Membrane Solubility Parameter and *In Situ* Release of Theophylline

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Abstract □ The solubility of theophylline in polyethylene glycol 400–water binary mixtures was analyzed in terms of solute–solvent interaction using the solubility parameter principle of Hildebrand. Preliminary *in situ* (rat gut permeation) studies with the solvent mixtures having varying polarity as expressed by the solubility parameter showed that (*a*) the more alike the solubility parameter of theophylline ($\delta_2 = 14$, as obtained from solubility studies) and the solubility parameter of the solvent mixture, the greater was the attraction of solvent for the drug (*b*) sufficient similarity must exist between the solubility parameter of theophylline and that of the intestinal mucosa to promote bioabsorption, and (*c*) from the above, it follows that there exists a competition between solvent and rat gut membrane for the drug. The solubility parameter of the solvent vehicle must be such that it does not impede absorption of the molecules into the intestinal mucosa.

Keyphrases □ Solubility parameter—theophylline in propylene glycol 400–water, *in situ* release in the rat gut, membrane solublity parameter □ Release rate—theophylline in propylene glycol 400–water, *in situ* rat gut model, membrane solubility parameter □ Solute–solvent interactions—effect on the solubility of theophylline in propylene glycol 400–water, *in situ* release in the rat gut, membrane solubility parameter

The principle of solute–solvent interaction and its influence on drug solubility and solubilization has been studied extensively (1–10). Recent works (11–13) have extended the Hildebrand–Scatchard model (1, 2) to handle solubility predictions of drugs in polar solvents.

This report examines the influence of solvent polarity, solvent attraction for the solute (theophylline), and the effect of this interaction on theophylline release. The method of Doluisio *et al.* (14), in which drug absorption is followed using an *in situ* rat gut preparation, was employed to monitor theophylline disappearance from various polyethylene glycol 400–water mixtures into the rat intestinal membrane. The results of this study are analyzed according to the postulates of previous work (3–5, 15–17).

EXPERIMENTAL

In Situ **Rat Gut Method**—Male Sprague-Dawley rats, 220–250 g, were fasted for 16 h with free access to water and housed in mesh screen cages to prevent coprophagy. The rats were anesthetized with 75 mg/kg ip injections of sodium pentobarbital. After the onset of anesthesia, a midline incision was made to expose the intestines. Two L-shaped glass cannulae were inserted into the intestine and ligated. The proximal cannula, which was placed just below the bile duct, and the distal cannula were spaced ~61 cm apart. Four-centimeter lengths of Tygon tubing were attached to each cannula, and a 30-mL hypodermic syringe was connected to each Tygon tube using a three-way stopcock as a connector. The proximal syringe was filled with a pH 7 phosphate buffer, previously warmed to 37°C, and the intestine was flushed until the perfusate was observed to be clear as it left the distal cannula. Nine milliliters of various polyethylene glycol 400–water mixtures, having a range of solubility parameters and resulting in varing solubility for the drug, were formulated with each containing 2 mg/mL of theophylline and 1200 cpm of ^{14}C-labeled polyethylene glycol 4000, which was used as a nonabsorbable marker to monitor water flux. These solutions were placed in the prepared gut *via* the distal cannula and flushed back and forth through the intestines several times to effect uniform mixing. Two time zero samples (0.1 mL each) of the solution were then removed. After sampling, the solution was returned to the intestine and the stopcocks were closed to maintain the solution in place. A stop watch was activated, and serial time samples were removed thereafter. The stop watch was stopped during sampling time and restarted when the solution was

returned to the gut. Samples were removed from alternate syringes at each time period. One of the two samples removed was placed in a 20-mL vial, 15 mL of scintillation cocktail was added, and the sample was counted in a liquid scintillation counter utilizing single-channel counting to monitor water flux. The second sample was added to a 10-mL volumetric flask, brought to volume with the same solvent that the drug was dissolved in, and the absorbance measured in a spectrophotometer[1] at 272 nm.

Solubility Studies—Data from an earlier investigation (11) on the solubility of theophylline in dioxane–water mixtures were utilized in the study to obtain the solubility parameter of theophylline and to assess its solubility in solvent mixtures of varying solubility parameters (δ values).

