

## Solubilization of griseofulvin by nonionic surfactants

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Four nonionic surfactants,  $\text{Me}[\text{CH}_2]_{15}[\text{OCH}_2\text{CH}_2]_x\text{OH}$  where  $x = 10, 22, 45$  and  $60$ , and polyoxyethylene glycols 200, 400 and 1000 increased the solubility of griseofulvin over its value in water. Cetomacrogol micelles solubilize two molecules of griseofulvin per micelle. The site of solubilization seems likely to be the polyoxyethylene part of the micelles. The partial molal heats and entropies of solution decrease as surfactant or polyoxyethylene glycol concentration is increased.

**SURFACTANTS** may play an important role in the dissolution step of an insoluble drug, such as griseofulvin, before absorption (Bates, Gibaldi & Kanig, 1966). Bates, Lin & Gibaldi (1967) have shown that lysolecithin is capable of solubilizing large amounts of griseofulvin. To effect an increase in absorption of griseofulvin by the body by artificial means, solubilized systems, or admixtures of detergent and drug, might be effective. Some nonionic detergents have been examined, as in general these are the least toxic of detergents.

### Experimental

The materials used were commercial detergents based on hexadecanol with varying numbers of ethylene oxide units (abbr. to  $\text{HE}_x$ ) e.g.  $\text{Me}[\text{CH}_2]_{15}[\text{OCH}_2\text{CH}_2]_x\text{OH}$ , where  $x = 10, 22, 45$  and  $60$  (Glovers Chemicals). The material with  $x = 22$  is Cetomacrogol B.P. The detergent P40 (Shell) or Triton X100,  $\text{Me}_3\text{C}\cdot\text{CH}_2\cdot\text{CMe}_2\cdot\text{C}_6\text{H}_4[\text{OCH}_2\text{CH}_2]_{10}\cdot\text{OH}(\text{OE}_{10})$  was used, and for comparative purposes, polyoxyethylene glycols (PG) 200, 400 and 1000. Deionization of these compounds did not affect the solubility results. The ethylene oxide content of the detergents was checked using the method of Siggia, Stark & others (1958). Apart from the nominal  $\text{HE}_{15}$  and  $\text{HE}_{60}$ , which contained 38 and 50 ethylene oxide units respectively, the detergents had the composition stated above.

Solubilities were determined by the method of Elworthy & Lipscomb (1968), and measurements were made at different temperatures to evaluate the partial molal heats ( $\Delta\bar{H}$ ) and entropies ( $\Delta\bar{S}$ ) of solution. The concentrations of the saturated solutions were determined by suitably diluting the solution to give a final concentration of 50% v/v ethanol; calibration curves were prepared in the same solvent, arranged to contain the same amount of detergent as present after dilution of the saturated solution.

The maximum wavelength of absorption was determined in the various "solvents" used giving the following results for  $\lambda_{\text{max}}$  (in  $\text{m}\mu$ ): water 296,  $\text{HE}_x$  detergents and polyoxyethylene glycols 295,  $\text{OE}_{10}$  294, benzene 291, heptane 287.

Viscosities of detergent solutions relative to water were measured at  $25^\circ$  in an Ostwald capillary viscometer.

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## Results and discussion

The results of the solubility determinations are given in Table 1, expressed as moles griseofulvin dissolved in 1000 g solution i.e., molality, counting the detergent or polyoxyethylene glycol as part of the solvent.

With the detergent HE<sub>10</sub>, cloudy solutions were formed at concentrations below 4%, and erratic results were obtained. In view of this experimental difficulty, the two results given in Table 1 for this detergent are considered approximate. Fig. 1 shows that solubilization in the detergent solutions increases linearly with detergent concentration. When the detergents are compared on a percentage basis (i.e., Table 1) the compounds containing the shortest polyoxyethylene chains appear to solubilize the largest amount of griseofulvin. However, when equimolar concentrations are compared (Fig. 1) the detergents containing the longest polyoxyethylene chains have greatest solubilizing power, solubilization decreasing with decreasing polyoxyethylene chain length.

