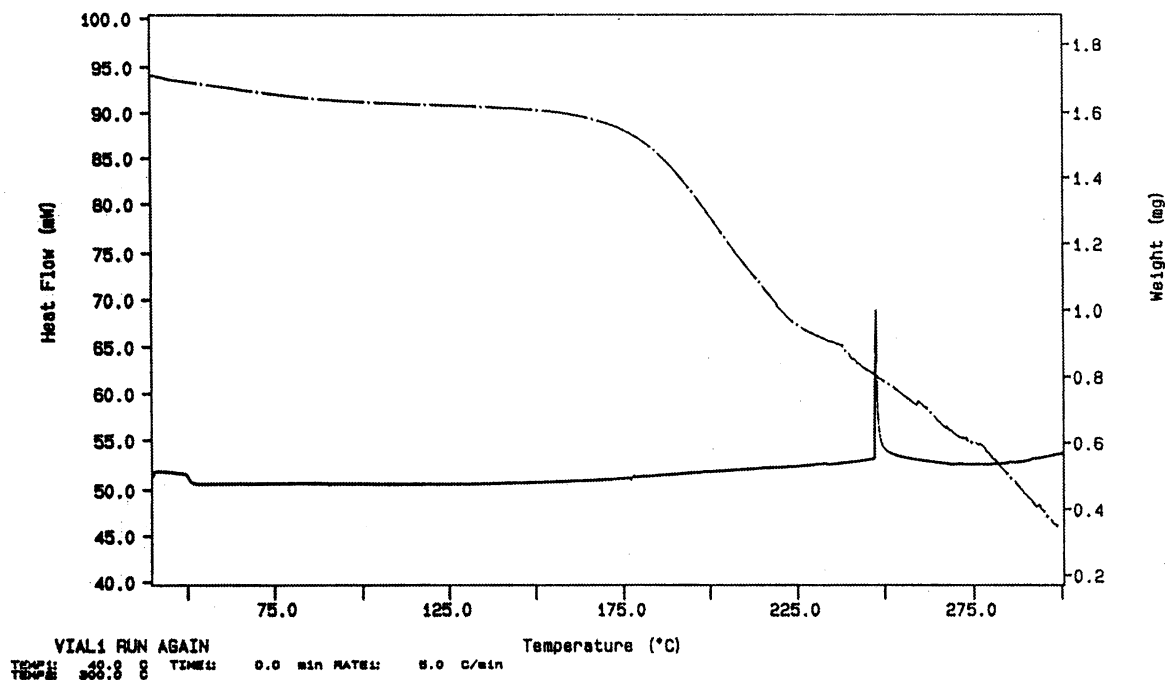Fig. 4. Powder X-ray diffraction of (A) PVP; (B) PVAP-PVP complex, and (C) PVAP.

Fig. 5. TGA and DSC thermographs of PVAP.

halo observed for PVAP had an angular range of $10° 2\theta$–$32.5° 2\theta$ and showed a maximum intensity at $22.5° 2\theta$. In contrast, PVP and the complex each showed two diffuse halos over the $10° 2\theta$–$35° 2\theta$ angular range (PVP: $10°$–$16° 2\theta$ and $16°$–$35° 2\theta$; PVAP-PVP: $10°$–$17.5° 2\theta$ and $17.5°$–$35°$ 2θ), with maximum counts at $11.6° 2\theta$ and $22° 2\theta$, and $13.8° 2\theta$ and $22° 2\theta$, respectively.

The TGA and DSC thermograms of PVAP, PVP, and PVAP-PVP complex obtained at a heating rate of $5°C$ min^{-1} are shown in Figs. 5–7. PVAP and the complex had a moisture content of 5.3 and 3.7%, respectively, whereas PVP contained 15.0% moisture. The endothermic peaks at 246 and $251°C$ for PVAP and the complex appear to be due a decomposition product since both materials exhibited a sharp decline in their weights at about $175°C$. In the case of PVP, the endothermic signal at $206°C$ is due to a solid-solid transition of some kind because (i) the sample showed no weight loss between 125 and $275°C$, and (ii) this peak disappeared when the sample heated to $225°C$ was cooled and reheated. Using a

hot stage microscope, PVP showed an off-white to light yellow coloration at about $246°C$, whereas PVAP and the complex turned dark brown in color at their respective decomposition temperatures.