RESULTS

Rate Constants for Absorption—The disappearance of theophylline from the solvent provided semilogarithmic plots, as observed in Fig. 1, which when analyzed, suggested the following model:

$$D_G \underset{k_2}{\overset{k_1}{\rightleftharpoons}} D_M \overset{k_3}{\rightarrow} D_B \tag{Eq. 1}$$

The quantity D_G represents the concentration of drug in the intestine, D_M is the drug concentration in the membrane, k_1, k_2, and k_3 are the rate constants for transfer of drug between the compartments, and D_B is the drug concentration in the blood.

Differential equations for the process represented by the above model were written from which the following solutions were obtained:

$$D_G = D\frac{(k_2 + k_3 - \alpha)e^{-\alpha t}}{(\beta - \alpha)} + D\frac{(k_2 + k_3 - \beta)e^{-\beta t}}{(\alpha - \beta)} \tag{Eq. 2}$$

where D represents the concentration of drug in the solution that was perfused into the intestine. The general form of Eq. 2 may be written as:

$$D_G = X_1 e^{-\alpha t} + X_2 e^{-\beta t} \tag{Eq. 3}$$

where α is the slope of the residual line feathered from the nonlinear initial phase of the curve in Fig. 1, and β is the slope of the terminal log-linear phase. The respective intercepts of these two straight lines are X_1 and X_2, and are written as:

$$X_1 = D\frac{(k_2 + k_3 - \alpha)}{\beta - \alpha} \tag{Eq. 4}$$

$$X_2 = D\frac{(k_2 + k_3 - \beta)}{\alpha - \beta} \tag{Eq. 5}$$

where D_G is defined at time zero, *i.e.*, D_{G0} by the expression:

$$D_{G0} = X_1 + X_2 \tag{Eq. 6}$$

k_1, k_2, and k_3 are obtained from the identities:

$$\alpha + \beta = k_1 + k_2 + k_3 \tag{Eq. 7}$$

and:

$$\alpha\beta = k_1 k_3 \tag{Eq. 8}$$

Substituting Eqs. 6 and 7 into Eq. 4 and rearranging yields:

$$k_1 = \frac{X_2\beta + X_1\alpha}{X_1 + X_2} \tag{Eq. 9}$$

which enables one to calculate k_3 from Eq. 8 and k_2 from Eq. 7.

Biological Partition Parameter and a Membrane Solubility Parameter—From the shape of the experimental curve of Fig. 1, it is assumed that equilibrium of theophylline exists between compartments G and M due to a par-
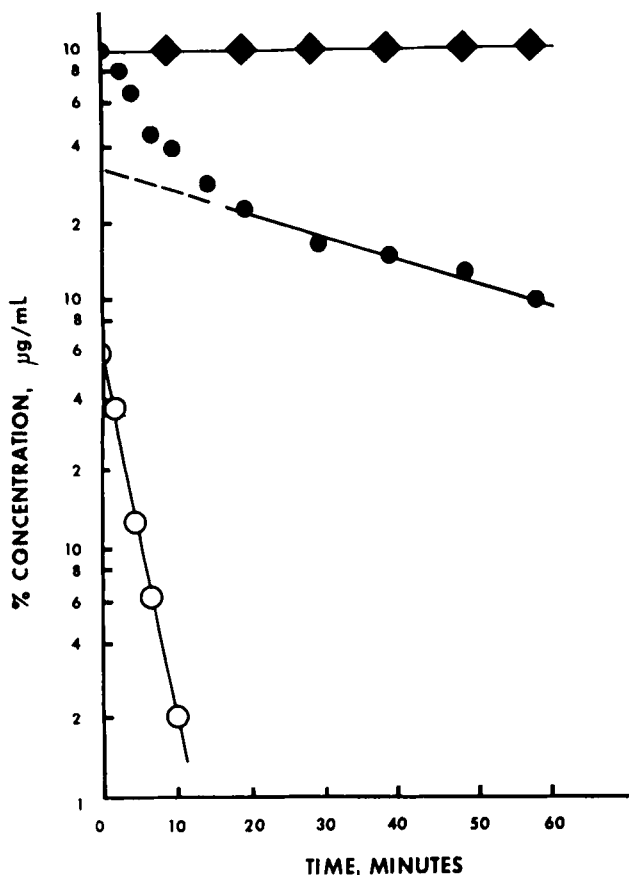
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[1] Beckman.

