at least at the 97.5% level of confidence, during the first 24 hr post-administration between the excretion rates of the metabolite following administration of the fine powder and of the ground mixture. There were significant differences among their cumulative amounts excreted during the initial time periods. The comparison of the sodium salt powder with the ground mixture, however, revealed no statistical differences in excretion rates and cumulative amounts excreted in a 0–24-hr period.

The present investigation showed that the improvement in the dissolution behavior of phenytoin due to vibrational ball milling with microcrystalline cellulose affected significantly the absorption characteristics of a drug whose absorption was dissolution rate limited. It is of interest to explore the vibrational ball milling of other poorly water-soluble drugs with microcrystalline cellulose.

REFERENCES

(1) S. A. Kaplan, in "Dosage Form Design and Bioavailability," J. Swarbrick, Ed., Lea & Febiger, Philadelphia, Pa., 1973, p. 20.

(2) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **58**, 1505(1969).

(3) E. I. Stupak, H. A. Rosenberg, and T. R. Bates, *J. Pharmacokinet. Biopharm.*, **2**, 511(1974).

(4) A. Ampolsuk, J. V. Mauro, A. A. Nyhuis, N. Shah, and C. I. Jarowski, *J. Pharm. Sci.*, **63**, 117(1974).

(5) S. Miyazaki, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **23**, 552(1975).

(6) K. Yamamoto, M. Nakano, T. Arita, and Y. Nakai, *J. Pharmacokinet. Biopharm.*, **2**, 487(1974).

(7) K. Arnold, N. Gerber, and G. Levy, *Can. J. Pharm. Sci.*, **5**, 89(1970).

(8) K. S. Albert, E. Sakmar, M. R. Hallmark, D. J. Weidler, and J. G. Wagner, *Clin. Pharmacol. Ther.*, **16**, 727(1974).

(9) L. Lund, *Eur. J. Clin. Pharmacol.*, **7**, 119(1974).

(10) A. J. Glazko and T. Chang, in "Antiepileptic Drugs," D. M. Woodbury, J. K. Penry, and R. P. Schmidt, Eds., Raven, New York, N.Y., 1972, p. 127.

(11) Y. Saitoh, K. Nishihara, F. Nakagawa, and T. Suzuki, *J. Pharm. Sci.*, **62**, 206(1973).

(12) A. J. Wilensky and J. A. Lowden, *Neurology*, **23**, 318(1973).

(13) H. J. Kupferberg, *Clin. Chim. Acta*, **29**, 283(1970).

(14) T. C. Butler, *J. Pharmacol. Exp. Ther.*, **119**, 1(1957).

(15) S. P. Agarwal and M. I. Blake, *J. Pharm. Sci.*, **57**, 1434(1968).

(16) A. J. Glazko, T. Chang, J. Baukema, W. A. Dill, J. R. Goulet, and R. A. Buchanan, *Clin. Pharmacol. Ther.*, **10**, 498(1969).

(17) A. J. Glazko and T. Chang, in "Antiepileptic Drugs," D. M. Woodbury, J. K. Penry, and R. P. Schmidt, Eds., Raven, New York, N.Y., 1972, p. 130.

(18) "Guidelines for Biopharmaceutical Studies in Man," APhA Academy of Pharmaceutical Sciences, Washington, D.C., 1972.

(19) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **60**, 1376(1971).

(20) W. A. Dill, J. Baukema, T. Chang, and A. J. Glazko, *Proc. Soc. Exp. Biol. Med.*, **137**, 674(1971).

ACKNOWLEDGMENTS AND ADDRESSES

Received October 1, 1975, from the *Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan, and the ‡Faculty of Pharmaceutical Sciences, University of Chiba, Yayoicho, Chiba 280, Japan.

Accepted for publication December 16, 1975.

The authors are grateful to Dr. S. Takahashi, Department of Neurology, Hokkaido University Hospital, and to Dr. T. Minagawa and Dr. T. Sakuma, Department of Microbiology, Hokkaido University Medical School, for the help in sampling blood. Thanks are also due to Dainippon Pharmaceutical Co. and Asahi Kasei Industrial Co. for generous supplies of the materials.

ˣ To whom inquiries should be directed.

Solubility of Nonelectrolytes in Polar Solvents IV: Nonpolar Drugs in Mixed Solvents

S. H. YALKOWSKY *ˣ, S. C. VALVANI *, and G. L. AMIDON ‡

Abstract □ The molecular and group surface area approach to solubility is shown to be applicable to mixed aqueous solvent systems. An equation is derived which is consistent with the exponential increase in the aqueous solubility of nonpolar drugs that frequently accompanies the addition of a cosolvent. This equation predicts that: (*a*) the ability of a drug to be solubilized by a cosolvent is proportional to its hydrophobic surface area per molecule, and (*b*) the ability of a cosolvent to solubilize any drug is inversely proportional to its interfacial tension against a reference liquid hydrocarbon. These predictions are experimentally verified with solubility studies of several alkyl *p*-aminobenzoates in propylene glycol–water mixtures and of hexyl *p*-aminobenzoate in mixtures of water with ethanol, methanol, ethylene glycol, propylene glycol, glycerin, and formamide.

Keyphrases □ Solubility—nonelectrolytes in mixed aqueous solvent systems, molecular and group surface area approach □ Nonelectrolytes—solubility in mixed aqueous solvent systems □ Polar solvents, mixed—solubility of nonelectrolytes, molecular and group surface area approach □ Cosolvent systems, polar—solubility of nonelectrolytes, molecular and group surface area approach □ Alkyl *p*-aminobenzoates—solubility in propylene glycol–water mixtures □ Hexyl *p*-aminobenzoate—solubility in mixed polar solvent systems

Cosolvents are routinely used to increase the solubility of drugs in an aqueous medium. In general, the selection of a mixed solvent system is performed in a hit-and-miss fashion. There are few if any useful guidelines for assessing the relative solubilizing efficiency of the available liquids. Dielectric constant and solubility parameter correlations are of only limited utility, especially for drugs having very low aqueous solubilities. Yet it is precisely for these poorly soluble drugs that solubilization is most important.

