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Solid state interaction of bromazepam with polyvinylpyrrolidone in the presence of moisture

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Solid state interactions involving drug and excipient may give rise to problems which are not immediately obvious or anticipated. The advent of such sophisticated analytical techniques as X-ray diffraction, differential scanning calorimetry (DSC) and high-pressure liquid chromatography (HPLC) have enabled researchers to detect active drug–excipient interaction far easier than ever before and it is common practice for all leading drug companies to embark on a rigorous preformulation programme to ensure compatibility of active ingredients and excipient(s).

While a drug product displaying a drug–excipient interaction may give rise to such deleterious effects as increased toxicity or reduced potency, there may be occasions that such interactions realise beneficial results, e.g. the coprecipitation of polyvinylpyrrolidone (PVP) with sparingly soluble drugs has resulted in superior in-vitro profiles accompanied by enhanced in-vivo absorptivities when compared to the active drug alone (Mayersohn and Gibaldi, 1966).

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Difficulties in formulating a new pharmaceutical dosage form have often been experienced because of such interactions. A literature survey indicates that interactions involving the formation of complexes in aqueous solutions have been studied extensively. Relatively few studies have been carried out on the solid state. This is probably because solid-state reactions are usually complicated by numerous parallel and consecutive reactions. A number of reports indicate delay in absorption (El-Masry and Khalil, 1974; Moriguchi and Kaneniwa, 1969; Nogami et al., 1969) or inactivation of for example preservatives as a result of adsorption onto solids commonly used in pharmaceutical dosage forms (McCarthy, 1969; Khalil and Nasipuri, 1973). Binding of oxymorphone to cross-linked disintegrants and interactions resulting from powder mixing and their effects on in vitro dissolution rate have also been reported (Chien et al., 1981; Chowhan and Chi; 1986).

The therapeutic response of any solid dosage form depends not only on the amount of active ingredient present but also on its availability to the patient once administered. Consequently, a

study of the solid state drug–excipient interactions is of prime importance. During preformulation studies of a bromazepam tablet in our laboratory, a number of excipients were investigated and extensive binding was noted between bromazepam and PVP in the presence of moisture.

Adsorption of bromazepam by PVP was determined at 25 °C by a method similar to that used by Sorby (1965) and Khalil and Moustafa (1973).

Chosen quantities of drug and polymer were accurately weighed on an analytical balance, thoroughly triturated and stored at room temperature for 7 weeks. Appropriate dilutions of the dissolved samples were made and magnetically stirred prior to final measurements on a UV spectrophotometer. Freshly prepared mixtures were used as controls.

The results were plotted according to the Freundlich equation:

$$\log(x/m) = \log K + \frac{1}{n} \log C_{EQ}$$

where C_{EQ} is the equilibrium concentration of bromazepam free in solution, x/m is the amount of bromazepam adsorbed by the quantity of adsorbent used in the investigation, and K and n are constants. The values of the Freundlich constants, K and n, were obtained from the intercept and slope of a regression line calculated by the method of least squares from the experimental data. Results of these studies are presented in Fig. 1.

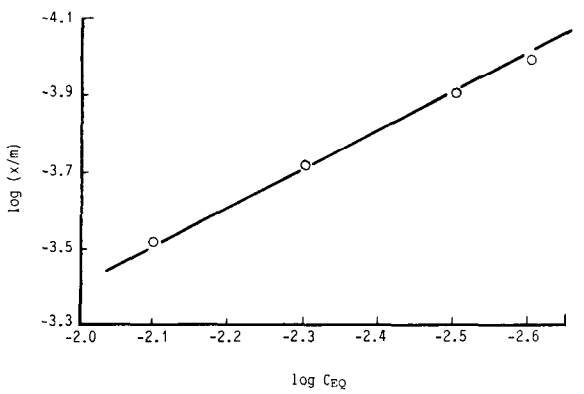

Fig. 1. Freundlich isotherm for adsorption of bromazepam at 25 °C by PVP; $K = -1.900$, $n = 1.204$ and $r = 0.993$.

The binding of bromazepam to PVP followed the Freundlich adsorption isotherm as shown in Fig. 1. It was found that the binding was sensitive to variation in solution pH and temperature. The aqueous solubility of bromazepam decreased with an increase in pH. The intrinsic dissolution rate measurements were conducted at pH 2 and 6 and found to be 0.41 and 0.012 mg/cm^2/min, respectively.

