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Dissolution Characteristics of Hydrophobic Drug-Soluble Carrier Coprecipitates (Ⅱ)

Dissolution Characteristics of Phenylbutazone-Polyvinylpyrrolidone Coprecipitates

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복용량이 비교적 적고, 난용성 醫藥品으로 antirheumatism에 사용되고 있는 phenylbutazone을 macromolecule polymer로서 water soluble carrier인 polyvinylpyrrolidone과 solvent method로 1:1, 1:5, 및 1:9(w/w)의 coprecipitate를 形成시켰으며, 이들 coprecipitate의 용출 속도를 pure drug 및 coprecipitate 형성 용매인 methanol에서 재결정한 recrystallized pure drug의 그것과 측정 比較하였다.

1:1, 1:5 및 1:9(w/w)의 coprecipitate는 recrystallized pure phenylbutazone보다 약 4.5배의 용출의 증가를 보였고, 이들 1:1, 1:5, 1:9(w/w)에서의 그 carrier의 量에 따른 용출에의 영향은 거의 없었다.

時間에 對한 log probit를 plot하여 求한 dissolution half life, $T_{50\%}$는 coprecipitate ratio 1:1(w/w)에서는 5.5분, 1:5에서는 10분, 1:9에서는 12.5분이었다.

This is a report of a preliminary investigation made to ascertain the dissolution characteristics of a relatively water-insoluble drug, phenylbutazone in the form of a coprecipitate or solid dispersion with polyvinylpyrrolidone(PVP).

Several investigations[1-11] demonstrated the formation of solid dispersion or coprecipitate of relatively water-insoluble drugs with various pharmacologically inert carriers can increase significantly in their *in vitro* dissolution rates.

In theory, the enhancement in the dissolution rate of a drug should facilitate its GI absorption rate if the absorption process is dissolution rate limited.

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Among the techniques that can potentially enhance the dissolution rate and, hence, the rate and/or extent of absorption of hydrophobic drug is the formation of coprecipitates with polymeric materials such as polyvinylpyrrolidone.

This physicochemical drug modification offers the advantage of possibly enabling one to administer the drug orally in a form from which it is most available for GI absorption.

And also, it has been reported[7~10] that a correlation between the solubility and/or *in vitro* the dissolution rates and the *in vivo* absorption pattern of drugs orally administered as polyvinylpyrrolidone coprecipitates was found in some water-insoluble drugs and its physicochemical drug modifications. The studies of solid dispersions or coprecipitates system have been much discussed but, ascertainable theoretical considerations have not been established.

EXPERIMENTAL

Materials-The phenylbutazone and polyvinylpyrrolidone employed in this study were pharmaceutical grade. The polyvinylpyrrolidone had an average molecular weight of 40000 (K-30).

All other chemicals used were reagent grade and were used as received.

Preparation of Test Systems- The 1:1, 1:5, and 1:9(w/w) phenylbutazone-polyvinylpyrrolidone coprecipitates system was prepared by dissolving both components in methanol and subsequently evaporating off the organic solvent *in vacuo*.

The residue was then dried to constant weight *in vacuo* and screened, and the phenylbutazone-polyvinylpyrrolidone weight ratio was analytically confirmed.

The 1:1, 1:5, and 1:9 (w/w) physical mixtures system was prepared by gently triturating appropriate quantities of phenylbutazone and polyvinylpyrrolidone in glass mortar.

The pure phenylbutazone was recrystallized in methanol, the solvent of the solvent method vehicles.

All powders were analyzed for the pure phenylbutazone contens and all particle size screened through standard mesh screen and the 150 to 200-mesh fraction collected for use in these dissolution rate studies.

All particulate dissolution rate expcriments were performed in at least duplicate.

Dissolution Assembly- The assembly consisted of a 1000ml three-neck round bottom flask immersed in a constant-temperature water bath adjusted to 37°±0.1. A

0.7×5.0cm glass stirring blade and shaft attached to a stirring motor was inserted in the centre neck. The motor was controlled at 100 RPM. Dissolution procedure carried out in simulated intestinal fluid TS (without the enzyme, USP XIX). All particulate *in vitro* dissolution rate experiments performed under the non-sink condition. At frequent intervals, 2 ml of samples were removed from the flask with the filter pipet and immediately replaced with the equal volume of fresh dissolution medium.

The filtrates were suitably diluted when necessary, and the concentration of drug in solution was determined spectrophotometrically at the wave length 264 nm. using a recording Beckman DU spectrophotometer. At this wave length, polyvinylpyrrolidone did not show any absorption of light and phenylbutazone yield excellent Beer's law plot.

