

# The solubility of some compounds in hexadecylpolyoxyethylene monoethers, polyethylene glycols, water and hexane

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The solubilities of a series of compounds of varying polarity, i.e. decane, benzene, sulphadiazine, *p*-hydroxybenzoic acid, ethyl and butyl *p*-hydroxybenzoate and methyl anisate in cetomacrogol 1000 and hexadecyl heptaoxyethylene ether solutions, have been determined. A comparison of these results with the solubilities of these compounds in water, *n*-hexane and polyethylene glycol solutions gives some evidence on the mechanism of solubilization. The results show that the solubilization of these compounds is not adequately described solely on the basis of solubility into the separate regions of the micelle. The micellar solubility of the compounds was dependent on the hydrocarbon solubility and the presence of groups in the molecule which can form hydrogen bonds. Butyl paraben was found to have a higher solubility in 10% cetomacrogol solutions than either ethyl paraben or methyl anisate. The hydrophil-lipophil characteristics of the detergents with the polarity of the solubilize molecule also affect solubilization. A non-polar molecule such as decane has a greater solubility in the more lipophilic detergent and the reverse is true of *p*-hydroxybenzoic acid.

One of the main advantages in the use of non-ionic detergents in formulation is that the oxyethylene and hydrocarbon chain lengths can be tailored to provide any particular hydrophilic-lipophilic characteristic and thus it is possible to solubilize a wide range of compounds by adjusting these parameters.

Theoretically it should be possible to calculate the maximum additive concentration (M.A.C.) of a compound in a detergent solution from the saturation solubilities of the compound in the different regions of the micelle. This approach is valid for only a few compounds solubilized by ionic detergents (Hartley, 1938). Micelles of non-ionic detergents have an oxyethylene-water complex region of indeterminate composition and consequently the simple "bulk solubility" approach is not adequate. For a detergent of a given hydrocarbon chain length a minimum hydrophilic chain length is required for the detergent to be water soluble provided this occurs, the smaller the hydrophilic chain in a series of surfactants, the more hydrocarbon can be solubilized (Saito & Shinoda, 1967).

It has been found that the M.A.C. of benzoic acid in a series of polyoxyethylene hexadecyl ethers increased from 1.0 mol benzoic acid/mol  $C_{16}n_{16}$  to 3.0 mol benzoic acid/mol  $C_{16}n_{96}$  (Humphreys & Rhodes, 1968). [Detergents are abbreviated thus  $CH_3(CH_2)_{15}\cdot O\cdot(CH_2CH_2O)_{16}H = C_{16}n_{16}$ .]

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The solubilizate molecule may itself affect the M.A.C. Nakagawa & Tori (1960) showed that, in  $C_{10}n_{10}$ , decane and decyl chloride were solubilized less than some other more polar decyl compounds. Similar results have been found for substituted benzoic acids and esters (Chakravarty, Lach & Blaug, 1957).

#### MATERIALS AND METHODS

*Heptaoxyethylene glycol monohexadecyl ether*, prepared according to Elworthy & Macfarlane (1963), was chromatographed (Macfarlane, 1963) to yield white crystals m.p. 37.8–38.2°. (Elworthy & Macfarlane, 1963, give m.p. 38.5°.)

*Cetomacrogol 1000 B.P.C.* (Macarthy's Ltd., Romford) was used as received. It was assayed for oxyethylene units by the method of Siggia, Starke & others (1958). The mean result of two determinations was 79.61% of oxyethylene units in the molecule. (B.P.C. limits: 76.52–81.36%.) Assuming the hydrocarbon chain to be the hexadecyl chain, this gives the number of oxyethylene units as 21.5. For all subsequent calculations the molecular weight was taken as 1210.

*Polyethylene Glycol 1000 (PEG)* was B.D.H. Laboratory Reagent and was used as received. The oxyethylene content was not determined but the molecular weight was taken as 986 for all calculations, and corresponded to an oxyethylene chain of 22 units.