Dry PVAP and PVP have been reported to exhibit a glass transition temperature (T_g) of $42.5°C$ at a scanning rate of $8°C$ min^{-1} (Porter and Ridgway, 1983) and $177°C$ at a heating rate of $25°C$ min^{-1} (Hancock and Zografi, 1994), respectively. As is evident from Figs. 5–7, no T_g could be detected for three materials at a scanning rate of $5°C$. Attempts to detect T_g using the heating rates reported in the literature and at $35°C$ min^{-1} also failed. In the case PVAP, owing to the presence of 5.3% moisture content, the T_g probably decreased to a value $< 40°C$, the minimum detection temperature range used in the study, and therefore could not be detected. However, for PVP with 15% moisture, according to Oksanen and Zografi (1990), an endothermic peak at about $75°C$ should have appeared. The failure to observe this peak, however, could be due to
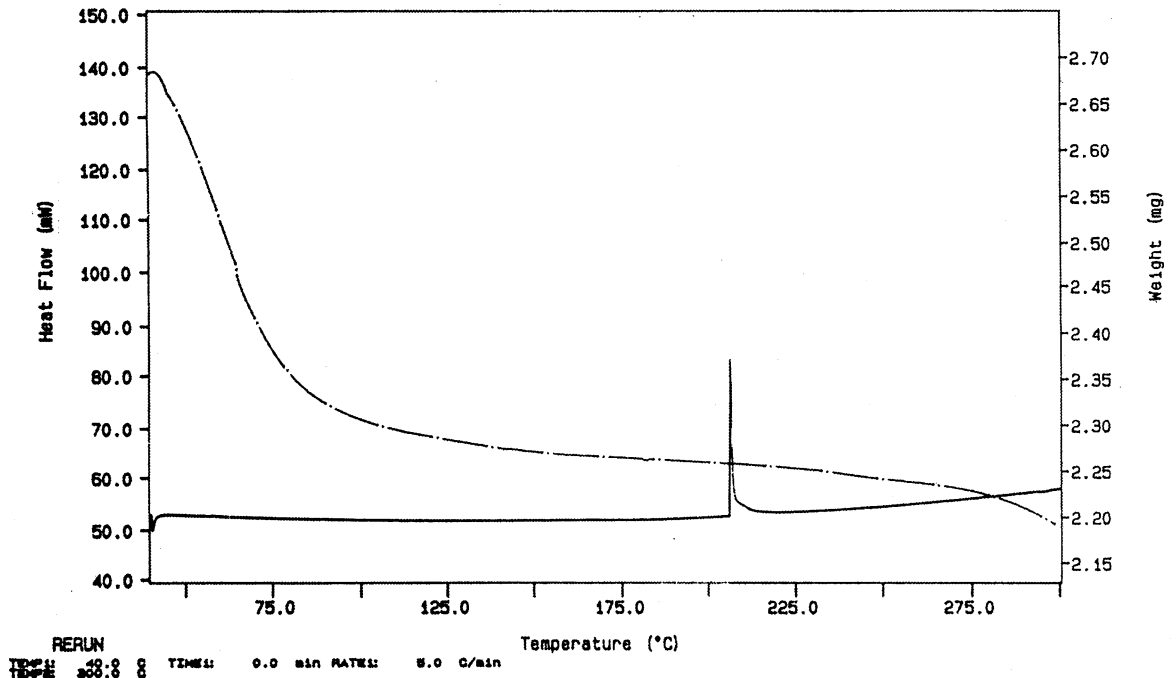
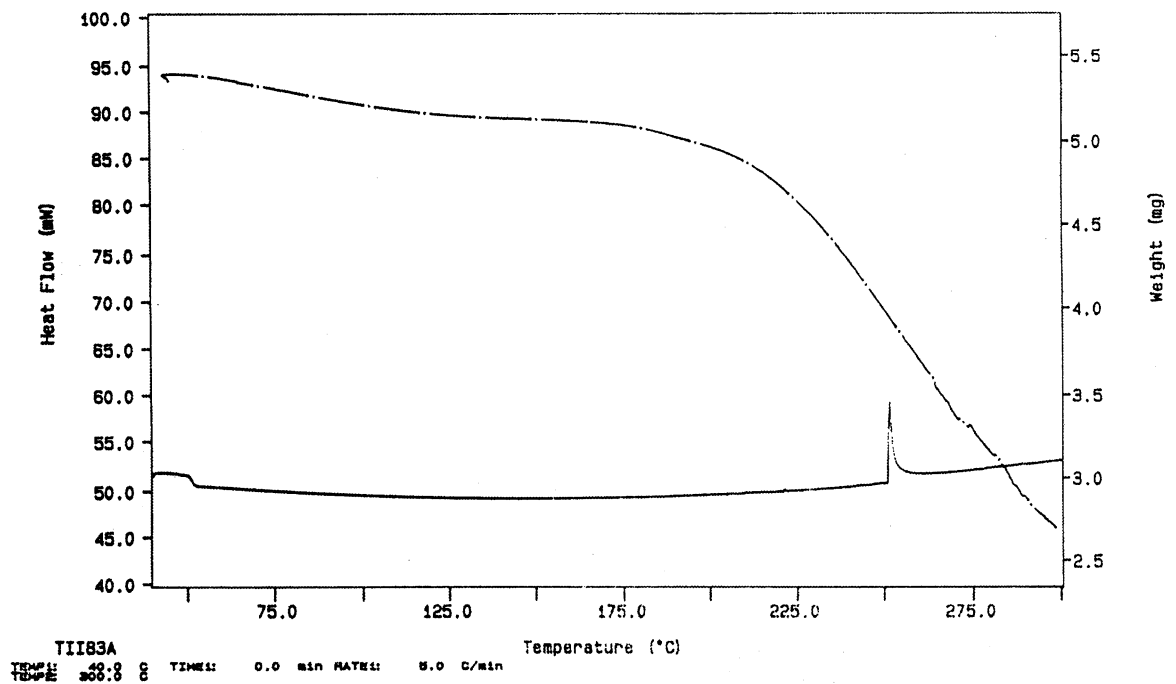Fig. 6. TGA and DSC thermographs of PVP.

