

Determination of Rate Constants for *In Vitro* Three-Compartment Transfer Using a Two-Phase System

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Abstract □ The use of two-phase studies to obtain the four rate constants involved in the transfer of drug between three compartments is described. The systems studied include the transfers of salicylic acid between pH 2 buffer, cyclohexane, and pH 7.4 buffer; erythromycin between pH 6.8 buffer, toluene, and pH 7.4 buffer; and erythromycin between pH 6.8 buffer, cyclohexane, and pH 7.4 buffer. The rate constants derived were shown to be independent of interfacial areas and phase volumes by studies in which these parameters were varied. Three phase curves showing the amount of drug in each phase *versus* time were drawn by an analog computer. The analog computer program included as parameters the four rate constants, the volumes of each of the three phases, and two interfacial areas. Thus, volumes and areas more likely to exist in biological systems, but impractical experimentally, can be selected to show drug transfer kinetics. Experimental points obtained from three-phase studies followed the computer-drawn curves closely.

Keyphrases □ Erythromycin transfer rate—two-phase system □ Salicylic acid transfer rate—two-phase system □ Transfer rate constants—salicylic acid, erythromycin, two-phase systems □ Distribution coefficients—salicylic acid, erythromycin, two-phase systems □ Interfacial area, phase volume, stirring rate, effects—transfer-rate constants

Absorption of drug from the gastrointestinal tract into the bloodstream is believed to occur by passive diffusion through a lipoidal membrane (1, 2). A number of workers used three-phase *in vitro* models to simulate the *in vivo* system to study the factors influencing drug transfer (3–9). Doluisio and Swintosky (4) devised an inverted rocking Y-tube, with aqueous phases in each of the two arms overlaid with a connecting layer of an immiscible organic liquid. Perrin (5) suggested a rectangular cell with a partition separating the two aqueous phases and the organic phase on top. These investigators demonstrated that drug transfer between three compartments can be described by four first-order rate constants.

In selecting a model for studying *in vitro* transport characteristics of erythromycin, it appeared that the four rate constants involved in transfer between three layers could most easily and accurately be determined by two-phase systems. Simulated three-phase curves can be obtained by using the rate constants in an analog computer program. This is in contrast to the approach taken by Khalil and Martin (6) who determined the rate constants from experimental curves by means of an analog computer.

This paper reports studies with salicylic acid and erythromycin using the described approach. Salicylic acid transfer between pH 2 and 7.4 buffers was selected as representative of gastrointestinal absorption of an acidic drug. Erythromycin transfer between pH 6.8 and 7.4 was studied primarily to develop *in vitro* data that could be related to systemic absorption of this drug from milk in the treatment of bovine mastitis. This

system can also be considered representative of absorption of a basic drug from the small intestine.

EXPERIMENTAL

Apparatus—The vessel chosen for the two-phase transfer studies consisted of a 2-l. round-bottom, three-necked, standard taper flask fitted with a ground-glass sealed stirrer in the center opening. A three-blade propeller was attached to the bottom of the stirring shaft which was driven by a variable speed stirrer.¹ A second three-blade propeller was placed on the stirring shaft 7.62 cm. (3 in.) above the first. When 1 l. of each phase was added to the flask, the stirrer was positioned so that the propellers were 3.81 cm. (1.5 in.) above and below the interface. Two glass tubes were inserted through a rubber stopper in one of the necks and extended into each of the liquid phases through which samples were withdrawn. The other opening served for introducing the liquid phases and was stoppered during the test. This flask gave an interfacial area of 194 cm.² For the purpose of studying the effect of phase volumes and interfacial area on transfer rate, a 2-l. graduated beaker was converted into a three-necked container with 24 × 40 taper joints. This vessel permitted changing volumes without affecting interfacial area. The interfacial area using this flask was 96 cm.²

The apparatus used for three-phase studies was a modification of the two-phase apparatus. Two 2-l. round-bottom flasks were placed next to each other, and the organic liquid phase was circulated between the two flasks by means of a tubing pump² and a siphon tube. Stirrers identical to those used for the two-phase study were used in each flask.

