Phenobarbital Solubility in Propylene Glycol–Glycerol–Water Systems

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Abstract □ Phenobarbital solubility in various binary and ternary propylene glycol–glycerol–water solvent systems was determined. Phenobarbital concentrations several times those of the ethanol-containing USP and BPC elixirs were obtained. From log solubility–solvent composition plots, a general equation was developed for phenobarbital solubility prediction in propylene glycol–water, glycerol–water, and propylene glycol–glycerol–water solvent systems. Solubility predictions using another equation, based on linear log solubility–dielectric constant relationships, were limited by the need to use different constants for different solvent blends. Heats of solution for phenobarbital determined in selected solvent blends as well as in USP and BPC elixirs varied within a very narrow range, suggesting similar solute–solvent interactions.

Keyphases □ Phenobarbital—solubility in various binary and ternary solvent systems □ Solubility—phenobarbital in binary and ternary solvent systems □ Solvent systems—various binary and ternary, phenobarbital solubility

Ethanol-free liquid preparations of phenobarbital and other drugs are needed for the treatment of alcoholic patients, children, the elderly, and peptic ulcer patients. Furthermore, ethanol is not a pharmacologically inert solvent, and its interactions with various drugs are well known (1). Ethanol is used in many prescription and nonprescription liquid preparations in proportions up to 90% (2, 3). It is used in drug products as a solvent, preservative, and stabilizer and for its pharmacological effects. Other compounds may be used in place of ethanol except when it is used as a solvent.

Various formulas were suggested as alternatives to official formulas for phenobarbital elixir (4–9). Most formulas, however, contained ethanol in proportions varying from 15 to 40%. Some solubilized systems of phenobarbital also were prepared and tested for stability and *in vitro* availability (10, 11). In the present study, phenobarbital solubility was determined in binary and ternary propylene glycol–glycerol–water systems, and solubility data were correlated to physicochemical properties of solvents and the solute. This study should provide a model for the development of ethanol-free pharmaceutical solutions of drugs that currently include ethanol in their formulations.

EXPERIMENTAL

Materials—Phenobarbital[1], propylene glycol[2], and glycerin[2] were used as supplied.

Solubility Studies—Excess quantities of phenobarbital were placed in 50-ml glass-stoppered flasks with 30 ml of the solvent system. The flasks were shaken in a thermostatically controlled water bath[3] until saturation. Four different temperatures were used; the temperature control was better than ±0.2°. Samples of the saturated solutions were pipeted, filtered through a 0.8-μm membrane filter[4], suitably diluted with the same solvent, and assayed for phenobarbital. In all solvent systems, 0.01 *N* HCl was used instead of water to suppress phenobarbital ionization.

Assay—Phenobarbital was assayed spectrophotometrically[5] according to a previously described method (12). A calibration curve was established for phenobarbital in every solvent blend.

RESULTS AND DISCUSSION

Equilibrium solubility data of phenobarbital in aqueous solvent blends containing different proportions of glycerol and/or propylene glycol are shown in Fig. 1. Phenobarbital concentrations up to 45 mg/ml (~10 times the concentration of USP or BPC elixirs) were obtained. The contribution of propylene glycol to the increase in phenobarbital solubility was greater than that of glycerol. Log solubility–solvent composition plots for both propylene glycol–water and glycerol–water systems (Fig. 2) were straight lines. Literature data (13) indicate that, in a propylene glycol–water system, the logarithm of the solubility of some drugs is linearly related to the fraction of propylene glycol present by:

$$\log S_t = \log S_0 + \alpha f \qquad \text{(Eq. 1)}$$

where S_t is the drug solubility in the solvent mixture, f is the volume fraction of propylene glycol, S_0 is the drug solubility in water, and α is a constant characteristic of the system under study.