TABLE 1. SOLUBILITY OF GRISEOFULVIN IN SOLUTIONS OF NONIONIC SURFACTANTS AND POLYOXYETHYLENE GLYCOLS

Concentration % w/v	Solubility (molality $\times 10^3$ ) at			
	15°	25°	35°	45°
<b>Cetomacrogol</b>				
0.007 .. ..	2.0 <sub>4</sub>	2.8 <sub>5</sub>	3.9 <sub>5</sub>	6.3 <sub>5</sub>
0.997 .. ..	16.9	17.9	21.9	26.4
5.500 .. ..	92.4	97.4	107.1	116.5
15.01 .. ..	245.5	257.5	285.5	344.5
<b>OE<sub>10</sub></b>				
0.30 .. ..	7.2	8.3 <sub>4</sub>	11.3	
1.005 .. ..	20.5	24.4	29.2	
5.019 .. ..	97.5	107.1	132.0	
10.02 .. ..	196.5	210.3	262.2	
19.74 .. ..	363	413	509.4	655
<b>HE<sub>10</sub></b>				
7.45 .. ..		128		
11.88 .. ..		203		
<b>HE<sub>35</sub></b>				
0.997 .. ..		13.0		
5.003 .. ..		56.5		
15.011 .. ..		169.4		
<b>HE<sub>60</sub></b>				
0.999 .. ..		12.5		
5.007 .. ..		50.5		
15.012 .. ..		155.5		
<b>PG200</b>				
18.35 .. ..	10.0	10.3	19.4	33.8
19.71 .. ..		12.0	18.6	33.0
45.90 .. ..	42.7	61.5	103.5	193.5
75.21 .. ..	293	398	567	831
112.8 .. ..	1737	2028	2531	3021
<b>PG400</b>				
11.15 .. ..		5.7		
21.35 .. ..		12.0		
33.69 .. ..	25.6	30.3	73.5	110.5
63.87 .. ..	228	248	409	782
86.18 .. ..	923	1104	1516	2445
112.9 .. ..	2880	3206	3852	4386
<b>PG1000</b>				
8.40 .. ..		4.8		
14.80 .. ..		7.1		
24.25 .. ..		15.7		
36.64 .. ..		35.6		
69.98 .. ..		414		
82.79 .. ..		1170		

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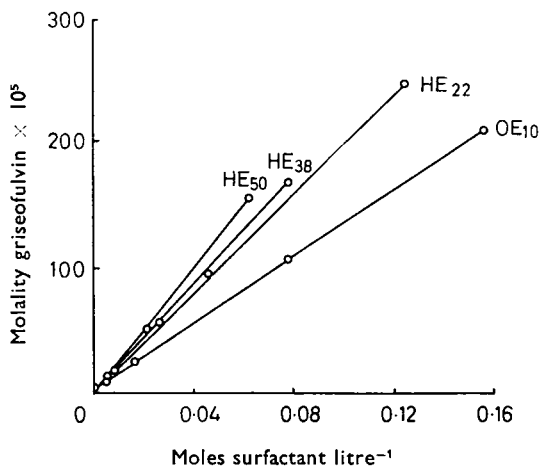


FIG. 1. Solubilization of griseofulvin by various nonionic surfactants.

But the detergents solubilize far more griseofulvin than polyoxyethylene glycol mixtures of equal concentration.

The ratios of mole detergent/mole griseofulvin solubilized calculated at 10% w/v detergent concentrations are:

Detergent	OE <sub>10</sub>	HE <sub>10</sub>	HE <sub>22</sub>	HE <sub>38</sub>	HE <sub>50</sub>
Molar ratio	74	(85)	49	46	40

As the critical micelle concentrations (CMC) of these detergents are very low, e.g., 0.007% for cetomacrogol (Elworthy, 1960a), the solubility of griseofulvin in water has been subtracted from the total solubility in the detergent solution, in calculating the ratio. Use of the solubility at the CMC would have been strictly correct, but the error introduced by using the solubility in water is small, as the CMC values are so low, and the detergent concentration high.