Several consequences of adsorption are possible, and from the results obtained it seems that significant amounts of bromazepam are lost either by physical complexation or activated adsorption. Thus the in vivo concentration of drug presented to the absorbing surfaces will be considerably less than when the same amount of drug is administered in simple solution. While adsorption of active components to insoluble cross-linked excipients could be anticipated, binding of drug of PVP needs further investigation. Dispersions of drugs

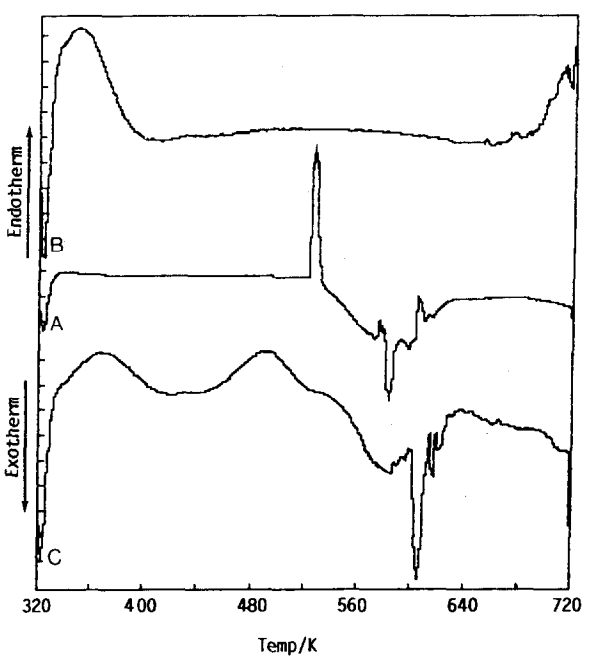

Fig. 2. DSC thermograms of bromazepam, PVP and their mixtures. A: bromazepam alone; B: PVP alone; C: physical mixture of bromazepam and PVP after 7 weeks of storage at room temperature.

in macromolecules such as PVP, methylcellulose and hydroxypropylcellulose have been extensively used to enhance the dissolution characteristics of sparingly soluble drugs (Florence et al., 1973; Shefter and Cheng, 1980; Corrigan et al., 1980; Oth and Moes, 1985). PVP is able to disperse a variety of compounds in its matrix. Higher dispersibility (solubility) resides with those compounds capable of interacting through hydrogen bonding with the pyrrolidone moiety of the polymer (Shefter and Cheng, 1980). On the other hand, activated adsorption might lead to complex and unstable equilibria.

Studies have been initiated to examine the nature of bromazepam PVP interaction by IR spectroscopy and DSC.

The infrared spectra of the mixtures in various proportions and combinations were determined on a Beckman IR-4 infrared spectrophotometer with potassium bromide optics. The mixtures yielded spectra almost identical to those of their pure samples.

The DSC traces of bromazepam and physical mixtures with excipients other than PVP, combined the features characteristic of the traces of individual components. However, the incorporation of PVP into the mixture of bromazepam had a profound influence on the characteristic features of bromazepam (Fig. 2). An endothermic peak around 512 K corresponded to the melting temperature of bromazepam, which was observed in the intact bromazepam (Fig. 2A). Reliable values

