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The influence of polyvinylpyrrolidone on the dissolution properties of hydroflumethiazide

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The incorporation of hydroflumethiazide with polyvinylpyrrolidone (PVP) was found to retard and to enhance the dissolution of the drug from compressed discs, the magnitude of the effect being dependent on the proportion of PVP present and its method of incorporation. The most active system dissolved sixteen times faster than pure hydroflumethiazide. Low concentrations of PVP were also found to decrease the apparent solubility of hydroflumethiazide while at high concentrations solubility was enhanced. X-ray and infrared analysis of systems suggested the presence of an amorphous form of hydroflumethiazide in coprecipitate systems. The dissolution data were consistent with a physical model which takes account of the roles played by crystalline and amorphous hydroflumethiazide together with the complexing and crystal growth inhibiting effect of PVP on hydroflumethiazide.

With the development of an awareness of the importance of dissolution rate in influencing biological availability, considerable attention is being paid to methods of enhancing this property. In 1965, Tachibana & Nakamura reported a novel method of preparing aqueous dispersions of β-carotene by using water soluble polymers such as polyvinylpyrrolidone (PVP). This coprecipitation technique was shown by Stupak & Bates (1972, 1973) to enhance the dissolution and biological availability of both reserpine and digitoxin. Simonelli, Mehta & Higuchi (1969) carried out extensive studies on the mechanism of increased dissolution rates from sulphathiazole—PVP systems using discs of constant surface area. They presented a model to explain the experimental data, which utilized a controlling sulphathiazole external layer at low PVP weight fractions and a controlling PVP external layer at higher PVP weight fractions. Gibaldi & Weintraub (1968), in studies on discs prepared from mechanical mixes of salicylic acid and PVP, reported a lowering of the dissolution rate of salicylic acid in the presence of PVP. The results were consistent with the model proposed by Higuchi, Mir & Desai (1965) for the dissolution of two non-interacting phases. In the present report, the effect of PVP on the dissolution properties of hydroflumethiazide from both mechanical mix and coprecipitate systems is reported.

MATERIALS AND METHODS

Preparation of PVP-hydroflumethiazide systems

Coprecipitates. A weighed quantity of hydroflumethiazide was dissolved in a minimum volume of ethanol and the required amount of PVP (Plasdone C15, molecular weight 10 000) was added to the solution. The ethanol was removed by evaporation and the dried material was powdered (sub 85 mesh sieve). Coprecipitates were made from mixtures of PVP and hydroflumethiazide containing different PVP weight fractions and assayed for hydroflumethiazide content.

Mechanical mixes. Mechanical mixes of PVP and hydroflumethiazide of weight fractions similar to those prepared for coprecipitate studies were made.

Assay procedure. PVP-hydroflumethiazide systems were assayed to determine the exact PVP weight fraction, by dissolving a known weight of the system in 0·1N HCl and measuring the absorbance at 273 nm. Corrections for the contribution of PVP to the total absorbance were made where appropriate.

Dissolution studies

Weighed quantities of each system were compressed into discs (13 mm diameter at a force of 3808 kg cm^{-2}), under vacuum, in a hydraulic punch die assembly (R11C Hydraulic Press C30). The discs were mounted on circular microscope cover slips with molten hard paraffin so that only the upper surface remained exposed. The disc was fixed to the centre of the base of the beaker (400 ml) using a water insoluble adhesive. The dissolution procedure used was similar to the beaker method of Levy & Procknal (1964) modified to allow continuous monitoring of hydroflumethiazide absorbance with time. The dissolution assembly was arranged so that the dissolution medium (400 ml 0·1N HCl) was pumped (peristaltic pump: Watson and Marlow, R. H. Flow Inducer) through silicone rubber tubing (Gallenkamp TX 800, internal diameter 3/16″) from the beaker to the ultraviolet spectrophotometer (Unicam SP800) and returned to the dissolution vessel. The volume of the tubing and flow through cell was 49 ml and the flow rate was 220 ml min^{-1}. The level of the tubing in the dissolution vessel was adjusted to midway between the surface of the dissolution medium and the stirrer blades. Determinations were carried out on at least three discs of each system and the results averaged. Reproducibility was within $\pm 4\%$ and in some cases curves were superimposable.