Figure 1—*Semilogarithmic plot showing first-order biexponential absorption of theophylline from the rat small intestine. Key: (◆) water flux as monitored using the nonabsorbable marker [^{14}C]polyethylene glycol 4000; the straight line shows concentration of the pure binary solvent in the rat intestine after correction for water flux; (●) theophylline concentrations in the rat intestine, $\beta = 0.021$; (O) residual feathered line representing the equilibrium phase of drug between contents of the gut and the rat intestinal membrane, $\alpha = 0.348$.*

titioning of the drug. The partition parameter, K_p, for this process (absorption and desorption of theophylline in the intestinal membrane) is written as:

$$K_p = \frac{k_1}{k_2} \qquad \text{(Eq. 10)}$$

The parameter K_p of Eq. 10, obtained from *in situ* rat gut data, should be related to the physicochemical properties of the drug-solvent carrier system. An equation, written in different forms by Davis (15), Cammarata and Rogers (18), Weimer and Prausnitz (19), Yeh and Higuchi (20), and Srebrenik and Cohen (21), and introducing δ_0 as the solubility parameter representing the rat gut membrane, is shown below:

$$\log K_p = \frac{V_2\phi_1{}^2}{2.303RT} [(\delta_1 - \delta_2)^2 - (\delta_0 - \delta_2)^2] \qquad \text{(Eq. 11)}$$

This equation may be used to analyze the data of the current study. The quantity R is the gas constant, T is the absolute temperature, and V_2 is the liquid molar volume of the solute, which for theophylline is 124 mL/mol. The terms ϕ_1 and δ_1 are, respectively, the volume fraction and the solubility parameter of the solvent, and δ_2 is the solubility parameter of the solute. Mullins (16) has reviewed various methods by which δ_0 for biological membranes may be obtained. He estimated from thermodynamic considerations that the δ_0 value of the frog sciatic nerve ranges from ~10.0 to 13.0. Mullins also noted for the frog nonsynaptic membrane that a value of 11.5 was in agreement with experimental results, whereas a value of 10.0 seemed more favorable for the δ value of synaptic nerve membranes. Cammarata *et al.* (17), using the erythrocyte membrane as a model for drug partitioning in biological systems, obtained a value of 8.05 as the apparent solubility parameter for the erythrocyte membrane.

Equation 11 does not account for entropic effects such as molecular size differences between solvent, solute, and membrane. Flory (22, 23) and Huggins (24, 25) introduced such size differences, *i.e.*, the molar volumes of solute and solvent, to account for deviations of solution phenomena from

Table I—Solubility of Theophylline, $\delta_2 = 14.0\ (cal/mL)^{1/2}$, $V_2 = 124$ mL/mol, in Selected Polyethylene Glycol 400-Water Mixtures at 25°C

Perecentage of Polyethylene Glycol 400	δ_1	ϕ_1	$(\delta_1 - \delta_2)^a$	Solubility, mg/mL	SD
100	10.5	0.9893	−3.5	15.539	±0.174
90	11.8	0.9879	−2.2	17.594	±0.102
80	13.1	0.9876	−0.9	17.937	±0.257
75	13.7	0.9885	−0.3	16.728	±0.096
70	14.4	0.9908	0.4	13.294	±0.231
65	15.0	0.9920	1.0	11.660	±0.058
60	15.7	0.9928	1.7	10.445	±0.034

^{a} δ_1 is the solubility parameter of the mixed solvent; δ_2 is the solubility parameter of the solute, theophylline.

ideality. The inclusion of these factors together with corrections for possible membrane metabolism and changes in solute molar volume across the biomembrane would seem warranted. Nevertheless, the present simplified approach was attempted as a first approach to the calculation of solute-solvent attractions and the estimation of δ_0 values in biological systems.

