

## THE SOLUBILIZATION OF SOME PARA-SUBSTITUTED ACETANILIDES IN AQUEOUS SOLUTIONS OF POLYOXYETHYLENE-POLYOXYPROPYLENE BLOCK COPOLYMERS

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Non-ionic surfactants in micellar concentrations have been used as solubilizing agents to increase the solubility of sparingly water soluble compounds. Several workers have reported relations between surfactant structure and extent of solubilization. Such relations have proved useful in the selection of surfactants for a particular purpose. However there is little information on the relations between the solubilizing capacity and structure of block copolymers. In this work the influence of structurally related block copolymers on the solubility of some p-substituted acetanilides has been investigated.

The solubilizates used were acetanilide, its 4-hydroxy, 4-fluoro, 4-chloro, 4-bromo, 4-iodo, 4-nitro, 4-methoxy and 4-ethoxy derivatives and 4-acetamidobenzaldehyde. The surfactants used were polyoxyethylene-polyoxypropylene block copolymers, poloxamers L62, L63, L64, P65 and F68 (marketed as Pluronic by Wyandotte Corporation). They are chemically similar, each possessing the same polyoxypropylene hydrophobe, but with different amounts of ethylene oxide in the hydrophil. The saturation solubilities of the acetanilides were measured at 37°C in aqueous solutions containing increasing concentrations of each poloxamer. The solubility of each compound increased linearly with increasing concentration of poloxamer, but some anomolous behaviour was seen in solutions of poloxamer P65.

When the increased solubility of the acetanilides was expressed as moles of drug solubilized per equivalent of ethylene oxide, the solubilizing capacity of the poloxamers decreased with increasing oxyethylene chain length. However, when considered as moles of drug solubilized per mole of poloxamer, the capacity increased with oxyethylene content for acetanilide, its 4-hydroxy, 4-methoxy and 4-ethoxy derivatives and 4-acetamidobenzaldehyde i.e. the less hydrophobic drugs. The hydrophobic nature of the solubilizates can be described using the  $\pi$  values of their functional groups (Fujita, Iwasa & Hansch, 1964). The slopes obtained from plots of moles of drug solubilized per mole of poloxamer against poloxamer oxyethylene content decreased to a limiting value as a function of the  $\pi$  value of the substituent group on the acetanilide molecule. The inter-relationship between the hydrophobic nature of the solubilizate, the site of solubilization on the poloxamer molecule and the solubilization efficiency of the poloxamer will be discussed.

A linear relation was found between log. aqueous solubility of the acetanilides and the  $\pi$  value of their functional groups. The effect of solubilizate structure on the extent of solubilization by an individual poloxamer can be measured from similar plots of log. moles of drug solubilized per mole of poloxamer against  $\pi$ . A linear plot was obtained for poloxamer F68. The moles solubilized per mole poloxamer P65 against  $\pi$  plot showed anomolous behaviour for the more hydrophobic compounds which may be explained in terms of polymer aggregation. The apparent aggregation number of poloxamer P65 in aqueous solution at 37°C is known to increase continuously and non-linearly over the concentration range used in this work, whereas it has been shown that poloxamer F68 does not aggregate at that temperature (Wong, 1974).

Fujita, T., Iwasa, J. & Hansch, C. (1964). J. Amer. Chem. Soc., 86, 5175-5180.  
Wong, C-K. (1974). M.Sc. Thesis, University of Manchester.