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Solubility of Acetaminophen in Cosolvents[1,2]

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The solubilities of acetaminophen (*N*-(4-hydroxyphenyl)acetamide) (ACA) were determined in various aqueous cosolvent mixtures, *i.e.*, ethanol–water, polyethylene glycol 400 (PEG 400)–water and polyethylene glycol 4000 (PEG 4000)–water, by ultraviolet spectrophotometry at 244 nm, a $30 \pm 2\,^{\circ}C$. The mixed solvents were prepared by mixing known volumes of solvents except in the case of PEG 4000–water where weight by volume (w/w) was used.

In the above aqueous cosolvent systems, the solubility of ACA increased with cosolvent concentration and the maximum appeared at about 80% cosolvent concentration. When the solubilities of ACA were plotted against the approximate dielectric constants, which were calculated from the sum of the product of the volume composition with the dielectric constants of the individual components, peaks were found at dielectric constant values of 25 and 35 for PEG 400–water and ethanol–water, respectively. The solubility was fitted to a log linear solubility equation proposed by Yalkowski *et al.*, which gave a good linear fit up to 40% cosolvent in all water–cosolvent mixtures. These results should be useful in the formulation of both oral and injectable ACA solutions.

Keywords——acetaminophen (*N*-(4-hydroxyphenyl)acetamide) solubility; aqueous cosolvent; ethanol–water; polyethylene glycol–water; dielectric constant–solubility correlation; solubility equation (log linear)

To formulate acetaminophen (*N*-(4-hydroxyphenyl)acetamide) solutions for oral or parenteral use, it is necessary to find suitable solvent systems which are physically and pharmaceutically acceptable. Cosolvents are usually employed to increase the solubility of drugs in an aqueous medium. Selection of such mixed solvent systems is generally performed in a hit-and-miss fashion. However, it would be preferable to have an experimental basis for such selection. An interesting use of approximate dielectric constant as a basis for blending solvent systems for new drug formulation has been described by Moore.[3] A correlation between solubility and dielectric constants in pharmaceutical systems has been demonstrated.[4] In most systems, there exist maxima showing that there is a narrow range of solvent composition (dielectric constant) which is optimum for solubility. This correlation is useful in that once the range of dielectric constant is known, it is often possible to translate this to other solvent systems of the same dielectric constant.

Recently, Yalkowski *et al.*[5] have used cosolvent systems to increase the solubility of nonelectrolytes in polar solvents and they found an empirical equation which describes the solubility as a function of nonaqueous composition. This correlation is useful in predicting the solubility of a drug in a mixed solvent with minimum experimentation.

The purpose of the present study was to determine the composition of mixed solvent systems that may be used as vehicles for acetaminophen solutions, as well as to find a means of predicting the solubility of acetaminophen in each solvent system.

Experimental

Materials——Acetaminophen (Paracetamol, product of Bayer AG, Germany) was the drug to be dissolved. The other ingredients used were ethanol, and polyethylene glycol (PEG) 400 and 4000 (Union Carbide). All materials were of USP-NF grade and were used as received.

Solubility Determination——Solubilities of acetaminophen were determined in a series of solvents (given as v/v, except for polyethylene glycol 4000–water, which is given as w/v). Excess acetaminophen was placed in screw-capped test tubes containing 10 ml of solvent system. The tubes were fixed to a rotator (Rototorque heavy duty, Cole–Palmer Instruments Co., U.S.A.) to provide continuous agitation and were equilibrated for 3 d at 30±2 °C. Samples were taken using glass wool-tipped pipets. Generally, duplicate samples were taken from each mixture at each time and were assayed independently. After suitable dilution, the absorbance was measured. The absorbance of acetaminophen solutions was read at a wavelength of 244 nm on a Beckman Acta CIII spectrophotometer (Beckman Instruments Inc., U.S.A.). Solubilities were determined from suitable calibration curves and consideration of dilution factors.

