International Journal of Pharmaceutics, 58 (1990) 177–184
Elsevier

IJP 01975

Research Papers

Thermodynamics of paracetamol solubility in sugar-water cosolvent systems

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(Received 7 April 1989)
(Modified version received 28 July 1989)
(Accepted 5 August 1989)

Key words: Solubility; Paracetamol; Sugar; Thermodynamics; Cosolvent; Sorbitol; Glucose; Sucrose

Summary

The solubility of paracetamol in different concentrations of sorbitol, glucose and sucrose solutions was studied at 20 and 37°C. There was an appreciable decrease in solubility of the drug at both temperatures, the effect generally being more apparent at the lower temperature as reflected by the solubility ratios. Sorbitol exhibited the greatest effect followed by glucose then sucrose. Thermodynamic parameters were calculated and showed the nonspontaneity of the solubility process (positive free energy values). Entropy changes were positive or of small negative values, while enthalpy changes were positive and of relatively small values. Such results are compatible with the occurrence of hydrophobic interactions that led to a reduction in the solubility of the antipyretic agent. However, the effect of sugar concentration on the thermodynamic parameters was not the same with the three sugars tested, suggesting differences in their solvency characteristics.

Introduction

The nature of the solvent-cosolvent interactions which lead to variation in the solubility of a solute in a cosolvent system is still uncertain (Shihab et al., 1971; Lindstrom and Lee, 1980; Shihab et al., 1988). Sugar vehicles are an example of a cosolvent system in which a significant increase or decrease in solubility of a solute may happen (Paruta, 1964; Paruta and Sheth, 1966; Sanghavi and Khatib, 1980; Eshra et al., 1988; Shihab et al., 1988). The results are sometimes so strongly inconsistent with the sugar concentration (Eshra et al., 1988) that there is no conclusive evidence to support the mechanism whereby solubility changes occur. The common use of sugars in the pharmaceutical industry of liquid formulations accordingly makes more information about their solvency characteristics of specific relevance. By considering the physical events which are accompanied by changes in free energy, heat content and entropy, a thermodynamic analysis would help rationalize the process of solubility changes.

Paracetamol is an antipyretic of choice for children. In a previous work (Walters, 1968) the solubility of paracetamol was studied in sorbitol solutions at concentrations from 0 to 8%. It would be interesting to extend the concentration range of sorbitol so as to reach nearly saturation and to investigate as well the effect of other sugar moie-

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ties on the solubility of the drug. The present report deals with some aspects of thermodynamics in an attempt to interpret paracetamol solubility in various sugar vehicles, by relating solute-solvent-cosolvent interactions, on a molecular basis, to the total solubility.

Experimental

Materials

Sorbitol (Wilkinson-Vickers, Wharfedale Labs, U.K.), paracetamol (Alexandria Pharmaceuticals, Alexandria, Egypt), glucose and sucrose (B.P. grade), were used.

Method

Excess amounts of paracetamol were added to aqueous solutions containing various concentrations of sorbitol, glucose or sucrose in glass stoppered flasks. The flasks were shaken in a constant temperature water bath at 20 or 37 °C for 6 h and allowed to stand for 18 h to attain equilibrium. Samples were then withdrawn, properly filtered, diluted and analysed spectrophotometrically (Unicam SP 1800, U.K.) at 244 nm for paracetamol.

Results and Discussion

The solubility results of paracetamol in water and in different sugar solutions at 20 or 37 °C are shown in Figs. 1 and 2 and Table 1.

The solubility of paracetamol as in the case of solids in general increased with temperature (endothermic) due to the lowered solubility of the crystal lattice (Chen et al., 1976). Fig. 1 shows the effect of sorbitol, glucose and sucrose on the solubility of paracetamol as a function of concentration. With increasing sugar concentration, the solubility of the drug decreased to a degree sometimes considerably lower than that in water. The decreasing effect of the various sugars on the solubility of the drug was in the following order: sorbitol > glucose > sucrose. Results at 20 °C qualitatively paralleled those at 37 °C and approx. similar solubility curves were obtained in all cases.

