Solubility Analysis of Multicomponent Systems Capable of Interacting in Solution

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Abstract □ The results obtained in this study show that individual solubility profiles may be of no value for predicting the equilibrium solubility of mixtures of drugs, particularly when the drugs are capable of interacting in solution to form a very insoluble complex.

Keyphrases □ Mixed solvent system—effect on drug solubility, drug–drug interactions □ Solubility analysis—mixed solvent system–mixtures of drugs, difficulties encountered in using individual solubility profiles □ Drug solubility—multicomponent systems capable of interacting in solution, deviation from individual solubility profiles □ Complexes, drug—in mixed solvent systems, effect on solubility

Many reports in the literature concern the use of mixed solvent systems to solubilize various compounds. Moore (1) attempted a semiempirical approach by trying to manipulate the dielectric constant of cosolvent blends to dissolve given amounts of drugs. This approach was the subject of several theoretical and practical studies (2–4). Other investigations of pharmaceutical interest noted that multiple peak solubilities may exist for a drug as a function of the solvent composition or dielectric constant (5–7).

Although the equilibrium solubilities of a number of drugs as a function of various solvent mixtures have been studied, no information is available concerning the effect of solvent composition on the solubility of multicomponent systems in which drug–drug interactions or complexation are likely to occur. Such information would be of interest since many liquid pharmaceuticals are formulations of more than one drug and since mixed solvents are frequently required in these preparations because of the limited water solubility of the solutes.

The two model compounds, theophylline and phenobarbital, were chosen for this study because they are known to form a complex in solution (8). Solubility profiles in several solvent systems were determined for each drug, for mixtures of the drugs, and for the known complex. These data were used to evaluate whether solubility profiles of the individual drugs can be utilized to predict the effect of solvent on the equilibrium solubility of binary solutes when complexation occurs between the two drugs.

EXPERIMENTAL

Materials—The following were used: chloroform A.R.; alcohol USP; sulfuric acid, reagent grade; sodium hydroxide pellets A.R.; dibasic (anhydrous) sodium phosphate A.R.,; propylene glycol USP; glycerin USP; Carbowax 400[1]; theophylline NF (anhydrous), recrystallized from water and dried at 105° for 4 hr., m.p. 270–274°; and phenobarbital USP (powder), recrystallized from ethanol and dried at 105° for 2 hr., m.p. 174–178°.

A pH 11.0 phosphate buffer was prepared by dissolving 28.4 g. of anhydrous dibasic sodium phosphate in 2000 ml. of distilled water and adjusting to pH 11.0 with 1.0 *N* sodium hydroxide.

Diluted sulfuric acid was prepared by adding 57 ml. of sulfuric acid to about 100 ml. of distilled water, cooling to room temperature, and diluting to 1000 ml. with distilled water.

The solvents were prepared on a percent volume basis with the organic component added by buret.

The theophylline–phenobarbital (2:1) complex, prepared as previously described (8), melted at 249–251°.

Anal.—Calc. for $C_{26}H_{28}N_{10}O_7$: C, 52.7; H, 4.73; N, 23.6. Found: C, 52.63; H, 5.12; N, 23.85.

The 1 *N* sodium hydroxide was prepared by dissolving 40 g. of sodium hydroxide pellets A.R. in sufficient distilled water to make 1 l. Standardization was against potassium acid phthalate.

Equipment—The samples were maintained at 25.0 ± 0.5° by immersion in a water bath shaker[2,3]. A spectrophotometer[4] was used for analysis of the solutes. A pH meter[5] was used in the buffer preparation.

Equilibration—An excess of theophylline, or phenobarbital, or the previously isolated complex was added to 10 ml. of the solvent mixture contained in a screw-top vial. The vial was closed, using a Parafilm[6] liner in the cap, and sealed with several turns of electrical tape. Equilibration was obtained by shaking in a constant-temperature bath at 25.0 ± 0.5° for at least 36 hr. The samples were then removed, and an appropriate volume of the supernatant liquid was withdrawn from each vial by pipet and prepared for assay. The pipets were fitted with a glass wool prefilter to exclude undissolved solids.

Mixtures of theophylline and phenobarbital were equilibrated under conditions identical to those already described. In each solvent system, the amount of theophylline added was in excess of its equilibrium solubility. The total amount of phenobarbital added to these systems was such that: (*a*) all the theophylline present (in solution plus excess solid) would be complexed, and (*b*) the equilibrium solubility of phenobarbital would be exceeded in all the solvent concentrations examined.