A survey of the pharmaceutical literature (1–10) revealed that there is an exponential increase in aqueous solubility for many nonpolar drugs as the cosolvent is added. This increase was observed for many chemical

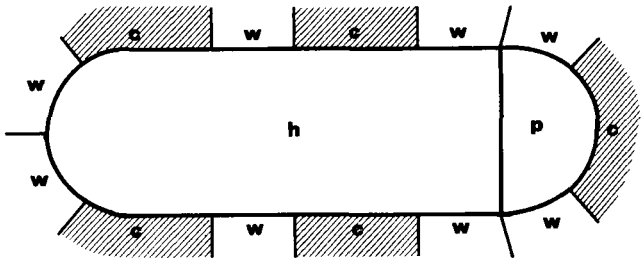

Figure 1—*Schematic diagram of a semipolar solute in a mixed solvent. Key:* h, *hydrophobic portion of solute;* p, *polar portion of solute;* c, *cosolvent; and* w, *water.*

classes of drugs in various mixed aqueous systems. The only requirement for plots of log (solubility) *versus* cosolvent composition to be linear appears to be that the solute must be less polar than the mixed solvent. Therefore, nearly all nonpolar drugs in most common mixed aqueous solvent systems are included. In spite of the ubiquitous nature of this phenomenon and its potential importance in pharmacy, there has been no systematic attempt to understand it or even to generalize about its applicability.

This work was initiated to fill this void and to elucidate the role of the cosolvent in the solution process. A simple model is developed for determining the activity coefficient and solubility of semipolar solutes in mixed solvents. The solubilities of hexyl *p*-aminobenzoate in various mixed solvent systems are used to substantiate the predictions of the model.

THEORETICAL

It is becoming increasingly popular (1–3, 11–15) to consider solute–solvent interactions in terms of solute molecular and group surface area of contact with the solvent. This concept was first proposed over 50 years ago by Langmuir (16) in his principle of independent surface action, but it received little attention until the recent development of a computer program for calculating molecular surface area (11). This program has been found useful in calculating functional group surface area as well as total molecular surface area (13).

To apply the molecular and group surface area approach to the solution of semipolar solutes in mixed solvents, all pairwise interactions between the various portions of the solute with the components of the solvent must be considered. It is assumed that the solute is sufficiently insoluble so that solute–solute contact is negligible, even in saturated solutions. This assumption restricts the applicability of the model to solutions containing low concentrations of solute. Before considering mixed solvents, the solute–solvent interactions between a drug and a pure solvent will be reviewed.

Pure Solvents—Previously (10, 13, 14), the molecular and group surface area (MGSA) approach was used to study the solubilities of hydrophobic solutes in water and other polar solvents. Based on this approach, the mole fractional solubility of a liquid solute in water, X_w^{liq}, can be related to the hydrophobic surface area, HSA, and the polar surface area, PSA, of the solute molecule by:

$$-kT \ln X_w^{liq} = (\gamma_{wh})(\text{HSA}) + (\epsilon_{wp})(\text{PSA}) \qquad \text{(Eq. 1)}$$

where γ_{wh} and ϵ_{wp} represent the microscopic surface free energy density, *i.e.*, free energy per unit area at the aqueous interface, with the hydrophobic and polar portions of the molecule, respectively, as described previously (13). [In one previous paper of this series (14), the term γ_{wp} was used instead of ϵ_{wp}.]

Equation 1 has been shown to be applicable to other polar solvents, provided that the appropriate microscopic surface free energy densities are used (14). That is:

$$-kT \ln X_c^{liq} = (\gamma_{ch})(\text{HSA}) + (\epsilon_{cp})(\text{PSA}) \qquad \text{(Eq. 2)}$$

where the subscript c denotes the solvent or cosolvent.

These equations can be extended easily to include crystalline drugs by the incorporation of the term $RT \ln X_i$, where X_i is the ideal mole fractional solubility of the drug (17, 18). Since the ideal solubility of a substance is independent of the nature of the solvent, Eqs. 1 and 2 become:

$$-kT \ln X_w = -kT \ln X_i + (\gamma_{wh})(\text{HSA}) + (\epsilon_{wp})(\text{PSA}) \qquad \text{(Eq. 3)}$$

and:

$$-kT \ln X_c = -kT \ln X_i + (\gamma_{ch})(\text{HSA}) + (\epsilon_{cp})(\text{PSA}) \qquad \text{(Eq. 4)}$$

respectively. These equations are, of course, based on the assumption that there is no specific solvation or self-association of the drug in the solvent.

The division of the solute according to its hydrophobic surface area and polar surface area is illustrated schematically in Fig. 1. There are several reasons for the choice of molecular surface area as a correlating parameter rather than molecular weight, volume, polarizability, or some other solute property. Correlation of the solubility of a large number of hydrocarbons and alcohols with surface area (13) and subsequently ethers, ketones, aldehydes, esters, acids, and olefins gives better results than with any other parameter considered. Moreover, the use of a single parameter for hydrophobic substituents eliminates the need to incorporate empirical correction factors to account for branching, ring formation, or positional isomerism. It is also possible to calculate molecular and group surface areas without performing any experimental measurements so that this parameter can be used in the design of nonexistent compounds. Finally, there is an intuitive relationship between solubility and the product of hydrophobic surface area and solvent hydrocarbon interfacial tension (10, 13, 14) which is consistent with existing theories of solubility.

Mixed Solvents—If a drug is dissolved in a mixed aqueous solvent, it will (on a microscopic level) be in contact with both water and cosolvent. According to Fig. 1 and to the proposed model, the solvent properties of a mixed solvent (*i.e.*, γ and ϵ) are a linear combination of the properties of its component species. Therefore, the mixed solvent can be described by multiplying Eq. 4 by the fraction of cosolvent, f_c, and Eq. 3 by the fraction of water, f_w, to get:

$$-kT \ln X_f = (f_c\gamma_{ch})(\text{HSA}) + (f_c\epsilon_{cp})(\text{PSA}) - f_c kT \ln X_i + (f_w\gamma_{wh})(\text{HSA}) + (f_w\epsilon_{wp})(\text{PSA}) - f_w kT \ln X_i \qquad \text{(Eq. 5)}$$

where X_f is the mole fractional solubility of the drug in the mixed solvent.