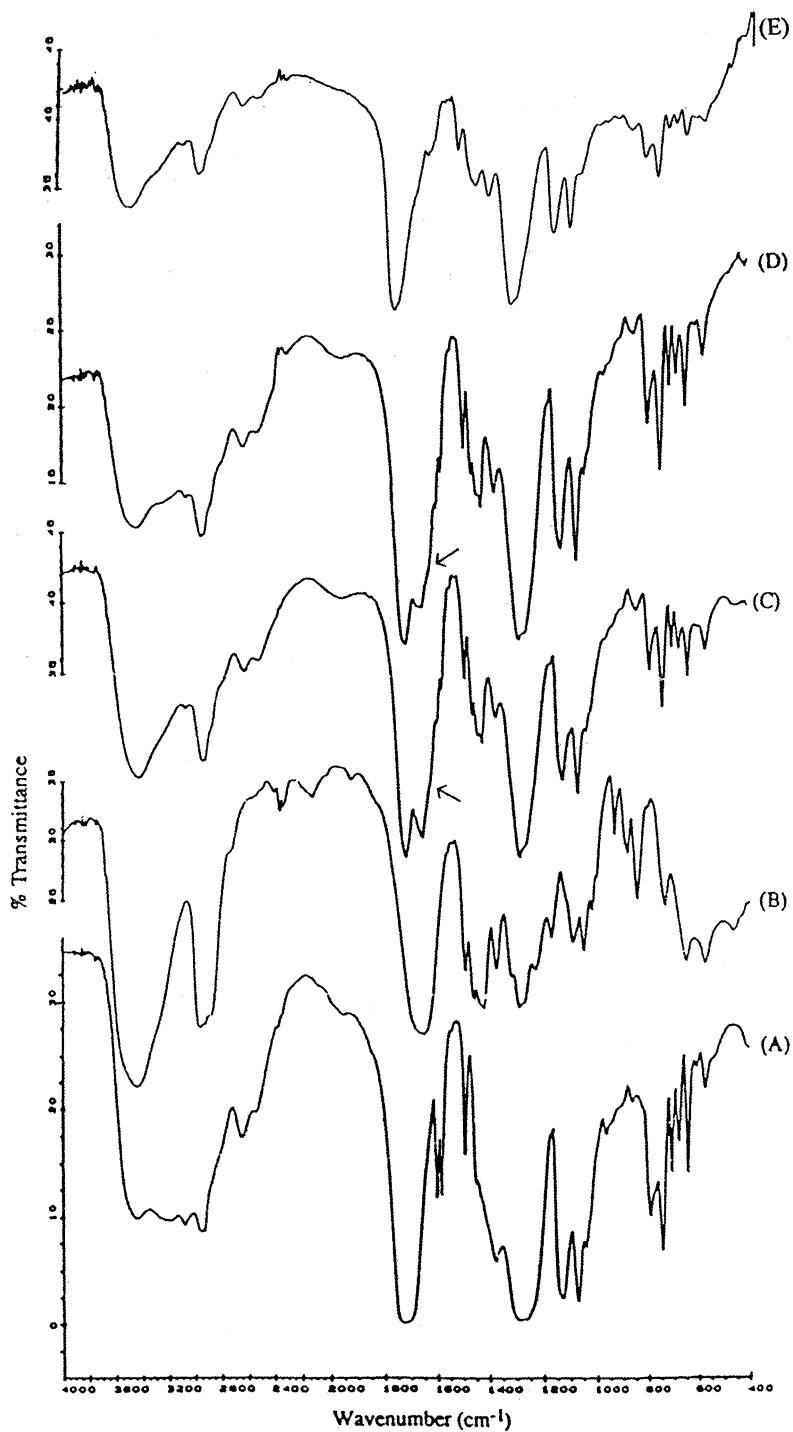Fig. 7. TGA and DSC thermographs of PVAP-PVP complex.

