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THE SOLUBILITY OF ALLOPURINOL IN AQUEOUS SOLUTIONS OF POLYVINYLPYRROLIDONE

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ABSTRACT

Saturation solubilities of allopurinol have been determined in aqueous solutions at pH 1.0 containing different molecular weight fractions of polyvinylpyrrolidone (P.V.P.). The P.V.P. was characterized using light scattering techniques.

Over the temperature range 15-40^{o} the solubilities increased linearly with concentration of P.V.P. For equal concentrations of different P.V.P. species the lower the molecular weight the greater is the increase in solubility of allopurinol. Solubility increases were never more than a twofold increase for any polymer species at any temperature. Binding ratios indicated a low affinity of allopurinol to all the P.V.P. species with the greatest affinity being for the lower molecular weight fraction.

The solubility data has been used to calculate enthalpy, free energy and entropy values for allopurinol/P.V.P. systems. Changes in these thermodynamic parameters did not suggest complex formation between allopurinol and P.V.P.

INTRODUCTION

There has been considerable interest in the use of water soluble polymers in the modification of the solubility and dissolution rate of drugs (1)(2). Various polymers have been used but P.V.P. has been the polymer of choice in many drug/polymer complexes (3)(4). Several workers have attempted to relate drug release rate from drug/polymer complexes to polymer molecular weight and have derived mechanisms of increased dissolution rate (5). Calculation of theoretical drug dissolution rates, from drug/polymer complexes based on these mechanisms requires certain basic data describing interactions between the drug and polymer.

In this work the solubility of allopurinol in solutions containing different molecular weight fractions of P.V.P. have been investigated. The aim is to characterize the interactions between P.V.P. and allopurinol. It is hoped that the solubility data may be of use in describing dissolution data to be obtained at a later date.

EXPERIMENTAL

Materials

Allopurinol B.P. (Burroughs Wellcome and Company, London) 150μ (100 mesh B.S.S.) was used for this work.

Polyvinylpyrrolidone (P.V.P.). Three molecular weight fractions of P.V.P. were used; P.V.P. K-15, K-30 and K-90 supplied by General Aniline Film Company. These fractions had nominal molecular weights of 10,000, 40,000 and 360,000 respectively.

HCl, AR (Fisons) as 0.01M and 0.1M solutions in distilled water were used as solvents and for pH adjustments in the solubility and dissolution experiments.

Methods

Light scattering methods were carried out using a photogonodiffusiometer (Fica 42000). The light scatter at angles between 45^{o} and 135^{o} was measured at 546 nm wavelength for a series of solutions containing different concentrations of each polymer species in 0.1N hydrochloric acid.

Differential refractometry. The change in refractive index with concentration of several dilute aqueous P.V.P. solutions (dn/dC) was determined at 0^{o} and 180^{o} using a differential refractometer (Polymer Consultants Ltd.). The scatter of the standard glass block was measured at 90^{o}.

Solubility. The saturation solubility of allopurinol was determined in a series of aqueous solutions at pH 1.0 containing con-

centrations of P.V.P. ranging from 1-10% w/v. Solubilities were determined at 15°, 25°, 35° and 40°.

Assay of solutions. The allopurinol content of the solutions was determined spectrophotometrically using a Unicam SP500. The wavelength of maximum absorption for allopurinol in 0.1M hydrochloric acid was 250 nm.

RESULTS

The Molecular Weights of P.V.P. Species

The relationship between the molecular weight (m), the change in refractive index with concentration (dn/dC) and the relative light scatter at 90° (S_{90}) is (6)

$$\frac{1}{m} = K^1(dn/dC)^2 \times \frac{C}{S_{90}}$$

where K^1 is a constant for the light scattering instrument. This relationship holds for molecules which are symmetrical or exhibit only a small asymmetry.

Values of S_{90} were calculated by dividing the observed light scatter at 90° by that for the standard glass block. Plots of S_{90} against concentration of P.V.P. were linear for each polymer species. Examination of light scatter values between the angles of 45° and 135° indicated that the amount of asymmetry in the system was small. Consequently reciprocals of $\frac{C}{S_{90}}$ presented in Table 1 could be used in the calculation of polymer molecular weight. The values of molecular weight are presented in Table 1

TABLE 1

Values of the Reciprocal Slope, Mean Values of dn/dC and Molecular Weight for P.V.P. K-15, K-30 and K-90.

P.V.P.	dn/dC	Reciprocal Slope $\frac{C}{S_{90}}$	M. Wt. from light scattering	Manufacturer's value
K-15	0.149	0.00518	14,006	10,000
K-30	0.151	0.00209	37,8222	40,000
K-90	0.148	0.00223	368,324	360,000

along with mean values of dn/dC and the manufacturer's specification.

Saturation Solubilities of Allopurinol at pH 1.0.