Solubility Parameters, Drug Release, and Bioabsorption—The terms of Eq. 11 describe solute-solvent and solute-membrane interaction forces due to polar interactions, in addition to dispersion or van der Waals forces as expressed by the classical Hildebrand equation (1). Analysis of the data using Eqs. 1, 3, and 7-10 provided pharmcokinetic parameters, which were correlated with solubility of theophylline and its release from the respective polyethylene glycol 400-water mixtures. A listing of these parameters is found in Tables I and II. Figure 2 shows that the closer the solubility parameter of theophylline $(14.0)^2$ and the solubility parameter of the particular solvent mixture (polyethylene glycol 400-water), the greater the attraction of solvent vehicle for the drug. A solvent whose solubility parameter is identical to that of theophylline would, according to regular solution theory, lead to the greatest solubility of the drug, barring solute-solvent interactions.

One would also expect an interplay of multiple physicochemical attractive forces in the drug release process due to differences between the membrane solubility parameter and that of the solvent and solute (Eq. 11). In this case,
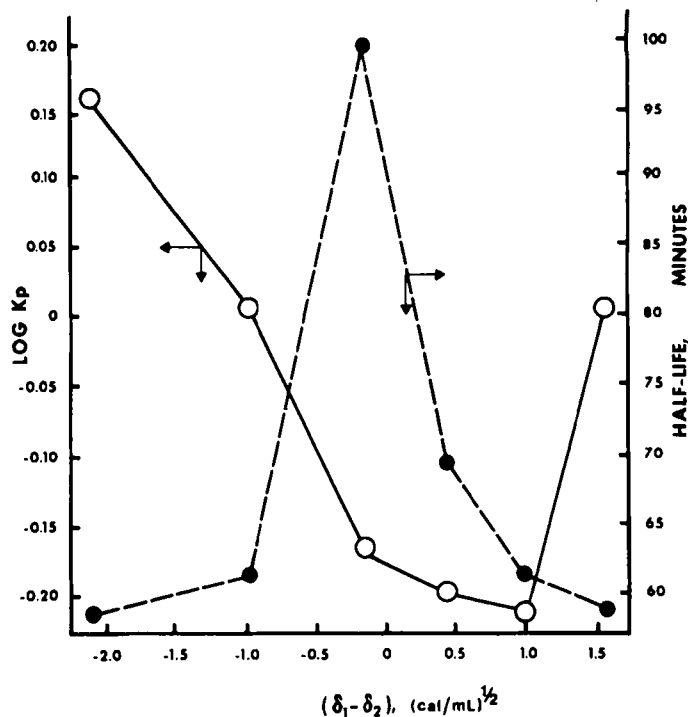

Figure 2—*Influence of solubility parameter difference ($\delta_1 - \delta_2$) on theophylline in situ partitioning (K_p) and the biological half-life ($t_{1/2}$) for absorption across the rat gut membrane. δ_1 is the solubility parameter of the mixed solvent; δ_2 is the solubility parameter of the drug, theophylline. Key: (●) half-life for theophylline absorption; (O) partition coefficient for theophylline absorption from solvent mixtures of varying solubility parameters.*

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[2] The solubility parameter of theophylline was taken from Ref. 12.

Percentage of Polyethylene Glycol 400	$t_{1/2,\beta}$, min	β, min⁻¹	α, min⁻¹	X_1, mg/mL	X_2, mg/mL	k_1, min⁻¹	k_2, min⁻¹	k_3, min⁻¹	$K_p{}^a$	log K_p	δ_0 high[b]/low
90	58	0.012	0.080	0.490	0.672	0.041	0.028	0.023	1.464	0.166	15.72 / 12.28
80	63	0.011	0.094	0.396	0.752	0.040	0.039	0.026	1.026	0.011	14.83 / 13.17
75	99	0.007	0.149	0.382	0.768	0.054	0.083	0.019	0.651	−0.186	14.53 / 13.47
70	69	0.010	0.143	0.302	0.750	0.048	0.075	0.030	0.640	−0.194	15.53 / 12.47
65	63	0.011	0.128	0.226	0.838	0.036	0.064	0.039	0.563	−0.250	15.98 / 12.02
60	58	0.012	0.090	0.340	0.740	0.037	0.036	0.029	1.028	0.012	15.66 / 12.34

$^a K_p = k_1 \div k_2$. ^{b} Membrane solubility parameters were calculated from the quadratic Eq. 11, and the two roots designated high and low are reported here.