Reagents and Buffers—All chemicals were reagent grade unless specified otherwise. Salicylic acid, erythromycin, monobasic sodium phosphate, dibasic sodium phosphate, potassium chloride, hydrochloric acid, cyclohexane, and toluene were used.

The pH 2 buffer was prepared by adding 65 ml. of 0.2 M hydrochloric acid and 250 ml. of 0.2 M potassium chloride to a 1-l. volumetric flask and adding water to volume. The pH 6.8 buffer was prepared by dissolving 28.9 g. of dibasic sodium phosphate (heptahydrate) and 8.05 g. of monobasic sodium phosphate (monohydrate) in sufficient water to make 1 l. The pH 7.4 buffer was prepared by dissolving 37.4 g. of dibasic sodium phosphate and 3.7 g. of monobasic sodium phosphate in sufficient water to make 1 l. The final pH of the 6.8 and 7.4 buffers was adjusted with hydrochloric acid. All pH measurements were made with a Corning model 7 pH meter.

Procedure—In the two-phase experiments, the drug was dissolved in 1 l. of either the organic liquid or the aqueous buffer, depending on which procedure was most satisfactory for measuring the transfer. One-half gram of salicylic acid and 2.0 g. of erythromycin were used in all of the studies. One liter of the aqueous phase was added to the vessel which was then immersed in a constant-temperature bath at 37 ± 0.05° and allowed to reach temperature. One liter of the organic liquid was heated to 37° and then added slowly onto the top of the aqueous phase so as not to disturb the interface. It was not considered necessary to pre-equilibrate the phases prior to the transfer studies because of the marked difference in polarity between the aqueous and organic phases employed. The system was stirred at 80 r.p.m., samples (2 ml.) of each phase were withdrawn at various time intervals, and the drug concentration in one or both

¹ Servodyne Mixer, model 4420, Cole-Parmer Instrument and Equipment Co., Chicago, Ill.

² Masterflex Pump, model 7015, Cole-Parmer Instrument and Equipment Co., Chicago, Ill.

Table I—Rate Constants and Distribution Coefficients from Two-Phase Transfer Studies

Drug	pH of Aqueous Phase	Organic Phase	Phase to which Drug Was Added	K_C	k_1 , cm. hr. ⁻¹	k_{-1} , cm. hr. ⁻¹
Salicylic acid	2	Cyclohexane	Organic	0.157	0.246	1.57
Salicylic acid	2	Cyclohexane	Aqueous	0.157	0.248	1.58
Salicylic acid	7.4	Cyclohexane	Organic	<0.002	<0.04	1.84
Erythromycin	6.8	Cyclohexane	Organic	0.0436	0.0309	0.670
Erythromycin	7.4	Cyclohexane	Organic	0.153	0.0959	0.625
Erythromycin	6.8	Toluene	Aqueous	1.679	0.573	0.341
Erythromycin	7.4	Toluene	Aqueous	6.52	0.699	0.107
Erythromycin	7.4	Toluene	Organic	6.52	0.710	0.109

of the two phases was measured. The volume of samples removed had an insignificant effect on the interfacial area.

In the three-phase experiments, 1 l. of the aqueous buffered drug solution (0.5 g./l. salicylic acid or 2.0 g./l. erythromycin) was added to one of the flasks and brought to 37°. One liter of the other aqueous buffer and one-half of the organic liquid were added to the other flask and brought to 37°. The remainder of the organic liquid was heated to 37° and then added to the flask containing the drug solution. Circulation of the organic liquid between the two flasks was maintained at 100 ml./min. with the pump. Samples (2 ml.) of each of the three phases were withdrawn at various time intervals, and the drug concentrations in each phase were determined.

Distribution coefficients (K_C) of the drugs between the organic liquids and the aqueous buffers, as well as the equilibrium amounts in the two phases, were determined in separate experiments by rapidly mixing the two phases (100 ml. of each) in a 250-ml. conical flask for 2 hr. at 37°, allowing the phases to separate, and determining the drug concentrations in each phase. Studies showed that 2 hr. of stirring was sufficient to reach equilibrium.