*Hexaoxyethylene glycol (Hexagol)*, prepared according to Elworthy & Macfarlane (1963) was a pale straw coloured liquid  $n_D^{25}$  1.4609. (Curme & Johnston, 1952, give  $n_D^{38}$  1.4589.)

*Benzene*, crystallizable (W. Jarvie Ltd.) was distilled before use,  $n_D^{18}$  1.5028. (Handbook of Chemistry and Physics 1966 gives  $N_D^{20}$  1.5011.)

*n-Decane*, olefine free (Fluka AG. Purum grade) was used as received,  $n_D^{18}$  1.4131. (Handbook of Chemistry and Physics 1966 gives  $N_D^{20}$  1.4119.)

*n-Hexane* (BDH spectroscopic grade) was used as received.

*Sulphadiazine B.P.* (Macarthy's Ltd., Romford) was recrystallized twice from dimethylformamide–ethanol mixture (1:3) and dried in a vacuum oven at 40° over phosphorous pentoxide: m.p. 254° (decomp). (British Pharmacopoeia 1968 gives m.p. 255 decomp.)

*p-Hydroxybenzoic acid* (BDH Ltd., Laboratory reagent) was recrystallized from distilled water and dried overnight at 40° in a vacuum over phosphorous pentoxide; m.p. 214°. (Vogel, 1956, gives 212°.)

*Ethyl p-hydroxybenzoate (ethyl paraben)* (BDH Ltd., Laboratory reagent) was recrystallized from distilled water, then dried overnight at 40° in a vacuum oven over phosphorous pentoxide; m.p. 112°. (Vogel, 1956, gives 111–115°.)

*n-Butyl p-hydroxybenzoate (butyl paraben)* (BDH Ltd., Laboratory reagent) was recrystallized from water–ethanol mixture (3:1) then dried in a vacuum at 40° over phosphorous pentoxide; m.p. 68°. (Merck Index, 1968, gives m.p. 68–69°.)

*Methyl p-methoxybenzoate (methyl anisate)* was prepared by esterification of anisic acid (Koch-Light Laboratories Ltd., Puriss grade) in the usual way. It was recrystallized from a methanol–water mixture (6:4) then dried in a vacuum over phosphorous pentoxide; m.p. 48.0–48.5° not raised by further recrystallization. (Lifschitz & Girbes, 1924, give m.p. 49.0–49.5°.)

*Water* used for the preparation of solutions was tap water distilled once from glass.

*Solubility measurements*

A small excess of decane was equilibrated with "solvent" (water or detergent) by shaking at 20° until saturation was reached. The saturated aqueous phase was assayed for hydrocarbon by gas liquid chromatography on a 6 ft Carbowax column at 75° using n-butanol as the internal standard.

Benzene was equilibrated in the same way and the benzene in the aqueous phase determined by ultraviolet spectrophotometry ( $\lambda_{\max} = 254$  nm). Saturation solubilities of solid compounds were determined as described by Elworthy & Lipscomb (1968a). Aqueous phases as well as hexane solutions were assayed by ultraviolet spectrophotometry.

*Phase diagrams* were constructed according to Boffey, Collison & Lawrence (1959).

## RESULTS AND DISCUSSION

*Solubility in water*

The most important properties of the solute molecules governing the solubility in water are the molecular volume and the presence of hydrophobic substituents requiring extensive structuring of the water molecules. The ability of substituent groups to participate in hydrogen bonding with the water molecules is less important. This is well illustrated by the results in Table 1.

Table 1. *The solubilities of compounds in pure liquids and the M.A.C.s in the detergent solutions (millimolal) at 20°.*

Solvent	Solute						
	Decane	Benzene	Sulpha- diazine	<i>p</i> -Hydroxy- benzoic acid	Ethyl paraben	Butyl paraben	Methyl anisate
Water	—	21.8	0.236	34.7	†4.91	1.065	3.87
n-hexane	∞	∞	0	0	1.04	4.48	636
1% w/v cetomacrogol	2.42	33.9	0.272	45.9	13.9	13.5	11.8
5% w/v cetomacrogol	9.72	125	0.535	90.8	45.1	58.3	29.6
10% w/v cetomacrogol	19.7	182	1.01	157	78.6	121	50.0
1% w/v C <sub>16</sub> n <sub>7</sub>	22.2	*261	—	45.0	15.9	—	12.0
2% w/v C <sub>16</sub> n <sub>7</sub>	38.2	—	—	56.9	27.6	—	20.5

\* in 12.5% cetomacrogol solution.