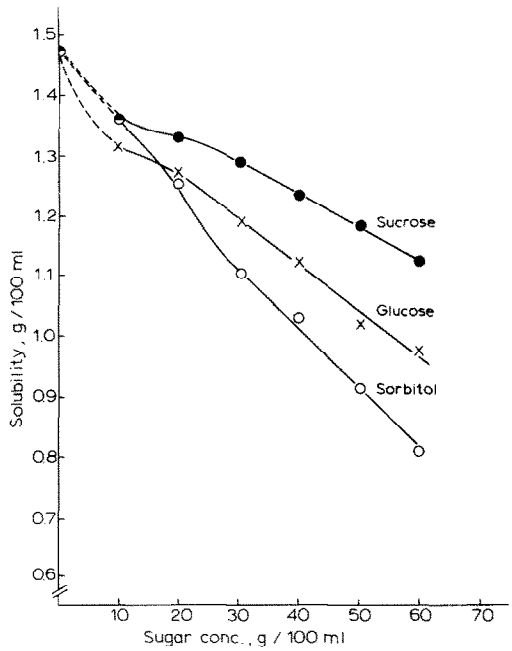

Fig. 1. Solubility of paracetamol in sorbitol (○), glucose (×) and sucrose (●), solutions at 20 °C.

However, the solubility ratios (solubility in sugar solution/solubility in water) (Table 1) were in general higher at 37 °C, indicating a greater effect at the lower temperature. Also, significant changes in the magnitude of solubility were noted between the different sugars. In 70% sorbitol solution at 20 °C, the solubility of the drug decreased dramatically (solubility ratio 0.47).

Sorbitol, glucose and sucrose were shown (Shihab et al., 1988) to decrease the dielectric constant of water, the effect increasing with sugar concentration. Nevertheless, the solubility results obtained in the present study are in contradiction with the dielectric constant concept which states that when the polarity of a solvent is decreased, it becomes a more favourable medium for the dissolution of nonpolar or relatively nonpolar drugs (Paruta, 1964). Similar unexpected results were previously reported (Paruta and Sheth, 1966; Shihab et al., 1988) and in such cases, the sugar solutions were considered as media in which the activity of water has been decreased by producing a statistically reduced number of available hydrogen bonding sites. The generally lower solubility

TABLE 1

Data for the solubility of paracetamol in sugar solutions

Sugar concentration (w/v)	S/S_o [a]						X [b]						K [c]					
	Glucose		Sucrose		Sorbitol		Glucose		Sucrose		Sorbitol		Glucose		Sucrose		Sorbitol	
	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C
10	0.888	0.962	0.918	1	0.92	0.94	0.0198	0.0108	0.0274	0	0.0146	0.0164						
20	0.857	0.892	0.898	0.981	0.85	0.89	0.0126	0.0153	0.0171	0.0051	0.0137	0.0155						
30	0.806	0.822	0.878	0.962	0.75	0.82	0.0114	0.0168	0.0137	0.0069	0.0152	0.0170						
40	0.755	0.752	0.827	0.873	0.70	0.77	0.0108	0.0176	0.0146	0.0171	0.0132	0.0164	0.049	0.0618	0.0584	0.0822	0.0878	0.0729
50	0.684	0.682	0.806	0.841	0.61	0.66	0.0112	0.0180	0.0130	0.0171	0.0139	0.0193						
60	0.663	0.662	0.755	0.771	0.54	0.61	0.0099	0.0159	0.0137	0.0205	0.0137	0.0188						
70			0.735	0.733	0.47	0.55			0.0127	0.0205	0.0135	0.0182						

[a] S/S_o = solubility in sugar solution/solubility in water

[b] X = no. of moles of drug precipitated per mole of sugar.

[c] K = salting out coefficient.

