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Relationships between poloxamer structure and the solubilization of some *para*-substituted acetanilides

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Saturation solubilities of several *para*-substituted acetanilides have been measured at 37 °C in aqueous solutions of structurally related polyoxyethylene-polyoxypropylene block copolymers–poloxamers L62, L63, L64, P65 and F68. These poloxamers differ only in the amount of ethylene oxide in the hydrophil. Solubilities increased with increasing poloxamer concentration. As the oxyethylene chain length of the poloxamer increased, then the solubilizing capacity per equivalent of oxyethylene decreased. The moles of acetanilide derivative solubilized per mole of poloxamer increased with poloxamer oxyethylene content in the case of the less hydrophobic acetanilides but was invariant in the more hydrophobic ones. The solubilizing capacities have been discussed in terms of the inter-relationships between the hydrophobic nature of the solubilizate and solubilizer and the site of solubilization on the poloxamer molecule.

The use of non-ionic surfactants as solubilizing agents is well established and the choice of surfactant for a particular drug can be made on a rational basis. Several workers (Goodhart & Martin 1962; Ismail et al 1970) have reported relations between surfactant structure and extent of solubilization. Other workers have considered the location of solubilizate molecules within surfactant micelles. Mukerjee (1971) related the distribution of some substituted benzoic acids between the hydrophobic core and the hydrophilic matrix of polyoxyethylene stearate micelles to solubilizate structure.

Recently there has been renewed interest in the use of polyoxyethylene-polyoxypropylene block co-polymers as solubilizing agents. There is little information in the literature which would permit selection of block copolymers to ensure optimum solubilization of a specified solute. This report describes the inter-relation between solubilizate and solubilizer structures and its effect on the solubilization and distribution of some *para*-substituted acetanilides in aqueous solution of a series of structurally related block co-polymers.

MATERIALS AND METHODS

Materials

The solubilizates used were acetanilide (BDH), its 4-hydroxy (BDH), 4-fluoro (Koch-Light), 4-chloro (BDH), 4-bromo (BDH), 4-iodo (Eastman), 4-nitro (Fisons), 4-methoxy (Eastman) and 4-ethoxy (BDH) derivatives and 4-acetamidobenzaldehyde (Koch-Light). The surfactants used were polyoxyethylene-polyoxypropylene block copolymers (marketed by the Wyandotte Chemical Company as 'Pluronics'), poloxamers L62, L63, L64, P65 and F68. The physical form, approximate molecular weight and chemical composition of each poloxamer can be determined from the so-called 'Pluronic Grid' (Wyandotte Chem. Corp. 1964). The products are designated L, P and F depending on whether they are liquid, paste or flakes. The chemical composition is indicated by a numerical key of two digits. The first digit is an indication of the molecular weight of the polyoxypropylene block. The second digit indicates the weight percentage of the oxyethylene group. All poloxamers were used as received from Ugine Kuhlmann Chemicals Ltd.

Method

The saturation solubilities of the *p*-substituted acetanilides were measured at 37 °C and pH 1·0 in aqueous solutions containing increasing concentrations of each poloxamer using procedures described previously (Collett & Withington 1972). Samples were assayed by ultraviolet absorption spectrophotometry. The presence of the poloxamers did not interfere with the assay.

RESULTS AND DISCUSSION

The saturation solubility of each acetanilide generally increased linearly with increasing concentration of poloxamer. Fig. 1 shows a typical solubility isotherm, for 4-hydroxyacetanilide. Both drug solubility and poloxamer concentration are expressed in mol litre^{-1}. A value for the amount of each drug solu-

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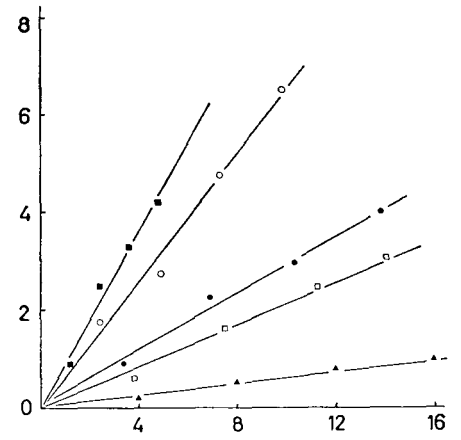