† The standard error of the solubility of ethyl paraben in water was found to be  $\pm 0.06$  millimolal.

*Solubility in hexane*

These results show the typical dependence of solubility in apolar solvents on the polarity of the solutes.

*Solubility in PEG solutions*

The solubilities of all the compounds was increased in polyethylene glycol solutions. If this increased solubility was dependent solely on the ability to form hydrogen bonds with the ether oxygen atoms it would be expected that solutions containing equal concentration by weight of the PEG 1000 and hexagol (PEG 300) would dissolve the same amount of solute.

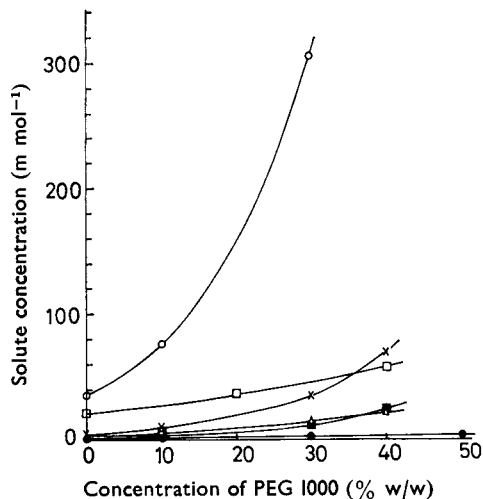


FIG. 1. The Solubility of compounds in PEG 1000 Solutions at 20° C. ○ *p*-Hydroxybenzoic acid. X Ethyl paraben. □ Benzene. △ Methyl anisate. ■ Butyl paraben. ● Sulphadiazine.

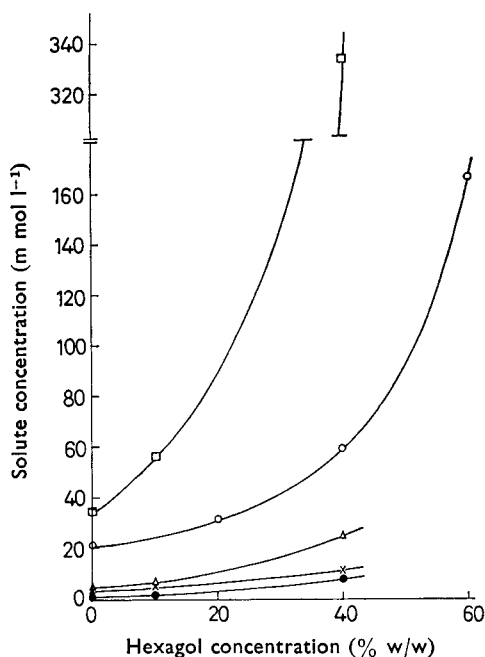


FIG. 2. The solubility of compounds in hexagol Solutions at 20° C. □ *p*-Hydroxybenzoic acid. ○ Benzene. △ Ethyl paraben. X Methyl anisate. ● Butyl paraben.

This does not occur, except with benzene. As can be seen from Figs 1 and 2 the longer chain polymer (PEG 1000) has a greater capacity to solubilize than has hexagol. This effect has also been reported by Blaug & Ahsan (1961) and may be due to the long polymer chain forming a partially coiled structure around the solute and thus increasing the solubility.

Paruta (1969) has shown that the paraben esters have a high solubility in solvents whose dielectric constant is about 30. At 20° the dielectric constant of ethylene glycol is 37.7; (water = 80.4, n-decane = 2.0), and if we assume, as is reasonable, that the dielectric constants of the PEGs are of a similar magnitude to that of ethylene glycol it would be expected that as the concentration of PEG is increased, the solubility of the parabens would increase markedly.

