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RESEARCH PAPER

Increasing the Aqueous Solubility of Acetaminophen in the Presence of Polyvinylpyrrolidone and Investigation of the Mechanisms Involved

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ABSTRACT

It was shown that the aqueous solubility of acetaminophen in the presence of polyvinylpyrrolidone (PVP) increased. The solubility at 25°C increased from 14.3 mg mL^{-1} in the absence of PVP, to 19.7 mg mL^{-1} in the presence of 4% w/v PVP, and to 26.7 mg mL^{-1} in the presence of 8% w/v PVP. Dialysis studies indicated that there is a potential of binding between PVP and acetaminophen in their aqueous solutions. Dialysis studies also revealed that the nature of interaction between PVP and acetaminophen is physical and reversible, and there was no strong binding between PVP and acetaminophen in their solutions. Infrared spectroscopy of acetaminophen/PVP solid dispersion indicated that the mechanism of interaction between PVP and acetaminophen is via hydrogen bonding. Therefore, the increase in solubility of acetaminophen in the presence of PVP is probably attributed to its ability to form a water-soluble complex with PVP.

Key Words: Acetaminophen; Polyvinylpyrrolidone; Solubility; Dialysis equilibrium; Complex formation; Infrared spectroscopy.

INTRODUCTION

There are some reports in pharmaceutical journals indicating the effect of polyvinylpyrrolidone (PVP) on the solubility of active substances. It has been reported that the aqueous solubility of trimethoprim increased 10 times in the aqueous solutions of 70% w/v PVP 40,000.[5] The solubility of naproxen increased by more than 6-fold in the presence of 10% w/v PVP 25,000.[1] In all cases, the increase in solubility of active substances in the presence of PVP has been attributed to their ability to form water-soluble complexes with PVP.

The objectives of the present study was first to investigate the effect of PVP on the aqueous solubility of acetaminophen and second to predict the possible interactions between PVP and acetaminophen.

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MATERIALS AND METHODS

Acetaminophen ($C_8H_9NO_2$) (*p*-hydroxyacetanilide) was obtained from Sterling Organics (Northumberland, UK). PVP as tradename Kollidon 30, with an average molecular weight of 50,000, was obtained from BASF (Aktiengesellschaft, Ludwigshafen, Germany). Anhydrous theophylline was obtained from BASF (Cheadle, Cheshire, UK). Absolute ethanol containing not less than 99.5% v/v C_2H_5OH was obtained from Hyman Ltd. (Witham, Essex, UK).

Determination of Acetaminophen Solubility in the Presence of PVP

To determine the aqueous solubility of acetaminophen in the presence of PVP, the following procedure was carried out. Samples of acetaminophen (3.5 g) were dispersed in 100 mL of freshly distilled water or aqueous solutions containing 0.5, 1, 2, 4, or 8% w/v PVP in stoppered 100-mL conical flasks. The flasks were shaken in a shaking water bath at $25 \pm 1^{\circ}C$ for a maximum of 48 hr. After 24 and 48 hr, the acetaminophen concentration was determined by spectrophotometry at 244 nm, in filtered solutions after appropriate dilution, using a calibration curve previously obtained. Aqueous PVP solutions had no absorbance above 240 nm; therefore, the presence of PVP in acetaminophen solutions did not interfere with the UV absorbance of acetaminophen at 244 nm.

Equilibrium Dialysis

Equilibrium dialysis was used to determine the interaction between acetaminophen and PVP in aqueous solution. Visking tube no. 5-24/32 (Medicell International, London, UK) with a molecular weight cutoff of 12,000 Da was used. Solutions containing PVP (4 or 8% w/v) were prepared by dissolving PVP in distilled water containing 1×10^{-2} M acetaminophen. Ten milliliters of these solutions were poured into dialysis tubes that previously had been prepared. A double knot had been tied at each end of the tube. The distance between two knots was about 11 cm in all experiments. Checks were made to ensure that the tubes did not leak. Each tube was immersed into the USP dissolution flask containing 1,000 mL of distilled water at $37 \pm 1^{\circ}C$, and the solution was stirred at 50 rpm using the USP apparatus II (paddle). The amounts of acetaminophen in solution surrounding the dialysis tube were determined, spectrophotometrically at 244 nm, every hour for up to 15 hr. Experiments were carried out in triplicate for each variable, and the mean values were reported. The same experiment was also carried out for theophylline. The amount of theophylline released from the dialysis tube was determined spectrophotometrically at 272 nm.