Equilibrium Solubility Studies- The equilibrium solubility of phenylbutazone was determined at 37°C in the dissolution medium. Excess quantities of pure phenylbutazone and the various test preparations were placed in 80ml glass-stoppered bottle together with 50ml of the medium. All bottles were closely, securely and mech anically shaken at 37°C until equilibrium was attained. Equilibrium was established by respectitive sampling and was found to occur with in 4~5 days. The equilibrated samples were then subjected to the filter pipet at 37°C, and the samples were assayed spectrophotometrically at 264 nm. for drug contents as the previously method.

RESULTS AND DISCUSSION

The comparisions of experimental equilibrium solubility of the pure drug and the various test preparations are shown in table I.

Table I Comarision of the Experimental Equilibrium Solubility of the Various Phenylbutazone Test Preparations

Test System	Equilibrium Solubility (mg/ml)
Pure Phenylbutazone	2.02
Pure Phenylbutazone*	2.30
Coprecipitates	
1 : 1(w/w)	1.90
1 : 5(w/w)	4.30
1 : 9(w/w)	5.07
Physical Mixtures	
1 : 1(w/w)	1.52
1 : 5(w/w)	2.67
1 : 9(w/w)	4.42

* Recrystallization in methanol, the vehicle of the solvent method.

The dissolution behavior of pure phenylbutazone, the pure drug of recrystallization in methanol and suspenoid pure drug at 37°C is shown in Fig. 1. The suspenoid pure drug is wetted with 2ml of the medium when it place in the dissolution medium.

A marked increase of dissolution rate in phenylbutazone, a very slightly soluble in water antirheumatics, when dispersed in the matrices of polyvinylpyrrolidone has been shown as in Figs. 2, 3, 4, and 5. The dissolution rates of phenylbutazone from coprecipitates system are increased about 4.5 fold as compared to those observed with pure phenylbutazone and about 2.5 fold to physical mixtures system(Figs. 2, 3, and 4.).

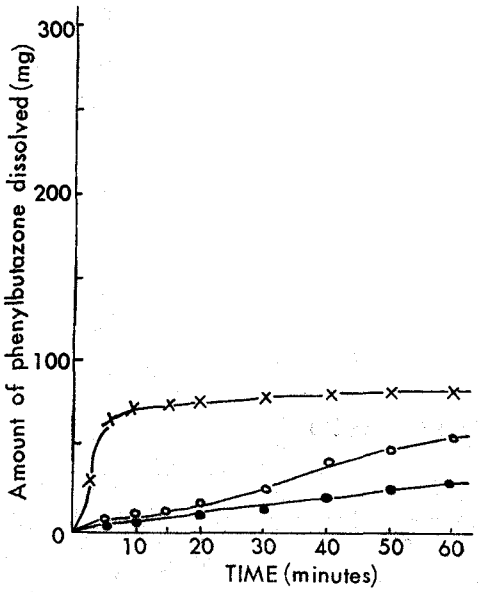

Fig. 1. Dissolution rates of phenylbutazone and phenylbutazone-PVP coprecipitates at 37°. Key: ×, suspenoid pure phenylbutazone; ○, recrystallized pure phenylbutazone; ●pure phenylbutazone.

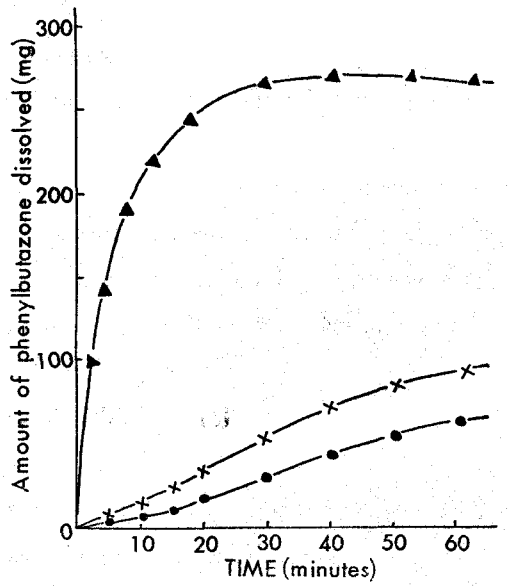

Fig. 2. Dissolution rates of phenylbutazone and phenylbutazone-PVP coprecpitiate at 37°.Key: ●, pure phenylbutazone, recrystallized; ×, 1:1 (w/w) phenylbutazone-PVP physical mixture; ▲, 1:1(w/w) phenylbutazone-coprecipitate.

