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The influence of polyvinylpyrrolidone on the dissolution and bioavailability of hydrochlorothiazide

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The dissolution properties of hydrochlorothiazide - PVP 10 000 mechanical mix and coprecipitate systems were qualitatively similar to those previously reported using hydroflumethiazide. Quantitative differences were dependent on the proportion of PVP present, its molecular weight and method of incorporation. Cumulative urinary excretion data from test capsule preparations showed that bioavailability was enhanced by the presence of PVP. However, the degree of enhancement was less than that expected from constant surface area disc rate studies. Dissolution tests on the capsule formulations, using the U.S.P. basket stirrer assembly, did not correlate with *in vivo* results. Using the Levy beaker method and a stirring speed of 40 rev min^{-1}, good correlation between amount dissolved in 30 min and amount excreted in urine after 24 h was obtained. The dissolution tests revealed that PVP retards the initial dissolution from capsule dosage forms, probably by retarding deaggregation and dispersion of drug particles.

In spite of their wide usage, little information exists on the bioavailability of thiazide diuretics. The bioavailability of hydrochlorothiazide dosage forms has been considered by some reviewers to be susceptible to formulation effects (Schneller, 1970). Greater urinary excretion of hydrochlorothiazide and of sodium was reported by Tannenbaum, Rosen & others (1968) from a tablet formulation containing hydrochlorothiazide and triamterene compared with a capsule dosage form. Cook, Chang & Mainville (1966), in studies on the dissolution properties of commercial hydrochlorothiazide tablets (50 mg), reported that, although all tablets met the specifications for disintegration time, variations between brands in the average time for 50% drug to dissolve of from 2 min to over 5 h were observed. A dissolution specification for hydrochlorothiazide tablets was included in the U.S.P. XVIII. McGilveray, Hossie & Mattok (1973) reported that hydrochlorothiazide tablets from ten of thirty-nine Canadian companies failed to meet U.S.P. XVIII dissolution requirements, while bioavailability data did not give correlations of predictive value with dissolution data.

A number of *in vitro* studies on the influence of formulation factors on the dissolution properties of hydrochlorothiazide have been published (Alam & Parrott 1971; Seth, 1972). These show that polyvinylpyrrolidone (PVP) can influence the dissolution properties of this drug. Sheen (1970) reported solid-solid interaction between PVP and hydrochlorothiazide and dissolution studies indicated that drug dissolution was decreased as the amount of PVP was increased.

In studies on a related diuretic, hydroflumethiazide, we have observed that coprecipitation with PVP can enhance dissolution rate 16-fold (Corrigan & Timoney, 1975). A detailed study of the influence of PVP on the dissolution and bioavailability of hydrochlorothiazide was therefore undertaken.

METHODS

The methodology used in the preparation and in the analysis of the physicochemical properties, of PVP - hydrochlorothiazide systems was similar to that previously reported (Corrigan & Timoney, 1975).

Preparation of capsule dosage forms

Capsules (size 0) containing 300 mg of a powder mix (particle size range 75–180 μm) which included 50 mg hydrochlorothiazide were prepared. Formulation A contained pure hydrochlorothiazide and lactose; Formulation B contained hydrochlorothiazide, PVP 10 000 coprecipitate 1:4 and lactose and Formulation C contained hydrochlorothiazide, PVP 10 000 physical mixture 1:4 and lactose.

In vitro *dissolution studies on capsule formulations*

The U.S.P. XVIII basket-stirrer assembly, using 1L flat based straight sided vessel containing 900 ml of dissolution medium at 37° was used initially. The dissolution medium consisted of dilute hydrochloric acid 1:100, which was stirred at 150 rev min^{-1}. In all other tests, purified water was employed. The beaker method of Levy & Hayes (1960), modified to allow determinations on capsules was also employed. A

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wire spiral was placed in the base of the beaker to hold the test capsule. The dissolution medium, 350 ml of purified water at 37°, was contained in a 400 ml beaker. Data points represent the mean value of six determinations. Samples were taken at regular time intervals, filtered through a millipore filter and the ultraviolet absorbance at 272 nm used to estimate the amount of drug in solution.

