

NON-IONIC SURFACE-ACTIVE AGENTS

PART I. THE SOLUBILITY OF CHLOROXYLENOL IN AQUEOUS SOLUTIONS OF POLYETHYLENE GLYCOL 1000 MONOCETYL ETHER

BY B. A. MULLEY AND A. D. METCALF

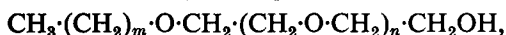
From the Pharmaceutics Laboratories, School of Pharmacy, Chelsea Polytechnic, London, S.W.3

Received June 26, 1956

NON-IONIC surface-active agents are being increasingly used in the pharmaceutical industry, mainly as emulsifying and solubilising agents. This paper is presented as part of a general study of the properties of these compounds and records the solubility at 20° C. of chloroxylenol (4-chloro-3:5-xyleneol) in aqueous solutions of polyethylene glycol 1000 monocetyl ether (cetomacrogol 1000, official in the B.P.C. 1954 and B. Vet. C. 1953) in concentrations up to 20 per cent. The ultra-violet absorption spectrum of chloroxylenol in solutions of the surface-active agent is used to show that a hydrogen-bonded complex is formed between the two substances by an interaction between the phenolic hydroxyl group and the ether oxygen atoms of the polyoxyethylene glycol chain. An interpretation of the solubility curve based on the formation of the complex is given.

EXPERIMENTAL METHOD AND RESULTS

Materials. Polyethylene glycol 1000 monocetyl ether of commerce (B.P.C. and B. Vet. C.) may be represented by the formula



where "m" may be 15 or 17 and "n" may be 19 to 23. The solubility of chloroxylenol in solutions of polyethylene glycol 1000 monocetyl ether was calculated using 23 and 15 as the values for "n" and "m" respectively.

Some confusion has arisen in the literature¹ concerning the correct values for "n". This seems to be caused by the formula given in the B. Vet. C. which we understand is to be amended. The limits for "n" are 19 to 23, corresponding to 20 to 24 ethylene oxide units in each molecule. It is well known² that commercial products of this type are not pure compounds but mixtures of materials of varying hydrophilic chain length. Statements referring to the chain lengths of these compounds normally indicate *average* chain length. The wordings of the official monographs are thus misleading.

Pure chloroxylenol was prepared by recrystallising a sample from light petroleum (b.pt. 100–120° C.) to constant m.pt. It formed colourless needles m.pt. 115.5–116° C. (uncorrected). Lesser and Gad³ reported m.pt. 115–116° C.

Distilled water was used for all solutions.

Method of determining the solubility of chloroxylenol in solutions of polyethylene glycol 1000 monocetyl ether. A suitable range of amounts

NON-IONIC SURFACE-ACTIVE AGENTS

of finely powdered chloroxylenol was weighed into a series of containers, to which were added equal volumes of a solution of the surface-active agent. The containers were immersed in a water bath at 20° C. and the mixtures equilibrated by shaking at intervals during 3 days. The limit of solubility was denoted by the appearance of turbidity in the solution, and the quantity of chloroxylenol dissolved was taken to be the mean of the amount contained in two adjacent solutions one clear the other turbid. Determinations of the solubility of chloroxylenol in solutions of the surface-active agent in concentrations of 10^{-5} M to about 0.2M were made in a similar manner. Equilibration for longer periods did not affect the end-point, which was determined to within approximately