Results in Fig. 2 show that Eq. 1 applies to the solubility of phenobarbital in glycerol–water and propylene glycol–water. Values for the constants (α) for propylene glycol and glycerol as calculated from the

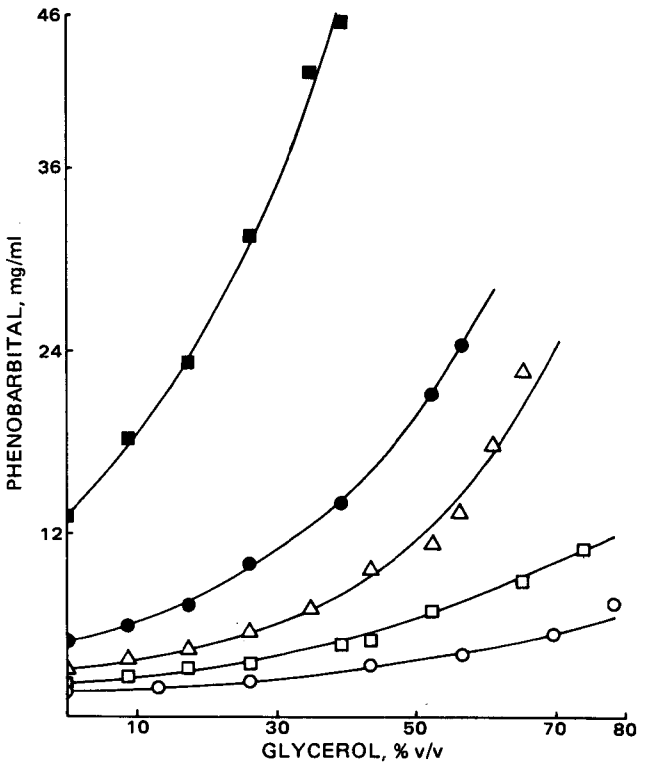

Figure 1—*Phenobarbital solubility in propylene glycol (PG)–glycerol–water systems at 32°. Key: ○, 0% PG; □, 10% PG; △, 20% PG; ●, 30% PG; and ■, 50% PG.*

[1] B.D.H. Chemicals Ltd., Poole, England.
[2] E. Merck, Darmstadt, West Germany.
[3] Kotterman, type 3407, Hanigsen, West Germany.
[4] Millipore Corp., Bedford, Mass.
[5] Pye-Unicam SP 600, Cambridge, England.

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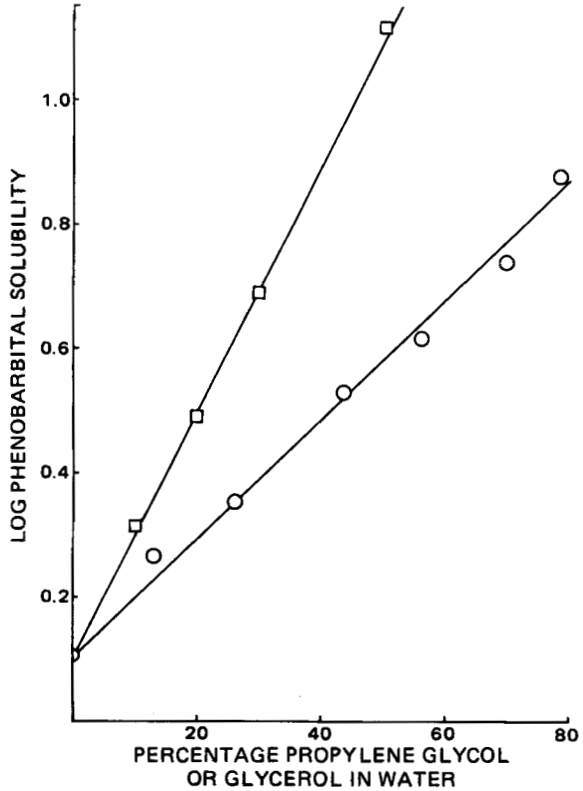

Figure 2—*Phenobarbital solubility in propylene glycol–water (PG–W) and glycerol–water (G–W) binary systems at 32°. Key: ○, G–W; and □, PG–W.*

slopes of the lines (Fig. 2) were 19.88 and 10.88×10^{-3}, respectively. In an attempt to extend the approach to the solubility of phenobarbital in propylene glycol–glycerol–water, the following equation was developed:

$$\log S_t = \log S_0 + \alpha_1 f_1 + \alpha_2 f_2 + \beta f_1^2 f_2 \qquad \text{(Eq. 2)}$$

where α_1 and α_2 are the constants for propylene glycol and glycerol, respectively, and f_1 and f_2 are the volume fractions of both solvents. The term $\beta f_1^2 f_2$ was determined from the fitting of some experimental solubility data to Eq. 2. It accounts for the increase in solubility due to solvent