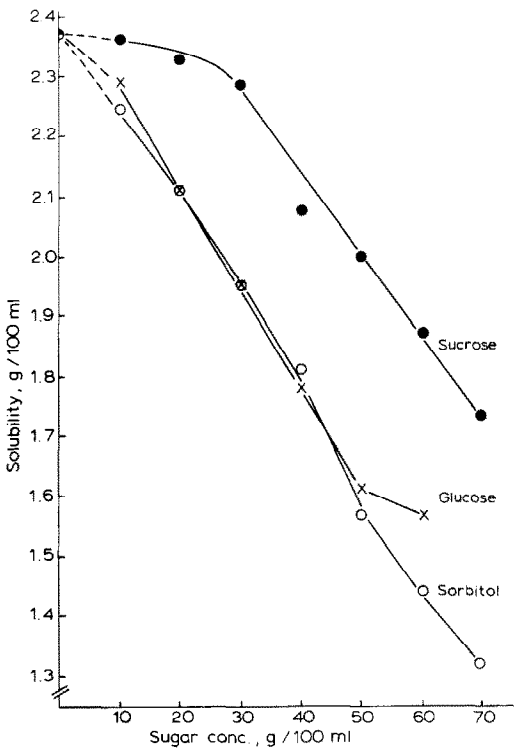

Fig. 2. Solubility of paracetamol in sorbitol (○), glucose (×) and sucrose (●), solutions at 37 °C.

ratios of the drug at 20 than 37 °C (Table 1) indicate that the effects are lower when the activity of water is higher (Shihab et al., 1988). There were exceptions in the case of glucose at concentrations from 40 to 60% and of sucrose at 70%, the ratios being slightly lower at 37 than at 20 °C. Another way of treating the data is to subtract the molar solubility of the drug in sugar solution from that in water. This should give the number of moles of drug that are precipitated because of the presence of sugar. Dividing this figure by the molar concentration of sugar would give the number of moles of drugs removed from solution by each mole of sugar. Table 1 shows that at all sorbitol concentrations and for concentrations higher than 10 and 30% for glucose and sucrose, respectively, the values were higher at 37 than 20 °C. No general trend in the values with change of sugar concentration could be observed at both temperatures for the three sugars.

Each nonelectrolyte in solution is assumed to occupy an element of volume. The 'effective pressure' of the surrounding medium will increase the energy required for maintaining this 'hole' and will thereby decrease the solubility of the nonelectrolyte (McDonald and Lindstrom, 1974). The strongly hydrophilic sugar moieties may produce in water localized environments different from pure aqueous dipoles. Irrespective of the mechanism by which the drug is squeezed out of water, comparatively little 'room' would be available for it. Thus a solubility decrease of paracetamol in the presence of sugars can be tentatively considered to be a nonspecific salting out effect. In a previous work (Collett and Flood, 1976), similar parameters were derived for the nonelectrolyte substance urea in its effect on the solubility of salicylic acid. For comparative purpose, salting-out coefficients K were therefore computed (Block and Patel, 1973) (Table 1). At 20 °C , sorbitol gave the highest K value, followed by sucrose. At 37 °C, K decreased for sorbitol as compared to the value obtained at 20 °C, while it increased in the case of glucose and sucrose. This again, may suggest some variations in the mechanism of solubility of paracetamol in the different sugar solutions.

An indication of the type of reaction occurring between solutes and solvent, may be obtained from values of the free energy ΔF associated with the solubility process

$$\Delta F = -2.303RT \log S_s/S_w \quad (1)$$

where S_s and S_w are the molar solubilities of drug in aqueous sugar solutions and water, respectively (Shihab et al., 1988). The changes in any system are spontaneous when the free energy of the system decreases, i.e. when ΔF is negative. This possibility is determined by three factors, the change of heat content ΔH (bonding strength), temperature T and entropy change ΔS (disordering or bond breaking). At a constant temperature, the free energy will be determined by the change in the heat content and the entropy change, the equilibrium considered being between the same standard states.

$$\Delta F = \Delta H - T\Delta S \quad (2)$$

TABLE 2

Thermodynamic parameters for the solubility of paracetamol in sugar solutions
Values between parentheses represent ΔF/mol sugar

