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COMMUNICATIONS

The release of some *p*-substituted acetanilides from solutions of structurally related Pluronics

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Polyoxyethylene-polyoxypropylene block co-polymers (poloxamers) have been shown to solubilize some drugs with low aqueous solubility (Parrott & Sharma 1967). More recently relationships between the efficiency of solubilization and poloxamer and solubilizate structure have been developed (Collett & Tobin 1979). However, an increased solubility does not necessarily imply an increased availability of a drug for systemic absorption since the amount of drug available for absorption from micellar solutions may be reduced due to micellar entrapment (Feldman & Gibaldi 1970). According to some workers, poloxamers behave differently in aqueous solution from many other non-ionic surfactants, for example they may not form micelles (Dwiggins et al 1960; Cowie & Sirianni 1966; Wong 1974). Consequently, if a solubilized drug is not within a micellar structure it should be free to move from a region of high concentration in poloxamer solution to one of low concentration. This report describes the use of a dialysis model, firstly to assess the influence of a series of structurally related poloxamers on the in vitro availability of some *para*-substituted acetanilides and secondly to investigate the relationship between dialysis rate and drug and poloxamer structures.

Materials

The Pluronics L62, P65 and F68;—*p*-substituted acetanilides (Collett & Tobin 1979) and dialysis cell (Withington & Collett 1973) have been described previously. Cellophane membrane (Visking Scientific Instrument Centre Ltd) was boiled for 10 min in each of three changes of distilled water to remove excipients such as sulphur, french chalk and glycerin (McBain & Hutchinson 1955) which could interfere with the spectrophotometric assay of the acetanilides. Membranes were stored in distilled water prior to use.

Method

The procedures used and the design of the dialysis cell have been described previously (Withington & Collett 1973).

Results and discussion

The transfer of solute across a membrane can be related by Fick's Law to the difference in concentration between the two sides of the membrane

$$\log (2Cd - Ci) = -Kt + \text{constant} \quad .. \quad (1)$$

where Cd = concentration of solute in the donor compartment at time t, Ci = initial concentration of solute in the donor cell and K = dialysis rate constant.

A plot of log (2Cd–Ci) against time is linear with slope —K. In this study the dialysis rates of any one solute in various concentrations of Pluronic L62, P65 and F68 were determined at pH 1·0 and 37 °C.

Values of K_{app}, the apparent dialysis rate constant, for substituted acetanilides in different concentrations of Pluronics L62, P65 and F68 were determined.† For any one solute the apparent dialysis rate constant decreases linearly with increasing concentration of each Pluronic. The slopes K* for plots of K_{app} against Pluronic concentration are shown in Table 1. The value of K* for each solute decreases in the order L62, P65, and F68. Plots of K* against the percentage of oxyethylene in the Pluronic molecule are linear. Table

Table 1. The Slope K*, for plots of K_{app} against Pluronic concentration for 4-substituted acetanilides dialysed from aqueous solutions of different Pluronics.

Compound	K* × 10^4 L62	P65	F68
Acetanilide	0·863	0·768	0·669
4-OH Acetanilide	0·634	0·620	0·588
4-OMe Acetanilide	0·800	0·798	0·701
4-OEt Acetanilide	0·802	0·734	0·544
4-F Acetanilide	1·006	0·827	0·592
4-Cl Acetanilide	1·703	1·424	0·983
4-Br Acetanilide	1·867	1·452	0·968
4-I Acetanilide	2·378	1·780	1·443
4-NO_2 Acetanilide	1·892	1·593	1·189
4-CHO Acetanilide	1·143	1·061	0·866

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† Individual values can be obtained from the authors.

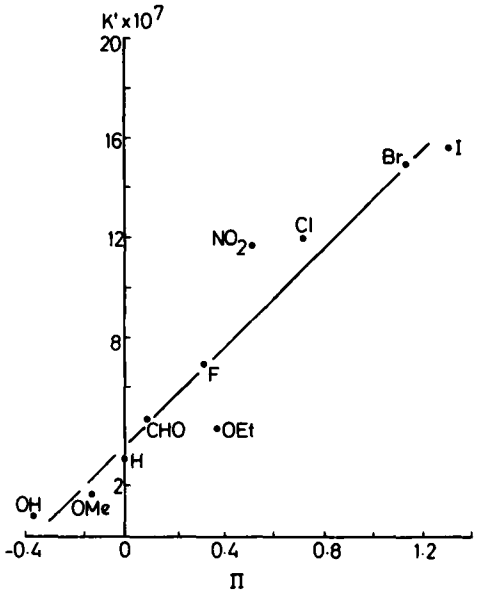

FIG. 1. Relationships between dialysis rate (K) and lipophilicity for *p*-substituted acetanilides in aqueous Pluronic solution.