Equation 5 is based on the assumption that the microscopic interfacial tension of a mixed solvent is an additive combination of its constituent values. Langmuir (16) used fractional surface area (mole fractions times molar surface area or volume fraction times surface area per unit volume) as a weighing factor instead of volume fraction. Since the surface areas per unit volume of each cosolvent used are remarkably close[1], the two unitless fractional quantities are virtually equivalent, but the latter is easier to utilize in practice.

The assumption of additivity and constitutivity is often used in calculating solubility parameters, dielectric constants, and other properties of mixed solvents. However, in the case of surface and interfacial phenomena, it is not always valid; experimentally determined tensions are generally less than would be predicted because, at a macroscopic aqueous interface, there is a buildup of a surface excess of less polar solutes (including cosolvent molecules) that makes the surface less polar than the bulk. This effect is clearly seen from the comparison of the experimental and calculated interfacial tensions of propylene glycol–water mixtures (Table VI in Ref. 3). The following brief arguments are submitted in support of the use of Eq. 3, which does not account for a surface excess.

Development of a macroscopic surface excess is a time-dependent process (19), because the cosolvent must diffuse from the bulk to the stagnant interface. The microscopic interface, on the other hand, is not stationary; the solute has a diffusivity comparable to that of the cosolvent. Therefore, in the absence of strong attractive interactions between solute and cosolvent, the accumulation of a significant surface excess of the latter about the rapidly moving (Brownian motion) solute molecules is less likely.

Since the development of a surface excess serves to lower the interfacial tension between two phases, a low interfacial tension would not favor such accumulation. Because of its curvature, the microscopic

[1] Unpublished data.

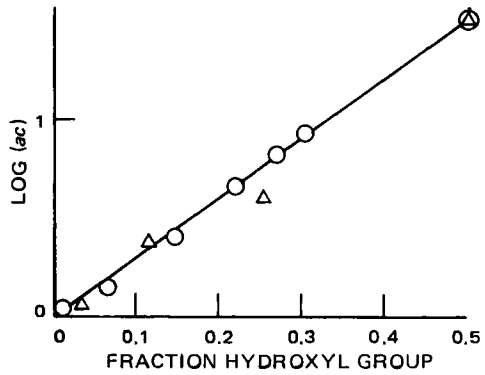

Figure 2—*Activity coefficients of heptane in pure alcohols* (△) *and ethanol–heptane mixtures* (○).

interfacial tension is much lower than a comparable macroscopic tension and thus should have a much smaller tendency to develop a surface excess.

Deal and Derr (20) showed that if the activity coefficient of *n*-heptane in various pure aliphatic alcohols and in mixtures of ethanol and heptane are plotted as a function of hydroxyl group concentration, the two sets of data fall on the same line (Fig. 2). If there is excess heptane from the mixed solvent at the microscopic interface, the triangles of Fig. 2 fall considerably above the line described by the circles; *i.e.*, the solute heptane molecules are surrounded by an excess of solvent heptane molecules.

On the basis of these arguments, it is believed that if there is a surface excess at the molecular interface, it is less than at the macroscopic interface. Since there is no way of determining its magnitude, it can, as a first approximation, be assumed to be negligible. This approximation can be made safely for aqueous glycerin and ethylene glycol, which are highly polar, but must be used cautiously for the more nonpolar cosolvents such as ethanol.

For low solute concentrations, f_w can be replaced with $1 - f_c$. Upon rearrangement of Eq. 5, the following is obtained:

$$-kT \ln X_f = (\gamma_{wh})(\text{HSA}) + (\epsilon_{wp})(\text{PSA}) - kT \ln X_i - [(\Delta\gamma)(\text{HSA}) + (\Delta\epsilon)(\text{PSA})]f_c \quad \text{(Eq. 6)}$$

where:

$$\Delta\gamma = \gamma_{wh} - \gamma_{ch} \quad \text{(Eq. 7)}$$

and:

$$\Delta\epsilon = \epsilon_{wp} - \epsilon_{cp} \quad \text{(Eq. 8)}$$

Equation 6 can be combined with Eq. 3 to give the following relationship, which serves as the basis for the rest of this paper:

$$kT \ln X_f = kT \ln X_w + [(\Delta\gamma)(\text{HSA}) + (\Delta\epsilon)(\text{PSA})]f_c \quad \text{(Eq. 9)}$$

This equation can successfully explain the exponential increase in the aqueous solubility of poorly soluble drugs that frequently accompanies the addition of cosolvent (1–10, 14). For convenience, Eq. 9 can be rewritten as:

$$\log X_f = \log X_w + \sigma f_c \quad \text{(Eq. 10)}$$

where:

$$\sigma = \frac{(\Delta\gamma)(\text{HSA}) + (\Delta\epsilon)(\text{PSA})}{2.303kT} \quad \text{(Eq. 11)}$$

(Note that Eq. 10 reduces to Eq. 1 or 2 when $f_c = 0$ or 1.)

Now the estimation of σ, the solubilizing power of a cosolvent for a drug, can be developed. In particular, the ability of various drugs to be solubilized by a particular cosolvent and the ability of various cosolvents to solubilize a particular drug will be predicted.

EXPERIMENTAL

Materials—The *p*-aminobenzoate esters studied were selected from those used in Ref. 21. All solvents were of USP grade and were used as received. The water was deionized.

Mixed Solvents—The mixed solvents were prepared by mixing 20, 40, 60, and 80 ml of cosolvent with 80, 60, 40, and 20 ml of water, respectively. The fraction of cosolvent present, f_c, is defined as the volume of cosolvent divided by the sum of the volumes of cosolvent and water.