It can be seen that the larger the polyoxyethylene chain, the greater is the amount of solubilization per mole of detergent. Because of the experimental difficulties, the molar ratio for HE<sub>10</sub> is approximate.

The micelle of the OE<sub>10</sub> compound has been shown to contain 140 detergent monomers (Kushner & Hubbard, 1954), while that of cetomacrogol contains 83 monomers (Elworthy, 1960b). For these detergents, roughly two griseofulvin molecules are solubilized per micelle. Micelle sizes for the HE<sub>38</sub> and HE<sub>50</sub> compounds are not known.

The solubilization of griseofulvin by detergent and polyoxyethylene glycol solutions increased with temperature; Fig. 2 gives the solubilities at different temperatures in cetomacrogol solution.

The solubility of griseofulvin is increased by polyoxyethylene glycols. Fig. 3 shows the relation between log molality of griseofulvin, and % w/w of polyoxyethylene glycol. Between 20 and 70% w/w, the graph is linear, and there appears to be very little difference between the

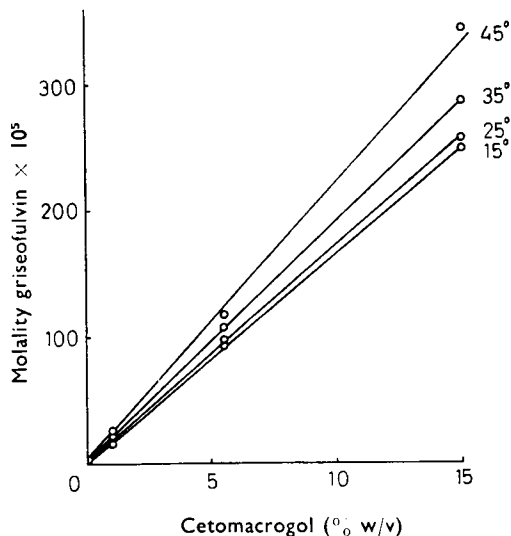


FIG. 2. Effect of temperature on the solubilization of griseofulvin in cetomacrogol solutions.

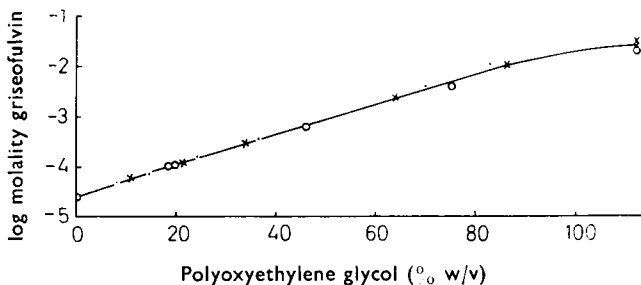


FIG. 3. Solubility of griseofulvin (log molality) in various polyoxyethylene glycol-water mixtures. ○ = PG200. × = PG400. ● = PG1000.

behaviour of griseofulvin in PG200, 400, or 1000. That the polyoxyethylene glycols increase the solubility of griseofulvin in water, and the length of the polyoxyethylene chain also affects solubility, may indicate that solubilization takes place in the polyoxyethylene-water layer of the micelles.

It has been shown (Elworthy, 1960b), that cetomacrogol forms spherical micelles, which are hydrated with 1.96 g water/g detergent. Similar conclusions on sphericity have been reached by Kushner & Hubbard (1954) for the OE<sub>10</sub> compound, and from their viscosity results a hydration of 1.26 g water/g detergent can be calculated from

$$[\eta] = 2.5 (\bar{v} + w v_1^c)$$

where  $[\eta]$  is the intrinsic viscosity, obtained by plotting the specific

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viscosity divided by the concentration against concentration, where

$$[\eta] = \left( \frac{\eta_{sp}}{c} \right) c = 0$$

$\bar{v}$  is the specific volume of detergent,  $w$  is the hydration, and  $v_1^\circ$  is the specific volume of water. Elworthy & Macfarlane (1963) have shown that micelles formed by monohexadecyl polyoxyethylene ethers were spherical when the numbers of ethylene oxide units present in the chain exceeded nine. It seems a reasonable assumption that the micelles of HE<sub>38</sub> and HE<sub>50</sub> are also spherical. Hence the measured viscosities are plotted in Fig. 4 giving intercept of 8.7 and 9.4 respectively, and the corresponding hydrations are 2.6 and 2.9 g/water/g detergent respectively.