Fig. 8. Infrared spectra of (A) PVAP; (B) PVP; (C) PVP-PVAP complex prepared in water; (D) PVP-PVAP complex prepared in ethanol (arrow points the 1632 cm^{-1} shoulder peak), and (E) 2:1 PVAP-PVP physical mixture.
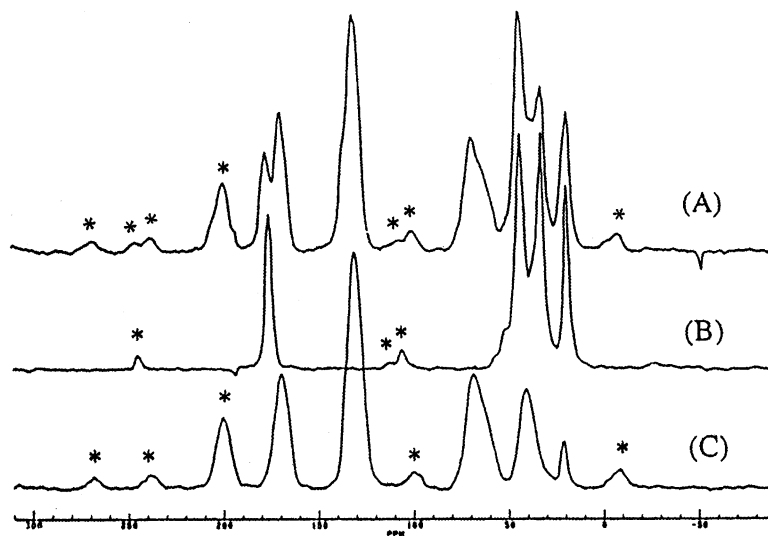
Fig. 9. ^{13}C CP/MAS solid-state NMR spectra of (A) PVAP-PVP complex; (B) PVP and (C) PVAP (* indicates spinning band).

small changes in specific heat involved, inability to attain near-equilibrium conditions during measurement, presence of impurities, and/or the faster rate of temperature change compared to the change in molecular rearrangement (Lee and Knight, 1965; Entwistle and Rowe, 1979; Porter and Ridgway, 1983).