Eq. 11 seems to suggest that δ_0, the membrane solubility parameter, would be important in evaluating the effects of solvent solubility parameters on drug absorption. Figure 2 shows that as the solubility parameter of the solvent gets closer to that of the solute, there is a rapid fall in the *in situ* partition parameter and a significant increase in the half-life for absorption (disappearance from the intestine) of theophylline. This is considered to be due to stronger interactions of solute and solvent. Conversely, when the solubility parameter of the solvent and solute are significantly different, the extent to which the drug and solvent molecules interact would be expected to be small. In such case, drug solubility would be reduced, resulting in greater release from the vehicle and a larger absorption rate constant.

Inspection of the lines in Fig. 2 and the parameters of Eq. 11 reveals a dependence of K_p (drug partitioning parameter) on δ_2 and δ_0, the membrane solubility parameter. A solvent mixture for optimum theophylline release and bioabsorption would have a solubility parameter that operates in conjunction with δ_2 and δ_0 so that solubility and partitioning effects were simultaneously changed. That is to say, the solubility parameter of drug and solvent (vehicle) must be sufficiently different to allow ready release of theophylline from the solvent, yet be similar enough to provide a reasonable concentration of the drug. And δ_2 and δ_0 must be sufficiently alike to favor drug absorption into the membrane.

To obtain quantitative measurements for the solubility parameter δ_0 of the rat gut membrane, the data summarized in Tables I and II were substituted into Eq. 11 for each polyethylene glycol 400-water solvent mixture, assuming $\phi_1^2 \simeq 1.00$. Average values for the two roots of the resulting quadratic equations were found to be 15.4 and 12.6. A δ_0 value of 12.6 for the rat gut membrane would seem to be more reasonable, since it is generally accepted that the intestinal membrane has low polarity. It is in fair agreement with the value of 11.6 suggested by Mullins (16) for synaptic nerve tissue. A value of 15.4 would suggest a *polar membrane in conflict with the relatively lipophilic character* of the intestinal mucosa (26).

Membrane solubility parameters may play a critical role in drug permeation and partitioning studies. The values may differ depending on the part of the intestines under consideration, such as for some antibiotics (27–29) for which "windows" or regions exist in the upper intestines where the drug is more readily absorbed.

DISCUSSION

Attempts have been made by some workers (30–32) to analyze the movement of drugs across cell membranes. These authors studied the kinetics of absorption of sulfonamides and barbiturates in the intestinal, gastric, and rectal regions of the GI tract. Utilizing theoretical models and introducing physical dimensions, some of which are associated with various membranes and others determined by *in vitro* experiments, these authors attempted to calculate physical constants consistent with the experimental data.

Khalil and Martin (5) studied the kinetics of [¹⁴C]carboxyl salicylic acid through model membranes and observed that the closer the δ value of the drug molecule to that of the lipoidal barrier, the faster the disappearance of the drug from an aqueous buffer layer of pH 2 (representing stomach contents) and the slower its appearance in an aqueous buffer of pH 7.4 (representing plasma). Khalil *et al.* (33, 34) employed the solubility parameter as an index of drug activity of several barbiturates. In their investigation, these authors observed that there was a linear relationship between the solubility parameter and logarithm of the partition coefficient reported in the literature for the various barbituric acid derivatives studied. They also observed a good correlation between solubility parameters of the barbiturates and their reported activities, and suggested that the solubility parameter concept might be a

possible substitute for the partition coefficient in structure-activity relationships. Pagay *et al.* (35) studied the influence of acetaminophen bioavailability and the dielectric properties of the vehicle. These studies, like those presented here, are attempts to understand the many factors that affect the solubility of drugs and their absorption properties.

