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THE INFLUENCE OF POLYVINYLPYRROLIDONE ON THE DISSOLUTION OF ALLOPURINOL

J.H. Collett
Department of Pharmacy, University of Manchester.

G. Kesteven
The Wellcome Foundation, Crewe.

ABSTRACT

Dissolution rates of allopurinol have been determined in non-disintegrating discs prepared from physical mixtures and from co-precipitates of allopurinol incorporating polyvinylpyrrolidone (P.V.P.). Four different molecular weight species of P.V.P., K-15, K-30, K-90 and Plasdone, were used. The results obtained indicate that the dissolution rate of allopurinol is not affected by changes in the amount of P.V.P. in the discs or by the molecular weight of the P.V.P. incorporated into the disc.

Dissolution rates of allopurinol into aqueous solutions of P.V.P. were less than those in solvent alone. The effect of P.V.P. in the dissolution media appears to be due almost entirely to the increase in bulk viscosity of the dissolution media.

INTRODUCTION

The dissolution of drugs with low aqueous solubility is often the rate controlling process in their absorption. Consequently those parameters which control dissolution rate assume special relevance. From a consideration of those controlling factors formulations can be prepared which can either enhance or inhibit the dissolution rate of sparingly soluble drugs.

Several approaches have been used in the control of drug dissolution. One such approach has been to add soluble hydrophilic polymers such as P.V.P. to the drug compound (1)(2). These polymers can affect the solution behaviour and transport properties of the drug molecules. There are conflicting reports in the literature as to whether P.V.P. enhances or retards drug dissolution from physical mixtures and from co-precipitates. Further there are reports that the molecular weight fraction of the P.V.P. contributes to its effect (3).

In this work the dissolution of allopurinol from physical mixtures and co-precipitates with P.V.P. of different molecular weight is investigated. Allopurinol was selected because of its low aqueous solubility. Three molecular weight species of P.V.P. were used including Plasdone, a pharmaceutical grade of the polymer. Plasdone complies with drug safety regulations in many countries and on this basis most emphasis is placed on allopurinol/plasdone systems. The aims of the work were firstly to determine the usefulness of P.V.P. in controlling the

dissolution of a drug with a low aqueous solubility, secondly to elucidate any controlling mechanism of P.V.P. on dissolution and finally to relate any effect of P.V.P. to its molecular weight.

EXPERIMENTAL

Materials and Apparatus

Dissolution measurements

Allopurinol B.P. and polyvinylpyrrolidone (P.V.P.) K-15, K-30 and K-90 have been described along with their characterization and assay procedures. In these experiments a pharmaceutical grade of P.V.P. (K-29 - 32, molecular weight 36,955) was also used.

Non-disintegrating discs (diameter 1.905 cm) of allopurinol and allopurinol/P.V.P. admixtures were prepared by compressing 2.0g of material in an Apex Type 14 hydraulic press at a compression load of 3,000 Kg.

Non-disintegrating discs of allopurinol/P.V.P. co-precipitates were prepared as follows. Appropriate amounts of allopurinol were dissolved in redistilled dimethylformarmide (Fisons) and the required amount of P.V.P. was then added to the solution. Dimethylformarmide was removed by evaporation and the dried material was powdered prior to the preparation of non-disintegrating discs.

The rotating disc type apparatus used for dissolution measurements has been described previously (4).

Viscosity measurements were made on an Epprecht Rheomat R.M.15 viscometer, Contraves A.G. Zürich. An MS-0 cup sustem was used for all viscosity measurements.

Methyl cellulose (Fisons) was used to adjust the viscosity of dissolution media where necessary.

RESULTS

Dissolution Rates of Allopurinol from Discs Containing Different Amounts of P.V.P.

Dissolution rates of allopurinol presented in Table 1 were determined from discs containing different proportions of allopurinol and P.V.P. (0-40% P.V.P.) using P.V.P. K-15, K-90 and Plasdone.

Dissolution rate constants are approximately equal for all admixtures used. The dissolution rates from discs containing P.V.P. K-90 were more variable than others. When dissolution

TABLE 1

Dissolution Rate Constants (g/sec) x 10^6 of Allopurinol into 0.1N Hydrochloric Acid from Discs Containing Different Amounts of P.V.P.

P.V.P.	% w/w P.V.P.						
Species	0.0	1	5	10	20	30	40
Plasdone	4.89	5.05	5.06	4.86	4.87	5.20	4.94
K-15	4.89	-	-	5.23	5.47	5.54	5.30
K-90	4.89	-	-	5.27	4.75	-	6.23

experiments were carried out on allopurinol/P.V.P. discs containing approximately 40% or more of P.V.P., the exposed surface of the discs released fragments of solid into the dissolution medium. Results from such experiments have no relevance to the studies since the condition of constant surface area was destroyed.