FIG. 1. The solubility of 4-hydroxyacetanilide in aqueous solutions of poloxamers L62 (▲), L63 (□), L64 (●), P65 (○) and F68 (■) at pH 1·0 and 37 °C. Ordinate: increased solubility (mol litre^{-1} × 10^2). Abscissa: concentration of poloxamer (mol litre^{-1} × 10^3).

bilized by each poloxamer can be obtained from the slopes of such plots. Table 1 presents the values of the moles of each drug solubilized mol^{-1} of poloxamer for each poloxamer. The less hydrophobic drugs i.e. acetanilide and the 4-hydroxy, 4-methoxy, 4-ethoxy and 4-aldehydic compounds, show increasing solubilization as the oxyethylene content of the poloxamer increases. The more hydrophobic drugs, however, 4-nitroacetanilide and the halogenated compounds, show a decrease in solubilizing capacity as oxyethylene content increases. When solubilization is expressed as the amount of drug solubilized per ethylene oxide group (see Table 2) then in general solubilization of the drugs decreased with increasing oxyethylene content. Similar results have been reported by Goodhart & Martin (1962) for the solubilization of some benzoic acid derivatives by a

Table 1. Mol of *p*-substituted acetanilide solubilized mol^{-1} of poloxamer in aqueous solution at pH 1·0 and 37 °C.

Substituent	L62	L63	L64	P65	F68
H	1·55	0·62	4·20	3·27	5·33
4-OH	0·63	2·12	2·65	5·20	9·51
4-OMe	1·73	1·20	1·50	1·65	2·58
4-OEt	0·38	0·65	0·41	0·36	0·56
4-CHO	1·92	1·66	3·24	2·31	4·21
4-NO_2	0·35	0·32	0·28	0·25	0·16
4-F	1·79	1·47	1·52	1·26	1·01
4-Cl	1·47	1·14	1·16	1·43	0·57
4-Br	0·84	0·70	0·67	0·73	0·21
4-I	0·67	0·56	0·46	0·56	0·16

Table 2. mMol of *p*-substituted acetanilide solubilized per equivalent of ethylene oxide in different poloxamers in aqueous solution at pH 1·0 and 37 °C.

Substituent	L62	L63	L64	P65	F68
H	139	34	159	81	35
4-OH	55	117	101	140	59
4-OMe	152	108	57	43	17
4-OEt	32	36	16	9·4	3·7
4-CHO	168	85	123	60	28
4-NO_2	31	16	11	6·4	1·0
4-F	158	81	58	33	0·7
4-Cl	129	59	40	37	3·8
4-Br	75	35	25	19	1·4
4-I	58	28	18	15	1·1

series of polyoxyethylene stearates, and by Gouda et al (1970) for the solubilization of some 5,5-disubstituted barbiturates by the same non-ionic surfactants. In both cases the solubilizing capacity of the surfactants increased with increasing oxyethylene chain length when results were expressed as mol of drug solubilized mol^{-1} of surfactant, but decreased when expressed as mol of drug solubilized per equivalent of ethylene oxide. The amount of acetanilide and 4-hydroxyacetanilide solubilized by the poloxamers used in this study could not be related directly to oxyethylene content. At the moment these results cannot be accounted for. One possible explanation for these anomalous results is that the two hydrophilic acetanilides have a selective influence on the aggregation properties of the poloxamers known to aggregate continuously (Wong 1974). Such an effect would lead to apparently random changes in the solubilizing capacities of the poloxamers.

Plots of mol of drug solubilized mol^{-1} of poloxamer against the percentage of ethylene oxide in the poloxamer molecule are linear. Slopes for these plots are given in Table 3. 4-Hydroxyacetanilide is typical of the less hydrophobic drugs: for those compounds the amount solubilized increases with increasing oxyethylene content and so the slope is positive. 4-Nitroacetanilide is typical of the more hydrophobic drugs which show decreasing solubilization with increasing ethylene oxide content and hence a negative slope. A similar relation can be seen for the solubilization of some 5,5-disubstituted barbiturates by a series of polyoxyethylene stearates (Gouda et al 1970). The amount of each barbiturate solubilized mol^{-1} of surfactant increases linearly with increasing oxyethylene chain length. The slope of the line increased with the increasing hydrophobicity of the barbiturate. The hydrophobic nature of the *p*-substituted acetanilides can be described using the π values (Fujita et al 1964) of their functional groups.