Preparation of Acetaminophen-PVP Solid Dispersion (Coevaporate)

A coevaporate of acetaminophen/PVP (1:2) was prepared by dissolving acetaminophen (2 g) and PVP (4 g) in 60 mL ethanol. This solution was then heated in a vacuum oven at $50 \pm 1^{\circ}C$ for 24 hr to evaporate the solvent. The produced crust was scrapped off, ground, and stored in a desiccator before use.

Infrared Spectroscopy

The infrared (IR) spectra of untreated acetaminophen and the 1:2 acetaminophen/PVP coevaporate were obtained using a Perkin Elmer FTIR 1600 spectrophotometer (Norwalk, CT) and potassium bromide disks.

RESULTS AND DISCUSSION

Solubility of acetaminophen in the presence of different amounts of PVP is illustrated in Fig. 1. The results after 24 or 48 hr were exactly the same, indicating the equilibrium has been achieved after 24 hr. It is obvious that PVP has a major effect on the solubility of acetaminophen. An increase in PVP concentration increased the solubility of acetaminophen. The solubility at $25^{\circ}C$ increased from 14.3 mg mL^{-1} in the absence of PVP, to 19.7 mg mL^{-1} in the presence of 4% w/v PVP, and to 26.7 mg mL^{-1} in presence of 8% w/v PVP. In fact, the solubility of acetaminophen in the presence of 8% w/v PVP increased more than 1.87 times.

There are some reports indicating the increase in solubility of some drugs in the presence of PVP. It has been reported that the aqueous solubility of trimethoprim increased from 0.4 mg mL^{-1} in water to more than 4 mg mL^{-1} in the aqueous solutions of 70% PVP

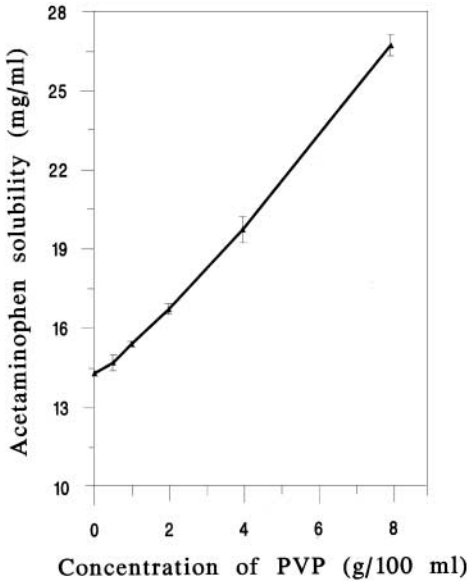

Figure 1. Effect of concentration of PVP on the aqueous solubility of acetaminophen.

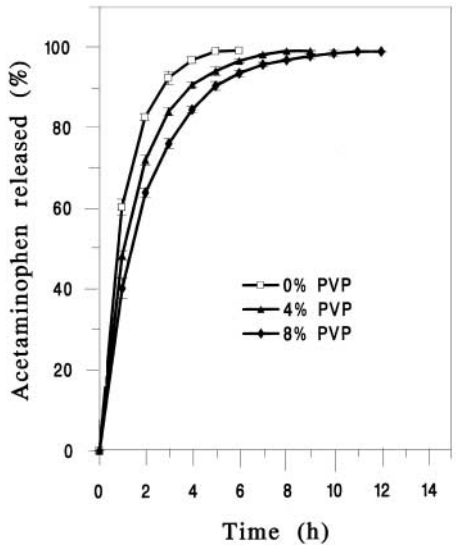

Figure 2. Passage of acetaminophen through the dialysis tube in the absence or presence of PVP.

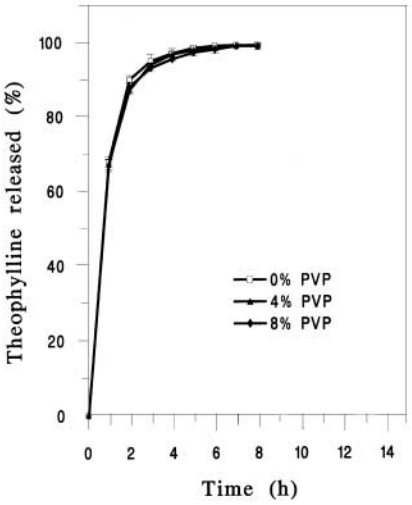

Figure 3. Passage of theophylline through the dialysis tube in the absence or presence of PVP.