Assay—Salicylic acid was determined spectrophotometrically with a Beckman DU-2 spectrophotometer at 297 nm. after an appropriate dilution with 0.1 N sodium hydroxide. Erythromycin was determined by the arseno-molybdate method (10). The cyclohexane and toluene samples were evaporated to dryness and reconstituted with water.

RESULTS AND DISCUSSION

Evaluation of Rate Constants—Two-phase transfer can be represented by the kinetic model:

$$C_A \xrightleftharpoons[k_{-1}]{k_1} C_B \tag{Eq. 1}$$

where C_A and C_B represent the concentration of drug in the two layers A and B , respectively, and k_1 and k_{-1} are the rate constants for the forward and reverse transfers, respectively. By considering the transfers to be first-order processes, the net rate of decrease in quantity of drug in layer A is given by the rate at which drug enters layer B less the rate at which drug returns from B to A . This is represented by

$$-\frac{dQ_A}{dt} = k_1' C_A - k_{-1}' C_B \tag{Eq. 2}$$

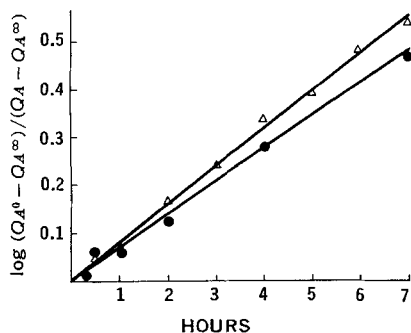


Figure 1—Rate of attaining equilibrium in the transfer of erythromycin from aqueous buffers (1 l.) to toluene (1 l.). Interfacial area equals 194 cm.². Key: Δ , pH 6.8; and \bullet , pH 7.4.

where Q_A is the quantity of drug in A , and k_1' and k_{-1}' are apparent rate constants. Since the transfer rate will be directly proportional to the interfacial area, S , and concentrations may be expressed as quantity divided by volume, Eq. 2 may be written:

$$-\frac{dQ_A}{dt} = k_1 \frac{SQ_A}{V_A} - k_{-1} \frac{SQ_B}{V_B} \tag{Eq. 3}$$

where k_1 and k_{-1} are rate constants independent of interfacial area and phase volumes with the dimensions of length per time (cm. hr.⁻¹).

It can be shown that Eq. 3 is related to Fick's law of diffusion by assuming that equilibrium is always present at the interface and the concentration gradient in phase A is rate determining (11). Thus, Eq. 4 may be written:

$$-\frac{dQ_A}{dt} = \frac{DS}{\Delta X} (C_A - \frac{C_B}{K_C}) \tag{Eq. 4}$$

where D is the diffusion constant, ΔX is the thickness of the diffusion layer, and K_C is the drug-distribution coefficient. Howard *et al.* (12) derived a similar equation to describe the transfer of a drug from an aqueous phase to an unstirred lipid sink. By expressing concentrations as quantities divided by volumes, Eq. 4 may be written:

$$-\frac{dQ_A}{dt} = \frac{DSQ_A}{\Delta XV_A} - \frac{DSQ_B}{\Delta XK_C V_B} \tag{Eq. 5}$$

where $D/\Delta X$ and $D/\Delta XK_C$ are equivalent to k_1 and k_{-1} in Eq. 3. Since D and ΔX have the dimensions of area per time and length, respectively, $D/\Delta X$ and $D/\Delta XK_C$ have dimensions identical to k_1 and k_{-1} , length per time.