Table 3. The slopes for plots of mol of *p*-substituted acetanilide solubilized mol^{-1} of poloxamer at pH 1·0 and 37 °C against the percentage of oxyethylene in the poloxamer molecule.

Substituent	Slope, K × 10^2	π[a]
H	6·30	0
4-OH	15·0	−0·36
4-OMe	2·74	−0·133
4-OEt	0·31	0·367[b]
4-CHO	5·20	0·091
4-NO_2	−0·32	0·499
4-F	−1·30	0·309
4-Cl	−0·78	0·714
4-Br	−1·03	1·130
4-I	−0·83	1·303

[a] From Dearden & Tomlinson (1971).
[b] Calculated from eqn 16, 17 and 19 of Fujita et al (1964).

Fig. 2 shows the relation between the π value for the *p*-substituent group of the acetanilides and the slope (K) of plots of mol of drug solubilized mol^{-1} of poloxamer against the percentage ethylene oxide in the poloxamer (from Table 3). For the less hydrophobic drugs K decreases linearly with π but beyond a π value of around 0·4 the value of K is reasonably constant.

These results indicate that the solubilization of *p*-substituted acetanilides in aqueous solutions of poloxamers can be divided into two types, depending on the hydrophobicity of the solubilizate. It is possible that the difference between the two groups may lie in the site of solubilization of the acetanilide on the poloxamer molecule. Mukerjee (1971) has shown that solubility data for some structurally related polyoxyethylene stearates can be analysed to give values for the amounts of drug solubilized in the core and in the oxyethylene mantle of the surfactant micelles. Although there is some divergence of opinion as to whether the poloxamers form micelles in solution (Mankowich 1954; Dwiggins et al 1960; Cowie & Sirianni 1966; Wong 1974), a similar analysis could yield information on the relative amounts of acetanilide bound to the propylene oxide hydrophobe and to the oxyethylene chain of the poloxamer molecule. The information is obtained from plots of equivalents of drug solubilized per equivalent of ethylene oxide (S/C_{EO}) against the propylene oxide-ethylene oxide mol ratio (C_R/C_{EO}). The plots are linear with an intercept A on the y axis representing the amount of drug bound to the oxyethylene chain and a slope B representing the amount of drug bound to the hydrophobe. A typical plot is shown in Fig. 3. Table 4 presents the values of A and B for each acetanilide and also the value of r the correlation coefficient for each plot. The values of B are much larger than the values of A in each case, indicating that most of the drug is bound to the hydrophobe. For simple hydrophobic bonding B should be directly proportional to π. Fig. 4 shows the plot of B against π. Again there is the division into

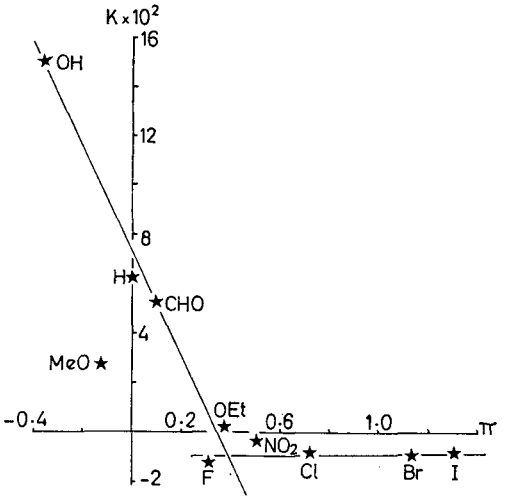

FIG. 2. Slope (K) for plots of mol of *p*-substituted acetanilide solubilized mol^{-1} of poloxamer against the percentage oxyethylene in the poloxamer molecule as a function of the π value of the substituent group on the acetanilide molecule.