40,000.[5] Cadwallader and Madan[2] reported that PVP significantly increased the aqueous solubilities of testosterone, progesterone, and diethylstilbestrol. The increase in solubility of these drugs in the presence of PVP was attributed to their ability to form water-soluble complexes with PVP.[2] Bettineti et al.[1] reported that the solubility of naproxen increased by more than 6-fold in the presence of 10% w/v of PVP 25,000. Tros-De-Ilarduya et al.[13] reported that solubility of sulindac was increased in the presence of PVP, and it was dependent on PVP concentration.

Equilibrium dialysis was used to determine the interaction between acetaminophen and PVP in aqueous solution. Dialysis membranes are thin films of highly polymerized substances (such as cellulose) that, in the presence of solvents, swell to form a molecular sieve where pores will retain polymer molecules with large molecular weights, but allow the diffusion of small molecules. Therefore, the drug molecules bound to the polymer do not pass through the tube membrane and remain inside the tube; only the unbound drug molecules pass through the membrane.[8]

The results of dialysis studies are presented in Fig. 2. It is obvious that PVP had a retardant action on the diffusion of acetaminophen from the dialysis tube, and this effect was dependent on the concentration of PVP in the solution. The slower release of acetaminophen from the dialysis tube in the presence of PVP may be attributed to a binding propensity between PVP and acetaminophen.

As a control study, the dialysis test was carried out using theophylline in place of acetaminophen. It has been reported that there is no binding affinity between PVP and xanthin derivatives, such as theophylline or caffeine.[6,15] The release of theophylline through the dialysis tube in the absence or presence of PVP is illustrated in Fig. 3. It is obvious that PVP had no effect on the release of theophylline

through the dialysis tube. Therefore, because there was no influence of PVP on the passage of theophylline compared with acetaminophen, the results of this part of the study suggest that there is a potential for bonding between PVP and acetaminophen.

Interaction of PVP in aqueous solution with various pharmaceutical agents has been investigated during the past years and it was found that PVP has a great tendency to bind with some drugs and preservatives. One of the most widely used methods to examine this kind of interaction is equilibrium dialysis. Plaizier-Vercammen and De Neve[9–11] showed there was an interaction between PVP with some aromatic compounds, such as benzoic acid and its derivatives in aqueous solutions using equilibrium dialysis and ultrafiltration. These workers showed that the increase in the concentration of PVP in solution increased the percentage of drug bound to PVP. Horn and Ditter[6] demonstrated that there is a binding affinity between PVP 49,000 and several drugs, using chromatographic technique and equilibrium dialysis.

The results of equilibrium dialysis in the present study (Fig. 2) indicated that acetaminophen concentration inside and outside the dialysis tube reached equilibrium after a long period (12 hr), and 99% of acetaminophen was released from the dialysis tube. This clearly shows that there was no strong binding between PVP and acetaminophen. In fact, these results revealed that the nature of interaction between PVP and acetaminophen is physical and reversible, and there is probably an equilibrium state between the amount of bound acetaminophen and free acetaminophen in the presence of PVP inside the dialysis tube as shown below:

$$\text{acetaminophen} + \text{PVP} \longleftrightarrow \text{acetaminophen} - \text{PVP}$$

The IR spectra for acetaminophen and for the 1:2 acetaminophen/PVP coevaporate are illustrated in Figs. 4 and 5, respectively. The IR spectrum of untreated acetaminophen (Fig. 4) shows a sharp band at 3,325 cm^{-1} due to O–H stretching, but this sharp peak has changed to a broad band in the coevaporate (Fig. 5). This may be attributed to the hydrogen bonding between the hydroxyl group of acetaminophen and the carboxyl group of PVP. To enhance the resolution of the vibrations in the IR spectrum of PVP–acetaminophen coevaporate, the vibration due to PVP was removed by spectral subtraction using the Fourier transform computer as reported by Doherty and York.[4] The resultant spectrum is shown in Fig. 6. This analysis shows that the O–H vibrations in acetaminophen had been significantly shifted to lower frequencies, which again