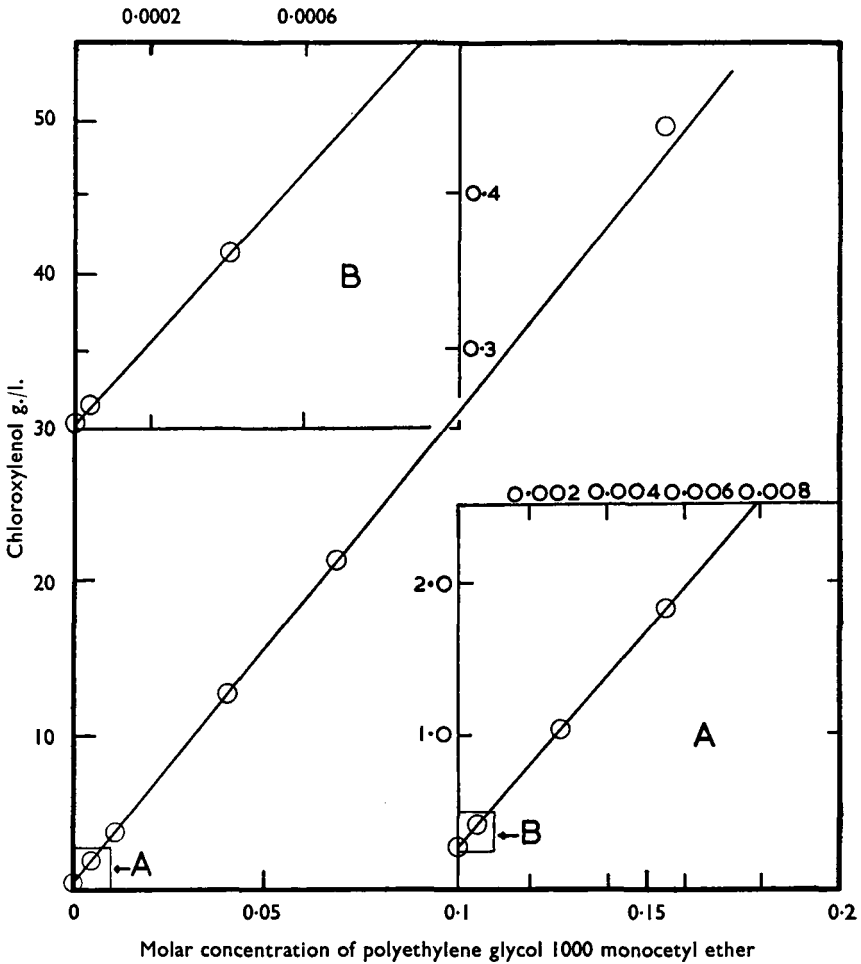


FIG. 1. The solubility of chloroxylenol in aqueous solutions of polyethylene glycol 1000 monocetyl ether. A is an enlargement of the section in the lower left corner of the diagram. B is an enlargement of the squared section of A.

± 1 mg. per litre at the lower concentrations of the surface-active agent. Results are shown in Figure 1.

The ultra-violet absorption spectra of chloroxylenol in water, cyclohexane and a solution of polyethylene glycol 1000 monocetyl ether. All measurements were made with a Unicam SP 500 spectrophotometer modified by Morton⁴. cycloHexane for spectroscopic purposes (B.D.H.) and distilled water were used as solvents. The spectra of chloroxylenol in water,

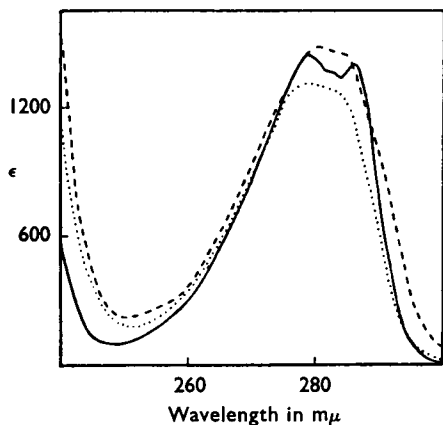


FIG. 2. Ultra-violet absorption spectra of chloroxylenol. The spectrum in cyclohexane is shown by the solid line, $\lambda_{\text{max.}}$ ($m\mu$), ϵ ; 279.5, 1440; 286.5, 1395; inflection at 283 $m\mu$, ϵ 1335. Spectrum in water (dotted line), $\lambda_{\text{max.}}$ 280 $m\mu$, ϵ 1305. Spectrum in solution of cetomacrogol (broken line), $\lambda_{\text{max.}}$ 281.5 $m\mu$, ϵ 1475.

cyclohexane and 0.00109M solution of cetomacrogol are shown in Figure 2. The concentration of the phenol in the two latter solvents was approximately 1 in 2000, and in water approximately 1 in 20,000. Beer's Law was found to apply to the solution in water over the concentration range 1 in 20,000 to 1 in 40,000.

Method of determining the solubility of chloroxylenol in water. A saturated solution of the phenol in water was prepared by shaking an excess of chloroxylenol with water at intervals for three weeks. The solution was equilibrated at 20°C. and the solubility was determined by

measuring the light absorption at 280 $m\mu$ of a dilution of the saturated solution equivalent to a concentration of about 1 in 30,000 of chloroxylenol.

DISCUSSION

The solubility curve shown in Figure 1 is not of the form normally exhibited when water-insoluble substances are dissolved in aqueous solutions of surface-active agents. There is apparently no rapid increase in solubility at a critical micelle concentration, and the solubility of chloroxylenol, when correction has been made for the solubility in water, which has a large effect at the lower concentrations of the surface-active agent, is directly proportional to the concentration of polyethylene glycol 1000 monocetyl ether over the concentration range studied. The phenol to surface-active agent molar ratio is about 1.9:1. Solutions of cetomacrogol 1000 gel above 25 per cent., so the solubility of the phenol was not investigated in this region.