Integration of Eq. 3 yields

$$\ln \frac{Q_A^0 - Q_A^\infty}{Q_A - Q_A^\infty} = S \left(\frac{k_1}{V_A} + \frac{k_{-1}}{V_B} \right) t \tag{Eq. 6}$$

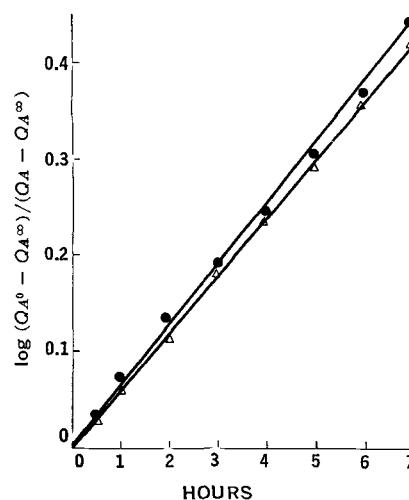


Figure 2—Rate of attaining equilibrium in the transfer of erythromycin from aqueous buffers (1 l.) to cyclohexane (1 l.). Interfacial area equals 194 cm.². Key: Δ , pH 6.8; and \bullet , pH 7.4.

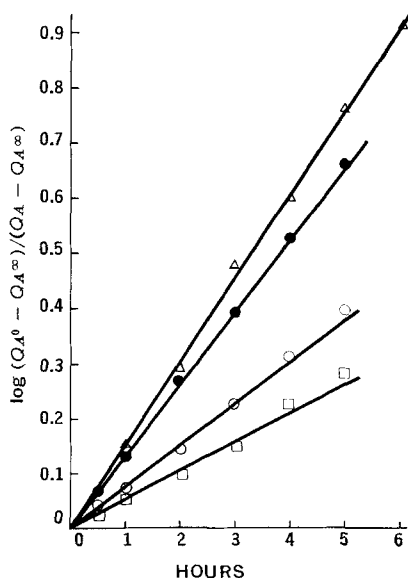


Figure 3—Rate of attaining equilibrium in the transfer of salicylic acid from cyclohexane (B) to pH 2 aqueous buffer (A). Key: Δ , $S = 194 \text{ cm}^2$, $V_B = 1 \text{ l.}$, $V_A = 1 \text{ l.}$; \bullet , $S = 96 \text{ cm}^2$, $V_B = 0.5 \text{ l.}$, $V_A = 1.5 \text{ l.}$; \circ , $S = 96 \text{ cm}^2$, $V_B = 1.0 \text{ l.}$, $V_A = 1.0 \text{ l.}$; and \square , $S = 96 \text{ cm}^2$, $V_B = 1.5 \text{ l.}$, $V_A = 0.5 \text{ l.}$

where Q_A^0 is the quantity of drug in layer A at zero time, and Q_A^∞ is the quantity of drug in layer A at equilibrium. A plot of $\log(Q_A^0 - Q_A^\infty)/(Q_A - Q_A^\infty)$ versus t should yield a straight line with an intercept of zero and a slope defined by Eq. 7:

$$\text{slope} = \frac{S}{2.303} \left(\frac{k_1}{V_A} + \frac{k_{-1}}{V_B} \right) \quad (\text{Eq. 7})$$

Since

$$K_C = \frac{C_B}{C_A} = \frac{k_1}{k_{-1}} \quad (\text{Eq. 8})$$

where K_C is the apparent distribution coefficient, substitution into Eq. 7 will allow evaluation of k_1 by the following expression:

$$k_1 = \frac{2.303}{S \left(\frac{1}{V_A} + \frac{1}{K_C V_B} \right)} \times \text{slope} \quad (\text{Eq. 9})$$

Then k_{-1} can be obtained from Eq. 8.

The half-life equation for attaining equilibrium may be derived from Eq. 7:

$$t_{1/2} = \frac{\ln 2}{S \left(\frac{k_1}{V_A} + \frac{k_{-1}}{V_B} \right)} \quad (\text{Eq. 10})$$

All experimental results obtained with the erythromycin and salicylic acid two-phase system followed the preceding relationships. Figures 1-3 are representative of the linearity obtained when the data are plotted according to Eq. 6. Rate constants and distribution coefficients for the two-phase systems used are shown in Table I.