Sugar concentration (w/v)	ΔF (cal mol^{-1})						ΔS (cal mol^{-1} deg^{-1})						ΔH (cal mol^{-1})		
	Glucose		Sucrose		Sorbitol		Glucose		Sucrose		Sorbitol		Glucose	Sucrose	Sorbitol
	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C	20 °C	37 °C			
10	69.81	24.16	49.91	0	49.91	36.61	2.685	2.685	2.937	2.937	0.615	0.624	856.4	910.56	230.05
	(125.8)	(43.5)	(170.8)	(0)	(91.0)	(66.7)									
20	90.34	71.07	63.08	11.96	97.37	71.07	1.137	1.136	3.008	3.008	1.347	1.358	423.34	944.56	491.91
	(81.4)	(64.0)	(108.0)	(20.5)	(88.7)	(64.7)									
30	126.32	121.81	76.56	24.16	172.6	121.81	0.269	0.269	0.083	3.083	2.669	2.686	205.04	980.02	954.52
	(75.9)	(73.2)	(87.3)	(27.6)	(104.8)	(74.0)									
40	164.61	177.08	111.66	84.5	205.64	161.51	−0.392	−0.411	1.601	1.606	2.778	2.768	94.7	580.61	1019.5
	(74.1)	(79.8)	(95.5)	(72.3)	(93.6)	(73.5)									
50	222.88	237.76	126.32	107.56	287.56	255.4	−0.643	−0.656	1.108	1.107	1.833	1.837	34.48	450.84	824.43
	(80.3)	(85.7)	(86.5)	(73.6)	(104.8)	(93.0)									
60	240.64	255.4	164.61	161.51	360.27	311.53	−0.772	−0.777	0.185	0.185	3.221	3.201	14.52	218.75	1803.87
	(72.3)	(76.7)	(94.0)	(92.1)	(109.4)	(94.6)									
70			180.7	193.05	443.29	366.08					4.226	4.243			1681.4
			(88.4)	(94.4)	(115.4)	(95.3)									

ΔH can be determined using the integrated form of the van't Hoff equation:

$$\Delta H = 2.303 \log \frac{(S_s/S_w)_2}{(S_s/S_w)_1} \cdot \frac{RT_2T_1}{T_2 - T_1} \quad (3)$$

The different thermodynamic parameters are listed in Table 2. In all cases, ΔF values were positive, indicating the nonspontaneous nature of the dissolution processes; in spite of a general favourable entropy increase. The entropy increase was, however, not large enough (even being of small negative value in some cases) to override an opposing enthalpy change. The free energy change values showed that increase in sugar concentration, provided a less thermodynamically suitable environment for the solubility of the drug (ΔF increase). On the other hand, the general decrease in ΔF values for each sugar system with increase of temperature is probably related to changes in the solvent structure (Wetlaufer et al., 1964). An exception was for glucose at high concentrations (40–60%) and for sucrose at 70%. For each particular system, values of ΔF/mol sugar gave approximately the same trend with increasing sugar concentration as the ΔF values themselves. However, the glucose and sucrose systems at 20 °C showed much less consistency in this respect.

Liquid water is known to be highly structured due to the formation of intermolecular hydrogen bonds (Elworthy and Worthington, 1968). The solubility of a weak acid like paracetamol in water is mainly controlled by the presence of polar groups on the aromatic ring but is also influenced by the hydrophobic surface of the molecule (Feldman and Gibaldi, 1967). Paracetamol is an aminophenol. It possesses both an OH and an NH group. The solubility of paracetamol in water is thus due largely to the presence of these polar groups permitting solvation by water through dipole interaction forces particularly hydrogen bond formation. This hydrogen bonding would tend to break the clusters of hydrogen bonded water molecules and replace them partially with hydrogen bonds between the polar portion of paracetamol and free water molecules (Feldman and Gibaldi, 1967). Sugars possess many hydrogen bonding sites which by interacting with water may affect its structuring and compete with the drug. Therefore, in the presence of sugars, the solubility of the drug will depend mainly on the interaction between the hydrophobic portion of the drug molecule and the water clusters. Essentially, the nonpolar portion of the solute becomes the fifth neighbour of the tetrahedral water molecules through van der Waal's interactions. The greater stability in this pentacoordinated state will promote an ordering effect on the solvent. An interaction of this type is called hydrophobic hydration and would tend to be a limiting factor on the solubility of the drug. When it becomes excessive, hydrophobic hydration produces a situation where the association of nonpolar portions through hydrophobic bonding (the sum of weak noncovalent interactions) becomes energetically more favourable as there would be more entropy to be gained by the system (Feldman and Gibaldi, 1967). In fact, hydrophobic bonding is driven by the entropic contribution since it originates from the diminution in the amount of ordered 'iceberg' structure in the water layer surrounding the nonpolar groups of the drug solute when two such groups associate to form a single cavity instead of occupying separate cavities in the water (Donbrow et al., 1976).

