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Influence of solvent composition on the solubilities and solid-state properties of the sodium salts of some drugs

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Summary

The solubilities of the sodium salts of some sulfonamides, barbiturates and hydantoins have been determined in mixtures of propylene glycol and water. In many cases, the solubilities of the salts in the mixed solvents were lower than those in water, however, several compounds exhibited enhanced solubilities in the mixed solvents. This unexpected increase in solubility was not related to the lipophilicity of the acidic forms of the drugs and occurred in at least one member of each group of compounds. Analysis of the solid phase which had been equilibrated with each solvent indicated the formation of crystal hydrates for most of the solutes, and in at least one instance, mixed solvates. These compounds could be categorized on the basis of their desolvation temperatures. Those compounds with low temperatures of desolvation had increased solubilities in propylene glycol-water mixtures while compounds with high desolvation temperatures had decreased solubilities in the mixed solvents. These data indicate that crystal hydrate formation plays a significant role in determining if a cosolvent can be used to enhance the solubilities of certain sodium salts.

In the last several years considerable interest has been devoted towards understanding and quantitating the influence of solvent blending, or cosolvency, on the solubilities of lipophilic solutes (Martin et al., 1979; Williams and Amidon, 1984; Yalkowsky and Rubino, 1987). Most of these studies considered the influence of solvent composition on the solubilities of nonelectrolyte solutes. However, few studies have examined the influence of solvent composition on the solubilities of salt forms of drugs. The combination of salt formation and consolvency might, in some instances, provide an alternative method of solubilization of a poorly water soluble weak electrolyte drug in cases where either technique alone is unsuitable due to reasons of poor chemical stability of the drug, toxicity due to high concentrations of cosolvents, or the inability of a single method to achieve the desired concentrations of drug in a formulation.

In theory, the addition of a cosolvent to an aqueous salt solution would be expected to reduce the solubility of the drug due to a reduction in the dielectric constant of the medium with a corresponding reduction in the solvation of the ions (Johnson, 1968). However, some studies have demonstrated that the addition of cosolvents to aqueous solutions of the salt forms of drugs has resulted in enhanced solubilities of the drugs

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(Kramer and Flynn, 1972; Agharkar et al., 1976). This apparent contradiction between the observed and expected behavior of salts in semi-aqueous solvent systems prompted further study of this phenomenon.

In the present study, the influence of solvent composition on the solubilities of the sodium salts of some representative poorly water soluble weak electrolyte drugs was examined. These included the sodium salts of some sulfonamides, barbiturates and hydantoins. The determination of the solubilities of the salts was performed at 25 ± 0.2°C in a constant temperature water bath. An excess amount of salt was equilibrated with 0, 10, 30 and 50% propylene glycol in water for 24–72 h. The supernatant was filtered through a 0.45 μm solvent-resistant filter, diluted with 0.1 N NaOH and assayed spectrophotometrically. Solubility determinations were performed in triplicate. The solid phase from the solubility experiments was collected onto filter paper, blotted free of excess solvent and dried under ambient conditions. Differential thermal analysis was performed on the solid phases using a Perkin Elmer DSC-2. Examination of the solid phase by thermal analysis was performed to ensure that the acid form of the drug did not precipitate during the equilibration procedure (Anderson and Conradi, 1985). In addition, it was reported previously (Rubino, 1989) that most of the compounds included in the present studies formed crystal hydrates when equilibrated with water. Thus, the drying time for the solid phases was dependent upon the rate of water loss from the crystal hydrate. Solvates with relatively low temperatures of desolvation were dried for 3 h; drying for longer periods of time resulted in significant changes in the transition temperatures. The more stable solvated solids were allowed to dry from 24 to 48 h without significant changes in their thermograms. The solvent com-

TABLE 1

Semi-aqueous / aqueous solubilities and transition temperatures (K) for desolvation [a]

Drug	log PC [c]	Fraction of propylene glycol			ΔH (cal K^{-1} $mol)^{-1}$ [b]
		0.10	0.30	0.50	
Sodium sulfadimethoxine [d]	1.56	1.14 (335)	1.18 (320)	1.31 (320)	1 800
Sodium sulfamerazine [d]	0.14	0.86 (390)	0.68 (390)	0.54 (385)	5 030
Sodium sulfamethazine [d]	0.27	0.90 (385)	0.78 (385)	0.69 (385)	3 100
Sodium sulfaquinoxaline [d]	1.68	0.98 [e] (385)	0.99 [e] (381)	0.98 [e] (381)	3 520
Sodium sulfathiazole [d]	0.05	1.07 (336)	1.34 (336)	1.80 (347)	1 050
Sodium amobarbital	2.07	1.01 [e]	1.02 [e]		
Sodium barbital	0.65	1.02 [e]	0.85 [e]	0.58	
Sodium butabarbital [d]	1.89	1.14 (350)	1.30 (350)	1.33	
Sodium phenobarbital	1.42	0.96 [e]	0.96 [e]	0.92	
Sodium 5-methyl-5-phenylhydantoin [d]	1.02	0.96 (395)	0.93 (395)	0.85 (395)	
Sodium phenytoin [d]	1.98	1.27 (330)	1.58 (345)	1.08 (345)	1 070