Dissolution Rates of Allopurinol from Discs Prepared from Allopurinol/Plasdone Co-Precipitates.

Co-precipitates were prepared containing from 10-90% Plasdone. The values of dissolution rate constants from the discs prepared from these co-precipitates are presented in Table 2.

Dissolution rate constants of allopurinol from discs containing 10% and those containing 20% Plasdone have similar values to those obtained from co-precipitates containing the same proportions of allopurinol/Plasdone. Discs containing 30% and more Plasdone were found to be pitted with a surface layer of white slurry after the completion of the dissolution test and

TABLE 2

Dissolution rate Constants (g/sec) x 10^6 of Allopurinol into 0.1N Hydrochloric Acid from Co-Precipitates of Allopurinol and Plasdone.

% w/w Plasdone						
0	10	20	30	40	60	90
4.89	5.14	5.15	5.94	5.64	8.03	15.66

consequently the dissolution rate constants obtained from these discs do not produce meaningful information.

Dissolution Rates of Allopurinol in Plasdone Solutions

The dissolution rates of allopurinol from non-disintegrating discs into water and aqueous Plasdone solutions were measured over a range of Plasdone concentrations at pH 1.0 and 6.0.

The dissolution rate is affected by both pH and concentration of Plasdone. At any given concentration of Plasdone, the dissolution rate at pH 1.0 is faster than at 6.0. The dissolution rate of allopurinol decreases with concentration of Plasdone at both pH 1.0 and 6.0.

Dissolution Rates of Allopurinol into Solutions Containing P.V.P. of Different Molecular Weight.

The range of concentrations of P.V.P. solutions was chosen so as to provide the same range of viscosity as the Plasdone solutions used in the previous experiments. Values of dissolution

TABLE 3

Dissolution Rate Constants (g/sec) x 10^6 of Allopurinol into Aqueous Plasdone Solutions at different pH.

	% w/v Plasdone						
pH	0	1	2	4	5	10	20
1.0	4.89	4.74	4.70	4.53	4.31	3.81	2.78
6.0	4.13	3.91	3.78	3.42	3.28	2.13	2.67

rate constants for allopurinol into solutions of different P.V.P. species of the same viscosity but different concentration are shown in Table 4. Dissolution rates decrease with increase in the concentration of P.V.P. but are approximately equal at a particular viscosity, suggesting that viscosity is a factor controlling the dissolution rate into P.V.P. solutions.

Dissolution Rates in Methyl Cellulose Solutions

The concentrations of P.V.P. used in the previous experiments provide a high viscosity relative to that of water. For this reason the influence of viscosity of dissolution media on dissolution rate was studied. Methyl cellulose was selected as a suitable substance to increase viscosity since it is relatively inert and readily available. The viscosities of the methyl cellulose solutions were equivalent to those of the P.V.P.

TABLE 4

Dissolution Rate Constants (g/sec) x 10^6 of Allopurinol into Aqueous Solutions of P.V.P. and of Methyl Cellulose with Equivalent Viscosity

Viscosity (centipoise)	P.V.P. K-15	K-30	K-90	Plasdone	Methyl cellulose
0.80	4.77	4.83	4.76	4.70	4.67
0.99	4.68	4.49	4.66	4.53	4.46
1.71	4.22	4.30	4.21	4.22	3.90
3.60	3.69	3.75	3.83	3.69	3.69

solutions. The dissolution rates of allopurinol decreased with increase in viscosity of the methyl cellulose solution (Table 4).

DISCUSSION

Three different molecular weights of P.V.P. were used in each of the groups of experiments. There were two main reasons for using each of the weight fractions rather than one polymer species. Firstly, it has been reported that the amount of P.V.P. released from non-disintegrating discs of P.V.P. decreases with increasing molecular weight fraction (3). Secondly, other workers found that the amount of sulphathiazole released from compressed tablets prepared from co-precipitates containing sulphathiazole and different molecular weight species of P.V.P. was a function of P.V.P. molecular weight. Thus, if P.V.P. influences the release of a drug from a non-disintegrating disc, then the choice of P.V.P. molecular weight is very important. If dissolution from polymer compresses obeys the Noyes-Whitney law then it might be expected that the polymer chain length producing the most significant increase in solubility of the drug would be most suitable. However, it has not been demonstrated conclusively that dissolution rates from polymer drug compresses are directly related to solubility in polymer solutions, therefore it is not reasonable to use one polymer only at this stage.