Goldberg et al.[12] in 1965 suggested the formation of solid solution to reduce the particle size to a minium, i.e., insoluble drugs dispersed moleculary in the matrix of soluble, inert carriers. This can increase not only the dissolution rate, but also the solubility of drugs. While the dissolution rates of phenylbutazone from physical mixtures system are increased about two (=1.75) fold as compared with the pure drug (Fig. 6). And, then the differences between the three coprecipitates system

and pure phenylbutazone are highly significant (Fig. 2,3,4 and 5.), but there is no statistical difference from the 1:1, 1:5 and 1:9 (w/w) coprecipitate systems and the physical mixture systems, too (Figs. 5 and 6)

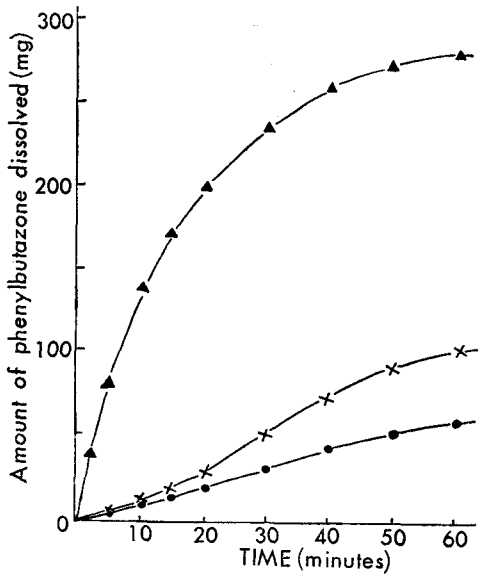

Fig. 3. Dissolution rates of phenylbutazone and phenylbutazone-PVP coprecipitate at 37°. Key: ●, pure phenylbutazone, recrystallized; ×, 1:5(w/w) phenylbutazone-PVP physical mixture; ▲, 1:5(w/w) phenylbutazone-PVP coprecipitate.

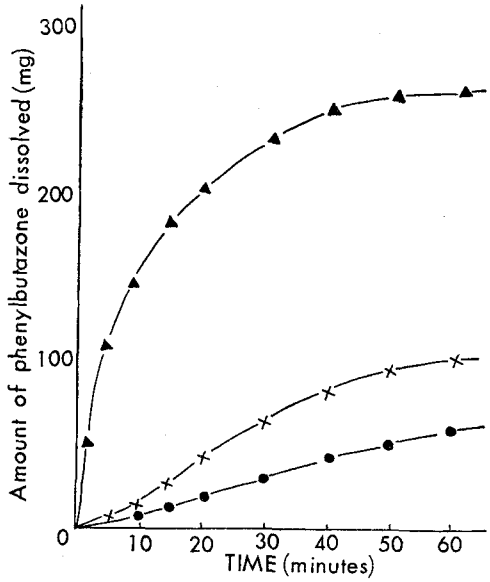

Fig. 4. Dissolution rates of phenylbutazone and phenylbutazone-PVP coprecipitate at 37°. Key: ●, pure phenylbutazone, recrystallized; ×, 1:9(w/w) phenylbutazon-PVP physical mixture; ▲, 1:9(w/w) phenylbutazone-PVP coprecipitate.

The dissolution rate half-lives ($T_{50\%}$) for the 1:1, 1:5, and 1:9(w/w) ratio phenylbutazone-polyvinylpyrrolidone coprecipitates at 37C° were determined by the log-probit methods.

A representative log-probit plots shown in Fig. 7 and the $T_{50\%}$ values obtained from plots of this nature are summerized in table II.

The data reveal that the rate of solution of phenylbutazone from the various ratio coprecipitate preparations decrease in the following order: 1:1〉〉1:5〉1:9〉〉1:0 (pure phenylbutazone recrystallized) 〉 1:0(pure phenylbutazone).

Table II. Effect of Drug-to-Polymer Ratio on the Dissolution Rate of Phenylbutazone from Phenylbutazone-Polyvinylpyrrolidone Coprecipitates and Physical Mixtures at 37°C.