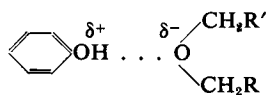
The critical micelle concentration of the non-ionic substances seems to be lower than that of other types of surface-active agent. Caution is necessary, however, when considering the properties of commercial materials because Kushner and Hubbard⁵, using the light scattering

NON-IONIC SURFACE-ACTIVE AGENTS

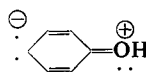
method, failed to observe a critical micelle concentration for Triton X-100, a failure which they suggested was due to the detergent being a mixture of materials of varying molecular weight. However, Gonick and McBain⁶ estimated by freezing point measurements that the critical micelle concentrations of Triton X-100 and nonaethylene glycol monolaurate were 9×10^{-4} and 6×10^{-4} molar respectively. There are indications⁷ that the critical micelle concentration may be even lower for non-ionic compounds of higher molecular weight.

Little detailed work has been published on the solubility of water insoluble substances in aqueous solutions of non-ionic surface-active agents, but it seems to be generally considered, by analogy with the soaps, that the increased solubility of such substances in solutions of the non-ionic compounds is due to the presence of micelles. The mechanism by which the presence of micelles increases the solubility has not apparently been considered in detail. McBain, Wilder and Merrill reported⁸ the solubility of Orange OT in three liquid non-ionic detergents at concentrations of 0 to 100 per cent. There was no indication of a critical micelle concentration, possibly because few results were given at low concentrations of the detergents. The differential solubilisation curves showed increased solubility per mole of the detergents, particularly at concentrations greater than 20 per cent. Similar results were given in more detail for the same dye and for one of the three detergents (Triton X-100) by McBain and Green⁹. Results obtained by Hadgraft¹, working with polyethylene glycol 1000 monocetyl ether and phenols which are soluble in water, indicate that the mechanism by which phenols dissolve in solutions of non-ionic surface-active agents might be unusual. He noted that oil-in-water emulsions prepared with cetomacrogol 1000 seemed to be incompatible with phenols and suggested that this was due to the formation of a complex between them. Rough determinations made by Hadgraft of the solubilities of resorcinol and phenol in 1 to 20 per cent. solutions of cetomacrogol 1000 showed them to be less soluble than in water. This supports the suggestion that complexes are formed. A plot of Hadgraft's results shows that the solubility of these phenols is approximately proportional to the cetomacrogol 1000 concentration.

It seems most likely that the formation of complexes between phenols and non-ionic surface-active agents containing polyoxyethylene glycol chains is due to hydrogen bonding (I). It is well known that strong hydrogen bonds are formed when the hydrogen atom concerned in the bond is acidic in nature.



(I)



(II)

This probably explains the strong hydrogen bonding tendency of the phenolic hydroxy group. In terms of resonance theory the acidic nature of the phenolic hydrogen atom is due to a reduction in the electronegative nature of the oxygen atom resulting from resonance between the possible

canonical forms of the molecule, e.g. (II). Higuchi and Lack¹⁰ showed that polyethylene glycols formed complexes with resorcinol, catechol and phenol, indicating that the interaction of phenols with non-ionic surface-active agents probably occurs at the ether portion of the molecules. The ultra-violet absorption spectra shown in Figure 2 were determined to see if hydrogen bonding between chloroxylenol and cetomacrogol 1000 could be detected. Phenols, in hydrocarbon solvents, usually show a relatively weak absorption band with well defined fine structure at about 280 m μ . The results recorded in Figure 2 for chloroxylenol in *cyclohexane* indicate that this phenol has a normal spectrum in this region. A slight shift of the band to longer wavelength, together with loss of fine structure, is observed when the solvent is water. This behaviour is typical of instances where association is possible with the solvent by hydrogen bonding¹¹⁻¹³. The effect is accentuated in aqueous solutions of the non-ionic surface-active agent. It therefore seems likely that chloroxylenol is associated with the polyoxyethylene glycol chain of the surface-active agent.

When solutions of cetomacrogol 1000 are mixed with a greater amount of chloroxylenol than will dissolve, an interaction occurs and the excess material is found to be an oily liquid and not crystalline phenol unless the amount of chloroxylenol added is very much greater than the amount which will dissolve. Related instances have been reported in the literature^{1,14,15}. The shape of the solubility curve in Figure 1 shows that the oily liquid is insoluble in water. The liquid probably consists of chloroxylenol together with surface-active agent and water. This has been demonstrated with *o*-chlorophenol and a non-ionic detergent¹⁵.

The most satisfactory interpretation of the results appears to be that the solubilisation of chloroxylenol by aqueous solutions of polyethylene glycol 1000 monocetyl ether by incorporation into the micelles is probably governed by the hydrogen bonding which occurs between the phenolic hydroxyl group and the ether chain of the non-ionic surface-active agent. When the molar ratio of phenol to surface-active agent exceeds about 1.9:1 it seems that the hydrophilic character of the micelle is decreased and a complex separates containing surface-active agent, chloroxylenol and water. The failure to observe a rapid increase of solubility of the phenol at a critical micelle concentration may be due to the fact that the surface-active agent used was not a pure substance or that a critical micelle concentration occurs at very low concentrations at which results were not obtained owing to the experimental difficulties involved.