Assay Procedure—*Individual Solubilities*—Filtered aliquots of the solutions containing either theophylline or phenobarbital were diluted with pH 11.0 phosphate buffer and analyzed spectrophotometrically *versus* buffer solution in 1-cm. silica cells at 275 and 240.5 nm., respectively. The concentration of theophylline or phenobarbital in the sample was calculated using an *a* (1%, 1 cm.) for theophylline of 635.7 and for phenobarbital of 417.5.

Solubility of Previously Isolated Complex—Filtered aliquots from solutions containing excess complex were diluted with pH 11.0 buffer and analyzed spectrophotometrically at 275 and 240.5 nm. in 1-cm. silica cells. The concentration of phenobarbital and theophylline in the original solution was calculated by solving the simultaneous equation for each component. The *a* (1%, 1 cm.) of theophylline at 240.5 nm. is 217.1; for phenobarbital at 275 nm., it is 24.7. The *a* (1%, 1 cm.) of theophylline and phenobarbital at 275 and 240.5 nm., respectively, was already given.

Solubilities in Mixture—Filtered 2-ml. aliquots were transferred to a separator containing 1 *N* sodium hydroxide to decompose the complex into its components (8). This solution was acidified with concentrated sulfuric acid, and diluted sulfuric acid was added. The acidic phase was extracted with chloroform; the chloroform layers were combined in a second separator and back-extracted with diluted sulfuric acid. The acidic phases were combined and

[1] Union Carbide Corp., New York, N. Y.

[2] Eberbach Corp., Ann Arbor, Mich.
[3] New Brunswick Scientific Co., New Brunswick, N. J.
[4] Model 240, Gilford Instrument Laboratories, Inc., Oberlin, Ohio.
[5] Radiometer-type PHM 26, The London Co., Westlake, Ohio.
[6] American Can Co., Neenah, Wis.

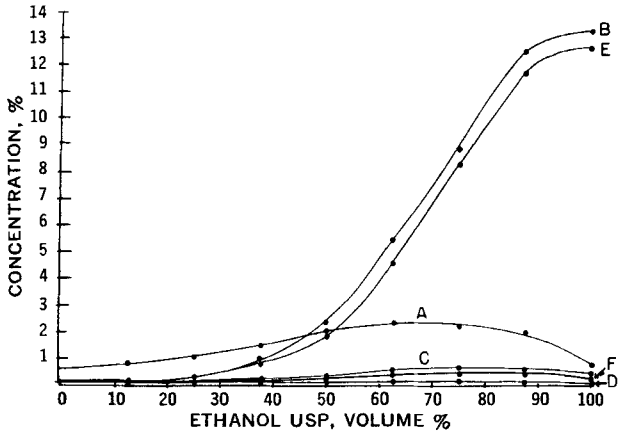

Figure 1—*Solubility profiles for single solutions of theophylline and phenobarbital, mixtures of the two compounds, and the previously isolated theophylline–phenobarbital complex in alcohol USP. Key: A, theophylline alone; B, phenobarbital alone; C, theophylline from previously isolated complex; D, theophylline from mixture; E, phenobarbital from mixture; and F, phenobarbital from previously isolated complex.*

made to a known volume. The absorbance was determined at 265.5 nm. *versus* diluted sulfuric acid in 1-cm. silica cells.

The chloroform layer was extracted with pH 11.0 buffer, and the aqueous extracts were combined and made to a known volume with buffer solution. The absorbance was determined at 240.5 nm. *versus* pH 11.0 buffer in 1-cm. silica cells.

Calculation of the theophylline and phenobarbital in the respective solutions was as follows: $Cu = Au/(A/c)$, where Au is the absorbance of the sample solution, Cu is its concentration, and A/c is the constant ratio of absorbance to concentration found with standard solutions at the same wavelength as the sample and under the same experimental conditions.

Preparation of Standards—Standard solutions were prepared which contained the following concentrations of theophylline and phenobarbital:

	Theophylline, mg./ml.	Phenobarbital, mg./ml.
Standard I	0.5	1.8
Standard II	1.0	12.0
Standard III	1.5	30.0
Standard IV	1.7	60.0
Standard V	1.3	120.0

Two milliliters of each standard solution was extracted and assayed as described under the assay procedure for the mixture. Absorbance and concentration values from the appropriate standard solutions were used as described previously to calculate the theophylline and phenobarbital in the mixture.