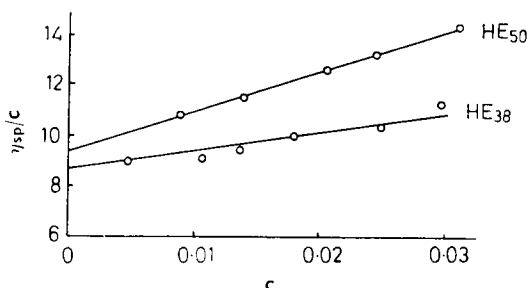


FIG. 4. Graph of  $\frac{\eta_{sp}}{c}$  against concentration ( $\text{g ml}^{-1}$ ) for HE<sub>38</sub> and HE<sub>50</sub>.

An attempt was made to calculate the solubility of griseofulvin in the micelles from the data on its solubility in polyoxyethylene glycols. In 1 g of cetomacrogol, which is associated with 1.96 g water, there is present 0.814 g glycol; thus we can consider the polyoxyethylene glycol-water part of the micelle as a 29.3% w/w solution. The solubility of griseofulvin in a solution of this concentration is  $26 \times 10^{-5}$  molal (Fig. 3) and 1 g of glycol is thus associated with  $0.09 \times 10^{-5}$  mole of griseofulvin. 1 g of cetomacrogol therefore has  $0.07 \times 10^{-5}$  mole griseofulvin theoretically solubilized in its glycol-water complex. From the solubility data, 1 g of cetomacrogol in a 10% w/v solution solubilized  $1.7 \times 10^{-5}$  mole of griseofulvin. Therefore about 25 times more griseofulvin is actually solubilized than can be accounted for on the basis of the calculation. The same picture emerges for the other detergents. For OE<sub>10</sub> the practical value at 10% w/v detergent concentration is  $2.1 \times 10^{-5}$  mole/g detergent ( $0.07 \times 10^{-5}$ ), for HE<sub>38</sub>  $1.1 \times 10^{-5}$  mole/g detergent ( $0.07 \times 10^{-5}$ ), for HE<sub>50</sub>  $1.0 \times 10^{-5}$  mole/g detergent ( $0.07 \times 10^{-5}$ ). The theoretical figures are in brackets.

For the cetyl chain-containing compounds, calculations of the solubility of griseofulvin in the hydrocarbon core, based on the solubility in pure heptane, give values  $10^3$ – $10^4$  times too small. For OE<sub>10</sub>, solubility data in an alkyl-aryl chain hydrocarbon resembling the hydrophobic

moiety of this detergent are not available, but even using the solubility data in benzene, a figure of 50% of the observed solubility is obtained; it must be borne in mind that the hydrocarbon chain of the OE<sub>10</sub> compound contains only about 40% of the phenyl group, so that the solubility of griseofulvin in it would be expected to be less than that in benzene, thus giving an even lower calculated solubility.

The above calculations have been based on the assumptions: (1) That the size and hydration of the micelles are unaltered when the solubilize is present. (2) That the solubility in bulk polyoxyethylene glycol-water mixtures, and in bulk hydrocarbon liquids can be used to calculate the solubility in the micelles. (3) That the polyoxyethylene-water layer is homogeneous from the surface of the hydrocarbon core to the micelle surface.