Fig. 8 compares the IR spectra of PVAP, PVP, PVAP-PVP physical mixture (2:1; w/w), and PVAP-PVP adducts prepared in ethanol and in an aqueous acidic medium. In the carbonyl frequency region, PVAP exhibited a strong band at 1723 cm^{-1} and PVP at 1656 cm^{-1}. The former is attributed to carbonyl groups of phthalate and acetate moieties, whereas the latter is due to cyclic amide groups. In contrast, the spectrum of the complex showed two strong bands at 1724 and 1657 cm^{-1} and a shoulder at 1632 cm^{-1}. The first two vibrational bands are obviously due to free carbonyl groups of PVAP and PVP, respec-
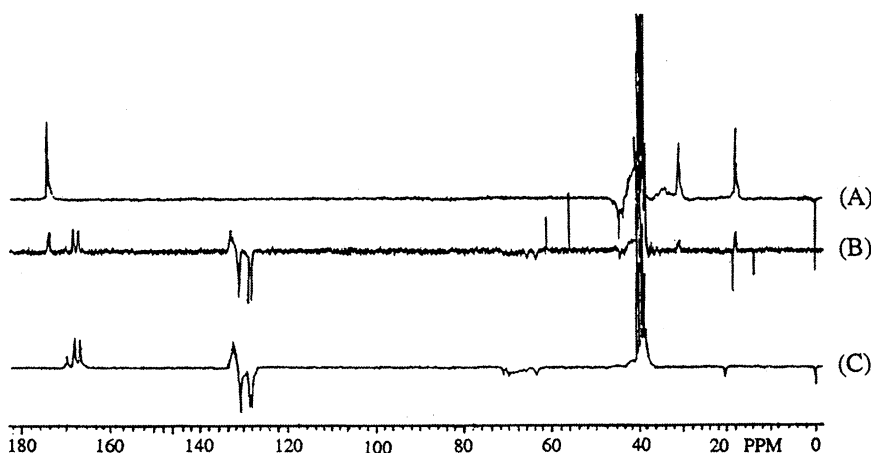

Fig. 10. ^{13}C solution NMR spectra of (A) PVP; (B) PVAP-PVP complex and (C) PVAP.

tively, as observed in the spectra of PVAP and PVP. The shoulder at 1632 cm^{-1} is attributed to carbonyl groups of PVP that formed hydrogen bonds with carboxyl groups of PVAP, in accordance with the assignment reported by Takayama and Nagai (1987) for a PVP-CP complex. The absorption band due to PVAP carboxyl carbonyl groups bound to PVP could not be identified in the spectrum because of the presence of other peaks in the region. The physical mixture, in contrast, showed a single peak at about 1721 cm^{-1}. These results clearly show that the PVAP-PVP complex formed in ethanol and aqueous acidic media is not a physical mixture, instead probably involves the formation of hydrogen bonds between carbonyl groups of PVP and carboxyl groups of PVAP at some point of the polymer chains.