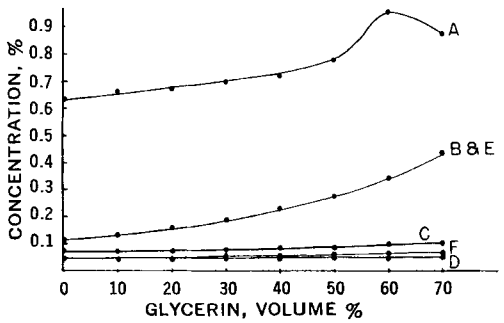

Figure 2—*Solubility profiles for single solutions of theophylline and phenobarbital, mixtures of the two compounds, and the previously isolated theophylline–phenobarbital complex in glycerin. Key: A, theophylline alone; B, phenobarbital alone; C, theophylline from the previously isolated complex; D, theophylline from the mixture; E, phenobarbital from the mixture; and F, phenobarbital from the previously isolated complex.*

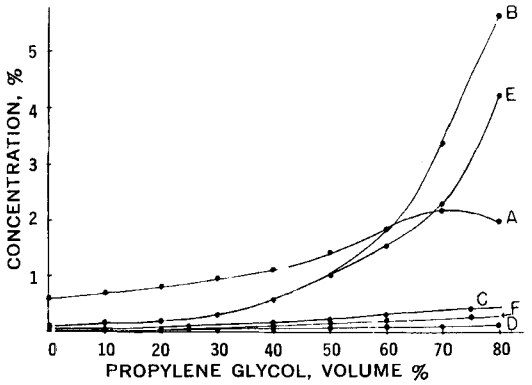

Figure 3—*Solubility profiles for single solutions of theophylline and phenobarbital, mixtures of the two compounds, and the previously isolated theophylline–phenobarbital complex in propylene glycol. Key: A, theophylline alone; B, phenobarbital alone; C, theophylline from the previously isolated complex; D, theophylline from the mixture; E, phenobarbital from the mixture; and F, phenobarbital from the previously isolated complex.*

The reported results are averages of at least duplicate runs on each material.

RESULTS AND DISCUSSION

Figures 1–4 show the equilibrium solubility profiles for single solutions of theophylline and phenobarbital, mixtures of the two compounds, and the previously isolated theophylline–phenobarbital complex in various aqueous organic solvent blends. Although the occurrence of multiple solubility maxima has been reported for certain compounds when increments of change in solvent composition or dielectric constant are small (5–7), the increments of organic solvent used in these experiments were too large to show whether multiple peak solubilities existed for these systems.

Since physical mixtures of theophylline and phenobarbital complex in solution (8), this complex was prepared, isolated, and equilibrated in each solvent blend, and the equilibrium solubilities were determined. Although the complex (T_2P) exists in solution as an equilibrium mixture of free (T,P) and interacting (T_2P) components, the absorption curve of the diluted sample was found to be a composite of the individual curves of the drugs in solution, and the total solubility of each component, regardless of molecular state, could be quantitated.

Only the solubility isotherms in ethanol–water are discussed in detail since these results are generally applicable to the other solvent systems studied.

The equilibrium solubilities of individual single solutions of theophylline and phenobarbital in hydroalcoholic blends are shown in Fig. 1. Examination of this figure shows that the solubility of phenobarbital (1-B) increases with increasing alcohol concentration, reaching maximum solubility in alcohol USP. Theophylline (1-A), on the other hand, reaches maximum solubility at about 60–65% by volume, alcohol USP, and further addition of alcohol results in a gradual decrease in solubility.

Also shown in Fig. 1 are the solubility isotherms for theophylline (1-C) and phenobarbital (1-F) obtained from equilibration of the previously prepared complex, where the concentration of theophylline and phenobarbital represents both free and complexed drug in solution. The equilibrium concentration of theophylline obtained from the dissolution of the known complex is very low compared with the concentration obtained when pure theophylline is equilibrated alone. Furthermore, although the solvent polarity has a significant effect on the solubility of the pure drugs, this effect is minimal with respect to the known complex. This finding is somewhat surprising since the theophylline–phenobarbital complex would be expected to be less polar than pure theophylline or phenobarbital. As a result, it would be reasonable to assume that the solubility of the known complex would increase significantly in solvents of lower polarity.

The data presented in the figures for the systems containing physical mixtures of theophylline and phenobarbital show that these solubility isotherms are complex and indicate that the individual