As there is only a small amount of solubilization, the first assumption is probably reasonable. The assumption on using bulk solubility in hydrocarbons for the purposes of calculation is perhaps not important, at least for the aliphatic hydrocarbon chain detergents, as the calculated solubilities are 10<sup>3</sup>-10<sup>4</sup> times too low. The third assumption, and part of the second relating to polyoxyethylene glycol-water mixtures require further examination. Schick (1963), has shown that in nonionic detergent micelles, the polyoxyethylene chain is arranged in an expanding spiral, i.e., a cone shape, with the narrower end of the cone at the surface of the hydrocarbon core. Macfarlane's work (1963) gave a similar idea, and molecular models showed that while there was plenty of room for hydrating water in the outer parts of the micelles, there was virtually no space for it close to the surface of the hydrocarbon core, due to crowding of the polyoxyethylene chain.

This region, adjacent to the hydrocarbon region, seems the most likely site for the griseofulvin within the micelles, as it is largely purely polyoxyethylene (rather than polyoxyethylene-water) in nature, and the solubility of griseofulvin in pure polyoxyethylene glycols is quite large. (Unfortunately, no calculation of theoretical solubility can be made, as the volume of the purely polyoxyethylene glycol region is unknown.) Also, the  $\lambda_{\max}$  values are quite close in the detergents and polyoxyethylene glycol solution (probably reflecting a somewhat similar environment), and different from those in heptane and benzene.

The thermodynamics of solubilization also indicate a similarity between the behaviour of griseofulvin in polyoxyethylene glycol-water mixtures, and in the detergents, and a distinct difference from the behaviour in water and hydrocarbons. The probable site of solubilization seems to be in the polyoxyethylene-water layer of the micelles, with the possibility of it being close to the hydrocarbon-polyoxyethylene boundary.

#### THERMODYNAMICS OF SOLUBILIZATION

Partial molal heats and entropies calculated as before (Elworthy & Lipscomb, 1968) are listed in Table 2. The "solvent" here is the detergent solution, so the thermodynamic properties relate to the change from the crystalline state to a very large amount of saturated solution.

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TABLE 2. THERMODYNAMIC PROPERTIES FOR SOLUTION OF GRISEOFULVIN IN NON-IONIC DETERGENT AND POLYOXYETHYLENE GLYCOL SOLUTIONS\* (% w/v)

		Temperature		
		20°	30°	40°
Water	$\Delta H$	5.1	6.5	10.0
	$\Delta S$	17	21	32
Cetomacrogol 1%	$\Delta H$	1.2	2.5	3.5
	$\Delta S$	4.1	8.3	11
Cetomacrogol 5%	$\Delta H$	1.2	1.7	2.1
	$\Delta S$	4.1	5.6	6.7
Cetomacrogol 10%	$\Delta H$	1.2	1.5	1.7
	$\Delta S$	4.1	5.0	5.4
Cetomacrogol 15%	$\Delta H$	1.2	1.5	1.6
	$\Delta S$	4.1	5.0	5.1
PG200 34%	$\Delta H$	6.5	9.5	10.7
	$\Delta S$	22	31	34
PG200 54%	$\Delta H$	6.0	8.4	9.3
	$\Delta S$	21	27	30
PG200 75%	$\Delta H$	5.3	7.6	8.5
	$\Delta S$	18	25	27
PG200 112.8%	$\Delta H$	3.1	3.6	3.8
	$\Delta S$	11	12	12
OE <sub>10</sub> 1%	$\Delta H$	2.2	4.2	—
	$\Delta S$	7.5	14	—
OE <sub>10</sub> 5%	$\Delta H$	1.4	3.2	—
	$\Delta S$	4.8	11	—
OE <sub>10</sub> 10%	$\Delta H$	1.4	3.6	—
	$\Delta S$	4.8	12	—
OE <sub>10</sub> 15%	$\Delta H$	1.3	3.7	—
	$\Delta S$	4.4	12	—
PG400 34%	$\Delta H$	6.4	11.3	14.5
	$\Delta S$	22	37	46
PG400 54%	$\Delta H$	4.6	9.2	12.6
	$\Delta S$	16	30	40
PG400 75%	$\Delta H$	3.0	6.8	10.8
	$\Delta S$	10.3	22	35
PG400 112.9%	$\Delta H$	2.3	2.8	3.1
	$\Delta S$	7.9	9.3	9.9

$\Delta H$  in kcal mole<sup>-1</sup>,  $\Delta S$  in cal mole<sup>-1</sup>deg<sup>-1</sup>.