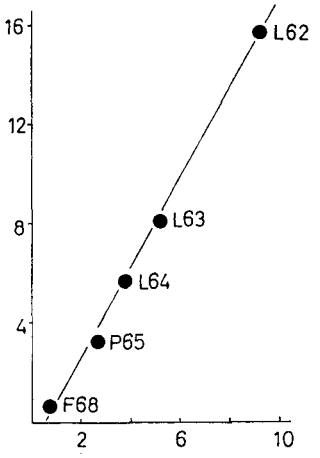

FIG. 3. Solubilization of 4-fluoroacetanilide in aqueous solutions of poloxamers L62, L63, L64, P65 and F68 expressed as equivalents of drug per equivalent of ethylene oxide against the poloxamer mole ratio. Ordinate: $S/C_{EO} \times 10^2$ (equivalents of drug solubilized per equivalent of ethylene oxide). Abscissa: $C_R/C_{EO} \times 10^2$ (propylene oxide-ethylene oxide mol ratio).

Table 4. The distribution of *p*-substituted acetanilides between the hydrophobe (B) and oxyethylene chain (A) of poloxamer molecules.

Substituent	A (eq/eq)	B (eq/eq)	r [a]
H	0·038	1·128	0·969
4-OH	0·064	1·514	0·603
4-OMe	0·002	1·622	0·996
4-OEt	0·002	0·332	0·998
4-CHO	0·026	1·543	0·902
4-NO_2	−0·002	0·351	0·995
4-F	−0·014	1·848	0·997
4-Cl	−0·010	1·384	0·993
4-Br	−0·005	0·825	0·991
4-I	−0·005	0·665	0·988

[a] r = correlation coefficient.

two groups. But in Fig. 4, B decreases as the hydrophobicity of the solubilizate increases. A possible explanation of this is that the oxyethylene chains are twisted round the hydrophobe forming a hydrophobic barrier that must be penetrated before the drug can bind to the hydrophobe. The ability to penetrate this barrier will decrease as π increases and hence B will decrease with increasing hydrophobicity. The division into two groups may be a result of drug binding to this oxyethylene barrier. From Table 4 it would appear that no drug is binding in the case of the more hydrophobic drugs (A values small and negative) but that for the less hydrophobic drugs small amounts are being bound to the oxyethylene chain leaving less free to bind to the hydrophobe. Weak interactions between the oxyethylene chains of non-ionic surfactants and some organic molecules have been shown by other workers (Bailey & Callard 1959; Wedderburn 1964).

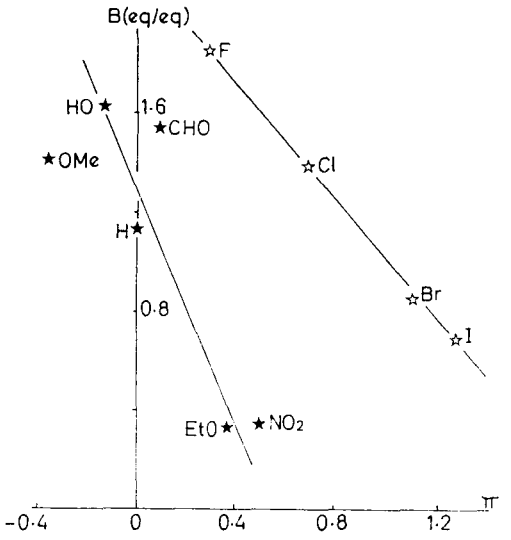

FIG. 4. The amount of *p*-substituted acetanilide solubilized by the hydrophobe of poloxamer molecules as a function of the π value of the substituent group on the acetanilide molecule.

The solubilization of *p*-substituted acetanilides in aqueous solutions of poloxamers thus appears to depend not only on the poloxamer structure but also on the nature of the solubilizate. The effect of the solubilizate is determined by its hydrophobicity which affects the site of solubilization on the poloxamer molecule. Further work will study the in vivo absorption of the *p*-substituted acetanilides from aqueous solutions of poloxamers. The differences in solubilization reported here may result in differences in the release rates of the drugs from aqueous solutions of poloxamers.

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