Solubility determinations

The effect of PVP concentration on the solubility of hydroflumethiazide, in 0·1 N HCl at 37°, was determined by a method similar to that of Shefter & Higuchi (1963). The concentrations of PVP used were 10, 7, 5, 2·5, 1·5 and 1%. At the higher PVP concentrations, even following dilution of samples, the PVP in solution contributed significantly to the total absorbance at 273 nm. A calibration curve of PVP aborbance at 273 nm against concentration was used to determine the correction required.

X-ray diffraction and infrared analyses

X-ray diffractograms of the samples were obtained using an X-ray powder diffractometer (Philips PW 1050/25) employing nickel filtered copper radiation.

A Perkin Elmer 157 sodium chloride infrared spectrophotometer was used to obtain infrared analyses of the samples.

RESULTS

Effect of PVP on hydroflumethiazide solubility

A linear relation between the apparent solubility of hydroflumethiazide and PVP concentration (over the range 1–10% in 0·1 N HCl at 37°) was observed and can be expressed as

$$C_f = 0{\cdot}0102C_p + 0{\cdot}046 \qquad r = 0{\cdot}9995,$$

where C_f and C_p are the apparent solubility of hydroflumethiazide and the PVP concentration in solution (g 100 ml^{-1}) respectively. However, the intercept on the C_f axis is lower than the solubility of pure hydroflumethiazide and the apparent solubility only rises above that of the pure drug when the PVP concentration in solution exceeds 1·4%.

Dissolution from mechanical mix systems

Dissolution profiles for hydroflumethiazide from mechanical mix systems were in all cases non-linear, the slopes of the curves decreasing with time over the initial period. During the first 40 s of a dissolution experiment some fine particles were observed rising from the surface of discs containing a PVP weight fraction greater than 0·5.

The initial and limiting dissolution rates (i.e. the rates over the first 4 min and 40 to 60 min period respectively) are plotted versus PVP weight fraction in Fig. 1. The initial dissolution rates of hydroflumethiazide increased non-linearly, the rate for the PVP weight fraction of 0·1 being lower than that of pure hydroflumethiazide. From the plot of the PVP to hydroflumethiazide ratio in the solid versus PVP weight fraction, superimposed on Fig. 1, it would appear that the increase in dissolution rate is directly related to the ratio of PVP to hydroflumethiazide in the solid. The limiting hydroflumethiazide dissolution rates for PVP weight fractions up to 0·6 were lower than that of the pure drug.

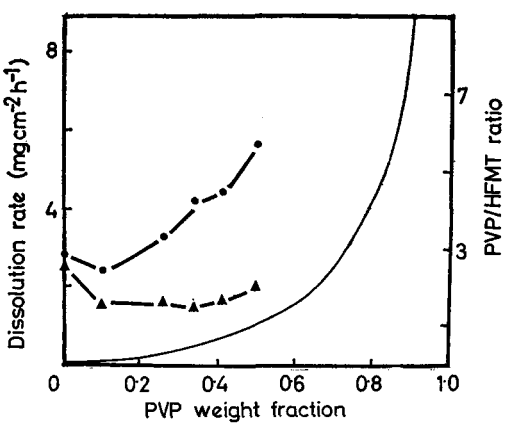

FIG. 1. Effect of PVP weight fraction on initial and limiting dissolution rate of hydroflumethiazide from mechanical mix systems at 37° in 0·1 N HCl using the automated beaker method. Superimposed is the PVP to hydroflumethiazide ratio as a function of PVP weight fraction. ● Initial dissolution rate, ▲ limiting dissolution rate.