Test System	$T_{50\%}$(min.)[a]	Percent Dissolved in 30 Minutes
Phenylbutazone[b]		11.7
Phenylbutazone[c]		25.5
Phenylbutazone[d]		79.6
Physical Mixtures		
1:1(w/w)		53.5
1:5(w/w)		63.4
1:9(w/w)		50.2
Coprecipitates		
1:1(w/w)	5.5	263.6
1:5(w/w)	10.0	229.4
1:9(w/w)	12.5	232.1

a) Determined from log-probit plots of dissolution data, *b*) Pure phenylbutazone *c*) Pure pheny lbutazone recrystallized, *d*) Suspenoid pure phenylbutazone

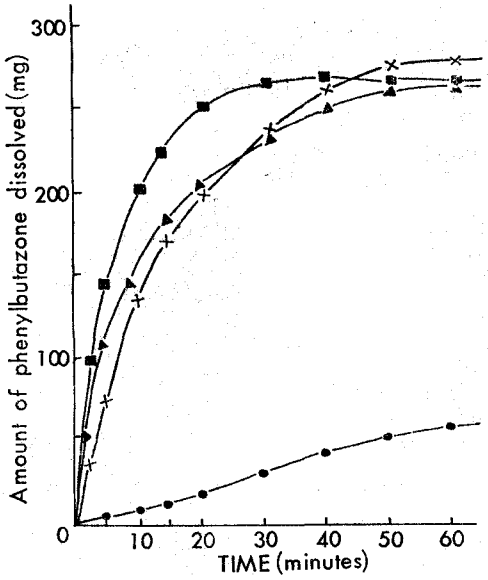

Fig. 5. Dissolution rates of phenylbutazone and phenylbutazone-PVP coprecipitates at 37°. Key: ●, pure phenylbutazone recrystallized; ■, 1:1 (w/w); ▲, 1:5(w/w); ×, 1:9(w/w) phenylbutazone-PVP coprecipitates.

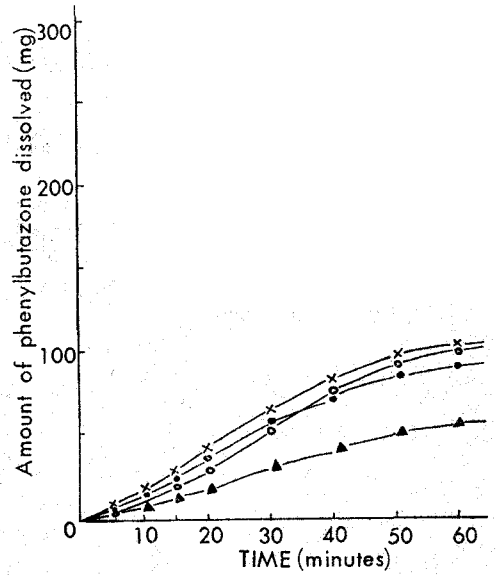

Fig. 6. Dissolution rates of phenylbutazone and phenylbutazone-PVP physical mixtures at 37°. Key: ▲, pure phenylbutazone, recrystallized; ●, 1:1(w/w); ×, 1:5(w/w); ○, 1:9(w/w) phenylbutazone-PVP physical mixtures.

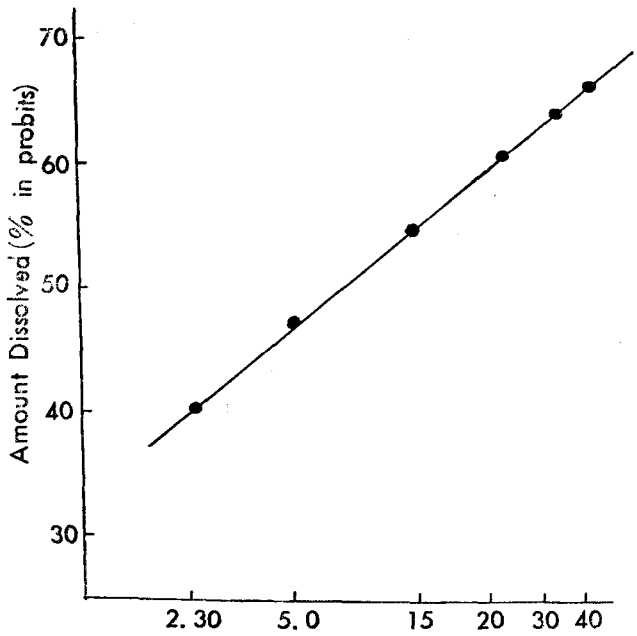

Fig. 7. Log-normal probability plot of dissolution rate data for phenylbutazone from a 1:1(w/w) ratio phenylbutazone-PVP coprecipitate at 37°C.

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