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

F. SHIHAB, J. SPROWLS, and J. NEMATOLLAHI

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, %	k
00	78.54
20	68.52
40	56.39
60	43.86
80	28.82
100	14.31
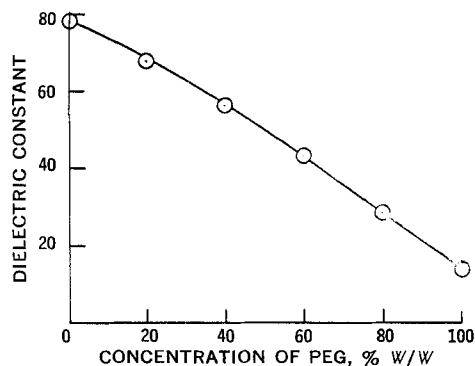
Figure 1—*Dielectric constant values of PEG–H₂O mixtures.*

Paraben		Concentration of Paraben, mole/liter					
R	R′	0.0	0.1	0.2	0.3	0.4	0.5
CH₃	H	43.86	43.36	43.01	42.65	42.22	41.57
C₂H₅	H	43.86	43.23	42.50	42.12	41.77	41.16
n-C₃H₇	H	43.86	43.12	42.18	41.71	40.59	40.12
n-C₄H₉	H	43.86	43.08	41.92	41.53	40.67	39.90
CH₃	CH₃	43.86	43.20				

EXPERIMENTAL

The dielectric constants of the solvents and the solutions were determined by using a Sargent chemical oscillometer, model V.

The solvents and solutions, whose dielectric constants were to be determined, were prepared by the previously reported procedure (1). The dielectric constants were determined according to the manual (2). The 10-ml. sample cell was washed with water, alcohol, and ether and dried thoroughly. The empty cell was then installed in position in the holder, and the instrument was adjusted to zero balance. Without removing the cell, the liquid under investigation was poured into the cell (about 1 cm. above the electrode). The instrument was again balanced, and the scale reading was recorded. The cell was then emptied, cleaned, and dried, and the procedure was repeated in the same manner for the next sample.

From the scale readings for two pure solvents with known dielectric constants, the cell constant, C_g, and the ratio of constants, C_g/C_0, were determined by employing the following formulas:

$$\frac{C_0}{C_g} = \frac{S_2(k_1 - 1) - S_2(k_2 - 1)}{k_1 S_1(k_2 - 1) - k_2 S_2(k_1 - 1)} \quad \text{(Eq. 1)}$$

Figure 2—*Solubility of methyl paraben as a function of dielectric constant (PEG–H₂O mixtures).*
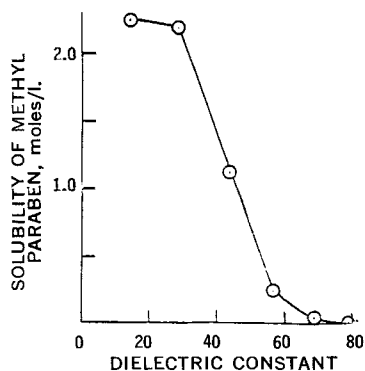
Envisioning the plausibility of physicochemical and biological applicability of solubility properties of parabens, in general, and the solubilizing potential of one paraben on the other, in particular, the authors attempted to elucidate the mechanism of solubility of parabens.

Two major influencing factors were considered to be involved in the solubility of parabens, irrespective of their use singly or in combination: (a) the dielectric constant of solvents or solutions in which one or two parabens were to be dissolved, and (b) hydrogen bonding between the ester molecules and between the solute and solvent molecules.

This communication is concerned with the evaluation of the solubility of parabens as a function of the dielectric constant. The experiments were designed to determine the dielectric constants of a number of solvents and solutions. These data were assumed to provide information leading to the elucidation of influencing factors responsible for the solubility enhancement of parabens.