In vivo *absorption studies*

Four healthy male adults received two capsules (100 mg hydrochlorothiazide) of each formulation on alternate weeks. Urine samples were collected at 30 min intervals up to 4 h after administration. Further samples were collected at 5, 7, 9, 14 and 24 h. Urinary volume and pH measurements were made on each sample, which were then stored at 4° while awaiting analysis. To ensure continuous flow of urine and to control fluid intake, 50 ml water was administered to each subject every 30 min up to the 4 h period, 100 ml on the fifth hour and after this time interval water intake was not controlled.

Assay of hydrochlorothiazide in urine

Samples (5 ml) of urine were extracted with 4 × 15 ml quantities of ethyl acetate, the extracts being pooled and evaporated to dryness.

Acetone (2 ml) was added to the residue to dissolve the soluble portion, 0·5 ml of the acetone solution was then spotted onto thin layer silica gel plates which had previously been cleaned with methanol and reactivated for 30 min at 110°. Plates were developed in a benzene–ether–acetone (3 : 3 : 4) solvent system, the development distance being 12 cm. Plates were then dried at 50° and the hydrochlorothiazide visualized using an ultraviolet lamp. The drug band was quantitatively removed and was placed in a conical flask to which 20 ml of absolute ethanol was added. The suspension was then centrifuged for 30 min at 3000 rev min^{-1}. The concentration of hydrochlorothiazide was determined from the ultraviolet absorbance at 272 nm. Preliminary investigations using samples of known drug concentration indicated that the above method was quantitiative.

RESULTS AND DISCUSSION

Physicochemical studies

The dissolution properties of hydrochlorothiazide: PVP 10 000 mechanical mix and coprecipitate systems were qualitatively similar to those reported previously for hydroflumethiazide systems. At low PVP weight fractions the relative decrease in hydrochlorothiazide dissolution rates were greater than in the corresponding hydroflumethiazide systems while at higher weight fractions dissolution rates were not enhanced to the same extent. The maximum enhancement of hydrochlorothiazide dissolution was ninefold (hydrochlorothiazide : PVP 1 : 4 coprecipitate system) compared with 16-fold in the case of hydroflumethiazide.

Replacement of PVP 10 000 by PVP 44 000 in mechanical mix systems led to initial and limiting dissolution rates which were on average 6 % lower than those observed using the lower molecular weight polymer. Coprecipitation of hydrochlorothiazide with PVP 44 000 did not enhance dissolution as markedly as when PVP 10 000 was employed, the maximum rate observed being seven times that of pure drug. The greater effectiveness of the lower molecular weight polymer in enhancing drug release from coprecipitate systems was reported also for sulphathiazole by Simonelli, Mehta & Higuchi (1969).

Low concentrations of PVP 10 000 and PVP 44 000 decreased hydrochlorothiazide apparent solubility while at concentrations above 0·1 % the apparent solubility increased. Similar findings were reported by Sheen (1970).

Comparison of the X-ray diffraction data for hydrochlorothiazide - PVP systems with that previously reported for hydroflumethiazide (Corrigan & Timoney, 1975) indicated that PVP was more effective in inhibiting hydroflumethiazide crystal growth during coprecipitation.

Lower X-ray peak intensities were observed from coprecipitates containing PVP 10 000 than from corresponding systems prepared using PVP 44 000. This observation is consistent with the report of Simonelli, Mehta & Higuchi (1970) that the larger the molecular weight of PVP the greater the quantity required to inhibit drug crystal growth.

Bioavailability study

Cumulative amounts of hydrochlorothiazide excreted from capsule formulations containing (A) pure drug, (B) coprecipitate and (C) physical mixture at various time intervals are shown in Fig. 1. It is evident that after each time interval the cumulative amounts excreted for formulations containing PVP were greater than those excreted from the pure drug formulation. These differences were statistically significant ($P < 0·05$) at 1·5, 4·0, 5·0, 14 and 24 h time intervals. Surprisingly the cumulative amount excreted up to 6 h was greater for the mechanical mixture formulation than for the coprecipitate, the