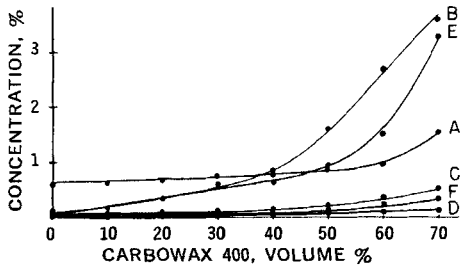

Figure 4—*Solubility profiles for single solutions of theophylline and phenobarbital, mixtures of the two compounds, and the previously isolated theophylline–phenobarbital complex in Carbowax 400. Key: A, theophylline alone; B, phenobarbital alone; C, theophylline from the previously isolated complex; D, theophylline from the mixture; E, phenobarbital from the mixture; and F, phenobarbital from the previously isolated complex.*

solubility profiles cannot be used to predict the equilibrium solubility of mixed components in systems where drug–drug interactions occur. In regard to the equilibration of the mixed components, it should be noted again that in each solvent system the amount of theophylline added was in excess of its equilibrium solubility. The total amount of phenobarbital added to these systems was such that: (*a*) all the theophylline present (in solution plus excess solid) would be complexed, and (*b*) the equilibrium solubility of phenobarbital would be exceeded in all of the solvent concentrations examined.

The solubility isotherm for theophylline obtained from equilibration of the mixtures in hydroalcoholic solvents is shown in Fig. 1-D. Since theophylline and phenobarbital do interact in solution to form a complex, the total amount of theophylline present in solution in the mixture samples is due primarily to the solubility of this complex. Therefore, it is interesting to compare this equilibrium theophylline concentration to the theophylline concentration present in systems containing only the isolated complex. Such a comparison shows that the concentrations in the two systems are significantly different. The concentration of theophylline in the systems containing only the isolated complex is higher and probably represents an apparent solubility due to the dissociated and undissociated complex. The lower solubility of theophylline in the mixture samples is probably the result of a decreased dissociation of the complex due to the excess phenobarbital present in solution. Therefore, the solubility of theophylline from the mixtures may represent the intrinsic solubility of the undissociated complex. The difference in solubility of theophylline obtained from equilibration of the known complex and the mixtures may be due to the fraction of the complex that dissociates in the former samples.

The equilibrium solubility of phenobarbital in the mixture samples is also shown in Fig. 1-E. Its solubility is lower than that obtained for the pure drug, which was unexpected since the mixture samples did contain excess phenobarbital. The factors responsible for this difference are not known, but several mechanisms may be operative. For example, although the complex solubility is very low, salting-out effects cannot be overlooked. Or, in the presence of excess phenobarbital, the possibility exists of changing stoichiometric ratios of the complex, as seen in Higuchi and Lach's studies (9). Or, perhaps, multiple equilibria may result in a multiordering.

Although all of the mixture samples contained excess phenobarbital, as previously discussed, it would be reasonable to assume that the reverse situation, systems containing enough theophylline to complex all the phenobarbital plus an amount in excess of its equilibrium solubility, would result in comparable solubility profiles.

From the results of this study, it would be expected that individual solubility profiles may be of no value in predicting the equilibrium solubility of mixtures of drugs, particularly when the drugs are capable of interacting to form a very insoluble complex. This can be illustrated by examination of the solubilities in 25% v/v alcohol USP. The equilibrium solubility of single solutions of theophylline and phenobarbital in this solvent is approximately 11 and 3 mg./ml., respectively. When a mixture of these compounds was equilibrated in the same solvent system, the apparent solubility of the complex which formed, calculated on the basis of theophylline in solution, was approximately 1 mg./ml. Furthermore, attempts to predict the solubility of this mixture, which contained excess phenobarbital, on the basis of the solubility of the known complex was also of little value, since the apparent solubility of a previously prepared complex in the same solvent system was found to be approximately 2.3 mg./ml. Therefore, the preparation of a formulation in which the solutes are totally soluble may present considerable difficulty, because the single drugs may be present in a concentration less than their saturation solubility but, because of the insoluble nature of the complex which may form, a precipitate results. The use of dielectric constants to predict solubility would probably, according to these preliminary data, lead to erroneous conclusions.

While this study reports results for saturated systems, similar results were obtained using more practical concentrations. For example, a 40% v/v alcohol USP solution containing 13 mg./ml. of theophylline and 0.8 mg./ml. of phenobarbital yielded a precipitate upon standing for a few hours. This occurred in spite of the fact that that individual components were soluble at this concentration level.

As previously mentioned, the results of this investigation were discussed only in regard to the hydroalcoholic systems. The results from the other solvent systems were qualitatively similar to the hydroalcoholic blends and, for this reason, were not discussed. The solubility studies were terminated in these blends at approximately 70–80% organic solvent by volume because the mixture samples became so viscous and contained so much precipitate that a clear solution could not be obtained for analysis.

Although only mixtures of two drugs were used in this study, the situation would probably become even more complicated if additional components are included that could also undergo complexation.

Further work is in progress on other multicomponent-containing systems where drug–drug interaction does not occur and in systems where such interactions occur, resulting in an increase in the solubility of the complex.

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