The results show that the rate of salicylic acid transfer from pH 2 to cyclohexane is about 70 times faster than from pH 7.4. Although the faster rate would be expected, the magnitude of the difference is much less than would be predicted on the basis of transfer of only unionized species. Based on a pKa of 3, the concentration of unionized salicylic acid at pH 2 would be more than 20,000 times greater than at pH 7.4. The closeness of the two reverse rate constants indicates that the pH of the aqueous phase has little effect on transfer rate out of cyclohexane. For the erythromycin-cyclohexane system, the rate constant from pH 7.4 buffer is 3.1 times greater than at pH 6.8. This compares with a ratio of 3.86 for the fraction of unionized species at the two pH levels (0.99% at pH 6.8 and 3.83% at pH 7.4 based on a pKa of 8.8 for erythromycin). The rate constants

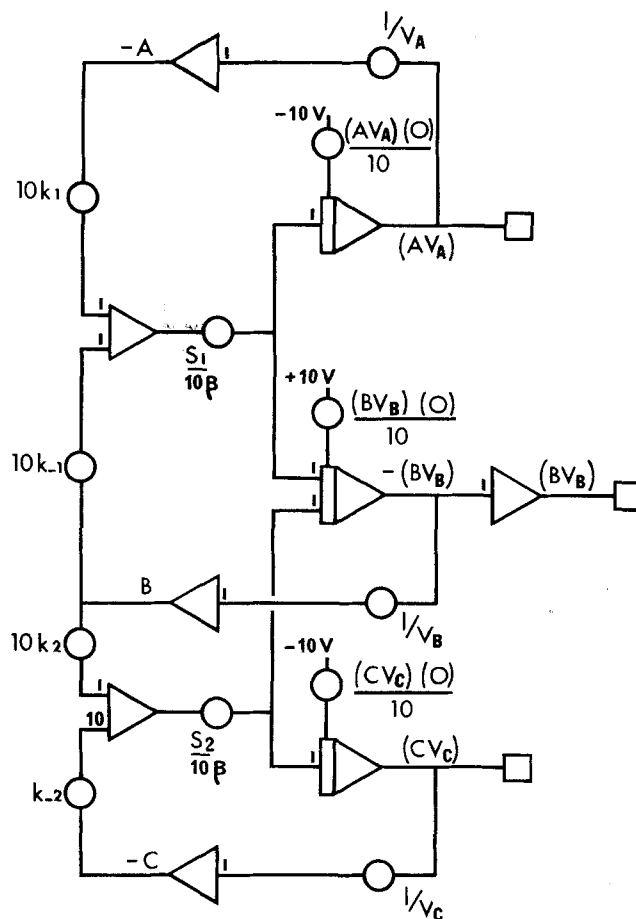


Figure 4—Analog computer program for obtaining three-phase drug transfer curves.

for the transfer of erythromycin from the aqueous phases into toluene are much greater than for cyclohexane. However, there is no correlation between the rate constants and the fraction of unionized species. The rate constant for the transfer from pH 7.4 buffer into toluene was only 1.2 times that from pH 6.8 versus the expected 3.86 ratio. A possible explanation for this lack of correlation might be the adsorption of the unionized erythromycin at the interface.

Distribution coefficients for unionized erythromycin were calculated from the apparent distribution coefficients by assuming that the drug in the organic phase was in the unionized form. In this manner, distribution coefficient values of 170 are derived for the toluene-pH 6.8 and toluene-pH 7.4 systems. The distribution coefficients of unionized erythromycin in the cyclohexane-pH 6.8

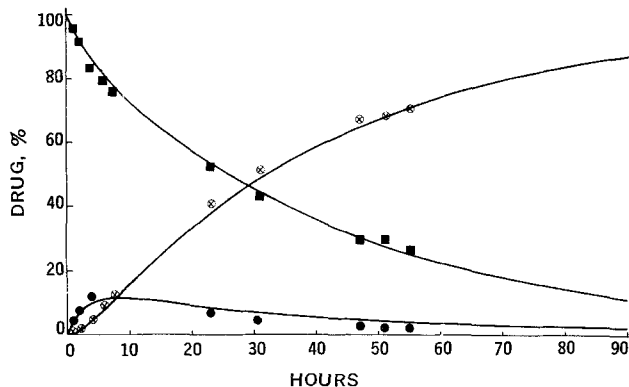


Figure 5—Transfer of salicylic acid from pH 2 buffer (1 l.) through cyclohexane (2 l.) to pH 7.4 buffer (1 l.). Lines were obtained from the analog computer program and points are experimental. Interfacial areas equal 194 cm^2 . Key: \blacksquare , pH 2.0 layer; \bullet , cyclohexane layer; and \diamond , pH 7.4 layer.

