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EFFECT OF DIFFERENT GRADES OF POLYVINYLPYRROLIDONE ON DISSOLUTION RATE OF CHLORPROPAMIDE AND ITS ABSORPTION THROUGH RAT STOMACH

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ABSTRACT

Coprecipitates of chlorpropamide and PVP 10000, 44000 and 700000 were prepared. Dissolution rate studies have shown that coprecipitate of Chlorpropamide and PVP 44000 (1:3.33) is by far the best combination. The same findings were also observed when all the three different coprecipitates were subjected to drug absorption studies through rat stomach. This increase in dissolution rate could be due to complex formation between the drug and the PVP irrespective of molecular weight, this was confirmed by T.L.C. and IR studies. It was also observed that the effect of PVP on increase in dissolution of insoluble drug reaches up to a certain molecular weight of PVP and decreases with further increase in molecular weight.

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INTRODUCTION

In our previous paper (1) we had reported that the dispersed mixture of chlorpropamide and PVP 44000 shows better dissolution rate as compared to other commonly available dispersing agents. We had further noted that the particle size of the coprecipitate within the range of 53 to 125 μm has little effect on the dissolution rate of the drug. Similarly it was also found that the increase in dissolution rate of the drug is not only due to high concentration of PVP but due to coprecipitate formation. The present report deals with the determination of behavioural differences (if any) with variation in molecular weight of different grades of PVP. Further since chlorpropamide is mostly absorbed through the stomach (2) it would be very useful to study whether dispersion technique has any effect on absorption of the drug through the rat stomach.

EXPERIMENTAL

Materials - Three grades of Polyvinyl-pyrolidone, approximately molecular weight 10,000, 40,000 and 700,000 (all from BDH), chlorpropamide, acetone, methanol, and other chemicals used were of BP or USP grade.

Preparation of Samples - Coprecipitates containing

chlorpropamide to PVP in the ratio of 1:3.33, using PVP 10000, 44000, and 700000, average molecular weight were prepared as described previously (1).

Dissolution Rate Studies - The coprecipitates and pure drug were tested for their rate of release following the tape method for multiparticulate system (3). The dissolution media was 400 ml. plain distilled water at $37^{\circ} \pm 0.5^{\circ}$. At the specified time intervals an aliquot (2 ml.) was withdrawn for analysis and replaced with an equal volume of distilled water maintained at the same temperature. After appropriate dilution with water the extinction was measured at 235 nm using 10 mm. cells in a Pye Unicam SP 30 Spectrophotometer. At this wave length polymers do not interfere with the measurement.

TLC Studies - TLC technique as described by Sunshine (4) with slight modification was used. One percent chloroform solution of chlorpropamide, PVP, and chlorpropamide-PVP coprecipitate mixture were spotted on a silica gel chromatogram. A 1.5 percent ammonia solution in methanol was used as the developing system. Development was allowed to proceed for half an hour, after which the plate was removed and dried in an oven at 120° for 10 minutes. Visualisation of the spots was carried out by one percent aqueous potassium permanganate solution.

Infra Red Spectra - A "Nujol" mull of each sample was smeared as a thin film between two sodium chloride plates and the IR spectrum was then recorded using Perken Elmer infra red spectrophotometer at the slow scanning speed to ensure maximum resolution of the bands.

Absorption in Rats - Absorption of the drug through rat stomach was studied by the in situ technique as described by Schanker et. al. (5).

Solutions of chlorpropamide and dispersed mixtures of chlorpropamide and different grades of PVP were prepared in isotonic hydrochloride citrated buffer at pH 2 (6) for the stomach absorption in the concentration of 200 to 204 µg/ml.

Male rats weighing 150 to 220 gm. were fasted for twenty-four hours prior to the experiment, however, water was allowed freely. The rats were anesthetized with pentobarbitone solution (5 mg/100 g. body weight). The stomach was exposed and the cardia ligated. The pylorus was ligated around a short polyvinyl cannula equipped with a stop-cock, care being taken to exclude major blood vessels from the ligatures.