Approximation of the Dielectric Constants——The values of approximate dielectric constants of solvent systems were calculated from the sum of the products of the volume composition with the dielectric constants of the individual components.[3] Thus, a mixture of 60% ethanol in water should have the following approximate dielectric constant

$$\varepsilon_{mixt}=0.6(\varepsilon_{eth})+0.4(\varepsilon_{water}) \quad (1)$$

where ε_{mixt}, ε_{eth} and ε_{water} are the dielectric constants at 30 °C of mixed solvent, ethanol and water, respectively. This approximation was valid for two of the solvent systems, but of course was inapplicable to the case of PEG 4000, which is a solid.

Results and Discussion

Analysis of Acetaminophen

The absorbance of acetaminophen was followed up to 15 μg/ml and was found to obey Beer's law. The molar absorptivity of acetaminophen in water was found to be 10050. There was no interference from the cosolvents at the concentrations present in the diluted samples.

Solubility of Acetaminophen

The solubility of acetaminophen at 30±2 °C in the various mixed solvent systems is shown in Table I. In aqueous cosolvent systems, *i.e.*, ethanol–water, PEG 400–water and PEG 4000–water, the solubility of acetaminophen increases with the concentration of the cosolvent. The maximum solubility appeared at about 80% cosolvent concentration. In general, large negative entropic effects can occur upon dissolution of a relatively nonpolar nonelectrolyte in water. Such an effect due to hydrophobic association considerably affects the

Table I. The Solubility of Acetaminophen in Aqueous Cosolvent Systems at 30±2 °C

Percent of cosolvent	Solubility (mg/ml)		
	Ethanol–water	PEG400–water	PEG4000–water
0	21	22	22
10	31	37	42
20	49	57	56
30	77	85	85
40	119	120	122
50	160	159	166
60	196	227	210
70	224	237	—
80	243	263	—
90	231	235	—
100	202	197	—

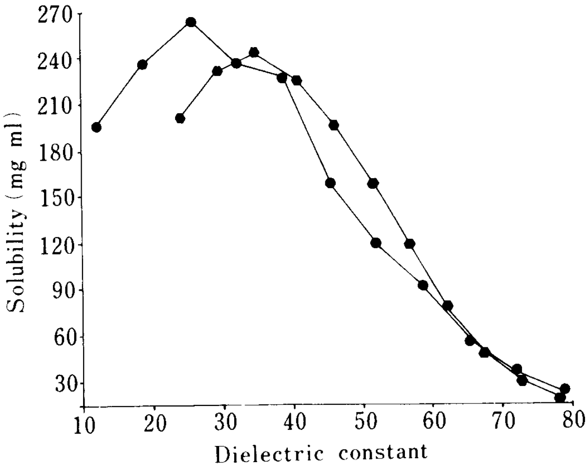

Fig. 1. Solubility of Acetaminophen in Aqueous Cosolvent Systems as a Function of Dielectric Constants

●, in ethanol–water; ●, in PEG 400–water.

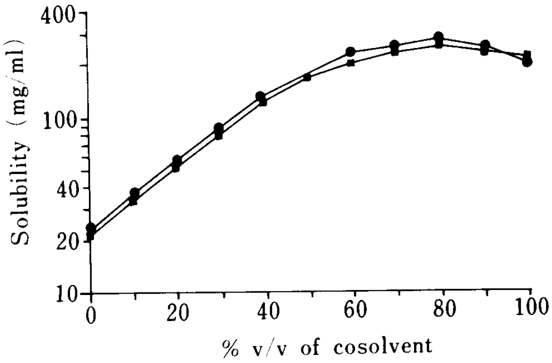

Fig. 2. Solubility of Acetaminophen at 30 °C as a Function of Cosolvent Content (v/v)

■, ethanol–water; ●, PEG 400–water.