Figure 4—*Solubility of propyl paraben as a function of dielectric constant (PEG–H₂O mixtures).*

Figure 5—*Solubility of butyl paraben as a function of dielectric constant (PEG–H₂O mixtures).*
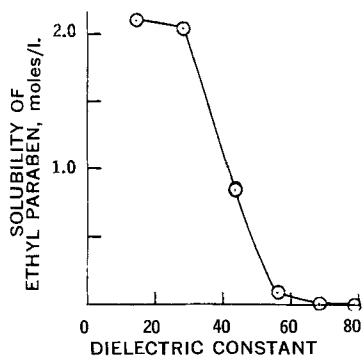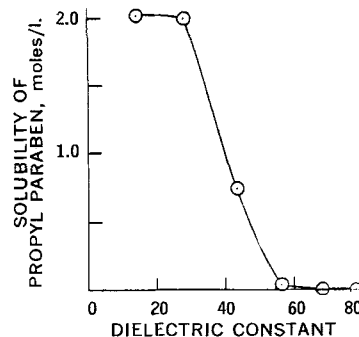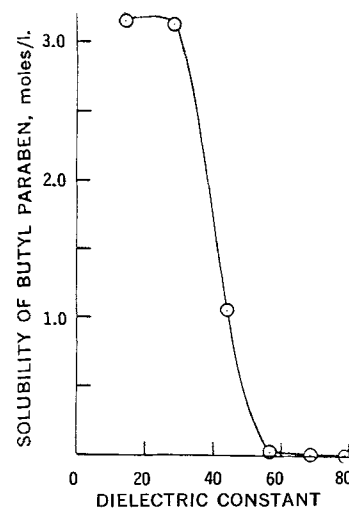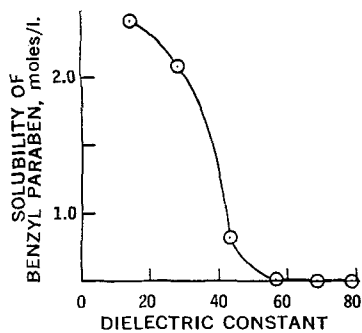

Figure 3—*Solubility of ethyl paraben as a function of dielectric constant (PEG–H₂O mixtures).*

Figure 6—*Solubility of benzyl paraben as a function of dielectric constant (PEG–H₂O mixtures).*

$$C_g = \frac{S(C_0/C_0 + 1) + kS(C_0/C_g + 1)}{k - 1} \quad \text{(Eq. 2)}$$

where C_0 = capacitance of the empty cell, C_g = capacitance of the cell with liquid, S = scale reading of a pure solvent, and k = dielectric constant.

The dielectric constant of each sample was then determined from its scale reading, using the following equation:

$$k = \frac{C_g + S(C_0/C_0 + 1)}{C_g - S(C_0/C_g + 1)} \quad \text{(Eq. 3)}$$

RESULTS AND DISCUSSION

The dielectric constant values of various concentrations of PEG–H₂O mixtures are depicted in Table I and Fig. 1. As expected, the dielectric constant of the solvent was inversely proportional to the concentration of PEG and gives a nearly linear relationship. The linearity is exact between 20 and 60% PEG, but beyond this amount the line bends slightly toward the x-axis (concentration axis). This could possibly be due to concentration effect.

Figures 2–6 depict the solubility of five parabens (methyl, ethyl, n-propyl, n-butyl, and benzyl paraben) individually as a function of the dielectric constant. The results coincide with those reported for other solvent systems (3, 4). All the curves have the shape of an inverted S. There seems to be an optimum solubility at the dielectric constant of about 30, beyond which there is a sharp drop in the solubility. Except for benzyl paraben, decreasing the dielectric constant value below 30 does not contribute to an increase in solubility.

The solubility features of methyl, ethyl, and n-propyl parabens are somewhat similar. The solubility of butyl paraben, however, differs from these three because it affords a significant increase in solubility upon adjusting the dielectric constants of the solvent to a value below 40. This difference in solubility property between butyl paraben and its lower homologs can be ascribed to the property of a long alkyl chain of the butyl group.