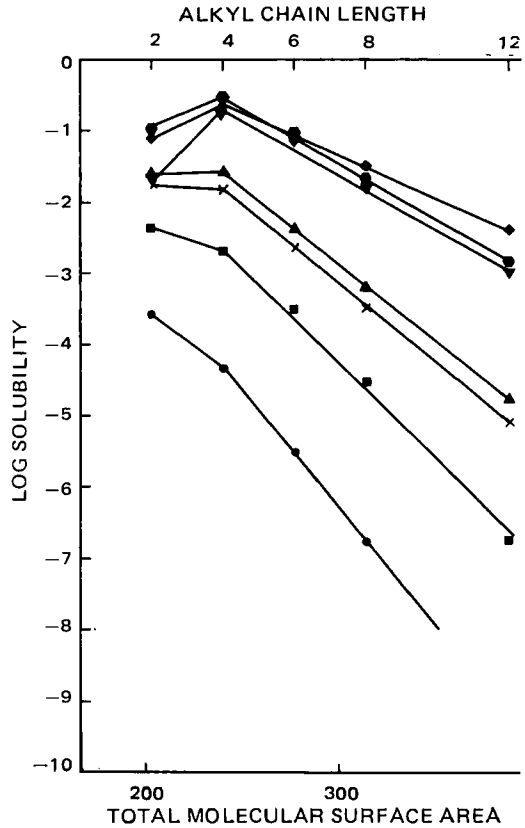

Figure 3—*Mole fractional solubilities of alkyl* p*-aminobenzoates in pure solvents. Key:* ●, *water;* ■, *glycerin;* ×, *formamide;* ▲, *ethylene glycol;* ▼, *propylene glycol;* ⬟, *methanol; and* ♦, *ethanol.*

Surface Area Calculations—The surface areas of the alkyl *p*-aminobenzoates were calculated by the preferred method described in Ref. 21. The hydrophobic surface area represents the alkyl and aryl portions of the molecules. The polar surface area is the sum of the amino and ester areas and is a constant 64 Å^2 for all esters.

Ideal Solubility Determinations—These values were calculated from the heat of fusion and the melting temperature (17, 18). The heats of fusion were determined by differential scanning calorimetry. The melting points were determined by hot-stage microscopy and differential scanning calorimetry as described previously (18).

Interfacial Tensions—The interfacial tensions were determined against tetradecane using the Wilhelmy plate method. The experimental details, along with the dependence of interfacial tension of hydrocarbon density, were described previously (22).

RESULTS

Pure Solvents—The mole fractional solubilities of the alkyl *p*-aminobenzoates studied in water, glycerin, ethylene glycol, propylene glycol, formamide, methanol, and ethanol are shown in Fig. 3. The relationship between log X and either chain length or total molecular surface area (TSA) was not linear in any of the solvents. The breaks in each curve were due to the fact that the ideal solubilities of the alkyl *p*-aminobenzoates showed a maximum at the butyl ester. This maximum was due to a change in the type of crystal formed in going from the lower to the higher homologs (18).

Since the solution interactions are of interest, it is more meaningful to look at the nonideal contribution to solubility. The nonideal solubility (often called the activity coefficient) is calculated by simply dividing the ideal solubility by the observed solubility. It is the solubility that the drug would have if it is converted to a liquid or oil by having its crystal structure destroyed. The activity coefficients (ac) of poorly soluble drugs are equivalent to the reciprocal of the liquid solubilities described by Eqs. 1 and 2.

When the observed solubilities of Fig. 3 are replaced by the nonideal

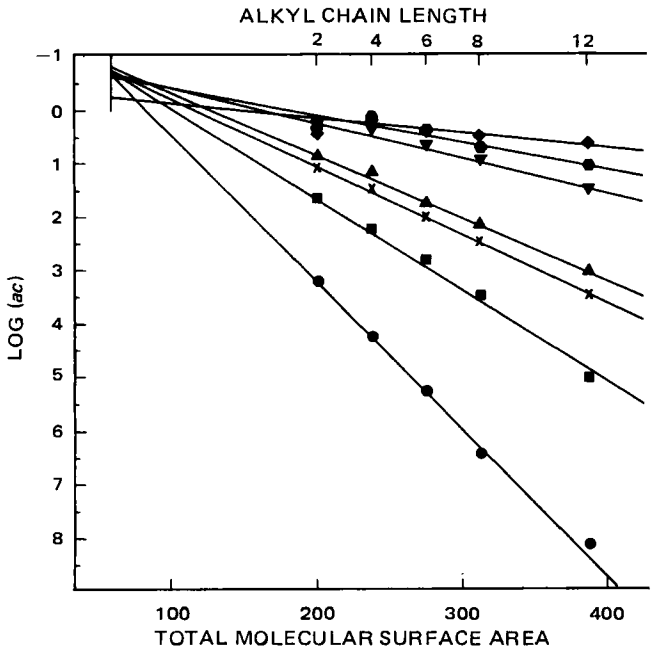

Figure 4—*Mole fractional activity coefficients of alkyl* p-*aminobenzoates in pure solvents. Key:* ●, *water;* ■, *glycerin;* ×, *formamide;* ▲, *ethylene glycol;* ▼, *propylene glycol;* ⬣, *methanol; and* ♦, *ethanol.*

solubilities, the data shown in Fig. 4 are obtained. In all solvents considered, there was good linearity between log (*ac*) and molecular surface area as predicted by Eqs. 3 and 4. The slopes of the lines appear to be related to the polarities of the solvents and the lines appear almost to converge at about 64 Å^2, the area of the polar moieties of the esters.

Mixed Solvents—The solubility data for the esters in 20, 40, 60, and 80% propylene glycol–water mixtures (Fig. 2 of Ref. 1) also show a break in the log solubility–surface area curves; when corrected for crystallinity, these data give the straight lines of Fig. 5. The data for the esters in the mixed solvents are qualitatively similar to the data

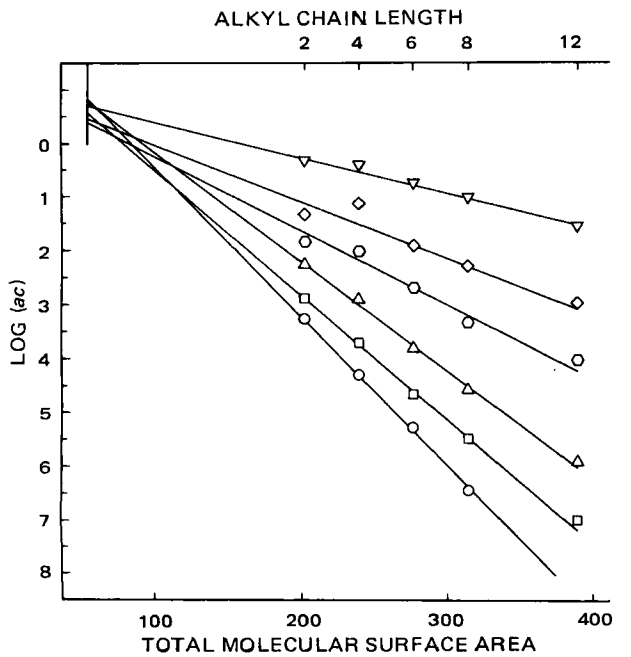

Figure 5—*Mole fractional activity coefficients of alkyl* p-*aminobenzoates in propylene glycol–water mixtures at 37°. Key:* ▽, *propylene glycol;* ◇, *80% propylene glycol in water;* ○, *60% propylene glycol in water;* △, *40% propylene glycol in water;* □, *20% propylene glycol in water; and* ○, *water.*