Dissolution from coprecipitate systems

Both the initial and limiting dissolution rates obtained for coprecipitate systems are plotted versus PVP weight fraction in Fig. 2. Non-linear dissolution profiles, with the slopes decreasing with time, were obtained from discs with PVP weight fractions up to 0·62. The limiting dissolution rate was reached during the course of the experiment only in systems of PVP weight fractions below 0·42. Discs with a PVP weight fraction of 0·67 gave linear plots over the time period studied. The dissolution profiles of systems with a weight fraction above 0·67 exhibited an increase in slope after the initial rate period. A maximum dissolution rate sixteen times that of pure hydroflumethi-

azide was obtained with the 0·84 weight fraction system. Comparison of the results obtained for coprecipitate systems (Fig. 2) with those for mechanical mixes shows that at all weight fractions the former method gave enhanced dissolution. The ratios of the initial dissolution rates for coprecipitate systems to those obtained with mechanical mix systems of similar weight fraction are superimposed on Fig. 2. These ratios indicate that coprecipitation brought about an approximate fourfold increase in dissolution rate. The variability in the ratios reflect the differences in the actual PVP weight fraction in the two types of systems.

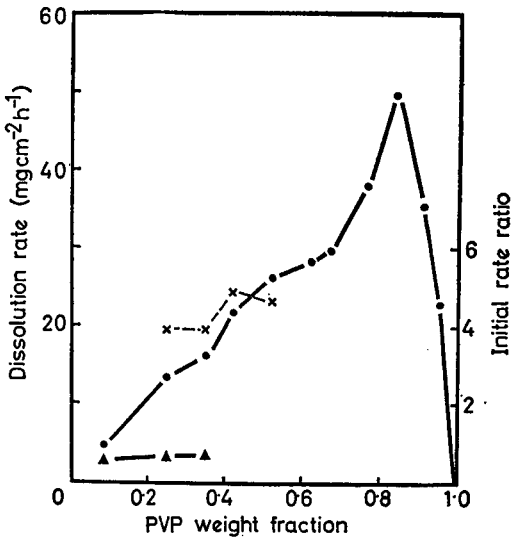

FIG. 2. Effect of PVP weight fraction on the initial and limiting dissolution rate of hydroflumethiazide from coprecipitate systems at 37° in 0·1 N HCl using the automated beaker method. Superimposed is the ratio of the initial rates to those obtained for mechanical mix systems as a function of PVP weight fraction × — ×: ● Initial dissolution rate, ▲ limiting dissolution rate.

X-ray diffraction and infrared analysis of samples

Pure PVP is amorphous and therefore showed no diffraction peaks. X-Ray diffraction patterns from mechanical mix systems exhibited characteristic hydroflumethiazide peaks, peak intensities decreasing with increase in PVP weight fraction and becoming undetectable above weight fraction of 0·91. Coprecipitates with a PVP weight fraction above 0·35 showed no diffraction peaks. Coprecipitates with lower fractions gave peaks of much lower intensity than the corresponding mechanical mix systems. These differences are evident from the scans for mechanical mixes and coprecipitates of PVP weight fractions of 0·35 and 0·42 in Fig. 3. The patterns obtained for coprecipitates were similar to that of the desolvated crystal form of hydroflumethiazide (Corrigan & Timoney, 1974). The absence of X-ray diffraction peaks indicates that hydroflumethiazide is present in an extremely fine dispersion, possibly in amorphous form.

Comparison of the infrared data from coprecipitates with mechanical mixes of corresponding PVP weight fractions indicated changes in peak resolution for coprecipitates above a PVP weight fraction of 0·35 which could be ascribed to a decrease in crystallinity.