The change in the dielectric constant values as a function of concentration of parabens in 60% PEG–H₂O is depicted in Table II and Fig. 7. Methyl, ethyl, n-propyl, and n-butyl parabens, together with methyl p-methoxybenzoate, in concentrations ranging from 0.1 to
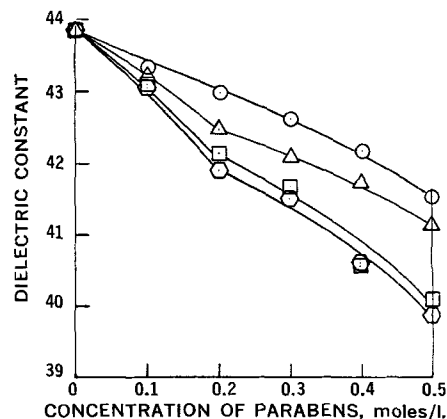

Figure 7—*Dielectric constant values of alkyl parabens in concentrations ranging from 0.1 to 0.5 M. Key:* ⊙, *methyl;* △, *ethyl;* ▢, *n-propyl; and* ○, *n-butyl.*
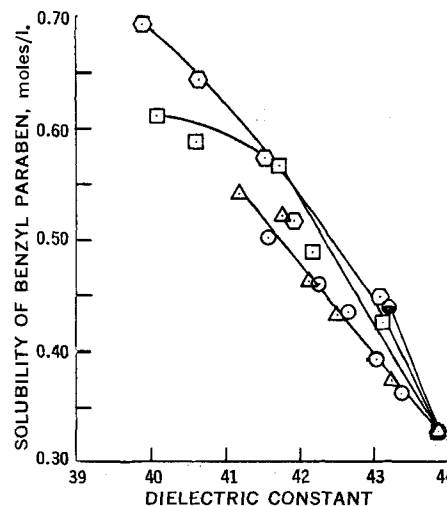

Figure 8—*Solubility of benzyl paraben in solutions of various concentrations (various dielectric constants) of alkyl parabens. Key:* ⊙, *methyl;* △, *ethyl;* ▢, *n-propyl;* ○, *n-butyl; and* ◕, *methyl p-methoxy.*

0.5 M were employed. The dielectric constant values decrease as the concentration values increase. The dielectric constant-lowering potential increases in an ascending order of the alkyl chain of the parabens.

The difference between the dielectric constant-lowering potential of two distant paraben homologs, methyl and butyl, is small at 0.1 M but increases significantly at 0.5 M (see Table II). This is probably

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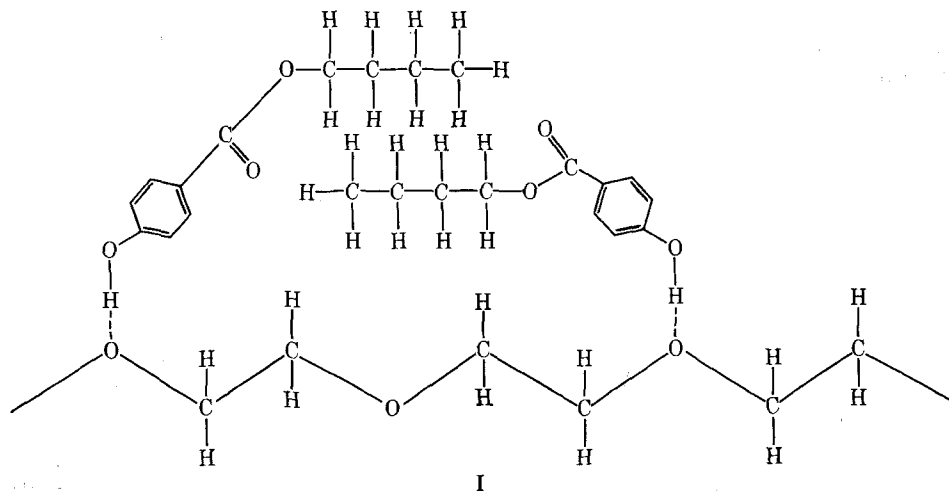
due to a difference in the length of the alkyl chain. Considering the preferred conformation of polyethylene glycol, the long alkyl chains of butyl parabens, whose OH are hydrogen bonded to alternate oxygens of the polyethylene glycol, can overlap and become stabilized by van der Waals' force. The semirigid structure illustrated in Structure I and/or analogously crosslinked structures, formed as a result of overlap between alkyl chains of butyl paraben, hydrogen bonded to two different polyethylene glycol molecules, can contribute to the lowering of the polarity of the medium upon increasing the concentration more than with methyl paraben, in which such linking is not possible.