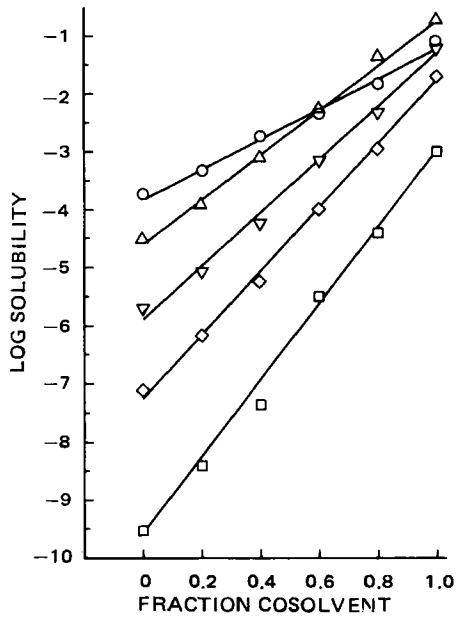

Figure 6—*Solubility of alkyl* p-*aminobenzoates in propylene glycol–water mixtures. Key:* ○, *ethyl;* △, *butyl;* ▽, *hexyl;* ◇, *octyl; and* □, *dodecyl.*

for the pure solvents. This finding indicates that a solvent blend of two liquids can indeed be treated as a pure solvent of intermediate polarity.

The data in Fig. 5 can be replotted to show the effects of altering solvent composition for each homolog. Figure 6 illustrates that increasing propylene glycol composition produces a linear increase in log X. It is apparent that the less water-soluble esters are solubilized most efficiently; *i.e.*, the solubilizing power of propylene glycol is greatest for the most nonpolar esters.

The relative solubilizing power of a variety of polar solvents for hexyl *p*-aminobenzoate can be seen from the slopes of lines of Fig. 7. The ability of the various solvents to solubilize hexyl *p*-aminobenzoate appears to be directly related to the nonpolarity of the solvent. The quantitation of these results with Eq. 11 will be discussed next.

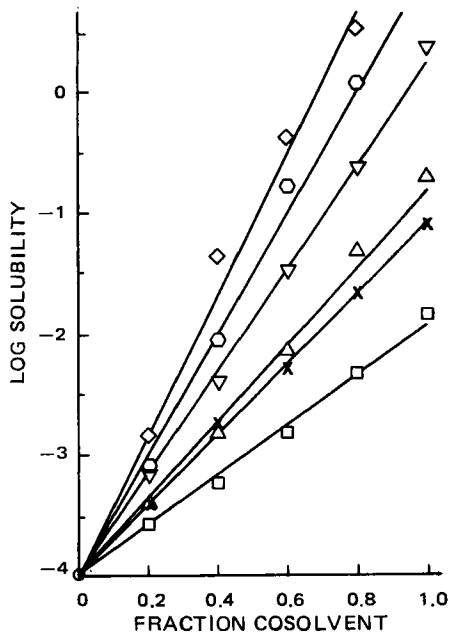

Figure 7—*Solubility of hexyl* p-*aminobenzoate in mixed solvent systems. Key:* ○, *water;* □, *glycerin–water;* ×, *formamide–water;* △, *ethylene glycol–water;* ▽, *propylene glycol–water;* ○, *methanol–water; and* ◇, *ethanol–water.*

Table I—Microscopic Interfacial Free Energy Densities for Several Solvents

Solvent, Temperature	γ, dynes/cm² (from Slope)	ϵ, dynes/cm² (from Intercept)	$\Delta\gamma$, dynes/cm² ($\gamma_w - \gamma_c$)	$\Delta\epsilon$, dynes/cm² ($\epsilon_w - \epsilon_c$)	$(\Delta\gamma)$ (HSA), dynes[a]	$(\Delta\epsilon)$ (PSA), dynes[a]
Water, 25°	28.3	10.2	0	0	0	0
Methanol, 25°	4.7	8.1	23.7	2.1	4968	143
Ethanol,[b] 25°	2.8	3.8	25.6	6.4	5367	412
Ethylene glycol, 25°	11.1	11.0	17.2	−0.8	3618	−44
Propylene glycol, 25°	6.5	8.5	21.8	1.7	4600	109
Glycerin, 25°	18.7	5.2	9.6	5.0	2026	324
Formamide, 25°	12.1	10.8	16.2	−0.6	3400	−32
Water, 37°	29.1	13.1	0	0	0	0
20% Propylene glycol, 37°	22.7	4.2	6.4	8.9	1346	569
40% Propylene glycol, 37°	20.3	9.3	8.8	3.8	1862	246
60% Propylene glycol, 37°	12.6	2.5	16.5	10.6	3456	667
80% Propylene glycol, 37°	9.9	4.3	19.2	8.8	4038	565
Propylene glycol, 37°	6.5	9.5	22.6	3.6	4739	230

[a] Hexyl *p*-aminobenzoate. [b] One data point was omitted.

DISCUSSION

Pure Solvents—*Comparison of* $(\Delta\gamma)(HSA)$ *and* $(\Delta\epsilon)(PSA)$—The relative importance of the hydrophobic and polar components of σ (Eq. 11) can be determined by the application of Eqs. 1 and 2 to the solute. The activity coefficients (or nonideal solubilities) of the esters in the various pure and mixed solvents described in Figs. 4 and 5 enable a comparison of $(\Delta\epsilon)$(PSA) and $(\Delta\gamma)$(HSA) for each ester. According to Eqs. 1 and 2, each line in these figures has a slope of $1/2.303\ kT \times \gamma$ (the microscopic interfacial free energy density at the hydrophobic portion of the solute and the pure or mixed solvent).