Table 2. *The solubilities of compounds in PEG solutions (millimolal) at 20°.*

Solvent	Solute					
	Benzene	Sulpha-diazine	<i>p</i> -Hydroxy-benzoic acid	Ethyl paraben	Butyl paraben	Methyl anisate
10% w/v PEG 1000	20% PEG 36.1	— 0.719	— 75.6	— 10.5	— 2.54	— 8.59
30% w/v PEG 1000	40% PEG 57.2	— 2.11	— 304	— 35.0	— 11.0	— 14.6
40% w/v PEG 1000	60% PEG 154.3	50% PEG 4.20	— 559	— 69.3	— 22.1	— 21.5
80% w/v PEG 1000	611	—	—	—	—	—
10% w/v hexagol	20% n <sub>6</sub> 31.9	—	— 56.6	— 7.38	— 1.96	— 5.11
40% w/v hexagol	59.4	—	334	25.5	8.02	11.4
60% w/v hexagol	167	—	—	—	—	—

#### *Solubilization in cetomacrogol solutions*

The solubility of all compounds is greater in cetomacrogol solutions than in water when the concentration of cetomacrogol is much greater than the cmc of 0.007% (Elworthy, 1960). This increase is linear with increase in concentration of the detergent above the cmc (Fig. 3). Sulphadiazine has a very low solubility in water, in hexane and in PEG solutions: it is solubilized by cetomacrogol solutions least of all of the compounds investigated. This may be due to the large size of the sulphadiazine molecule. Elworthy & Lipscomb (1968b) found a correspondingly low solubility for griseofulvin in cetomacrogol.

*p*-Hydroxybenzoic acid is insoluble in hexane but its high solubility in PEG solutions results in the highest M.A.C. of all of the compounds in surfactant solutions.

The other compounds studied are soluble in water, PEG solutions and in hexane and so their M.A.C.s are, in part, a reflection of these properties.

Table 3 shows the solubilities of the compounds expressed as mol of solubilize/mol of detergent (cetomacrogol or C<sub>16</sub>n<sub>7</sub>) and this is a function of the solubility of the compounds in the micelles. It can be seen that butyl paraben is as soluble in the

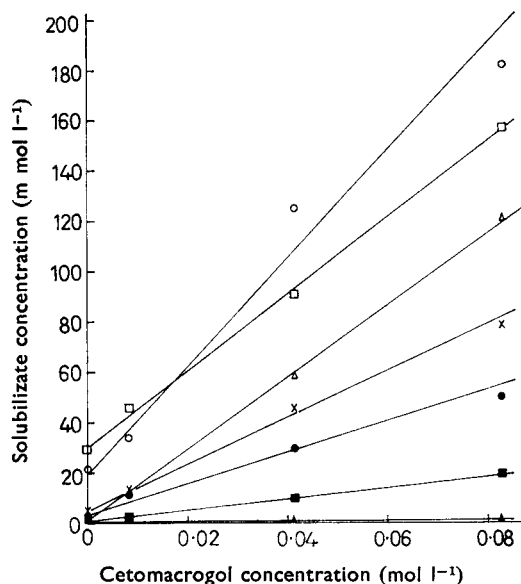


FIG. 3. The solubility of compounds in cetomacrogol solutions at 20° C. ○ Benzene. □ *p*-Hydroxybenzoic acid. △ Butyl paraben. × Ethyl paraben. ● Methyl anisate. ■ Decane. ▲ Sulphadiazine.