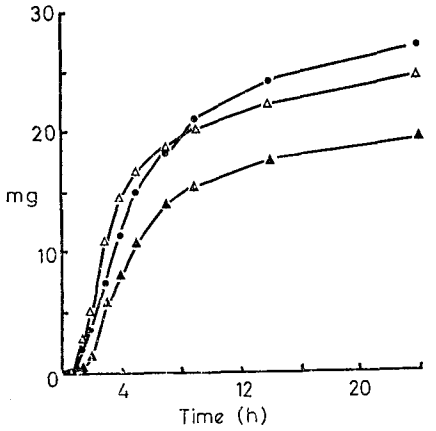

FIG. 1. Mean cumulative amounts of hydrochlorothiazide excreted (mg) at various times after ingestion of 100 mg of drug in capsule formulations containing ● hydrochlorothiazide—PVP 10 000 coprecipitate, △ hydrochlorothiazide—PVP 10 000 mechanical mixture and ▲hydrochlorothiazide.

difference being statistically significant after 3 h. Although these results show that PVP can enhance the absorption of hydrochlorothiazide, the enhancement is less than might have been expected from the constant surface area disc studies.

Dissolution tests were therefore carried out on the capsule formulations. Plots of cumulative percentage drug dissolved from the three formulations, using the U.S.P. test and the recommended stirring speed of 150 rev min^{-1}, are shown in Fig. 2. All three formulations were well within specifications, 60 % of drug being released in less than 12 min. The percentages released within the 30 min period are not in rank order agreement with the urinary excretion results. The initial drug release is fastest from the pure drug formulation, there being a lag in the release from the PVP containing formulations. Over the time studied, drug release from the mechanical mix preparation was lower than that from pure drug. Lowering the agitation by reducing the stirring speed to 50 rev min^{-1} decreased the initial dissolution from the pure drug preparation but did not alter the ranking of the preparations. It would appear that using the U.S.P. apparatus pure drug particles were rapidly dispersed in the dissolution medium giving a large initial surface area. However, formulations containing PVP exhibited a smaller surface area, the PVP retarding deaggregation and preventing the initial rapid dispersion of drug. Using the beaker dissolution test method at a stirring speed of 59 rev min^{-1}, more pronounced lags in the release from PVP containing formulations were evident and drug release from all preparations was further slowed. The percentages released after 30 min were 94, 70 and 66·2 % for coprecipitate, pure drug and mechanical mix capsule formulations respectively. The effect of reducing the stirring speed to 40 rev min^{-1} in the beaker method is illustrated in Fig. 3. The resulting decrease in dissolution from the pure drug formulation was sufficient to allow rank order correlation of the dissolution data from the 9 to the 30 min time with the cumulative urinary excretion of drug from 8 h to 24 h. The critical importance of low agitation conditions in *in vivo-in vitro* correlations using the beaker method was also reported for aspirin by Levy Leonards & Procknal (1965).

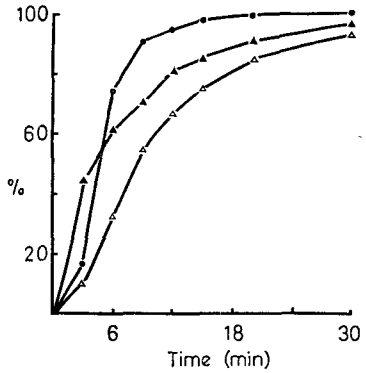

FIG. 2. Dissolution profiles of capsule formulations containing 50 mg of hydrochlorothiazide, determined in 1 % HCl at 37°, using the U.S.P. basket stirrer assembly with a stirring speed of 150 rev min^{-1}. ● hydrochlorothiazide—PVP 10 000 coprecipitate; △ hydrochlorothiazide—PVP 10 000 mechanical mixture; ▲ hydrochlorothiazide. y axis—% drug dissolved.

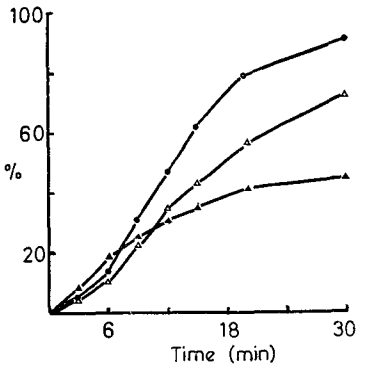

FIG. 3. Dissolution profiles of capsule formulations containing 50 mg of hydrochlorothiazide, determined in water at 37°, using the modified Levy beaker method with a stirring speed of 40 rev min^{-1}. ● hydroclorothiazide—PVP 10 000 coprecipitate; △ hydrochlorothiazide—PVP 10 000 mechanical mixture; ▲ hydrochlorothiazide. y axis—% drug dissolved.

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