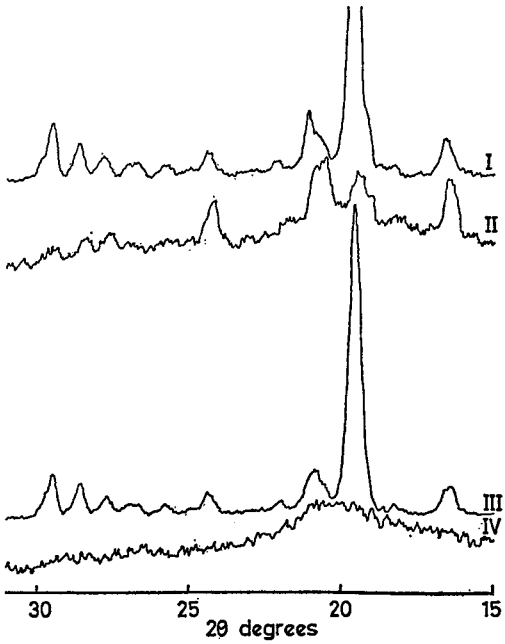

FIG. 3. X-ray diffraction patterns of hydroflumethiazide—PVP systems. I. Mechanical mix of PVP weight fraction 0·35. II. Coprecipitate of PVP weight fraction 0·35. III. Mechanical mix or PVP weight fraction 0·42. IV. Coprecipitate of PVP weight fraction 0·42.

DISCUSSION

The increase in the solubility of hydroflumethiazide in the presence of PVP is indicative of the formation of soluble complexes. The linear relation suggests that such complexes may be of the first order in PVP (Higuchi & Connors, 1965). The ability of low concentrations of PVP to depress apparent solubility of drugs has been previously reported by Breuninger & Goettsch (1965) and Gibaldi & Weintraub (1968). The latter authors, studying salicylic acid, observed a gradual increase in solubility with time, true equilibrium only being established after two weeks. Extended studies were not possible with hydroflumethiazide because of decomposition problems.

Higuchi & others (1965) applied the diffusion layer (film) theory of mass transfer to the dissolution of a mixture of two solids which form a 1:1 soluble complex. Qualitative application of this theory to the PVP-hydroflumethiazide systems predicts that (i) as the PVP weight fraction is increased, non-linear dissolution profiles should be obtained and (ii) the dissolution rates, initial and limiting, should increase with increase in PVP weight fraction up to a maximum and then fall to zero, both these occurrences being due to the presence of soluble complexes. The results for mechanical mix systems are in general agreement with these expectations with the exception that rates lower than that of pure hydroflumethiazide were observed.

It would appear from the X-ray diffraction and infrared results that the fourfold enhancement in dissolution rate brought about by coprecipitation is due to the presence of an amorphous form of hydroflumethiazide in coprecipitate systems. With increasing PVP weight fraction, sufficient PVP is present to retard the conversion of amorphous hydroflumethiazide to the stable crystalline form. The ability of PVP to retard

hydroflumethiazide crystal growth has been reported previously (Corrigan & Timoney, 1974). Consideration of the solubility enhancing (carrier) effect, together with the presence of an amorphous form of drug adequately explains the results obtained up to a PVP weight fraction of 0·84. At higher PVP weight fractions, the concentration of hydroflumethiazide rapidly declines and it is possible, as suggested by Chiou & Riegelman (1971), that molecularly or colloidally dispersed drug is involved in the release. The increase in the dissolution rate after the initial period, observed for discs with PVP weight fractions above 0·67 is probably due to an increase in surface area of the discs as a result of swelling of PVP. Nogami, Nagai & Kondo (1970), in studies on the dissolution of pure PVP in an acetone–water system, observed an increase in rate after the intial stage which they attributed to swelling of PVP. It is of interest that in the investigation of sulphathiazole—PVP systems by Simonelli & others (1969), the presence of an amorphous form of drug was indicated. In the current work, the much greater contribution of the PVP carrier effect is probably a reflection of the differing diffusion layer thicknesses, 25×10^{-4} cm (Simonelli & others, 1969) in the sulphathiazole—PVP study and 69×10^{-4} cm in the current work. The results underline the important influence of agitation intensity on dissolution rate from these systems.

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