Table 3. *The solubilities of compounds per mol of each detergent at 20°.*

Solute	$C_{16}n_7$		Cetomacrogol	
	Solubility as mol/mol	Solubility as mol/oxyethylene unit	Solubility as mol/mol	Solubility as mol/oxyethylene unit
Decane .. ..	0.888	0.127	0.232	0.0106
Benzene .. ..	—	—	2.33	0.106
<i>p</i> -Hydroxybenzoic acid	0.616	0.088	1.460	0.0664
Ethyl paraben	0.630	0.090	0.911	0.0414
Butyl paraben ..	—	—	1.45	0.066
Methyl anisate ..	0.430	0.061	0.618	0.0281
Sulphadiazine ..	—	—	0.0099	0.00045

micelles as is *p*-hydroxybenzoic acid. This cannot be explained by summing the solubilities of these compounds in hexane and in polyoxyethylene-water mixtures, as, although the butyl ester is more soluble than the *p*-hydroxybenzoic acid in the hydrocarbon core, it is less soluble in the oxyethylene-water complex. Therefore, there may be a significant change in the micelle structure on solubilization of these two compounds.

The micellar solubility of the other compounds in both cetomacrogol and  $C_{16}n_7$  (Table 3) shows a decrease in the order *p*-hydroxybenzoic acid > ethyl paraben > methyl anisate > decane. This is the order of *decreasing* solubility in water alone and in PEG solutions and of *increasing* solubility in hydrocarbon solvents. Blaug & Ahsan (1961) reported similar results for other paraben-non-ionic systems.

Benzene seems to have an anomalously high solubility in the cetomacrogol micelles (Fig. 1): it is much less soluble in PEG solutions than *p*-hydroxybenzoic acid, although it is miscible in all proportions with hydrocarbon solvents. These results all show

that the M.A.C.s of the compounds in cetomacrogol cannot be rationalized simply in terms of their solubility in typical constituent parts of the micelle. Changes in the structure of the micelles must also be important factors in the mechanism of solubilization.

#### *Solubilization in C<sub>16</sub>n<sub>7</sub> solutions*

The solubility of decane, *p*-hydroxybenzoic acid, ethyl paraben and methyl anisate increases with increasing concentration of C<sub>16</sub>n<sub>7</sub>. Butyl paraben causes separation of C<sub>16</sub>n<sub>7</sub> solutions into two immiscible phases at 20°; it was also found to coacervate with cetomacrogol solutions at temperatures higher than 22°. Butyl paraben has been reported to coacervate in solutions of Myrj 52 and Tween 80 (Blaug & Ahsan, 1961).

Table 3 shows that decane displays the greatest micellar solubility, whereas methyl anisate is less soluble in the micelles than either ethyl paraben or *p*-hydroxybenzoic acid.

#### *Comparison of the M.A.C.s in cetomacrogol and C<sub>16</sub>n<sub>7</sub> solutions*

Solubilities in C<sub>16</sub>n<sub>7</sub> solutions were always greater than in cetomacrogol solutions even when the differing sizes of the micelle core in the two cases was considered.

The hydration of the oxyethylene layer around the C<sub>16</sub>n<sub>7</sub> micelles is significantly less than that of cetomacrogol in the simple detergent solutions, and is equivalent to that in an 80 and 30% solution of PEG respectively (Elworthy, 1960; Elworthy & McDonald, 1964).

Therefore, comparing solutions of the two detergents containing the same amount of oxyethylene chains, the C<sub>16</sub>n<sub>7</sub> solution has a greater capacity for solubilization at all sites providing that the act of solubilizing a compound does not significantly change the aggregation number and hydration of the micelles. This is reflected in the data in Table 4.

Table 4. *Solubilities in different parts of the micelle.*

Compound	Solubility		*Solubility—proportion in hydrocarbon	
	†0.01 mol litre <sup>-1</sup> cetomacrogol	†0.03 mol litre <sup>-1</sup> C <sub>16</sub> n <sub>7</sub>	0.01 mol litre <sup>-1</sup> cetomacrogol	0.03 mol litre <sup>-1</sup> C <sub>16</sub> n <sub>7</sub>
<i>p</i> -Hydroxybenzoic acid ..	48.3	52.7	48.3	52.7
Ethyl paraben .. ..	14.75	22.0	14.75	22.0
Methyl anisate .. ..	9.8	17.0	8.3	12.7

\* The solubility of the compounds after subtracting the amount of the compound that dissolves in the relevant proportions of hydrocarbon in each detergent.