It can be seen (Table 2) that at any one temperature the saturation solubilities are dependent on both the molecular weight and the concentration of P.V.P. As the molecular weight of P.V.P. is increased, the saturation solubility of allopurinol is decreased for a given concentration of P.V.P. indicating a greater affinity of the short polymer chains for allopurinol compared to that of the long polymer chains. The affinity of P.V.P. for allopurinol may be accounted for by interactions of polymer groups on the P.V.P. chain with polar groups in the allopurinol molecule, or entrapment of allopurinol molecules within the coil structure of P.V.P.

Binding Ratios of P.V.P. with Allopurinol.

The number of P.V.P. polymer units for a particular molecular weight species at a given temperature, associated with one

TABLE 2

Saturation Solubilities of Allopurinol (g/litre) in olutions of P.V.P. at pH 1.0 and at Different Temperatures.

% w/v P.V.P.	K-15				K-30				K-90			
0	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)
0	0.345	0.569	0.885	1.084								
2	0.389	0.644	0.983	1.220	0.369	0.615	0.960	1.181	0.363	0.564	0.909	1.175
4	0.495	0.728	1.117	1.330	0.420	0.669	1.035	1.272	0.385	0.602	0.956	1.219
6	0.562	0.810	1.221	1.469	0.449	0.726	1.128	1.369	0.480	0.633	1.000	1.268
8	0.611	0.916	1.356	1.645	0.524	0.787	1.203	1.444	0.533	0.662	1.018	1.313
10	0.697	0.987	1.476	1.760	0.544	0.863	1.283	1.530	0.436	0.726	1.038	1.373

a, 15°; b, 25°; c, 35°; d, 40°.

molecule of allopurinol is obtained from the slope of a plot of moles of P.V.P. repeating unit per litre against moles of allopurinol per litre. The binding ratios obtained in this way are presented in Table 3.

Whilst the affinity of the polymer for allopurinol is low, it increases with increase in temperature and decreases with increase in molecular weight.

The binding of allopurinol on to P.V.P. chains may also be considered on a "mole for mole" basis. The number of moles of allopurinol bound to one mole of P.V.P. polymer species decreases in the order:- K-90 > K-30 > K-15. This reversal of the binding ratio trend shown in Table 3 is to be expected

TABLE 3

Binding Ratios of Allopurinol on to P.V.P. at Different Temperatures for Different Molecular Weight Species.

Molecular Weight Species	Temperature °C 15		25		35		40	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
K-15			286.5	0.318	206.8	0.229	178.4	0.198
K-30	563.8	0.181	416.9	0.116	305.1	0.0847	275.3	0.0764
K-90	1342.4	0.0414			736.4	0.0227	442.9	0.0137

(a) moles of P.V.P. repeating unit per mole of allopurinol.

(b) moles of P.V.P. per mole of allopurinol.

since the number of polymer repeating units is much greater for the high molecular weight polymer species.

ΔHs, the Differential Heat of Solution.

The differential heat of solution for allopurinol in P.V.P. K-15 and K-30 decreases with increase in P.V.P. concentration, suggesting a possible complex formation between allopurinol and P.V.P.. Values for ΔHs at a particular concentration of polymer increase with increase in molecular weight.

ΔHp, The Heat of Partitioning

The present system can be considered as a distribution of allopurinol between 0.1M hydrochloric acid (in which the mole fraction of allopurinol is n_o) and the various concentrations of polymer in 0.1N hydrochloric acid (in which the mole fraction of allopurinol is n_a). The heat of partitioning may be obtained from

$$\log \frac{n_a}{n_o} = -\frac{\Delta Hp}{2.303RT} + \text{a constant}$$

TABLE 4

Differential Heats of Solution (Kcals per Mole) for Allopurinol in P.V.P.

Molecular Weight Species	% w/v P.V.P.					
	0	2	4	6	8	10
K-15	8.248	8.198	7.163	6.991	7.163	6.637
K-30	8.248	8.423	7.995	8.074	7.359	7.481
K-90	8.248	8.456	8.236	8.595	8.737	8.031

The ΔHp values in P.V.P. K-15 and K-30 solutions become increasingly negative as the concentration is increased but no conclusion may be drawn for the K-90 solutions. The effect of increasing molecular weight appears to make the ΔHp values less negative for a given concentration of P.V.P.

ΔGp, The Free Energy of Partitioning

The free energy of partitioning may be calculated from

$$\Delta Gp = -2.303RT \log \frac{n_a}{n_o}$$

ΔGp values in Table 6 are small and negative ranging from -0.01 to -0.375 Kcals per mole and become increasingly negative with increasing polymer concentration at a particular temperature.

DISCUSSION

In the present study, the criterion for solubility equilibrium was that daily assays on three consecutive days agreed to within

TABLE 5

Differential Heats of Partitioning (Kcals per mole) for Allopurinol in Different Molecular Weight Species of P.V.P. Solutions at pH 1.0.