Some workers (3–5, 33–38) have suggested that solubility parameters and dielectric requirements affect the bioavailability of drugs *in vivo*. Others (18, 19, 39–44) have concluded that permeability and the partition coefficient are useful parameters to be employed in monitoring drug absorption. Hansch *et al.* (45) have reported on a optimum log P for drug partitioning or penetration into the central nervous system which appears to be remarkably constant at a value of 2.0. The work reported in this paper suggests that not only the solubility parameter of the drug and solvent (drug carrier) but also the δ_0 of biological membranes should be considered by formulators in drug design work. However, the solubility parameter for the membrane as well as for the solute and solvent will probably have to be redefined to reflect the polar and hydrogen-bonding interactive forces involved in solute-solvent attraction and the permeation of the membrane by the solute. This problem has been studied (11–13) and is the subject of continuing work.

CONCLUSIONS

A method has been developed to optimize *in vivo* release characteristics of drug molecules based on solute-solvent interactive forces and use of the Hildebrand solubility parameter. A solubility parameter of 12.6 for the rat gut membrane has been estimated and is used to demonstrate the role of solute-solvent interactive forces in drug release studies. This method for obtaining the solubility parameter of a membrane uses an *in situ* drug absorption approach and a living membrane (rat gut) as the permeation barrier. The results obtained from this preliminary work are encouraging. However, further work must be done with various pharmaceutical drug-solvent systems before definitive conclusions can be made. Extended testing may provide improved solubility and penetration parameters characteristic of various living membranes and tissues which would prove useful in physical medicinal chemistry and quantitative drug design. It is suggested that theophylline, and possibly other poorly soluble drugs whose solubility and biological activity require careful control for optimum therapeutic effects, may be formulated using a generalized solubility parameter approach. Relative interaction of drug molecules with the vehicles in which they are formulated and the biological membranes they penetrate must be assessed in a number of systems before fundamental principles can be established.

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Synthesis and Properties of Some 13-*cis*- and All-*trans*-retinamides

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Abstract □ Several 13-*cis*-retinamides were synthesized from 13-*cis*-retinoic acid *via* either 13-*cis*-retinoyl chloride or 13-*cis*-1-retinoylimidazole. All-*trans*-retinoylglycine was prepared from all-*trans*-retinoyl chloride and ethyl glycinate. Detailed procedures were developed for the preparation of other all-*trans*-retinamides on a large scale for studies of the chemoprevention of cancer.

Keyphrases □ 13-*cis*-Retinamides—synthesis and chemical properties □ All-*trans*-retinamides—synthesis and chemical properties □ Synthesis—13-*cis*- and all-*trans*-retinamides, chemical properties

Compounds of the vitamin A group (retinoids) are essential for normal cellular differentiation and for the growth of epithelial tissues (1–4). During recent years, many studies, reviewed by Sporn and co-workers (3–9) and Bollag and co-workers (10–12), have shown that retinoid deficiency in animals enhances susceptibility to chemical carcinogenesis, that epithelia in certain organ cultures develop preneoplastic lesions in the absence of retinoids, and that administration of certain retinoids may prevent or reduce carcinogen-induced neoplasia in epithelial tissues of animals, as well as preneoplasia (6, 13–16) in organs in culture. In particular, certain derivatives and analogues of all-*trans*-retinoic acid (tretinoin, also known as vitamin A acid; Ia) exert a prophylactic (and, in some cases, a therapeutic) effect on the development of preneoplastic and malignant epithelial lesions (*e.g.*, 11, 16–25). Among the more interesting derivatives of retinoic acid and its analogues are the amides (retinamides and retinamide analogues). The purpose of this report is to describe the preparation of several all-*trans*-retinamides (II) and 13-*cis*-retinamides (IV) for long-term studies of chemoprevention in animals. Only one 13-*cis*-retinamide, the primary amide (IV, R = H), had been previously described (without a synthesis procedure) in the literature (26).

RESULTS AND DISCUSSION

The preparation of all-*trans*-retinamides IIa–d (27) and IIe (28) has been briefly outlined in the patent literature, but the characterization data (mp, UV) were sparse. The 4-hydroxyphenyl amide (all-*trans*-*N*-(4-hydroxyphenyl)retinamide; IIm) was synthesized originally by Gander and co-workers (24, 28). The preparation of IIf–l has not been described previously, but IIf–i