Table II—Effect of Phase Volumes and Interfacial Area on Rate Constants in the Transfer of Salicylic Acid from Cyclohexane into pH 2 Buffer

Experiment	Volume of pH 2 Buffer, l.	Volume of Cyclohexane, l.	Interfacial Area, cm. ²	<i>t</i> _{1/2} , hr.	<i>k</i> ₁ , cm. hr. ⁻¹	<i>k</i> ₋₁ , cm. hr. ⁻¹
1	1	1	194	1.97	0.246	1.57
2	1	1	96	3.92	0.249	1.59
3	0.5	1.5	96	4.77	0.250	1.52
4	1.5	0.5	96	2.24	0.252	1.53

and cyclohexane-pH 7.4 systems are 4.4 and 4, respectively. The fact that the distribution coefficients are nearly the same at both pH's for toluene and cyclohexane indicates that essentially only the unionized species is transferring into these solvents.

Table I shows that the same rate constants are obtained regardless of whether the drug is added to the aqueous or the organic phase. This is shown for the transfer of salicylic acid between pH 2 and cyclohexane and erythromycin between pH 7.4 and toluene. Therefore, the drug can be dissolved in either phase to determine the rate constants. Generally, it is most advantageous to add the drug to the phase in which the drug is least soluble.

Toluene and cyclohexane were selected for the lipoidal phases after studying distribution coefficients with a number of organic solvents. Although these solvents have similar delta values, they gave quite different rate constants. The magnitude of the difference was similar to that reported by Khalil and Martin (6) for the transfer of salicylic acid into these two solvents. Although both toluene and cyclohexane have a lower density than water, rate constants may be as easily determined with solvents heavier than water. In most previously described three-compartment models, only solvents lighter than water could be used.

Effects of Stirring Rate, Phase Volumes, and Interfacial Area—Since the transfer-rate constants are dependent on the ΔX in Eq. 5, it is important that this parameter does not vary. The most likely cause of change in the diffusion layer would be variations in the stirring rate. The effect of stirring rate on salicylic acid transfer was studied over a range of 50–130 r.p.m. The rate constants were found to be constant over the range 70–90 r.p.m. Increasing rates observed from 110 to 130 r.p.m. can be explained by a decrease in diffusion layer thickness, while a slight decrease in rate obtained at 50 r.p.m. can be attributed to insufficient stirring of the layers. On the basis of these results, a stirring speed of 80 r.p.m. was used in all experiments.

Several experiments were run to demonstrate that the rate constants defined in Eq. 3 are independent of phase volumes and interfacial area. Figure 3 and Table II show the results obtained when these parameters were varied in the transfer of salicylic acid from cyclohexane into pH 2 buffer. Experiments 2, 3, and 4 demonstrate that changes in phase volumes affect the rates of achieving equilibrium but not the rate constants. Experiments 1 and 2 (Table II) show that when the interfacial area is approximately halved, the half-life is doubled while *k*₁ and *k*₋₁ remain constant. The fact that the rate constants did not change when two vessels of different shape were

used would indicate that the diffusion layer thickness remained constant in these experiments. However, Augustine and Swarbrick (13) showed that the design of the transfer cell can be important. The agitation intensity and thus the resulting diffusion layer thickness achieved at a given stirring rate may be dependent on the shape of the vessel.