Since the polar surface area is the same for all esters (approximately 64 Å²), ϵ can be determined for each solvent from the extrapolated activity coefficient at TSA = PSA = 64 Å². The values of ϵ and γ in each solvent system studied are listed in Table I. The values of ϵ are not greatly different from that of water for any solvent, so $\Delta\epsilon$ is quite small in all cases. On the other hand, $\Delta\gamma$ is usually quite large. The values of $\Delta\epsilon$ and $\Delta\gamma$ are also given in Table I. It is also known that the value of HSA is significantly greater than the value of PSA for all esters studied. The last two columns of Table I show that for hexyl *p*-aminobenzoate, a typical poorly soluble solute, the value of $(\Delta\gamma)$ (HSA) is much greater than $(\Delta\epsilon)$(PSA) for all of the cosolvents considered. This finding leads to the following very useful approximation to Eq. 11:

$$\sigma \cong \frac{(\Delta\gamma)(HSA)}{2.303kT} \qquad \text{(Eq. 12)}$$

This approximation, which is applicable to solutes of low polarity, allows σ to be described in terms of a single property of each pure solvent component (γ_w and γ_c, the microscopic free energy density at the molecular hydrophobic surface) and of the pure solute (HSA, the molecular hydrophobic surface area).

Although the microscopic hydrocarbon surface areas of the solute can be calculated (21), the free energy per unit of molecular hydrocarbon surface area cannot be determined directly. However, this microscopic property can be related to the free energy per unit area at a suitable macroscopic hydrocarbon–solvent interface. This latter quantity, which is the hydrocarbon–solvent interfacial tension, is easily measurable for most polar solvents. To make this correlation, a model liquid hydrocarbon must be chosen for the macroscopic determinations and the differences between the macroscopic and microscopic interfacial tensions then must be considered.

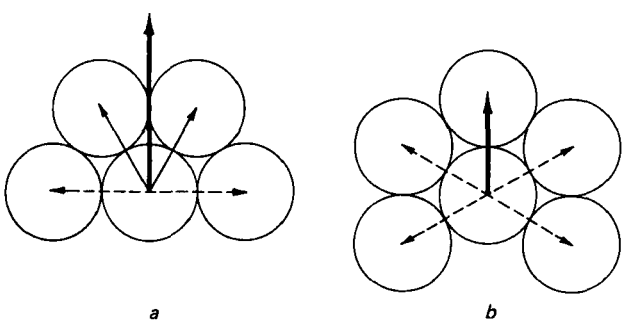

Figure 8—*Schematic diagram of the forces acting on a surface molecule of solvent at a planar interface* (a) *and at an interface having a radius of curvature equal to the solvent radius* (b).

Comparison of Macroscopic and Microscopic Interfacial Tensions—The choice of a model hydrocarbon for the macroscopic determinations is somewhat arbitrary and is governed primarily by experimental convenience. Low molecular weight hydrocarbons such as hexane are too volatile and tend to be miscible with some semipolar solvents such as ethanol. The very high molecular weight hydrocarbons are solid and cannot be used to get unambiguous interfacial tension values. Tetradecane is convenient to work with (22) and was used in all interfacial tension measurements.

The major difference between the microscopic and macroscopic interfacial tensions results from the extremely high degree of curvature of the molecular surface. The effect of high curvature can be conceptualized by consideration of the interfaces depicted in Fig. 8. Figure 8*a* shows a group of closest packed spheres at a macroscopic planar interface. (For simplicity, the region above the surface is treated as a perfect void so no transinterfacial forces have to be considered.) The balanced forces and their resultant force are indicated by solid arrows.

Figure 8*b* is a comparable diagram for the molecules surrounding a microscopic void space the size of a solvent molecule. The balanced forces are again indicated by dotted arrows. Since there is only one unbalanced interaction for each molecule surrounding the void space, this force (indicated by a solid arrow) is the resultant force. Since the

Table II—Calculation of Curvature Correction Factor from Single Solvent Data

Solvent, Temperature	γ, dynes/cm² (from Slope)	γ^0, dynes/cm² (Experimental, 25°)	c (γ/γ^0)
Water, 25°	28.3	51.9	0.55
Methanol, 25°	4.7	4.2[a]	—[a]
Ethanol, 25°	2.8	—[a]	—[a]
Ethylene glycol, 25°	11.1	19.3	0.58
Propylene glycol, 25°	6.5	12.5	0.52
Glycerin, 25°	18.7	35.2	0.53
Formamide, 25°	12.1	31.2	0.39
Water, 37°	29.1	51.9	0.56
20% Propylene glycol, 37°	22.7	44.1	0.52
40% Propylene glycol, 37°	20.3	36.2	0.56
60% Propylene glycol, 37°	12.6	28.3	0.45
80% Propylene glycol, 37°	9.9	20.4	0.49
Propylene glycol, 37°	6.5	12.5	0.52

[a] Experimental γ cannot be determined accurately because of the miscibility of the solvents with tetradecane.

Table III—Calculation of Curvature Correction Factor from Propylene Glycol–Water Data for Alkyl *p*-Aminobenzoates

Ester	HSA, A²	Slope (σ)	c
Ethyl	146	2.66	0.44
Butyl	178	3.82	0.52
Hexyl	210	4.72	0.54
Octyl	242	5.50	0.55
Dodecyl	306	6.61	0.52

imbalance of forces at the interface gives rise to the interfacial tension, the tension about a highly curved interface will be less than at a planar interface.

There is no definitive means of quantitatively predicting the effect of curvature on interfacial tension. However, several investigators proposed relationships of the same general form as the one proposed by Tolman (23):

$$\frac{\gamma^0}{\gamma} = \frac{1}{1 + \frac{2\delta}{r}} \qquad \text{(Eq. 13)}$$

where γ and γ^0 are the microscopic and macroscopic interfacial tensions, respectively; δ is a constant related to the size of the solvent (for water, $\delta \simeq 1.0$); and r is the radius of the microscopic interface in Angstroms. For cavities the size of the solvent molecule, the curvature correction factor is expected to be about 0.33; for nearly spherical solutes such as methane, neopentane, and adamantane, the factor increases to about 0.5, 0.65, and 0.77, respectively. It is not known whether nonspherical solutes can be treated as spheres of the same volume or whether some other means must be used to compute the appropriate radius of curvature.