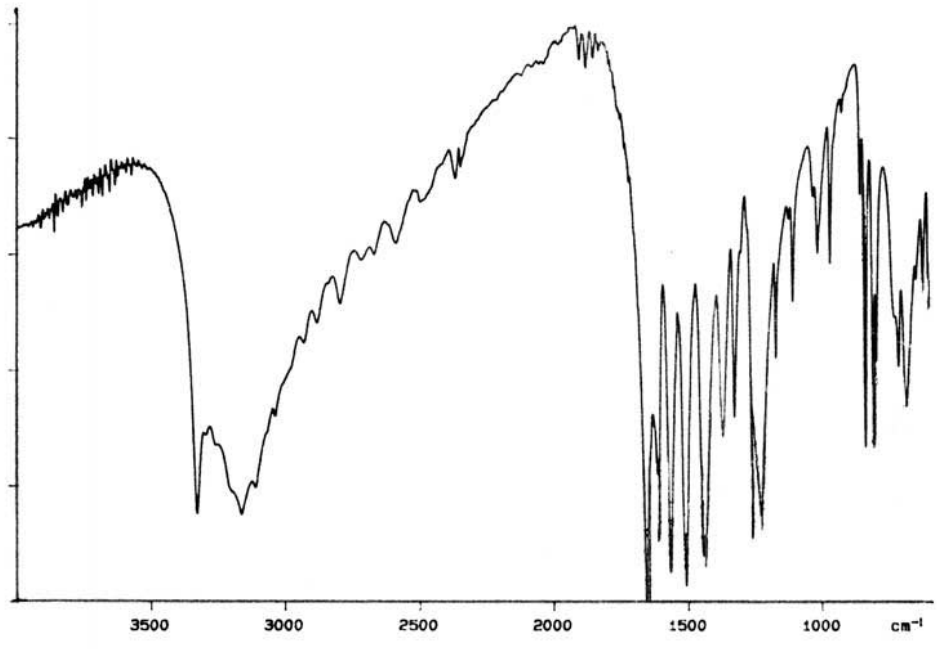

Figure 4. IR spectrum of pure acetaminophen.

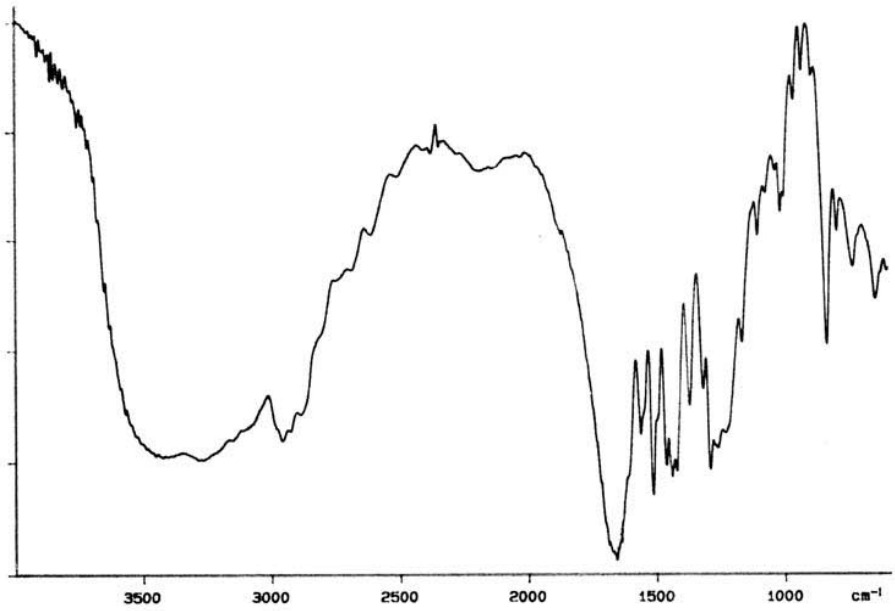

Figure 5. IR spectrum of 1:2 coevaporate of acetaminophen and PVP.