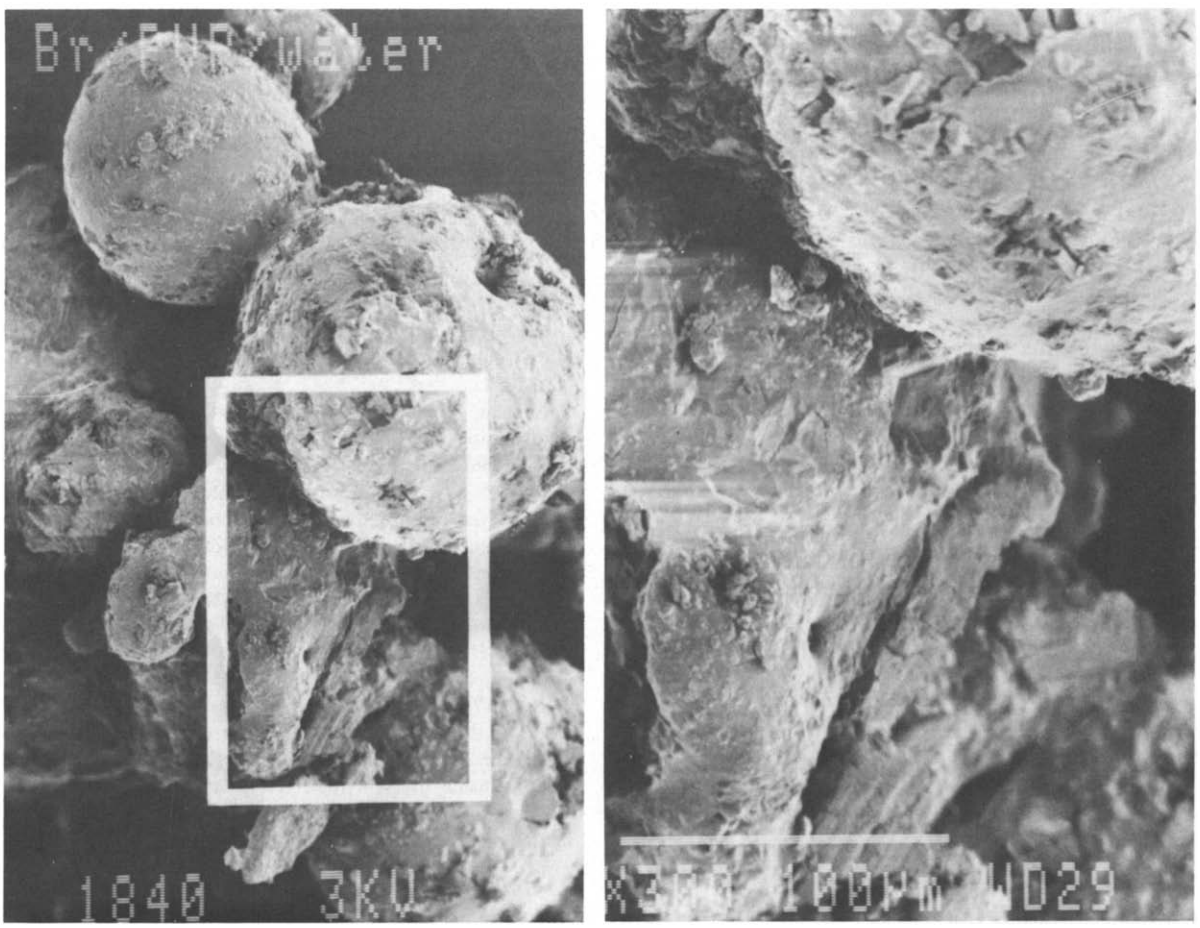

Fig. 3. Scanning electron micrographs of powder mixture of bromazepam and PVP in the presence of moisture. Surface deposition of drug particles on the PVP grains is shown. ×300.

for the entropy of fusion of PVP could not be determined experimentally. The compounds lost moisture upon heating and finally sublimed well beyond the melting range of bromazepam, as evidenced by a coating of the compound around the inside of the calorimeter cell. The loss of moisture and decomposition was noted when the signals deviated from the original baseline for PVP (Fig. 2B). The DSC trace of bromazepam-PVP mixture (Fig. 2C) shows an endotherm similar to that of pure PVP, while that of bromazepam has been obliterated. This disappearance of the endothermic peak may be attributed to the complex formation with a new endothermic peak corresponding to 480 K, or to the formation of an eutectic mixture. It is thus clear that PVP is capable of binding bromazepam extensively, and lower recovery resulted on dissolution testing. Self-association of bromazepam molecules within the PVP structure may account for the observed dissolution effects. In addition, hydrolytic cleavage of benzodiazepines at temperatures as low as 30 °C has been reported (Inotsume and Nakano, 1980). Further investigation is necessary to elucidate the mechanism(s) of such interactions and their biological significance. It is important to note that actual coprecipitation of bromazepam and PVP from organic solvents may yield a product displaying improved solubility profiles and this possibility is to be investigated.

A scanning electron microscope was used to examine the nature of solid-state interactions in an effort to understand the results obtained above. When bromazepam and PVP were thoroughly mixed and stored under ambient conditions for several weeks, particle–particle interactions resulted in the surface deposition of drug particles on the PVP grains (Fig. 3), exhibiting much less drug recovery in dissolution studies. In contrast, those drug particles that adhere randomly to the PVP grains would easily go into solution. The hydrophobic nature of bromazepam film deposits on PVP grains can hinder liquid penetration and reduce the rate of drug dissolution.

In conclusion, data obtained in this study indicate that PVP can interfere with bromazepam. The degree of interference is dependent on the amounts of adsorbing agent and moisture present. Further work will be necessary before a complete understanding of the effect of adsorption on uptake of the drug is achieved.

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