Since there is no firm basis for choosing any particular relationship between γ and γ^0, the curvature correction must remain as an adjustable parameter, c, whose value lies somewhere between 0.33 and 1.0. Because all solvents considered are of comparable radius compared to that of the alkyl *p*-aminobenzoates, the value of c is expected to be a constant that is nearly independent of the solvent, so that:

$$\gamma = c\gamma^0 \qquad \text{(Eq. 14)}$$

applies to these systems.

The approximate constancy of c can be confirmed by another analysis of the data in Figs. 4 and 5. According to Eqs. 1 and 2, the slopes of the lines in the figure are equal to $\gamma/2.303kT$ for each solvent. The values of γ calculated from these slopes are listed in Table II along with the experimentally determined γ^0 values. It can be seen from the last column that there is very little difference in the curvature correction factors for the solvents. The values for methanol and ethanol appear to be exceptions but probably are due to the difficulties in determining interfacial tensions that result from the partial miscibility of these two pure solvents with the reference hydrocarbon, tetradecane.

Mixed Solvents—The assumed constancy of the curvature correction factor, c, allowed σ to be related directly to the measurable solvent hydrocarbon interfacial tension. Combining Eqs. 12 and 14 gives:

$$\sigma = \frac{c(\gamma_w{}^0 - \gamma_c{}^0)\text{HSA}}{2.303kT} = \frac{c\Delta\gamma^0\text{HSA}}{2.303kT} \qquad \text{(Eq. 15)}$$

which, when combined with Eq. 10, gives:

$$\log S_f = \log S_w + \frac{c}{2.303kT}\Delta\gamma^0\text{HSA}f_c \qquad \text{(Eq. 16)}$$

If c is always constant, Eq. 16 can be tested in two ways: (*a*) by relating the solubilizing power of a particular solvent system (having a constant $\Delta\gamma^0$) to the hydrophobic surface area of a series of solutes, and (*b*) by relating the solubilizing power of a series of cosolvents (having different values of $\Delta\gamma^0$) for a single solute.

According to Eq. 16, the slopes of the lines in Fig. 6 are each equal to:

$$\text{slope} = \frac{c(\gamma_w{}^0 - \gamma_{\text{PG}}{}^0)}{2.303kT} \times \text{HSA} \qquad \text{(Eq. 17)}$$

From the known values of $\gamma_w{}^0$, $\gamma_{\text{PG}}{}^0$, and HSA for each ester, the corresponding apparent values of c can be calculated. These values (Table III) are in good agreement with the values of Table II.

Table IV—Calculation of Curvature Correction Factor from Mixed Solvent Data for Hexyl *p*-Aminobenzoate

Cosolvent	σ[a]	$\Delta\gamma$, dynes/cm² (from σ)	$\Delta\gamma^0$, dynes/cm² ($\gamma_w{}^0 - \gamma_c{}^0$)	c ($\Delta\gamma/\Delta\gamma^0$)
Water	0	0	0	—
Glycerin	2.04	9.3	16.7	0.56
Formamide	2.71	12.3	20.7	0.59
Ethylene glycol	3.77	17.0	32.6	0.52
Propylene glycol	4.72	21.3	39.4	0.54
Methanol	5.45	24.6	47.7	0.52
Ethanol	6.35	28.7	51.9	0.55

[a] Calculated from $(\Delta \log X)/\Delta f_c$.

The slopes of the lines of Fig. 7 are, according to Eq. 16, equal to $(c/2.303kT)\,\Delta\gamma^0 \times \text{HSA}_{\text{hexyl }p\text{-aminobenzoate}}$. The values of c calculated for each solvent from these slopes are given in Table IV. Again, the values obtained are in agreement with all previous values. Further confirmation of the constancy of c is seen from the dependence of σ on $\Delta\gamma^0$ ($c = 0.57$ from Fig. 1 of Ref. 14) and from the slope of log (solubility) *versus* surface area for over 200 hydrocarbons and monofunctional aliphatic compounds in water [$c = 0.55$ (21)]. On the basis of the preceding observations, a constant value of 0.55 can be chosen for c and can be used in the equations.

The fact that c is constant is highly significant in that it makes Eq. 16 useful for predicting how well a particular cosolvent can solubilize a specific nonpolar drug. Table V lists the expected value of σ (both on a mole fraction scale, σ, and on a molar scale, σ_m) for each solvent considered. The last two columns of Table V list the predicted and observed increases in hexyl *p*-aminobenzoate solubility with each 10% increase in cosolvent composition. In all cases, the agreement between the two is quite good.

The constancy of c also makes it possible to predict the effect of HSA on the alkyl chain length on the solubility of a series of homologs in a given polar solvent. Table VI compares the observed decrease in the activity coefficient of the alkyl *p*-aminobenzoates in each of the pure and mixed solvents studied with the value predicted by Eq. 2 (with $c = 0.55$ and 18 Å²/methylene group). Again, the agreement between theory and experiment is quite good.

The utility of Eq. 16 extends far beyond hexyl *p*-aminobenzoate and the discussed solvents. It can be applied to nearly any nonpolar drug in a binary aqueous solvent system, even if the values of c and HSA are not explicitly known. The authors have observed[1] that the ability of propylene glycol to solubilize a number of drugs is directly related to the hydrophobicity of the drug and that the degree to which a drug is solubilized by a cosolvent is inversely proportional to its aqueous solubility. This result is expected because both aqueous solubility (corrected for crystal effects) and σ are related to hydro-

Table V—Predicted Effects of Cosolvents on Solubility of Hexyl *p*-Aminobenzoate[a]

Cosolvent	σ_X (Predicted)	σ_M (Predicted)	Factor by which Aqueous Molar Solubility Increases with Addition of 10% Cosolvent: Predicted	Observed
Water	0	0	1.0	1.0
Glycerin	2.02	1.43	1.4	1.6
Formamide	2.52	2.18	1.7	2.0
Ethylene glycol	3.97	3.48	2.2	2.2
Propylene glycol	4.79	4.19	2.6	2.6
Methanol	5.80	5.45	3.5	3.2
Ethanol	6.31	5.81	3.8	3.9

[a] All predicted values were based on a value of 0.55 for c.