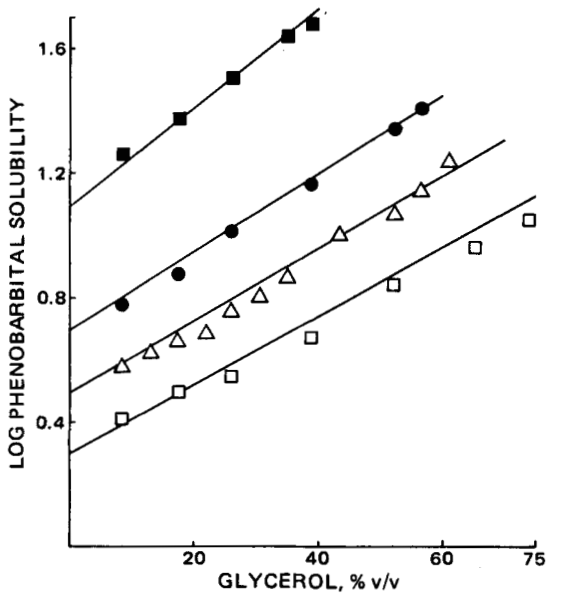

Figure 3—*Agreement of experimental solubility of phenobarbital in propylene glycol–glycerol–water (PG–G–W) ternary systems with values predicted from Eq. 2. Key: —, theoretical; □, 10% PG; △, 20% PG; ●, 30% PG; and ■, 50% PG.*

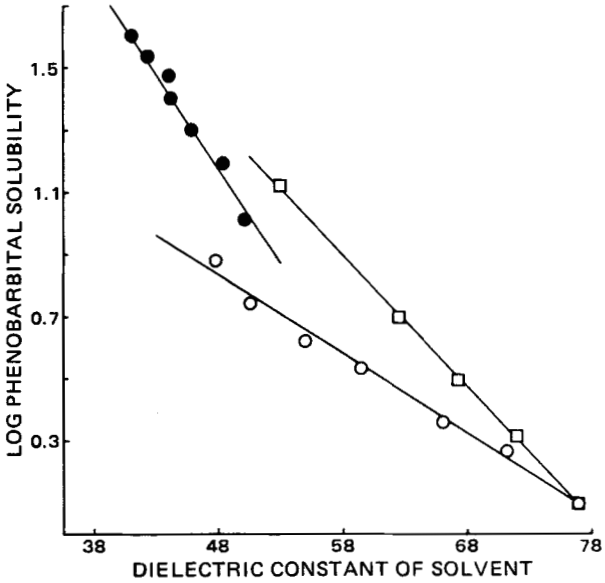

Figure 4—*Relationship of phenobarbital solubility to the dielectric constant of the solvent system. Key: ○, glycerol–water; □, propylene glycol–water; and ●, propylene glycol–glycerol–water.*

interactions. When f_1 and f_2 are equal to zero, Eq. 2 reduces to:

$$\log S_t = \log S_0 \qquad \text{(Eq. 3)}$$

which is the logarithm of phenobarbital solubility in 0.01 N HCl.

When f_1 is variable and $f_2 = 0$, Eq. 2 is reduced to:

$$\log S_t = \log S_0 + \alpha_1 f_1 \qquad \text{(Eq. 4)}$$

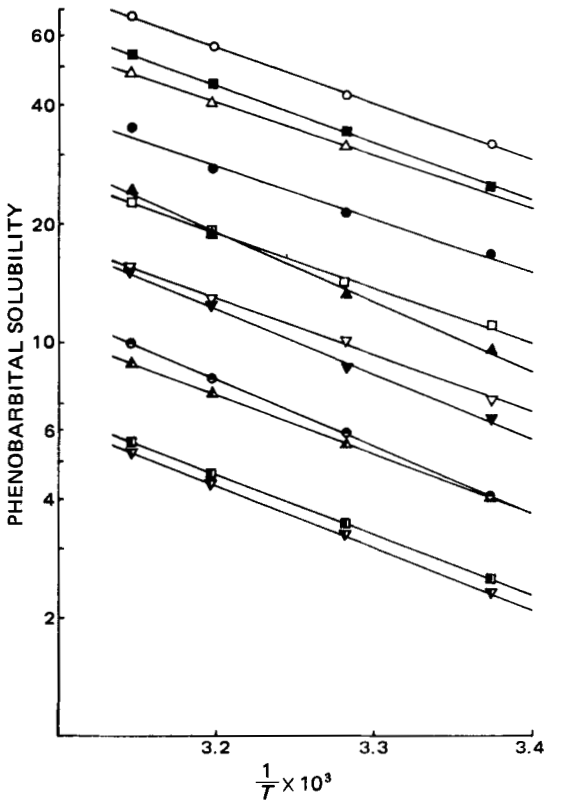

Figure 5—*Effect of temperature on phenobarbital solubility (propylene glycol, PG; glycerol, G; and water, W). Key: ○, BPC elixir; ■, 50% polyethylene glycol 400–50% W; △, 50% PG–26% G–24% W; ●, 30% PG–52% G–18% W; □, 30% PG–39% G–31% W; ▲, 50% PG–50% W; ▽, 30% PG–26% G–44% W; ▼, USP elixir; ◓, 30% PG–9% G–61% W; ▲, 20% PG–26% G–54% W; ◧, 10% PG–26% G–64% W; and ▼, 44% G–56% W.*

which describes the solubility of phenobarbital in propylene glycol–water.

When $f_1 = 0$ and f_2 is variable, Eq. 2 reduces to:

$$\log S_t = \log S_0 + \alpha_2 f_2 \qquad \text{(Eq. 5)}$$

which describes the solubility of phenobarbital in glycerol–water binary systems. Figure 3 shows the fitting of theoretical lines calculated on the basis of Eq. 2 to experimental points determined in the present study. The good fit suggests the possible use of such an equation for solubility predictions in ternary propylene glycol–glycerol–water systems.

Gorman and Hall (14) reported a linear relationship between the logarithm of secobarbital solubility and the dielectric constant of the binary solvent systems which have similar bonding characteristics: ethanol–water, glycerol–water, and propylene glycol–water. In the present investigation, the log solubility–dielectric constant (calculated) relationship for phenobarbital in propylene glycol–water and glycerol–water was also linear (Fig. 4). When this approach was extended to phenobarbital solubility in propylene glycol–glycerol–water, an essentially linear relationship was observed (Fig. 4). However, this linearity does not seem to extend to solvent systems containing high proportions of water since the line does not intersect with the other two lines at 100% water solvent composition. This result does not allow for solubility predictions over a wide range of solvent compositions as is possible when Eq. 2 is utilized.

The effect of temperature on phenobarbital solubility in 12 selected solvent systems was studied. Equilibrium solubilities were determined at 23, 32, 40, and 45 ± 0.2°, and the log solubility–$1/T$ relationships were plotted (Fig. 5). The heats of solution calculated from Fig. 5 varied in the relatively narrow range of 6–8 kcal/mole for the different solvent systems. The relatively nonpolar phenobarbital molecule is believed to dissolve in the relatively polar solvent blends through hydrogen bonding of the electronegative oxygen of the phenobarbital carbonyl groups to the hydrogen of hydroxyl groups in water, glycerol, or propylene glycol. The close values of heats of solution suggest similar types of solution mechanism and bonding.

Results of the present investigation showed that phenobarbital solubility can be effected through the use of mixed ethanol-free solvents to produce concentrations well above those required to formulate a phenobarbital elixir. The correlation of solubility data to specific solvent contributions enabled solubility predictions from a knowledge of solvent composition. Evaluation of the stability and bioavailability of phenobarbital in these solvent systems will be reported later.

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COMMUNICATIONS

Single-Point Maintenance Dose Prediction: Role of Interindividual Differences in Clearance and Volume of Distribution in Choice of Sampling Time

Keyphrases ☐ Pharmacokinetics—single-point maintenance dose prediction, theoretical analysis ☐ Single-point maintenance dose prediction—pharmacokinetics, theoretical analysis

To the Editor:

Experimental observations of very strong correlations between a single determination of concentration after the first dose of a drug and the eventual steady-state concentration have been observed experimentally for lithium, nortriptyline, imipramine, and desipramine (1–5). Such a relationship also exists for drugs with short half-lives based on simulations and clinical studies of chloramphenicol and theophylline (6–8).

If a single determination of concentration after the first dose of drug correlates with the eventual steady-state concentration, then, over the linear range, this correlation provides the basis for the prediction of maintenance dose necessary to achieve a desired steady-state concentration. In an attempt to clarify this very powerful method of maintenance dose prediction, a theoretical analysis of the relationship was carried out to determine the: (*a*) source

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