The breaking up of water clusters surrounding the nonpolar portions requires heat ($+\Delta H$) and increases the randomness ($+\Delta S$). From a mechanistic point of view, hydrophobic bonding actually places a limitation on the solubility of the drug as it would tend to pull it out of solution (Feldman and Gibaldi, 1967). From the data in Table 2, the overall picture shows that the entropy changes were generally positive or of very small negative value, while the enthalpy changes were positive, a fact that eliminates the possibility of a complexation mechanism between the sugars and the drug (Feldman and Gibaldi, 1967). Moreover, the values of enthalpy change were relatively small, as is generally observed in hydrophobic events (Lindstrom and Lee, 1980). In addition, the possibility of a complex between paracetamol and sorbitol has been ruled out in a previous study (Walters, 1968). With increasing sorbitol concentration, ΔS and ΔH increased, suggesting that the water available to dissolve the drug was stripped off progres-

sively more by the sugar as its concentration increased. The gradual increase in enthalpy with sugar concentration, will thus correspond to the reduced solvent structure near the nonpolar areas, as they associate together through hydrophobic bonding. It should be noted that ΔS values were generally slightly lower at the lower temperature.

In the case of glucose, there was a decrease in enthalpy with increasing sugar concentration. At the same time, the entropy decreased with increase in sugar concentration at both temperatures. It even became negative at higher concentrations. This may indicate a gradual decrease in solubility by polar groups contribution and an increase of hydrophobic hydration. ΔH values decreased gradually with increasing concentration of glucose, suggesting that the net breaking of water-solute (drug or sugar) bonds decreased. This is compatible with hydrophobic hydration events (Feldman and Gibaldi, 1967). At the same time, ΔS values decreased and became even negative leading to increase in the ordering of the system. The entropy change implies a far greater disorder of paracetamol molecules in solution than in the crystal. At high concentrations of sugar, the amount of water available for the drug decreases. This may represent a state closer to that in the crystal than in the dilute sugar solution (Elworthy and Worthington, 1968).

Regarding sucrose, at low concentrations, an increase in entropy and enthalpy occurred, then after 40%, there was a decrease in both values. This suggests that at low concentrations, hydrophobic bonding took place, then after 40% was reached, there was a gradual decrease in the breaking of water solute bonds (ΔH decrease) and a decrease in ΔS leading to less disordering in the system. The overall decrease in the number of water molecules available at high sugar concentrations, may be partly responsible for this peculiar behaviour. It also seems possible that a complicated series of equilibria between water and the sugar are in operation as well as possible associations between the complexed solvents and the solute (Elworthy and Worthington, 1968).

It should be noted that ΔS values were generally the same at 20 and 37 °C or slightly higher at 20 °C for both glucose and sucrose systems. In the case of glucose, however, the differences were more pronounced.

In spite of the rather similar nature of the three solvent systems studied, the thermodynamic parameters determined provide substantial evidence that change in the mechanism of drug solubility with sugar concentration was not essentially the same for the various sugars. On the other hand, a practical implication of the results obtained is that the preparation of a liquid pediatric form of paracetamol in the sugar solutions tested, will obviously not provide the required dose (120 mg) in a teaspoonful (5 ml). Since there is a tendency to substitute sorbitol solution (B.P.C, U.S.P) for glycerol in pharmaceutical preparations (Martindale, 1982) and since paracetamol is approx. 3.5-times more soluble in glycerol than in 70% sorbitol solution at 20 °C, the present data would serve to obviate such a tendency. Moreover, the possibility of precipitation with thermal variation below ambient will be of concern, particularly that with sorbitol, ΔS values being lower at the lower temperature tested.

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