[a] Numbers in parentheses are transition temperatures.
[b] Calculated per mole of water in crystal after equilibration in 10% propylene glycol.
[c] Log octanol/water partition coefficient of acid form.
[d] Indicates compounds which form crystal hydrates.
[e] Indicates ratio not significantly different from 1.00 at $p < 0.05$.

position of the solid phase was determined from the loss of weight after heating in the DSC, or from the spectrophotometric absorbance of a known weight of the solid phase, as reported previously (Rubino, 1989). The presence of propylene glycol in the solid phase was determined using high-performance liquid chromatography with a refractive index detector. The stationary phase was a 10 μm, 25 cm, C-18 column and the mobile phase consisted of 30% methanol in water. The flow rate was 1 ml/min. In order to verify further the presence of the sodium salt after equilibration, the solid phase in many cases was also examined using a Phillips X-ray powder diffractometer. This was also performed to detect possible structural changes in the various solvates which were identified.

The results of the solubility determinations are presented in Table 1 along with the log octanol/water partition coefficient of each drug (Leo et al., 1971). The data are listed as the ratio of the solubility of the drug in mixed solvent/water. Aqueous solubilities were reported in a previous publication (Rubino, 1989). For many of the compounds, the addition of cosolvent resulted in a reduction in the solubility of the drug as would be expected based on a reduced dielectric constant of the solution. However, four compounds unexpectedly exhibited enhanced solubility upon addition of the cosolvent. These four compounds belonged to different chemical groups of drugs, indicating that the phenomenon was not related to a particular class of compound or ionic group. Likewise, the trends in the solubility data are apparently not related to the lipophilicity of the corresponding unionized form of the drugs. For example, the order of the partition coefficients for the sulfonamides is: sulfaquinoxaline > sulfadimethoxine > sulfamethazine > sulfamerazine > sulfathiazole. However, the order of the solubility changes in 30 and 50% propylene glycol from Table 1 is: sulfathiazole > sulfadimethoxine > sulfaquinoxaline > sulfamethazine > sulfamerazine.

The rank order of the solubility changes for the barbiturate salts likewise does not follow the order of the partition coefficients of the unionized forms of the drugs. In the case of the hydantoin salts, the more lipophilic phenytoin demonstrated some enhanced solubility in the mixed solvent systems compared with the 5-methyl-5-phenyl derivative, but the solubility profile is unusual in that a maximum was reached in 30% propylene glycol. These results indicate that the magnitude and direction of change of the solubilities of these salts do not appear to depend on the lipophilic nature of the conjugate acid.

The results of the DSC analysis confirmed that in each case, the solid phase was composed of the salt form of the drug. Thus, the solubility data reported in Table 1 are representative of the salt-solution equilibrium. These results also indicate that the saturated salt solutions were sufficiently basic to prevent precipitation of the acid form of the drugs in all cases but one. It was reported previously (Rubino, 1989) that thermal and X-ray analysis of samples of sulfathiazole sodium revealed evidence of precipitation of the acid form of the drug after equilibration with water, but most of the solid phase was composed of the sodium salt. As in the case of the purely aqueous systems, most of the compounds included in the present study formed hydrates, and in the case of phenytoin sodium, evidence of mixed solvates was found (see below).

Hydrate and solvate formation have been shown previously to influence the solubilities of nonelectrolyte drugs (Pfeiffer et al., 1970; Fokkens et al., 1983; Gould et al., 1989), however few studies have reported the effects of this phenomenon on electrolyte solubility. Fung and Nealon (1974) reported that the solvent composition of the dissolution medium can have a significant effect on the dissolution behavior of a given solvated form of a drug. In purely aqueous solvent systems, crystal hydrate formation has been associated with reduced solubilities, compared to anhydrous crystals, however, in semi-aqueous solvents their behavior might be quite different if a favorable interaction takes place between the cosolvent and the solvate or hydrate molecule. This may be the case in the propylene glycol-water system where an exothermic reaction between the two components has been noted (Borghesani et al., 1989).