SUMMARY

1. The solubility curve of chloroxylenol in aqueous solutions of polyethylene glycol 1000 monocetyl ether at 20° C. is reported. The increased solubility of the phenol is due to its incorporation into the micelles. The curve shows that the solubility of the phenol is directly proportional to the concentration of the surface-active agent and that the solubility limit is reached at a molar ratio of phenol to surface-active agent of about 1.9:1.

2. Evidence is given, based on the ultra-violet absorption spectra of

NON-IONIC SURFACE-ACTIVE AGENTS

chloroxylenol in *cyclohexane* and in a solution of polyethylene glycol 1000 monocetyl ether, that hydrogen bonds are formed between the phenolic hydroxyl groups and the ether chains of the non-ionic surface-active agent.

3. It is suggested that a hydrogen-bonded complex of the phenol, surface-active agent and water is precipitated at the limit of solubility due to a reduction in the hydrophilic character of the micelles.

The authors thank Dr. H. S. Bean for help which enabled them to undertake this work. The polyethylene glycol 1000 monocetyl ether was kindly given by Glovers (Chemicals) Ltd.

REFERENCES

1. Hadgraft, *J. Pharm. Pharmacol.*, 1954, **6**, 816.
2. Mayhew and Hyatt, *J. Amer. Oil Chem. Soc.*, 1952, **29**, 357.
3. Lesser and Gad, *Ber. dtsh. chem. Ges.*, 1923, **56B**, 963.
4. Morton, *J. Pharm. Pharmacol.*, 1954, **6**, 148.
5. Kusher and Hubbard, *J. phys. Chem.*, 1954, **58**, 1163.
6. Gonick and McBain, *J. Amer. chem. Soc.*, 1947, **69**, 334.
7. Hsiao and Dunning, *J. phys. Chem.*, 1955, **59**, 362.
8. McBain, Wilder and Merrill, *J. phys. Chem.*, 1948, **52**, 12.
9. McBain and Green, *ibid.*, 1947, **51**, 286.
10. Higuchi and Lack, *J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 465.
11. Coggeshall and Lang, *J. Amer. chem. Soc.*, 1948, **70**, 3283.
12. Nagakura, *ibid.*, 1954, **76**, 3070.
13. Nagakura and Baba, *ibid.*, 1952, **74**, 5693.
14. Weiden and Norton, *J. Colloid Sci.*, 1953, **8**, 606.
15. Livingston, *ibid.*, 1954, **9**, 365.

DISCUSSION

The paper was presented by DR. B. A. MULLEY.

MR. J. W. HADGRAFT (London) wondered whether the formation of complexes accounted for the loss of activity of phenols in the presence of non-ionic surface-active agents, because possibly the affinity of the phenol for oxyethylene compounds was greater than its affinity for bacterial protein. Further, if the complex formation were concerned only with the oxygen in the ether chain of the surface-active agent, it should be possible to demonstrate the formation of complexes between phenols and the simple polyethylene glycols.

DR. L. SAUNDERS (London) said that his own work on the critical micelle concentrations of non-ionic surface-active agents confirmed the conclusions of the authors. He suggested that some diffusion measurements might help in elucidating the structure of some of those complexes.

MR. J. H. OAKLEY (London) asked whether there was the same suppression of bactericidal activity if the proportion of non-ionic surface-active agent to chloroxylenol was increased over the minimum necessary for solubilisation as in the case of formulations with soap. It was well known that if more soap were put in the solution than was necessary a lowering of bactericidal effect occurred. Did the authors feel that the non-ionic approach to chloroxylenol presentation would overcome some of the incompatibilities which ionic formulations gave?

B. A. MULLEY AND A. D. METCALF

DR. B. A. MULLEY, in reply, said that the object had been to try to find out whether chloroxylenol associated with non-ionic surface-active agents. No work had been done on the activity of such solutions. There had been a suggestion in the literature that phenols and glycols formed complexes in solution, but there was a difference compared with the alkyl substituted polyethylene glycols because the complex which separated out was not solubilised by the addition of further glycol, and that made relationships completely different from the surface-active agents. He agreed that diffusion measurements might be helpful. The solubility curve method used was not sensitive enough at the very low concentrations which were probably necessary to show the critical micelle concentration. It might be that a high concentration of non-ionic surface-active agent in excess of that needed to solubilise phenol might well give lower activity. The ratio of non-ionic surface-active agent to phenol was obviously important.