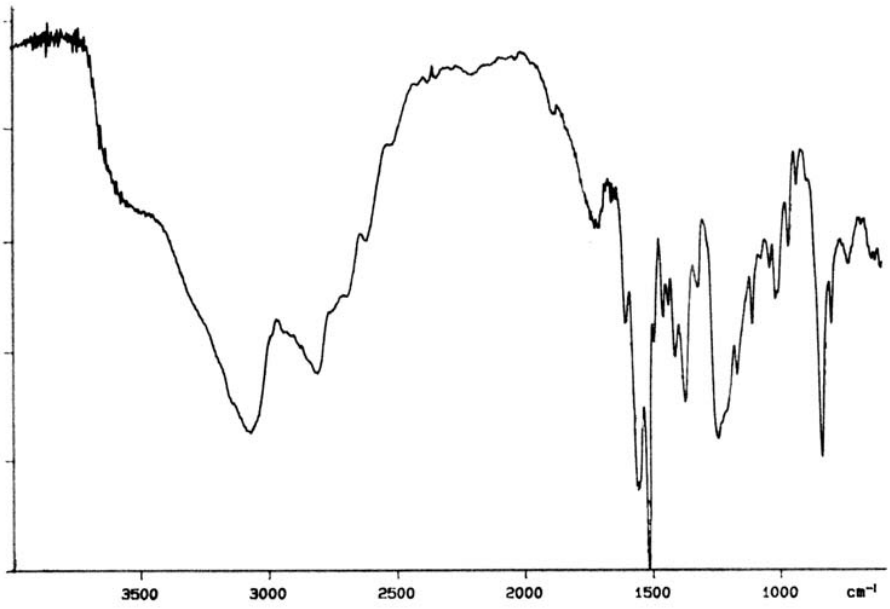

Figure 6. IR spectrum of 1:2 coevaporate of acetaminophen and PVP after subtraction of the PVP spectrum.

proves the formation of hydrogen bonding between PVP and acetaminophen.

De Villiers et al.[3] used a powder x-ray diffraction technique to quantify the relative amount of crystalline acetaminophen in coprecipitates of acetaminophen–PVP prepared by different methods and different solvents. They showed that the crystallinity of acetaminophen only decreased in coprecipitates in which both acetaminophen and PVP were soluble or partially soluble in the solvent used,

such as ethanol or water. As was shown in this study, acetaminophen and PVP bind together in their solutions via formation of hydrogen bonding. This is probably responsible for the formation of amorphous solid solution in their coevaporate, as reported by De Villiers et al.[3]

It has been shown that temazepam and PVP interact via formation of the hydrogen bond between the OH of temazepam and the C=O of PVP, using IR spectroscopy.[14] Tantishaiyakul et al.[12] demonstrated the presence of intermolecular hydrogen bond between piroxicam and PVP in their solid dispersion, using IR spectroscopy. Matsumaru et al.[7] demonstrated a weak hydrogen bond between the C(21)-hydroxyl group of ajmaline and the carboxyl group of PVP, in their coprecipitate, using nuclear magnetic resonance spectroscopy. Doherty and York[4] investigated the interactions between fursemide and PVP in a solid dispersion system using IR spectroscopy. They showed the existence of hydrogen bonding between the sulfonamide group in fursemide and PVP. Nuclear magnetic resonance data confirmed IR results.

The IR studies of acetaminophen/PVP coevaporate in this study demonstrated that acetaminophen and PVP interact via hydrogen bonding. This is expected because PVP contains a recurring carboxyl group, which allows it to hydrogen bond with the hydroxyl group of acetaminophen.

CONCLUSIONS

This study revealed that the aqueous solubility of acetaminophen in the presence of PVP increased. The solubility at 25°C increased from 14.3 mg mL^{-1} in the absence of PVP, to 19.7 mg mL^{-1} in the presence of 4% w/v PVP, and to 26.7 mg mL^{-1} in the presence of 8% w/v PVP. Dialysis studies indicated that there is a potential of binding between PVP and acetaminophen in their aqueous solution. Dialysis studies also revealed that the nature of interaction between PVP and acetaminophen is physical and reversible, and there was no strong binding between PVP and acetaminophen in their solutions. Infrared spectroscopy of acetaminophen/PVP coprecipitate indicated that the mechanism of interaction between PVP and acetaminophen is via hydrogen bonding. Therefore, the increase in solubility of acetaminophen in the presence of PVP is probably attributed to its ability to form a water-soluble complex with PVP.

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