Solubility of Nonelectrolytes in Polar Solvents

Keyphrases ☐ Solubility—nonelectrolytes in polar solvents ☐ Nonelectrolyte solubility—polar solvents

Sir:

It is generally recognized that established solubility relationships dealing with ideal and regular solutions are not well suited to the needs of the pharmaceutical chemist, because he is concerned primarily with aqueous and semiaqueous solutions of relatively nonpolar substances. The need for an understanding of the factors that govern solubility in polar solvents, for which regular solution theory is not applicable, is quite clear. Persuant to this need, we have concerned ourselves with the investigation of solubility relationships which are useful in determining solubility in aqueous and other polar media.

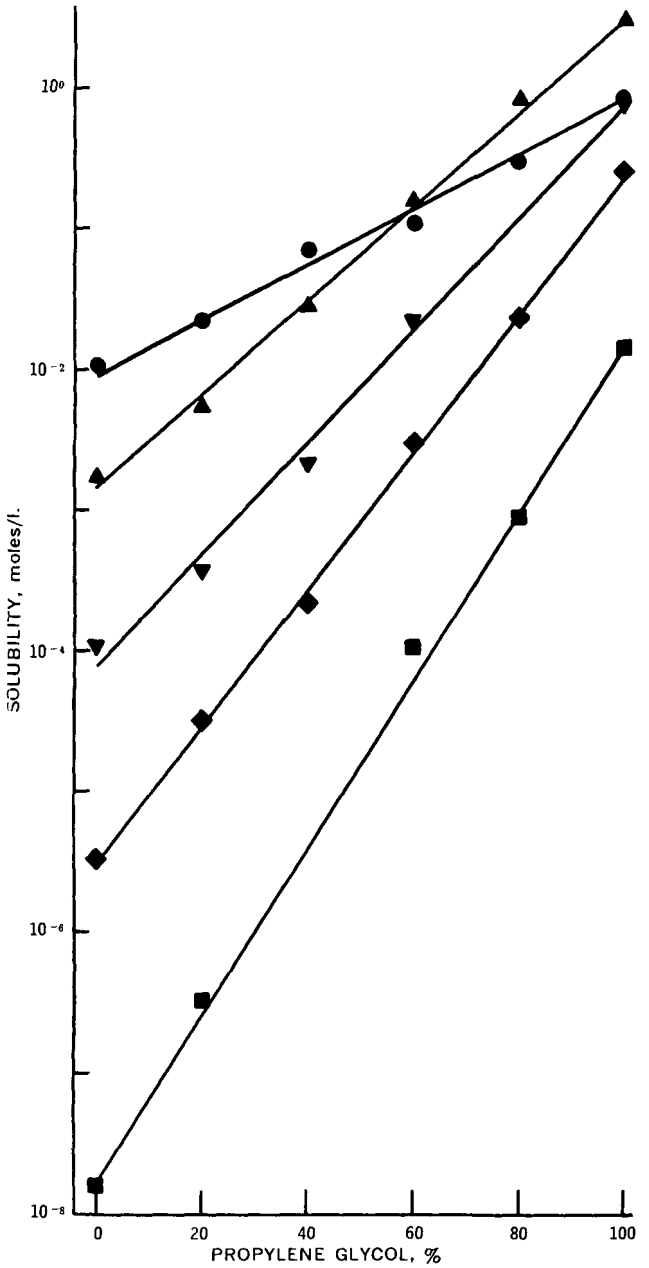

Figure 1—*Dependence of solubility of some alkyl* p*-aminobenzoates upon solvent composition. All measurements were performed at 37°. Key: ●, ethyl; ▲, butyl; ▼, hexyl; ◆, octyl; and ■, dodecyl.*