The solid-state CP/MAS and solution ^{13}C NMR spectra of PVAP, PVP, and PVAP-PVP complex are shown in Figs. 9 and 10, respectively. Both solution and solid-state NMR spectra of the complex showed peaks that were linear combinations of those observed in the spectra of PVAP and PVP. There were no new peaks in the spectrum of the complex, and no significant change in intensity, position, or shape of the peaks occurred. According to the additive rules for predicting ^{13}C chemical shifts (Brown 1985), the ester carbonyl carbons and carboxylic acid carbons should appear in the region from 167 to 172 ppm. Thus, the peak at 170 ppm in the ^{13}C solid-state spectrum of PVAP is assigned to carbonyl carbons belonging to both ester and free carboxylic groups in PVAP, whereas the peak at 177 ppm is due to cyclic amide carbonyl carbons. The signal at 137 ppm corresponds to the phthalyl aromatic carbons, whereas peaks at 18, 34, 45, and 65 ppm are attributed to methylene and methine carbons of the vinyl backbone and pyrrolidone ring. The chemical shifts, along with their assignment, for various carbons in the solution ^{13}C NMR spectra of PVP, PVAP, and the complex in dimethylsulfoxide-d$_6$ are listed in Table 2. As was observed with the solid-state ^{13}C NMR spectrum, the solution NMR spectrum of the complex also showed no change in chemical shifts with respect to those observed in the spectra of PVAP and PVP. These

Table 2
^{13}C Chemical shifts of PVAP, PVP, and PVAP-PVP complex

Chemical shift (δ, ppm)			Assignment[a]
PVP	PVAP	PVAP-PVP	
17.9	–	17.9	–^{4}CH$_2$– (pyrrolidone ring)
–	20.6	20.6	–CH$_3$ (acetyl)
30.9	–	30.9	–^{3}CH$_2$– (pyrrolidone ring)
38.4	–	38.5	–^{5}CH$_2$– (pyrrolidone ring)
[b]	–	[b]	–^{7}CH$_2$– (vinyl polymer)
–	41.0	41.0	–CH$_2$– (vinyl backbone)
44.5		44.5	>^{6}CH– (pyrrolidone ring)
	63.7	63.7	–CH–OH (vinyl backbone)
	69.9	69.9	>CH– (vinyl backbone)
	128.1	128.1	>CH– (phenyl ring)–
	128.5	128.6	>CH– (phenyl ring)–
	130.4	130.5	>CH– (phenyl ring)–
	130.6	130.7	>CH– (phenyl ring)–
	132.3	132.3	>C= (phenyl ring quaternary carbons)
	132.4	132.4	>C= (phenyl ring quaternary carbons)
	166.7	166.7	–COOH (phthalyl)
	167.9	167.8	–C(O)O (acetyl)
	169.6	169.6	–C(O)O (phthalyl)
173.5	–	173.5	–^{6}C(O)– (cyclic amide)

[a] See Fig. 1 for structure and numbering scheme.
[b] Signals masked due to NMR solvent.

results suggest that either the complex dissociates and exists as PVAP and PVP in dimethylsulfoxide or the complexation between PVAP and PVP is weak and the carbonyl carbons involved in interaction remain magnetically equivalent.