The solubility of benzyl paraben in various solutions of each alkyl paraben (methyl, ethyl, n-propyl, and n-butyl) with known dielectric constants were determined. The plots are depicted in Fig. 8. The results indicate that the solubility of benzyl paraben in a solution of alkyl paraben is not solely dependent on the dielectric constant-lowering potential of the alkyl paraben. Reference to Fig. 8 and solubility values of benzyl parabens in various concentrations of alkyl parabens, reported in the previous communication (1), clarifies this contrast. The 0.4 M concentrations of butyl paraben and propyl paraben have dielectric constants $k = 40.59$ and $k = 40.67$, respectively. The solubility of benzyl paraben in these solutions is 0.52 and 0.59 M, respectively, obviously opposite of what would have been expected from their dielectric constant values. The most conspicuous results were obtained from 0.1 M ethyl paraben and

0.1 M methyl p-methoxybenzoate, both with $k = 43.2$, in whose solutions the solubility of benzyl paraben was found to be 0.37 and 0.44 M, respectively.

In summary, there exists a relationship between the dielectric constant and solubility of parabens. The solubility data of combinations of two parabens, however, indicate the involvement of factors other than dielectric constants. A theoretical consideration of these will be given in a future communication.

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Inhibited Dissolution of Drug Crystals by Certified Water-Soluble Dyes II

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Abstract ☐ Experiments on dissolution inhibition of poorly water-soluble drug crystals (sulfathiazole and diethylstilbestrol) in the presence of low concentrations of certified water-soluble dyes are presented. The effect of the degree of undersaturation and the dependence of dissolution rate on the inhibitor concentration of powder systems were investigated. Data obtained are consistent with previous findings and suggest preferential adsorption at the primary dissolution sources on the crystal surface. Further dissolution studies in the presence of 0.04 M sodium cholate showed that the dye caused substantial reduction in surface dissolution of the sulfathiazole single crystal. Biological implications in these systems are considered.

Keyphrases ☐ Dyes, water-soluble—drug crystal dissolution, inhibition ☐ Dissolution rates, crystals—water-soluble dye effect ☐ Crystals, sulfathiazole, diethylstilbestrol—dissolution rates, dye effect ☐ Sodium cholate effect, dissolution—crystals–dyes

In previous communications, the effect of low concentrations of FD&C Blue No. 1 on the dissolution rate of certain crystalline drugs was reported (1, 2). Concentrations of 5–10 mcg./ml. were sufficient to exert a remarkable inhibition on the surface dissolution of sulfathiazole, sulfaguanidine, and phenobarbital monohydrate single crystals. Additional dissolution experiments on compressed disks of the pure drug gave similar results. Studies made on a powder system showed a marked inhibition of the dissolution rate; however, the results of only one powder system were insufficient to draw definite conclusions.

The present work was undertaken to: (a) determine the influence of the dye incorporated in a compressed

disk rather than dissolved in the test media; (b) define the manner in which undersaturation of the solution and concentration of the dye affect dissolution in powder systems; and (c) investigate the influence of the dye on micellar solubilization.

EXPERIMENTAL

Materials—Sulfathiazole Form I crystals were obtained using the method previously described (1). Diethylstilbestrol,[1] sodium chlorate,[1] and 0.90% NaCl solution[2] were USP grade; all other solvents were purified before use.

Dissolution-Rate Studies—Dissolution experiments to determine the influence of FD&C Blue No. 1 incorporated in a compressed disk were carried out using sulfathiazole Form I as a test material. Tablets of drug crystals alone and of drug crystals containing 5 mg. of the dye were compressed under the same pressure (Fig. 1). The dissolution rate was determined using a method described in a previous communication (1).

To substantiate earlier results obtained in the surface dissolution studies, a series of experiments was carried out on a powder system using diethylstilbestrol as a model substance. The Coulter counter method, described by Higuchi and Saad (3, 4) and by Edmundson and Lees (5), was used in these experiments. A suspension of diethylstilbestrol was prepared using the following method: 1 ml. of ethyl alcohol containing 10 mg. of diethylstilbestrol was added to 150 ml. of 0.90% NaCl solution. Magnetic stirring was maintained for 2 hr. The suspended crystals were then sonified for 2 hr. (using a Sonifier Cell Disruptor model W, 140 D)[3] to get a particle size

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