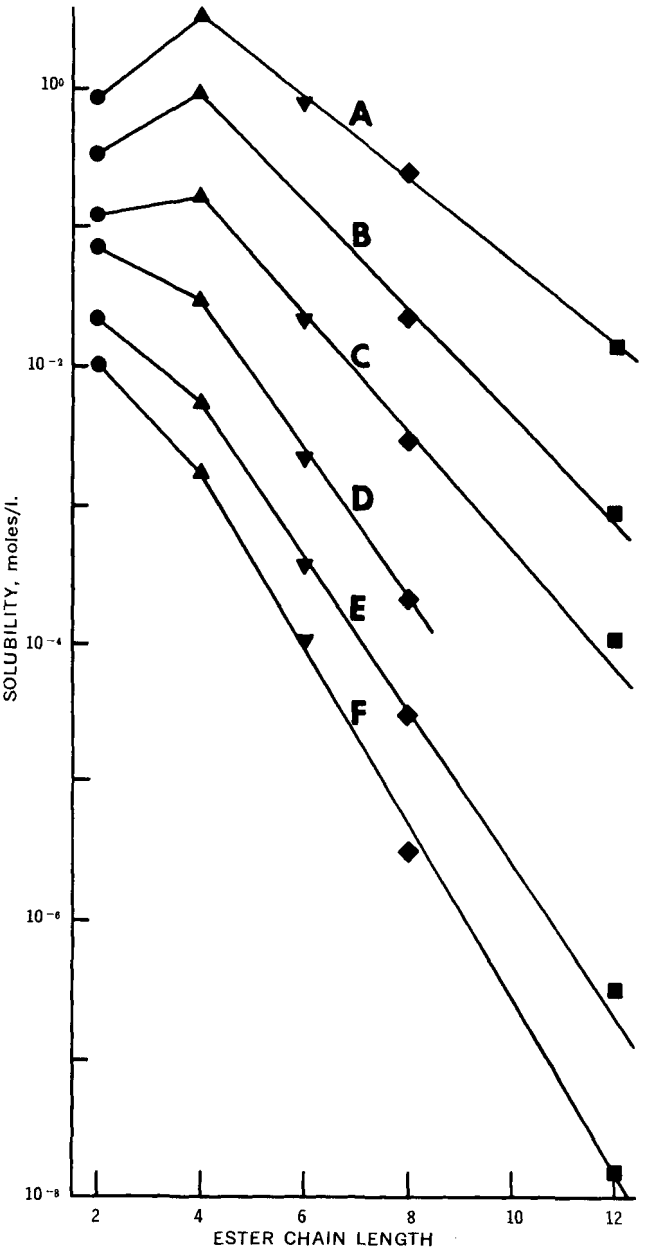

Figure 2—*Dependence of solubility upon chain length in various solvent mixtures. This graph contains the same data as Fig. 1 but replotted to show the linearity of chain length effects. Solvent: A, propylene glycol; B, 80% propylene glycol; C, 60% propylene glycol; D, 40% propylene glycol; E, 20% propylene glycol; and F, water. The breaks in the curves at four carbons were explained previously (7).*

Observations to date of our own data and literature data (1–5) indicate that for many drugs and druglike substances in binary aqueous systems:

$$\log S_f = \log S_{f=0} + \epsilon f \qquad \text{(Eq. 1)}$$

where S_f is the solute solubility in a mixed binary aqueous solvent consisting of volume fraction f of nonaqueous cosolvent; thus, $S_{f=0}$ is the solubility in water. The value of the constant ϵ is characteristic of the system under study. Results of investigations on the solu-

bility of some *n*-alkyl *p*-aminobenzoates in various binary solvent systems consisting of propylene glycol and water are shown in Fig. 1. It can be seen from the data in Fig. 1 that the slopes of the lines (*i.e.*, the value of ϵ) increase with the increasing chain length of the ester. In other words, the more nonpolar the homolog, the greater is its dependence upon the volume fraction of the nonaqueous component.

It has been noted (5–10) that frequently in water and other pure solvents:

$$\log S_n = \log S_{n=0} - \delta n \qquad \text{(Eq. 2)}$$

where S_n is the solubility of the homolog having n carbons in its alkyl chain, and $S_{n=0}$ is the intercept at a real or hypothetical chain length of zero. We have also noted that this relationship can be valid for homologous series in mixed solvents of any composition. As can be seen from the slopes of the lines in Fig. 2, the value of δ for the alkyl *p*-aminobenzoates is highly dependent on the solvent composition. [The breaks in the curves at four carbons were explained previously (7).]

It was postulated by other investigators (10–15) that solubility is determined in part by the combined energy required to create a cavity in the solvent which can accommodate the solute molecule and the energy involved in the insertion of a solute molecule into the cavity. For nonpolar materials, these processes can be highly influenced by the molecular hydrophobic surface area. To be specific, we have observed that the above δ and ϵ values can be related to the interfacial tension between the polar solvent or solvent mixture and a low energy hydrocarbon surface such as hexane, multiplied by the hydrophobic surface area of the homolog that would be exposed to the polar solvent. This work and some of its ramifications will be reported more completely in a forthcoming publication[1].

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Magnesium Lauryl Sulfate—Soluble Lubricant

Keyphrases ☐ Magnesium lauryl sulfate—evaluation as tablet lubricant ☐ Lubricants, tablet—evaluation of magnesium lauryl sulfate ☐ Tablet lubricants—evaluation of magnesium lauryl sulfate

Sir:

Lubricants are usually required in tablet and capsule formulations. Magnesium stearate is the most widely used lubricant, but its waterproofing properties can retard disintegration and dissolution. Thus, surfactants, such as sodium lauryl sulfate, are often added to formulations to counteract the waterproofing action of magnesium stearate (1, 2). We searched for a compound with the lubricating properties of magnesium stearate but without its waterproofing liability. We found one effective in three of four formulations studied.

The criteria against which the lubricants were measured were:

1. Will the formulation run?
2. What is the unit tablet or capsule weight variation from the mean (*i.e.*, the variance)? In each study, we tested for differences in weight variability given by two different batches by forming the ratio of these variances. If the two batches give weight distributions having equal variances, this ratio has the F distribution and one can test the hypothesis of uniform variance. In the first study, a tablet granulation with terra alba (89.9%), α-cellulose (4.8%), acacia (1.2%), and sucrose (4.1%) was used. Starch (5%) and the lubricant (Table I) were added with adequate mixing, and the granulations were

Table I—Tablets

	Lubricant	Mean Tablet Weight[a], mg.	*CV*, %
0.5%	Magnesium lauryl sulfate	1191.9	1.80
0.25%	Magnesium lauryl sulfate	1238.5	1.77
0.125%	Magnesium lauryl sulfate	Would not compress	
0.5%	Magnesium stearate	1191.2	1.84
0.25%	Magnesium stearate	1229.0	1.88
0.125%	Magnesium stearate	1200.5	2.10
0.0625%	Magnesium stearate	Would not compress	
0.5%	Sodium lauryl sulfate	1233.5	2.59
0.25%	Sodium lauryl sulfate	1246.1	2.65
0.0125%	Sodium lauryl sulfate	Would not compress	
0.5%	Talc	Would not compress	
0.5%	Polyethylene glycol 6000	Would not compress	
0.5%	Dioctyl sodium sulfosuccinate (85%) and sodium benzoate (15%)	Would not compress	
None		Would not compress	

[a] Twenty tablets were taken at regular intervals during a run, and 20 tablets were taken at random from a completed batch. Statistical evaluation of tablet weight variation data showed that sequential weight data and random weight data had roughly equal variability; variance estimates from the two sets were, accordingly, pooled.