Table VI—Predicted Effects of Chain Length on Activity Coefficients

Solvent	γ, dynes/cm²	Factor by which Room Temperature Activity Coefficient Decreases with Addition of Methylene Unit to Solute: Predicted	Observed
Water	51.9	3.46	3.31
Glycerin	35.2	2.19	2.13
Formamide	31.1	2.11	1.73
Ethylene glycol	19.3	1.59	1.69
Propylene glycol	12.5	1.35	1.33
Methanol	4.2	1.10	1.24
Ethanol	0	1.00	1.13

phobic surface area (Eqs. 1 and 12).

An interesting and important consequence of Eq. 16 is that the relative ability of the various cosolvents to solubilize a drug is independent of the drug (provided that it is sufficiently hydrophobic for this treatment to be applicable) and is related only to $\Delta\gamma^0$. Therefore, for any very insoluble drug, ethanol will be the most efficient solubilizer of the solvents considered, with the other solvents following in the order listed in Table IV.

SUMMARY AND CONCLUSIONS

The solubility of poorly water-soluble compounds in mixed aqueous solvents is treated as a linear combination of terms representing the pairwise interactions of each solvent component with each topographical component of the drug.

The interactions involving the hydrophobic portion of the solute are the major factors that determine how well it can be solubilized, and these interactions can be related directly to the interactions of a pure liquid hydrocarbon with the solvent components.

On this basis, an equation is derived that explains the exponential increase in the aqueous solubility of insoluble drugs with the addition of a cosolvent. This equation further predicts that the magnitude of the increase in solubility produced by the cosolvent is exponentially related to the surface (interfacial) properties of the solvent components and the hydrophobic surface area of the solute.

REFERENCES

(1) T. Higuchi, M. Gupta, and L. W. Busse, *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 157(1953).

(2) C. F. Peterson and R. E. Hopponen, *ibid.*, **42**, 540(1953).

(3) P. H. Elworthy and H. E. C. Worthington, *J. Pharm. Pharmacol.*, **20**, 830(1968).

(4) B. J. Poulson, E. Young, V. Coquilla, and M. Katz, *J. Pharm. Sci.*, **57**, 928(1968).

(5) E. R. Garrett and P. B. Chemburkar, *ibid.*, **57**, 950(1968).

(6) I. M. Korenman, *Russ. J. Phys. Chem.*, **45**, 1011(1971).

(7) Y. Kato and T. Ohuchi, *Yakugaku Zasshi*, **92**, 257(1972).

(8) A. J. Kapadia and J. Autian, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 380(1960).

(9) G. L. Flynn and S. H. Yalkowsky, *J. Pharm. Sci.*, **61**, 852(1972).

(10) S. H. Yalkowsky, G. L. Flynn, and G. L. Amidon, *ibid.*, **61**, 893(1972).

(11) R. B. Hermann, *J. Phys. Chem.*, **76**, 2754(1972).

(12) M. J. Harris, T. Higuchi, and J. H. Rytting, *ibid.*, **77**, 2694(1973).

(13) G. L. Amidon, S. H. Yalkowsky, and S. Leung, *J. Pharm. Sci.*, **63**, 1858(1974).

(14) S. H. Yalkowsky, G. L. Amidon, G. Zografi, and G. L. Flynn, *ibid.*, **64**, 48(1975).

(15) J. A. Reynolds, D. B. Gilbert, and C. Tanford, *Proc. Nat. Acad. Sci. USA*, **71**, 2925(1974).

(16) I. M. Langmuir, *Colloid Sym. Monogr.*, **3**, 48(1925).

(17) J. H. Hildebrand and R. L. Scott, "Regular Solutions," Prentice Hall, Englewood Cliffs, N.J., 1962.

(18) S. H. Yalkowsky, G. L. Flynn, and T. G. Slunick, *J. Pharm. Sci.*, **61**, 852(1972).

(19) A. W. Adamson, "Physical Chemistry of Surfaces," Interscience, New York, N.Y., 1970.

(20) C. H. Deal and E. L. Derr, *Ind. Eng. Chem.*, **60**, 28(1968).

(21) S. C. Valvani, S. H. Yalkowsky, and G. L. Amidon, *J. Phys. Chem.*, **80**, 829(1976).

(22) G. Zografi and S. H. Yalkowsky, *J. Pharm. Sci.*, **63**, 1533(1974).

(23) R. C. Tolman, *J. Chem. Phys.*, **17**, 333(1949).

ACKNOWLEDGMENTS AND ADDRESSES

Received October 6, 1975, from **Pharmacy Research, The Upjohn Company, Kalamazoo, MI 49001*, and the *‡School of Pharmacy, University of Wisconsin, Madison, WI 53706*

Accepted for publication December 10, 1975.

ˣ To whom inquiries should be directed.

Bioavailability of 11 Sulfisoxazole Products in Humans

GERALD W. A. SLYWKA *, ARMEN P. MELIKIAN, ARTHUR B. STRAUGHN, PHILIP L. WHYATT ‡, and MARVIN C. MEYER ˣ

Abstract □ Single lots of 11 commercially available 500-mg sulfisoxazole tablets were evaluated *in vitro* and *in vivo*. All products tested met USP XVIII specifications for weight variation and product assay. However, three products failed to meet the USP XVIII dissolution requirement. The only statistically significant difference observed between the 11 products was a lower peak plasma level exhibited by one product. No useful correlation was observed between the *in vivo* and *in vitro* studies for the dosage forms tested.

Keyphrases □ Sulfisoxazole—weight variation, dissolution, and bioavailability, *in vivo* and *in vitro* evaluation, commercial dosage forms □ Weight variation product assay—USP test, sulfisoxazole, commercial dosage forms □ Dissolution—USP test, sulfisoxazole, commercial dosage forms □ Bioavailability—sulfisoxazole, *in vivo* and *in vitro* evaluation, commercial dosage forms □ Antibacterial agents—sulfisoxazole, weight variation, dissolution, and bioavailability, commercial dosage forms

Sulfisoxazole is a sulfonamide antibacterial agent employed in the treatment of urinary tract infections. Although the metabolism, distribution, and elimination of sulfisoxazole have been studied in animals and humans (1–4), few studies have been undertaken to evaluate the bioavailability of commercially available