Use of Rate Constants in Three-Phase Systems—Three-phase transfer can be represented by the model:

$$C_A \xrightleftharpoons[k_{-1}]{k_1} C_B \xrightleftharpoons[k_{-2}]{k_2} C_C \quad (\text{Eq. 11})$$

where *k*₁ and *k*₂ are the rate constants for the forward transfer, and *k*₋₁ and *k*₋₂ are the corresponding reverse transfer constants. *C*_A and *C*_C represent the drug concentration in the two aqueous phases, and *C*_B is the drug concentration in the organic liquid. Rate equations for the transfer of drug from each of the three phases can be written as extensions of Eq. 3:

$$-\frac{dQ_A}{dt} = k_1 \frac{SQ_A}{V_A} - k_{-1} \frac{SQ_B}{V_B} \quad (\text{Eq. 12})$$

$$-\frac{dQ_B}{dt} = -k_1 \frac{SQ_A}{V_A} + k_{-1} \frac{SQ_B}{V_B} + k_2 \frac{SQ_B}{V_B} - k_{-2} \frac{SQ_C}{V_C} \quad (\text{Eq. 13})$$

$$-\frac{dQ_C}{dt} = -k_2 \frac{SQ_B}{V_B} + k_{-2} \frac{SQ_C}{V_C} \quad (\text{Eq. 14})$$

These equations differ from those presented by Perrin (5) and Khalil and Martin (6) for transfer of drug between three phases. Their equations show that the rate of transfer of total drug is a function of volume times concentration (quantity) rather than concentration in each phase. In their relationship, different values for the rate constants would be obtained each time the volumes are changed.

An analog computer³ was programmed to represent three-phase transfer based on Eqs. 12–14. The program is given in Fig. 4. The four rate constants can be determined by the two-phase studies described. Rate constants *k*₁ and *k*₋₁ are from a two-phase experiment employing phases *A* and *B*, while *k*₂ and *k*₋₂ are determined similarly from

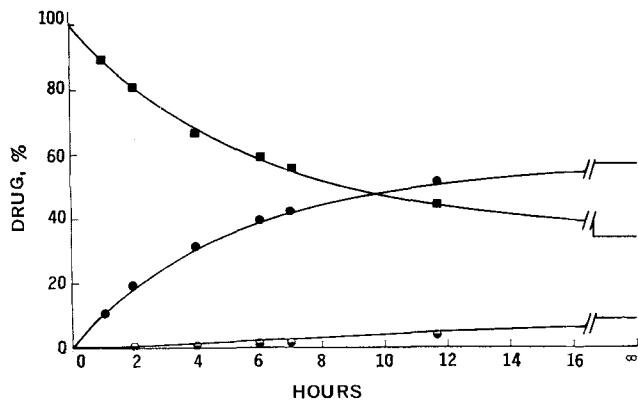


Figure 6—Transfer of erythromycin from pH 6.8 buffer (1 l.) through toluene (1 l.) to pH 7.4 buffer (1 l.). Interfacial areas equal 194 cm.². Lines were obtained from the analog computer program and points are experimental. Key: ■, pH 6.8; ●, toluene; and ○, pH 7.4.

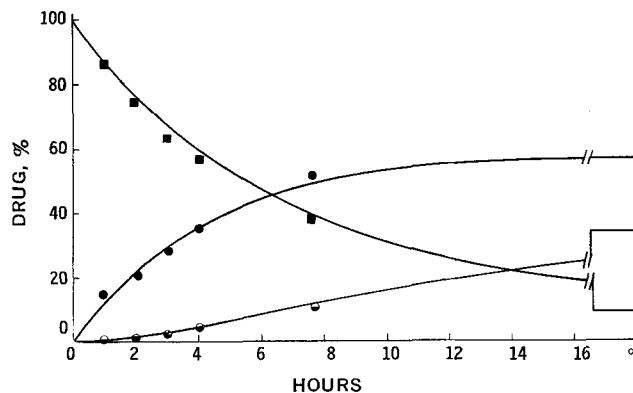


Figure 7—Transfer of erythromycin from pH 7.4 buffer (1 l.) through toluene (1 l.) to pH 6.8 buffer (1 l.). Lines were obtained from the analog computer program and points are experimental. Interfacial areas equal 194 cm.². Key: ■, pH 7.4 layer; ●, toluene layer; and ○, pH 6.8 layer.

³ Pace TR-48, EAI, Long Branch, N. J.