The stomach was first washed with saline until the washings were clear and then three times with drug solution warmed to body temperature. The abdominal incision was then closed. Ten ml. of the

drug solution was drawn into a syringe and 3 ml. were introduced into the stomach and then withdrawn into the syringe. This procedure was repeated several times to insure thorough mixing. Three to four ml. of the mixed drug solution (2.5 ml. per 100 g. of body weight) were introduced into the stomach and the stop-cock was closed. The solution remaining in the syringe was called initial solution. The drug solution was withdrawn from the stomach after each 15 minutes interval till the end of 1 hour and this was called the final solution. The estimation of the drug was carried out spectrophotometrically at 235 nm. after appropriate dilution. For each set of reading three rats were used.

RESULTS AND DISCUSSION

Dissolution Rate Of Coprecipitates - All the dissolution studies were based on two to three tests and were highly reproducible. Experimental technique used for dissolution rate studies was the same as described in our previous report (1). While comparing the effect of molecular weight of PVP on dissolution rate it was observed that the molecular weight indeed significantly changed the dissolution rate of chlorpropamide, the 44000 molecular weight being the most rapid of the three systems, (figure 1). This is also true in case

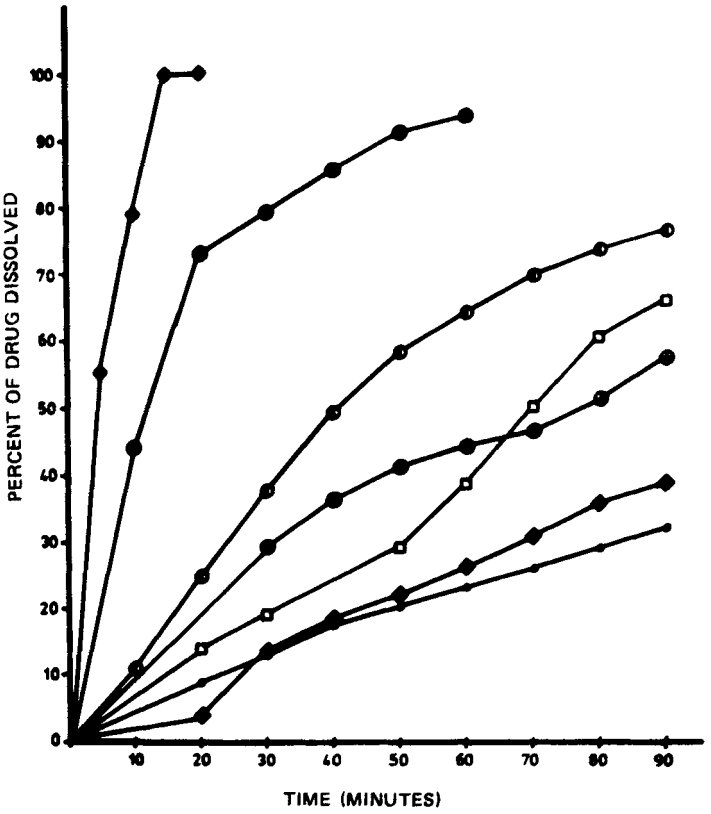

FIGURE 1

Dissolution rate of 1:3.33 w/w Chlorpropamide - PVP Coprecipitates at 37° (amount equivalent to 5 mg of Chlorpropamide). Pure Chlorpropamide —●— .

	Coprecipitate	Physical Mixture
PVP 10000	◇	◈
PVP 44000	◆	◕
PVP 700000	◉	⊗

of their physical mixtures. The inhibitory effect of PVP on the crystalization of several drugs to clarify the mechanism of coprecipitation of the drug with PVP has been reported by Sekikawa et al (7). The inhibi-

tory effect of crystalization was also noted in our case. Differential scanning colorimeter studies have shown that Chlorpropamide is molecularly dispersed in amorphous state in the coprecipitate mixture. The inhibitory effect decreased in the following molecular weight order; 44000 700,000 10000 as shown in figure 1.