It is reasonable to suspect, therefore, that crystal hydrate or solvate formation might play a role in the trends in the solubility data for the sodium

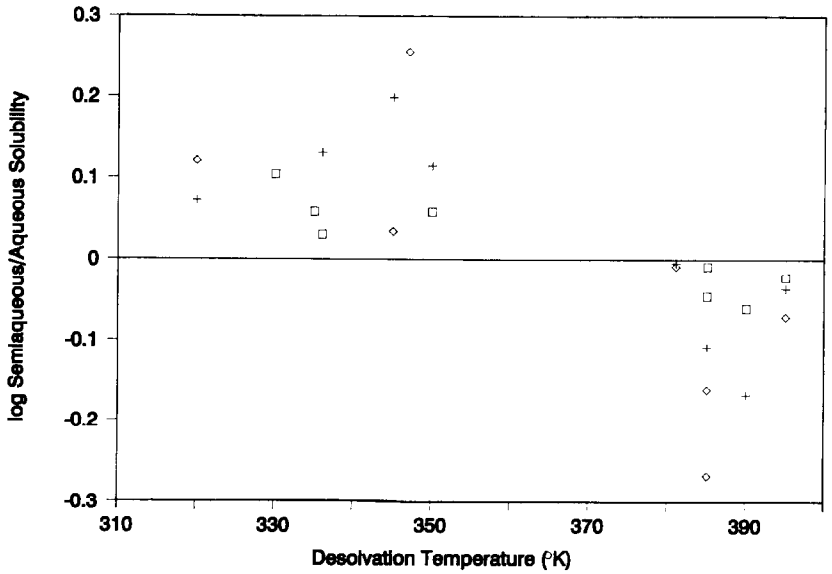

Fig. 1. Solubility in semi-aqueous/aqueous solvents vs temperature of desolvation. (□) 10% propylene glycol, (+) 30% propylene glycol, (◇) 50% propylene glycol.

salts reported in the present study. A plot of the log semi-aqueous/aqueous solubilities vs the desolvation transition temperatures is presented in Fig. 1 for those compounds that formed crystal hydrates. The temperatures for the onset of desolvation are listed in Table 1. The plot indicates that the salts appear to fall into two groups, 'low' and 'high' transition temperature solvates. Compounds which possess low temperatures of desolvation have increased solubilities in propylene glycol-water while those with high transition temperatures have decreased solubilities in the cosolvent-water mixture. The enthalpies of desolvation of the solid phase obtained after equilibration with 10% propylene glycol are reported in Table 1 for several of the compounds. These values are expressed as the enthalpy per mole of water present in the solid phase. The high transition temperature solvates were found to possess 3–5-fold greater enthalpies of desolvation per mole of water compared to the low transition temperature compounds. This observation is consistent with those of Fung and Nealon (1974) who observed that a high transition enthalpy, *t*-butylamine solvate of fluprednisolone did not demonstrate an enhanced dissolution rate in water while the lower transition enthalpy solvate of griseofulvin did show enhanced dissolution rates in water. It can also be noted from Table 1 that the solubilities of those compounds which did not show evidence of hydrate formation were either reduced or insignificantly influenced by the addition of the cosolvent. This observation agrees more closely with the anticipated effects of the addition of a polar cosolvent to an aqueous solution of a strong electrolyte.

The unusual solubility profile of phenytoin sodium in propylene glycol-water may also have been due to a change in the solid state of the drug. X-ray diffraction patterns of the solid phases were different after equilibration with each solvent system examined. Compositional analysis of the solid phase indicated a change in the crystal from a hexahydrate to a monohydrate when the solvent was changed from 10 to 30% propylene glycol, respectively. In addition, the solid phase incorporated one molecule of propylene glycol after equilibration in 30% propylene glycol. The remaining compounds retained only fractional amounts of propylene glycol in their solid phases. In 50% propylene glycol, the solid phase of phenytoin

sodium retained approx. 3 molecules of water and 1.5 molecules of propylene glycol.

Although the results obtained from the present studies do not provide a quantitative relationship of the effects of cosolvents on the solubilities of salts, the generality observed in Fig. 1 does seem to indicate that crystal solvation plays a significant role in determining whether the sodium salts of these drugs demonstrate enhanced solubilities in mixed solvent systems. The accurate prediction of the solubilities would most likely require numerous thermochemical data (Fokkens et al., 1983) as well as a knowledge of the dielectric constants of the saturated solutions. This might require that each drug be considered on an individual basis. Nonetheless, a consideration of solvate formation and its thermal behavior may help decide if a cosolvent will improve the solubility of a sodium salt. Finally, although the solubility increases observed for some of the compounds were relatively modest in the propylene glycol-water system, other solvent systems might result in greater solubility increases.

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