Molecular Weight Species	% w/v P.V.P.				
	2	4	6	8	10
K-15	-0.109	-0.388	-0.608	-0.741	-0.795
K-30	+0.136	-0.255	-0.174	-0.901	-0.771
K-90	+ 0.207	-0.014	+0.571	+0.408	-0.216

TABLE 6

Free Energies of Partitioning (Kcals per Mole) for Allopurinol in P.V.P. Solutions at pH 1.0 and Different Temperatures

% w/v P.V.P.	K-15				K-30				K-90			
	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)
2	-0.077	-0.082	-0.073	-0.084	-0.047	-0.055	-0.060	-0.063	-0.036	-0.040	-0.026	-0.060
4	-	-0.165	-0.162	-0.152	-0.130	-0.116	-0.115	-0.120	-0.085	-0.052	-0.067	-0.093
6	-	-0.238	-0.226	-0.219	-0.177	-0.173	-0.178	-0.175	-0.216	-0.092	-0.105	-0.128
8	-	-0.320	-0.301	-0.301	-0.275	-0.241	-0.228	-0.219	-0.285	-0.128	-0.126	-0.161
10	-	-0.375	-0.362	-0.353	-0.306	-0.296	-0.278	-0.266	-0.181	-0.194	-0.149	-0.200

(a) 15^{o}

(b) 25^{o}

(c) 35^{o}

(d) 40^{o}

experimental error. Equilibrium was achieved within seven days. During the course of the solubility experiments the physical appearance of the undissolved allopurinol did not change. The solubility of salicylic acid in P.V.P. solutions at pH 1.0 was investigated by Gibaldi and Weintraub (7). These workers found an irregular approach to equilibrium, which was not reached until about fourteen days. Furthermore, excess crystalline salicylic acid used in the solubility tests appeared to be transformed into an amorphous plastic precipitate.

When aqueous solutions of P.V.P. are used as the solvent then the solubility of allopurinol is greater than in the aqueous solutions themselves. This increase in solubility is presumably caused by either entrapment of allopurinol molecules within the coil structure of the polymer or, more probably, by adsorption on to P.V.P. chains. The affinity of P.V.P. for allopurinol is low, as is demonstrated by the binding ratios which range from 178 to 1342 units of P.V.P. associated with each molecule of allopurinol. However, as expected, the extra amount of allopurinol dissolved does increase proportionally with the amount of P.V.P. present in the dissolution media.

The samples of P.V.P. used in these studies are classified according to their mean molecular weights. But, molecular weight species considerably above and below the mean value are also present. It has been shown (8) that P.V.P. of molecular weight fractions below 10,000 exhibit viscosities characteristic of polyelectrolytes. The quantity of P.V.P. of molecular weight

less than 10,000 contained in the samples used in these studies should increase in the order K-15 > K-30 > K-90 and in consequence the ionic character of the samples should also increase in the same order. If it is assumed that allopurinol is bound to the P.V.P. chains by the interaction of its polar groups with polar sites on the chains, then the affinity of P.V.P. for allopurinol should increase in the order K-15 > K-30 > K-90. Examination of Table 3 reveals this to be the case.

Differential heats of solution (ΔHs) values (Table 4) decreased with increase in P.V.P. concentration for P.V.P. K-15 and K-30. In the case of P.V.P. K-90, the differences in ΔHs values were of the order of those expected from experimental error, nevertheless ΔHs values appear to remain approximately constant.

In an effort to produce more meaningful data, changes in the enthalpies of partitioning (ΔHp) with change of P.V.P. concentration were calculated. However, results calculated by this method are also subject to significant errors because the mathematical methods are rather too sensitive for the experimental techniques used. These difficulties were also encountered by Feldman and Gibaldi (8) in their study of the effect of urea on the aqueous solubility of benzoic and salicylic acids. In the calculation of enthalpies it is necessary to obtain the partitioning ratios $^{n}a/n_{o}$. Small errors in $^{n}a/n_{o}$ become large errors when log $^{n}a/n_{o}$ is calculated and can produce large errors in enthalpy values. Consequently it is more meaningful to discuss trends rather than

individual results when interpreting the thermodynamic data. In all cases ΔHp values tend to become more negative as the concentration of P.V.P. in solution increases, these values range from from +0.207 to -0.795 Kcals/mole. These values are much lower than those normally obtained for hydrogen-bond formation (approximately 3-5 Kcals/mole). The free energies of partitioning (ΔGp) are all negative indicating that the adsorption process is always spontaneous. The more negative ΔGp is, the more spontaneous is the process. From Table 6 it can be seen that the process becomes more spontaneous with increase in P.V.P. concentration. Temperature appears to have little effect on ΔGp. The magnitudes of the ΔGp values are again too small to indicate hydrogen-bond formation.

In view of the small ΔHp and ΔGp values obtained it is to be expected that the ΔSp values tend to become more negative (indicating an ordering of the system) as the concentration of P.V.P. is increased.

In summary, the thermodynamic parameters indicate that the association between allopurinol and P.V.P. is spontaneous. The bonds formed are probably weak dipole interactions between polar groups on the allopurinol molecule and polar sites on the P.V.P. chains. It is also possible for water molecules to collect at the surface of the P.V.P. chains if by doing so they reduce the interfacial free energy between water and P.V.P. This ordering of water and the resulting loss of entropy (which would increase

with increasing P.V.P. concentration) may make a contribution to the negative ΔSp values obtained.

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