These results indicate that the effect reaches maximum at a certain molecular weight, and decrease with further increases in molecular weight. For this reason the 44000 - molecular weight PVP has ben utilized for all future studies.

Infra-Red Spectra - Figure 2 shows the high frequency region of the IR spectra of chlorpropamide, PVP and chlorpropamide PVP co-precipitate. The IR spectrum of chlorpropamide shows a sharp band at $3450^{cm^{-1}}$, while the IR spectrum of the chlorpropamide: PVP system shows a broad band in this region. This broad band is present in all the three different chlorpropamide: PVP (different mol. wt.) coprecipitates in the same region. The broad band shown in the above combination is attributed to the presence of hydrogen bonding between the N-H group of chlorpropamide and the carbonyl group of the PVP. This is an indication of complex formation in all the cases. These findings were supported by T.L.C. studies which has clearly

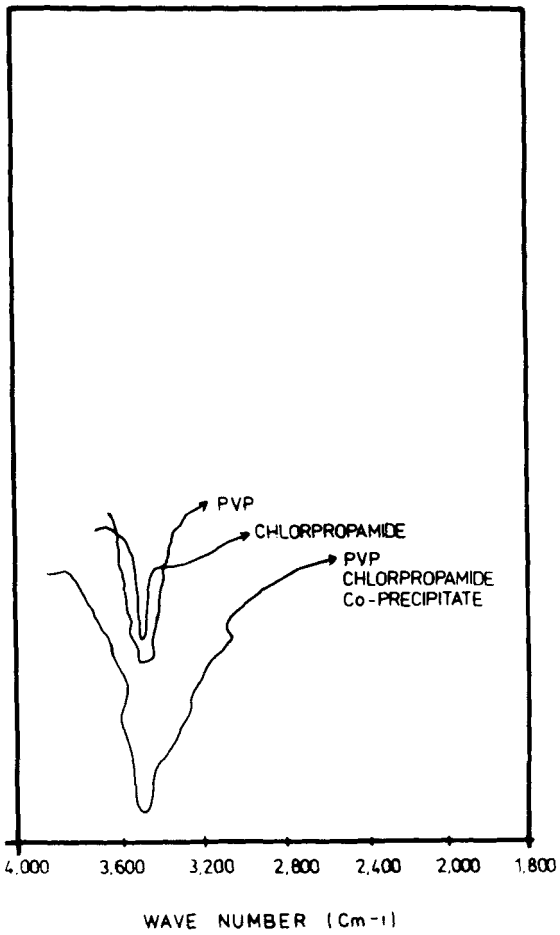

FIGURE 2

High frequency region of the I.R. spectra of Chlorpropamide, PVP 44000, and their Coprecipitate.

shown that the coprecipitate mixture travels quite slower than the pure drug (figure 3). The occurence of this complexation between chlorpropamide and PVP may explain the mechanism underlying the increase in the dissolution rate of medicament. The insoluble chlorpropamide is rendered more soluble by the attach-