2 shows the slope, K′, and the correlation for plots of K* against oxyethylene content for each *p*-substituted acetanilide. Dialysis of *p*-substituted acetanilide from aqueous solutions of Pluronics appears to be directly related to the oxyethylene content of the Pluronic.

Collett & Tobin (1979) have shown that the solubilization of *p*-substituted acetanilides in aqueous solutions of Pluronic can be related to the lipophilicity of the acetanilide molecule using π, the hydrophilic-lipophilic constant. Since the driving force for dialysis is a concentration gradient across a membrane and since the Pluronics affect the concentration of solute in the donor half cell then it is possible that a relationship will also be found between dialysis rate and lipophilicity. The amount of drug solubilized by poloxamer solutions is inversely related to π (Collett & Tobin 1979). Since the rate of dialysis depends on the concentration of free drug, then a direct relationship between dialysis rate and π should exist.

Fig. 1 shows the relationship between K′ and π for *p*-substituted acetanilides. The relationship is linear and can be expressed as

$$K' \times 10^7 = 3{\cdot}692 + 9{\cdot}907\ (\pm\ 1{\cdot}04)\ \pi \qquad (2)$$

n	r	s	F
10	0·958	1·675	90·39

It would appear from equation 2 that solubilized drug is not available for transfer across the membrane since drugs with the highest dialysis rates are the least solubilized by the Pluronic. However, the linear dependence of dialysis rate on percentage of oxyethylene in the Pluronic indicates that the compounds are solubilized at a particular site rather than in a particular structure. Another important finding of this work is that it is possible to predict the in vitro release rates of acetanilides from specified Pluronics agents used as solubilizing agents. Thus, for an acetanilide of known lipophilicity it is possible to select the Pluronic providing the required release rate.

Table 2. The slope, K′, and correlation for plots of K* against the percentage oxyethylene in the Pluronic molecule for 4-substituted acetanilides dialysed from aqueous solutions of different Pluronics.

Compound	π [a]	K′ × 10⁷	Correlation
Acetanilide	0	3·237	0·999
4-OH	−0·36	0·767	0·975
4-OMe Acetanilide	−0·133	1·650	0·875
4-OEt Acetanilide	0·367[b]	4·298	0·965
4-F Acetanilide	0·309	6·900	0·997
4-Cl Acetanilide	0·714	12·00	0·992
4-Br Acetanilide	1·130	14·98	0·999
4-I Acetanilide	1·303	15·58	0·987
4-NO_2 Acetanilide	0·499	11·72	0·996
4-CHO Acetanilide	0·091	4·617	0·973

[a] From Dearden, J. C., Tomlinson, E. (1968). J. Pharm. Pharmac. 23: 738

[b] Calculated from eg 16, 17 and 19 of Fujita, T., Iwasa, J., Hansch, C. (1964) J. Am. Chem. Soc. 86: 5175–5180

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REFERENCES

Collett, J. H., Tobin, E. A. (1979) J. Pharm. Pharmacol. 31: 174–177

Cowie, J. M. G., Sirianni, A. F. (1966) J. Am. Oil Chem. Soc. 43: 572–578

Dwiggins, C. W., Bolen, R. J., Dunning, H. N. (1960) J. Phys Chem. 64: 1175–1178

Feldman, S., Gibaldi, M. (1970) J. Pharm. Sci. 59: 579–589

McBain, M. E. L., Hutchinson, E. (1955) Solubilization and Related Phenomena. Academic Press London.

Parrott, E. L., Sharma, V. K. (1967) J. Pharm. Sci. 56: 1341–1343

Withington, R., Collett, J. H. (1973) J. Pharm. Pharmacol. 25: 273–280

Wong, C. K. (1974) M.Sc. Thesis. University of Manchester