At pH 1.0 the dissolution rates of allopurinol from allopurinol/Plasdone non-disintegrating discs prepared from physical

mixtures are within the range 4.94 to 5.06 (g. sec^{-1}) x 10^6 with a mean of 4.97 and standard error of mean 0.46. These values may be regarded as constant, indicating that the dissolution of allopurinol is independent of the concentration of P.V.P. up to 40%. Dissolution rates of allopurinol from non-disintegrating discs of allopurinol/P.V.P. K-15 and allopurinol/P.V.P. K-90 were also constant (within experimental error) when the discs remained intact during the experiment. Such dissolution behaviour is consistent with the theoretical model for dissolution from a two phase mixture in which the two components do not interact with each other (5). Upon exposure to the solvent, both components should tend to dissolve at rates proportional to their solubilities and diffusion coefficients. After a certain time, usually one of the phases would become depleted at the solid liquid interface. In view of the relatively high solubility of P.V.P. compared with allopurinol, it is likely that P.V.P. becomes depleted from the surface of the disc leaving a layer of allopurinol. Theoretical dissolution curves for P.V.P. from drug/polymer discs have been calculated by Gibaldi and Weintraub using the following relationship ( ).

$$(DR)_B = \frac{N_B}{N_A} (DR)^o_A$$

where $(DR)^o_A$ is the intrinsic dissolution rate of component A, $(DR)_B$ is the dissolution rate of B and N_A and N_B are the original amounts of A and B in the mixture. Dissolution curves can also

be constructed for P.V.P. from allopurinol/P.V.P. admixtures. The dissolution profile can be compared to that reported by Gibaldi and Weintraub (6). It can be seen that the shape of the dissolution curves are similar for P.V.P. dissolving from discs of salicylic acid/P.V.P. and allopurinol/P.V.P. mixtures.

One assumption of this analysis is that the dissolution rate of P.V.P. is independent of the molecular weight of P.V.P. whereas Nogami reports that the dissolution rate of P.V.P. from non-disintegrating discs of P.V.P. alone is influenced by the molecular weight of the polymer. It may not be regarded as legitimate to compare dissolution rates of P.V.P. from P.V.P. discs alone to those of P.V.P. from P.V.P./drug mixtures (because of the influence of P.V.P./drug complexes on the dissolution rate of P.V.P.). However since it has been found that complexes of the type formed between allopurinol and P.V.P. do not influence the dissolution rate of the drug (6) then it is reasonable to use the dissolution profiles of P.V.P. obtained by Nogami (7) in the discussion of the current results. The dissolution profiles demonstrate an induction period at the beginning of the release process followed by a quasi steady state release. The length of the induction period increased with increasing molecular weight whereas the quasi steady state decreased. One explanation of the induction period is that the polymer matrix swells prior to dissolution (8). The uptake of solvent in this layer results in a continuous volume expansion of the matrix and at a distance

h from the "swollen matrix" boundary the matrix structure of the polymer does not exist. In this region the transport of polymer proceeds as a diffusion controlled process. The thickness of the diffusion layer is now governed by the hydrodynamics of the system. It is possible to calculate the concentration of P.V.P. at the solid-liquid boundary $C_{P.V.P.}$ from the following relationship (5).

$$C_{P.V.P.} = \frac{G_{P.V.P.}\, h}{D_{P.V.P.}}$$

where $G_{P.V.P.}$, $D_{P.V.P.}$ and h are the dissolution rate, diffusion coefficients and diffusion layer thickness of P.V.P. It can be calculated that the solid-liquid boundary concentration did not reach a concentration of 1% until the P.V.P. weight fraction in the discs was greater than 0.75.

In the current work the solubility of allopurinol was only slightly influenced by the presence of 1% P.V.P. Other workers have reported that the solubility of hydroflumethiazide (9) and of sulphathiazole is less in solutions containing 1% P.V.P. than in 0.1N HCl. Thus if increased dissolution rate from P.V.P./ drug mixtures is due to enhanced drug solubility in the diffusion layer due to the presence of P.V.P., then one possible explanation for the apparent none effect of P.V.P. on dissolution rate is the low concentration of P.V.P. in the diffusion layer. This explanation is complicated however by observations of increased drug dissolution rates from co-precipitate systems containing

drug/P.V.P. in the same proportions as those used in physical mixtures.