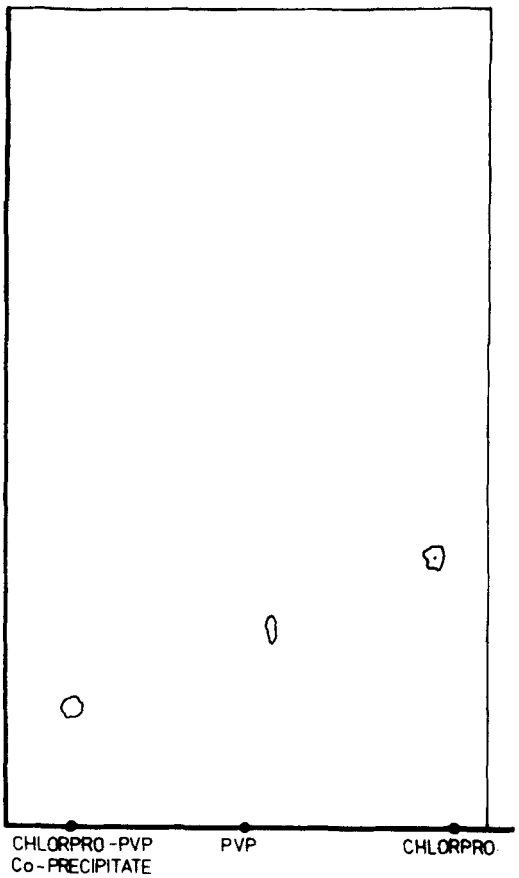

FIGURE 3

Chromatogram of Chlorpropamide, PVP 44000, and their Coprecipitate (almost identical chromatograms were obtained by other two ranges of PVP and their Coprecipitates with drug.)

ment of the molecules via hydrogen bonding to the high energy centres of the PVP.

Absorption of Drug Through Rat Stomach - Chlorpropamide is a water insoluble drug and this may affect its bioavailability through gastrointestinal tract due to

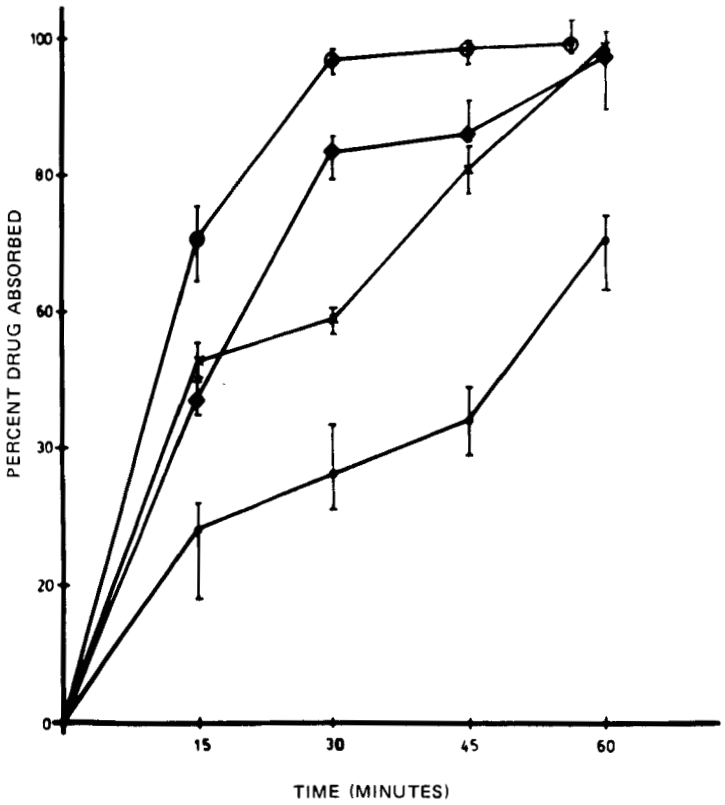

FIGURE 4

Drug absorbed levels through Rat Stomach.

Key:- Pure Chlorpropamide ⊢⊣ ; Coprecipitates:- Chlorpropamide - PVP 10000 ⊢⊣; Chlorpropamide - PVP 44000 ⊢⊣ ; Chlorpropamide - PVP 700000 ⊢⊣ .

(Each point indicates the mean of three experiments with the standard error of the mean).

slower dissolution rate in the G.I.T. To confirm this assumption, the disappearance of chlorpropamide from rat stomach was examined.

It was observed that in the first 15 minutes about 28.75% the dose of pure chlorpropamide disappeared

from the solution injected in the rat stomach. Similarly in the same time, about 48.28%, 71.07% and 47.67% of the drug administered disappeared from rats stomach from coprecipitates of PVP 10000, 44000 and 700,000 respectivelly. The overall absorption in case of coprecipitates occured in about 60 minutes. Generally it can be said that the disappeared amount of drug may be equal to pure absorbed amount. This experiment also confirms that the coprecipitate mixture of 44000: drug shows better absorption as compared to other two PVP: drug coprecipitates, (figure 4).

In conclusion, it can be said that the coprecipitate prepared out of PVP 44000, chlorpropamide shows the best results and can be developed further for formulation.

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