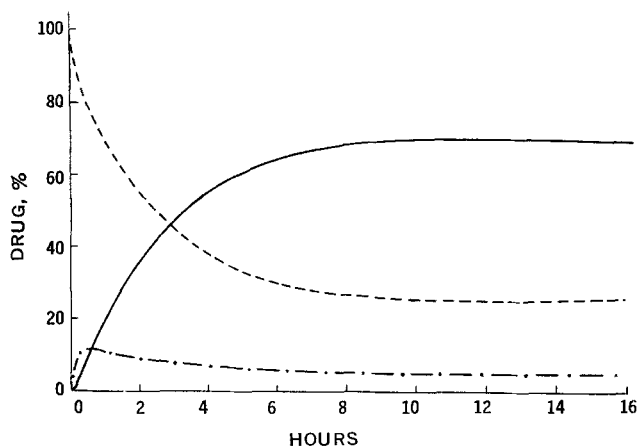


Figure 8—Transfer of erythromycin from pH 6.8 buffer (1 l.) through toluene (0.1 l.) to pH 7.4 buffer (10 l.). Interfacial areas equal 194 cm.². Curves were obtained from the analog computer program. Key: --, pH 6.8 buffer; - · -, toluene; and —, pH 7.4 buffer.

another two-phase experiment using phases B and C. Curves showing the amount of drug in each phase can then be obtained by putting these rate constants, along with desired phase volumes and interfacial areas, into the computer fitted with an X-Y recorder.

To demonstrate that rate constants from two-phase systems can be extended to this model, several three-phase runs were made and the experimental points were plotted against computer-drawn curves. The results are shown in Figs. 5–7. The experimental points followed the curves closely in all cases.

An advantage of the proposed method is that different volumes and interfacial areas can be fitted into the analog computer program. Thus, values more characteristic of those existing in the body can be used to simulate drug transport. For example, with the conditions described in Fig. 6, the percent of erythromycin in phase C at equilibrium is less than 10 and its $t_{1/2}$ is about 12 hr. However, if the

volumes of phases A, B, and C are assigned 1, 0.1, and 10 l., respectively, and the interfacial area is increased 10-fold, the curves in Fig. 8 are obtained. Under these conditions, the percent of erythromycin in phase C at equilibrium is increased to 73 and its half-life is decreased to 2 hr. These latter conditions would be impractical to use experimentally with the three-phase apparatus reported.

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Solubility of Alkyl Benzoates II: Effect of Dielectric Constant on the Solubility of Substituted Alkyl Benzoates

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Abstract □ The solubility of a homologous series of alkyl parabens, ranging from methyl to butyl together with benzyl paraben and methyl *p*-methoxybenzoate, were evaluated in solvents consisting of polyethylene glycol and water in various proportions. The relationship between dielectric constant value and mutual solubilizing effect, which was observed upon combining two parabens (benzyl paraben with any one of the parabens in the series), was evaluated. Decreasing the dielectric constant value of the solvent induced solubility of these esters. The dielectric constant, however, was observed to be not the sole factor, and there seems to exist a concentration effect of one paraben on the solubility of the other.

Keyphrases □ Solubility—substituted alkyl benzoates □ Dielectric constants, parabens—solubility relationship □ Parabens—mutual solubilizing effect □ Oscillometry—dielectric constant determination

In an earlier communication (1), the authors reported some solubility features of alkyl *p*-hydroxybenzoates (parabens). The data of these previous experiments, ob-

tained as a result of determining solubility of a combination of each paraben in a homologous series (methyl, ethyl, *n*-propyl, *n*-butyl paraben) and benzyl paraben, were indicative of the existence of a mutual solubilizing phenomenon among parabens. As compared to the solubility of a single paraben in polyethylene glycol (PEG) and water, there was an enhancement of solubility when a combination of two different parabens was allowed to dissolve.

Table I—Dielectric Constant of PEG-H₂O Mixtures

PEG, %	<i>k</i>
00	78.54
20	68.52
40	56.39
60	43.86
80	28.82
100	14.31