For example, Simonelli (3) and Corrigan (9) reported enhanced dissolution of sulphathiazole and hydroflumethiazide from co-precipitates. Dissolution profiles obtained by both workers were non-linear showing a rapid initial dissolution followed by a slower limiting dissolution rate. The rapid initial stage of dissolution was thought to be due to a high energy polymorph in each case rather than a direct effect of P.V.P. The later slower stage was assumed to be due to a P.V.P. carrier effect. In the current work, plots of amount dissolved as a function of time were linear. It is unlikely that an effect due to a polymorphic form would be expected, thus any effect of the polymer must be due to a P.V.P. carrier effect. The magnitude of the contribution of the P.V.P. carrier effect is probably a function of the diffusion layer thickness as evidenced by the results of Simonelli and of Corrigan (a twofold increase in the diffusion layer thickness halved the dissolution rate).

One of the principle ways in which P.V.P. exerts its influence on mass transfer through the diffusion layer and subsequently on dissolution rate is its contribution to viscosity which in turn affects the drug diffusion coefficient.

A series of experiments were designed to investigate the dissolution of allopurinol into solutions containing different concentrations of P.V.P. with different molecular weights. In

all cases the dissolution rate decreased as the concentration of P.V.P. increased. Furthermore for equal concentrations of P.V.P. the decrease in dissolution rate increased with increase in the P.V.P. molecular weight. P.V.P. dissolution media containing equal concentrations of different molecular weight P.V.P. have different viscosities.

It was decided to prepare solutions of P.V.P. K-15, K-30 and K-90 possessing viscosities equal to the viscosities of the Plasdone solutions used as the dissolution media in the previous dissolution experiments. The concentrations of P.V.P. K-15, K-30 and K-90 necessary to produce such solutions were obtained from the viscosity/concentration relationships determined previously. Solutions prepared in this way were used as dissolution media in further experiments. The dissolution rate constants for allopurinol discs into these media are reported in Table 4 . It can be seen that the rate constants in any medium of P.V.P. species are approximately equal to the rate constants obtained in solutions of Plasdone of the same viscosity. The dissolution rate of allopurinol in these systems appears to be related to viscosity. Further indications of the dissolution rate dependence on viscosity were demonstrated by carrying out dissolution rate determinations into solutions of methyl cellulose of known viscosity at pH 1.0. Plots of dissolution rate constants against viscosity for all the P.V.P. molecular weight species and methyl cellulose are approximately equal at pH 1.0.

The slopes obtained for Plasdone at pH 6.0 were of lower magnitude, probably due to the lower solubility of Plasdone at this pH. Thus it would appear that one of the main influences of P.V.P. on the dissolution rate is by way of its increase in the viscosity of the diffusion layer. Such an increase brings about a decrease in the diffusion coefficient of the drug or drug/polymer complex. During the course of this investigation, other workers (10) reported confirmatory findings. They observed that the dissolution rate of sodium chloride from compressed discs into dissolution media containing P.V.P. (molecular weight 360,000) decreased as the concentration of P.V.P. increased. The decrease in dissolution rate was attributed to an increase in the bulk viscosity of the dissolution media. More recently it was reported that the addition of 10% $^{w}/_{v}$ P.V.P. (molecular weight 360,000) to discs of sodium chloride or ephedrine or panioic acid reduced the dissolution rate of these compounds by 90%, 59% and 44% respectively (10). The saturation solubilities of these compounds decreased in the ratio 19.4 : 4.1 : 1.

For drugs exhibiting appreciable saturation aqueous solubilities, the incorporation of P.V.P. into non-disintegrating discs of these drugs is effective in retarding the drug dissolution rate from the discs. The more soluble the drug, the more effective is P.V.P. in retarding the drug dissolution rate. Usually, for drugs with low aqueous solubility, the dissolution rate is unaffected by the incorporation of P.V.P. into non-

disintegrating discs of such drugs. The only instances where the dissolution rate of poorly soluble drugs has been affected by the presence of P.V.P. in the discs are when the drugs exhibit polymorphism. Preparation of a co-precipitate between drugs exhibiting polymorphism and P.V.P. can result in the formation of a high energy (high solubility) polymorph being produced. In these systems drug dissolution may be increased. Different molecular weights of P.V.P. may have an effect on the dissolution rates of drugs from discs prepared using co-precipitates if the drug has different affinities for different chain length polymer species. The chain length associated with the highest solubility of the drug would be expected to produce the greatest increase in the dissolution rate. Usually the shorter the chain length of P.V.P., the greater is the increase in the dissolution rate.

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