† A 0.01 molar solution of cetomacrogol contains the same quantity of oxyethylene chains as a 0.03 molar solution of C<sub>16</sub>n<sub>7</sub>.

For compounds which are solely present in the micellar core, the M.A.C. should be the same in solutions of equal molarity of each detergent. A study of Figs 3 and 4 shows that this is not true for any system, even the decane solutions. This must mean that some additional factors are present.

The differences between the solubilities in each detergent increase in the order, methyl anisate, ethyl paraben, *p*-hydroxybenzoic acid. This suggests that the

solubility of *p*-hydroxybenzoic acid is more dependent on the oxyethylene content or the surface area of the micelles, than is the solubility of methyl anisate. Table 3 also shows this. This points to a high solubility in the micelle core for methyl anisate.

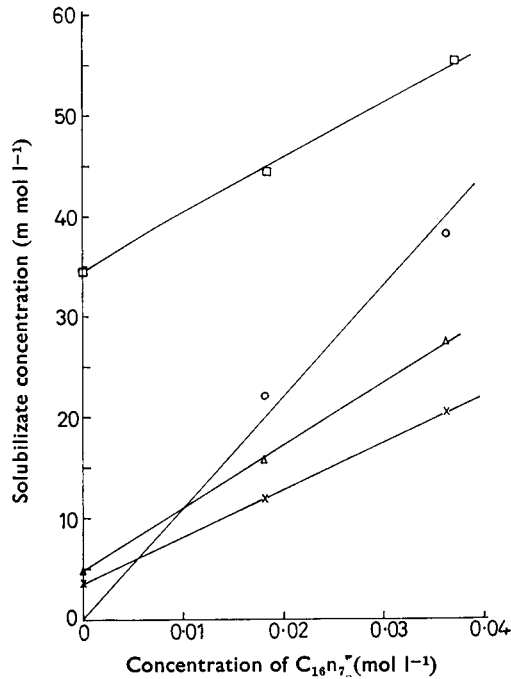


FIG. 4. The solubility of compounds in  $C_{16}n_7$  solutions at 20°C. □ *p*-Hydroxybenzoic acid. △ Ethyl paraben. X Methyl anisate. ○ Decane.

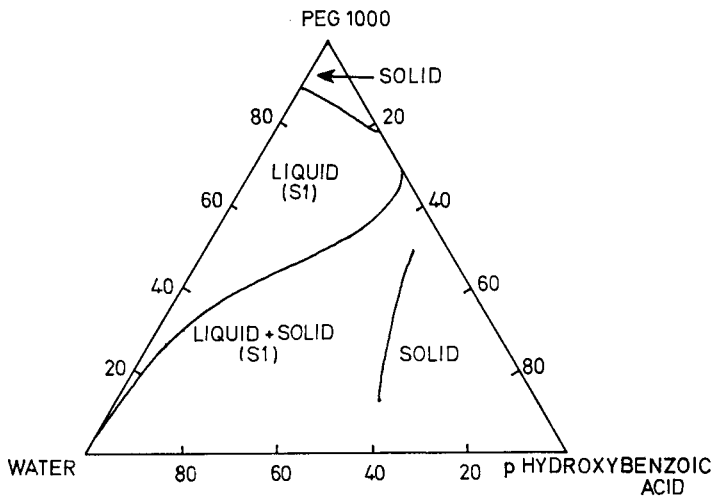


FIG. 5. Phase diagrams of *p*-hydroxybenzoic acid—PEG 1000—water mixtures. ( $S_1$  = water miscible phase).