\* Solubilities used for calculation of the thermodynamic properties were obtained from smoothed curves of solubility against concentration for surfactants, and log solubility against concentration for polyoxyethylene glycols.

As either detergent or polyoxyethylene glycol concentration is increased the thermodynamic properties decrease, e.g.,  $\Delta H$  and  $\Delta S$  become less positive. In 15% cetomacrogol and pure PG400, at 20°,  $\Delta H$  is 1.2 and 2.3 kcal mole<sup>-1</sup>, and  $\Delta S$  is 4.1 and 7.9 cal mole<sup>-1</sup> deg<sup>-1</sup> respectively. These figures are less than half the value obtained in pure water. Inspection of Table 2 reveals some correspondence of the thermodynamic values obtained in detergent solutions and in concentrated polyoxyethylene glycols, which indicates the possibility that griseofulvin is held in a polyoxyethylene glycol environment when solubilized in the micelle. These figures cannot be expected to correspond exactly because of the difference in the types of solutions being compared. Above 10% cetomacrogol and OE<sub>10</sub> concentrations,  $\Delta H$  lies in the regions 1–2 kcal mole<sup>-1</sup>

and  $\Delta S$  4–5 cal mole<sup>-1</sup> deg<sup>-1</sup>, which corresponds moderately well with figures obtained at high polyoxyethylene glycol concentrations,  $\Delta H$ , 2–3 kcal mole<sup>-1</sup>,  $\Delta S$ , 8–11 cal/mole<sup>-1</sup> deg<sup>-1</sup> (values at 20°). In the less concentrated polyoxyethylene glycol solutions the thermodynamic properties are fairly close to those obtained in water.

Considering concentrated detergent solutions and pure polyoxyethylene glycols, the lower entropies obtained suggest that the griseofulvin is in a more ordered state than when dissolved in pure water, possibly due to its association with the glycol or detergent.  $\Delta H$  is also lower than in water, and as the heat required to break up the crystal will be the same for dissolution in water as in a detergent or polyoxyethylene glycol solution, either the heat of dilution differs from that in water, or an interaction between griseofulvin and its polyoxyethylene “environment” accounts for the different heat changes.  $\Delta H$  is also less temperature-dependent in concentrated detergent solutions and in pure polyoxyethylene glycols than in water. This again may reflect the “environment”, as water structuring breaks down with temperature increase (see Elworthy & Lipscomb, 1968), while the polyoxyethylene “environment” of micelles will be maintained.

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## References

- Bates, T. R., Gibaldi, M. & Kanig, J. L. (1966). *J. pharm. Sci.*, **55**, 191–199.  
 Bates, T. R., Lin, S. L. & Gibaldi, M. (1967). *Ibid.*, **56**, 1492–1495.  
 Elworthy, P. H. (1960a). *J. Pharm. Pharmac.*, **12**, 293–299.  
 Elworthy, P. H. (1960b). *Ibid.*, **12**, 260–266.  
 Elworthy, P. H. & Lipscomb, F. J. (1968). *Ibid.* **20**, 790–792.  
 Elworthy, P. H. & Macfarlane, C. B. (1963). *J. chem. Soc.*, 907–914.  
 Kushner, L. M. & Hubbard, W. D. (1954). *J. phys. Chem., Ithaca*, **58**, 1163–1167.  
 Macfarlane, C. B. (1963). Ph.D. Thesis, University of Glasgow, p. 159.  
 Schick, M. (1963). *J. Colloid Sci.*, **18**, 378–389.  
 Siggia, S., Starke, A. C., Garis, J. J. & Stahl, C. R. (1958). *Analyt. Chem.*, **30**, 115–116.