The ^{1}H NMR spectra of PVAP, PVP, and the complex are shown in Fig. 11. The ^{1}H NMR spectrum of PVP has been reported by Aldeyeye and Barabas (1993). Thus, by analogy, the cluster of proton signals appearing in the region between δ 1.2 ppm and δ 2.4 ppm in the spectrum of PVP was attributed to polyvinyl methylene protons (H-7) and those located on C-2 and C-3 in the pyrrolidone ring (Fig. 1B). The signals due to
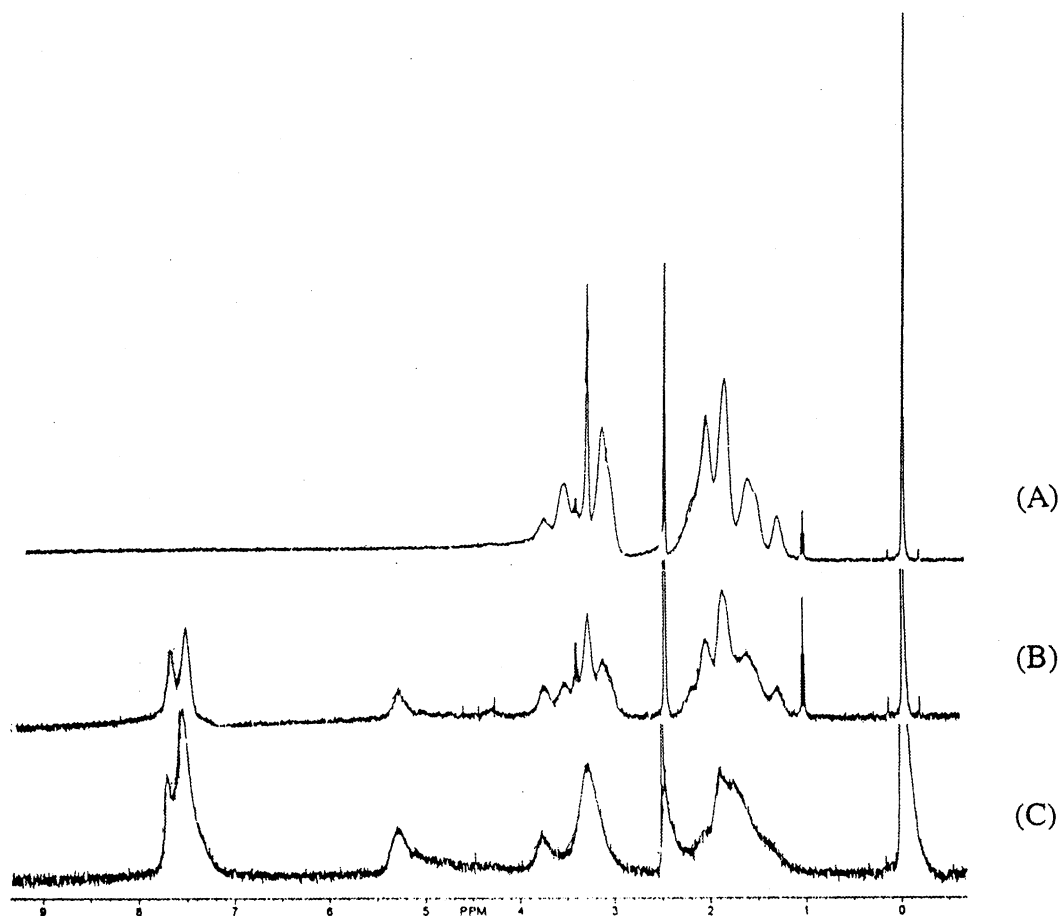
Fig. 11. ^{1}H NMR spectra of (A) PVP; (B) PVAP-PVP complex, and (C) PVAP in DMSO-d$_6$ at 50°C

methylene protons (H-5) bonded to carbon located next to the nitrogen atom in the PVP ring and polyvinyl methine proton appear in the region δ 2.9–4.0 ppm. In the spectrum of PVAP, the peaks centered at δ 7.5 ppm corresponded to the phthalyl protons, whereas polyvinyl methine protons appeared at δ 7.5 ppm. The peak at δ 5.2 ppm is attributed to the hydroxyl proton bonded to the vinyl backbone. As was observed with the solution and solid-state ^{13}C NMR spectra of the complex, the ^{1}H NMR also did not show any change in the chemical shifts.

4. Conclusions

The results presented show that PVAP and PVP readily reacts in ethanol and acidic aqueous solutions to produce an insoluble, amorphous complex. The appearance of a shoulder at 1632 cm^{-1} in the infrared spectrum of complex suggests that the interaction between PVP and PVAP initially involves the formation of hydrogen bonds between carbonyl group of PVP and carboxylic group of PVAP at some point of the polymer chains. This makes the hydrophilic parts of the two flexible polymer chains strongly hydrophobic, causing the polymer chains to coil up into a compact structure and, consequently, precipitate out from the solution as an insoluble solid. The solution and solid-state ^{13}C NMR spectra of the complex showed peak profiles that were linear combinations of those of PVAP and PVP, further lending support to the formation of a weak PVAP-PVP complex.

An investigation to produce palatable drug granules suitable for use in the preparation of chewable tablets using this in-situ complexation between PVAP and PVP is in progress. The preliminary data show that the entrapment by this method is nearly quantitative and result in partial amorphinization of drugs.

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