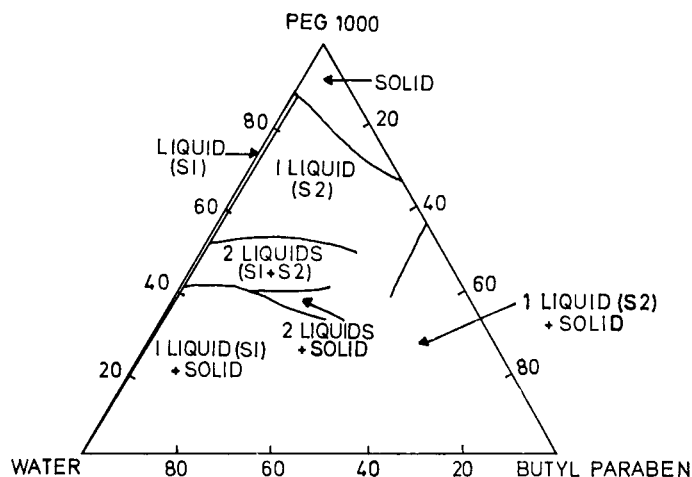


FIG. 6. Phase diagram of butyl paraben—PEG 1000-water mixtures. ( $S_1$  = water miscible liquid,  $S_2$  = water immiscible liquid).

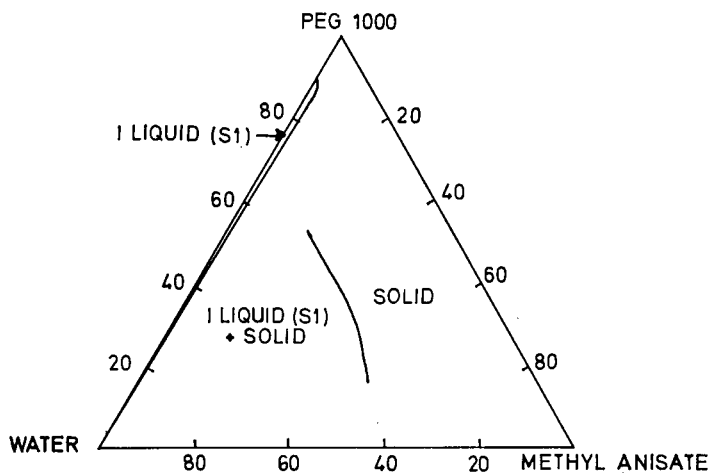


FIG. 7. Phase diagram of methyl anisate—PEG 1000-water mixtures. ( $S_1$  = water miscible liquid).

### Phase diagrams

The chief difference between the three diagrams (Figs 5, 6 and 7) is the presence of the water immiscible liquid in the butyl paraben system.

Comparison of the diagrams for *p*-hydroxybenzoic acid and methyl anisate shows the different degree of interaction between these two compounds and the PEG. The hydrogen bonding of the acid on to the oxyethylene chains results in a fluid system at much lower concentrations of water than in the methyl anisate system. The solubility of the acid in the PEG–water mixtures is much greater.

In the butyl paraben system the solubility of the ester in the PEG solutions is low but at low water concentrations and at the higher PEG concentrations, the second liquid phase appears. The probable difference between the two systems is that when a PEG molecule is associated with hydrogen bonded acid molecules it is still hydrophilic; when the ester molecule hydrogen bonds to a PEG molecule, the butyl chain

of the ester renders the complex hydrophobic and so a water-immiscible phase is formed. This provides an explanation of the coacervation noted in some of the butyl paraben systems in the solubility studies. There is no similar water-immiscible phase present in the methyl anisate system and this shows the lack of interaction between the ester and the PEG. The small increase in solubility of the ester which does occur at the higher PEG concentrations may be due to the solute molecules being trapped in the lattice of intermolecularly hydrogen bonded PEG chains.

Using this information it is possible to tentatively suggest the site of solubilization of the compounds investigated. Sulphadiazine and *p*-hydroxybenzoic acid are probably solubilized solely within the palisade layer, the acid being more concentrated in the deeper region of the layer. Ethyl and butyl paraben, methyl anisate and benzene are probably present throughout all regions of the micelle with increasing concentration in the core in the listed order above. Decane is probably nearly all solubilized within the core of the micelle.

#### *Acknowledgement*

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