Table II. Semi-empirical Correlation of Solubility of Acetaminophen with Cosolvent Content[a)]

Cosolvent mixtures	S_w (mg/ml)	σ	r
Alcohol–water	23	1.95	0.9700
PEG400–water	23	1.81	0.9858
PEG4000–water	23	1.77	0.9827

a) Regression line from 0 to 40% cosolvent.
S_w: solubility of acetaminophen in water. σ: parameter in Eq. (2). r: coefficient of correlation.

solubility. It is conceivable that the mixed solvent systems bring about a reduction in hydrophobic association. Thus, the use of cosolvents may increase the solubility of acetaminophen by increasing the entropy of solution.

Correlation of the Solubility with Dielectric Constants

Figure 1 shows a plot of the solubility of acetaminophen against the approximate dielectric constant of solvent mixtures. It can be seen that there are peak solubilities in the PEG 400–water and ethanol–water systems at dielectric constant values of 25 and 35, respectively. This finding is in general agreement with the results of Paruta *et al.*,[4)] who studied the solubility of acetaminophen in the dioxane–water system and found three peaks of solubility at dielectric constants of 14, 28 and 33—37. These values may serve as a guideline in blending of other solvent systems. The compositions of solvent mixtures should provide a dielectric constant close to the dielectric requirement of acetaminophen at the above peaks in order to obtain optimum solubility.

Semi-empirical Correlation

Yalkowski *et al.*[5)] introduced a log linear equation:

$$\log S = \log S_w + \sigma f \qquad (2)$$

which describes the solubility of some drugs in binary aqueous systems, where S is the solubility in the mixed aqueous system containing the volume fraction f of nonaqueous solvent, S_w is the drug solubility in water, and σ is a parameter representing the solubilizing power of the cosolvent for the drug and depends on the polarity of the drug and cosolvent. The log linear solubility equation is not without theoretical support. Martin *et al.*[6] have derived it beginning with the extended Hildebrand approach. A good linear fit for semipolar drugs in a number of water–cosolvent mixtures, including a strong solvating agent for the solute, was also demonstrated.

In a manner similar to that described above, a plot of solubility on log scale against the cosolvent content is shown in Fig. 2. A linear fit is obtained from 0 to 0.4 volume fraction of nonaqueous solvent. The values of σ for each cosolvent system are shown in Table II. Thus, if the aqueous solubility of a drug and the solubility at one cosolvent content are known, one can estimate the solubilities at other solvent compositions.

Selection of Cosolvents for Acetaminophen

Oral acetaminophen liquids are intended for use in pediatric and elderly patients. In the selection of suitable vehicles, one of the most important factors to be considered besides the solubility of acetaminophen is the palatability of the product. Therefore, the concentration of nonaqueous solvent is often kept to a minimum. Sweetener, color, flavor and preservative may also be added. The minimum concentration of nonaqueous cosolvent required may be estimated from Eq. (2) or Fig. 2. For an acetaminophen solution of 24 mg/ml, the concentration of nonaqueous components is sufficiently low that unpleasant tastes can be masked by minor adjustment of adjuvants. At the concentration of 100 mg/ml, acetaminophen may be solubilized by 36% ethanol or 34.5% PEG 400 or PEG 4000 at 30 °C. Higher concentrations of nonaqueous solvent will be required at lower temperatures. At these concentrations it is difficult to mask the undesirable tastes of ethanol and PEG 400. Propylene glycol and/or glycerin may be used in place of ethanol and PEG 400. The amount of propylene glycol or other solvent required to replace part or all of the ethanol or PEG 400 may be estimated from the dielectric constants (Eq. (1)). PEG 4000–water is a mixed solvent of choice because it is relatively tasteless. However, the bioavailability of the product should be evaluated, because there is a possibility of strong interaction between PEG 4000 and acetaminophen.

A 150 mg/ml acetaminophen injection requires 44.8% ethanol or 44.2% PEG 400. These concentrations of nonaqueous solvents are so high that they cause pain at the injection site and tissue damage may result. Multicomponent systems should be further investigated as a possible vehicle for acetaminophen injection.

References and Notes

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