

THE SOLUBILITY OF IODINE IN AQUEOUS SOLUTIONS OF NON-IONIC SURFACE-ACTIVE AGENTS

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The solubility of iodine in aqueous solutions of Cetomacrogol 1000 B.P.C., polyethylene glycol 1540 and cetyl and lauryl ethers of polyoxyethylene glycol has been determined. In the region of the critical micelle concentration of cetomacrogol the solubility is below that in water. Well above the CMC, the solubility increases linearly with the concentration of cetomacrogol. Over the temperature range 20–50° the solubility of iodine in aqueous cetomacrogol solution increases with rise of temperature. When a solution is heated and cooled the amount of iodine in the cooled solution is greater than can be obtained by equilibration at that temperature alone. Not all the iodine added to the surface-active agent systems is available for titration with sodium thiosulphate; the unavailable iodine can be accounted for as hydrogen iodide. For 200 g./litre solutions of polyoxyethylene glycol cetyl and lauryl ethers, the available iodine in solution decreases with the number of ethylene oxide units of the ether, but the molecular ratio of iodine to ether increases with the number of ethylene oxide units. The evidence indicates that formation of a complex between iodine and the surface-active agents is in some way involved in the mechanism of the solubilisation process.

THE use of iodine as an antiseptic began soon after Courtois discovered the element in 1811 and the history of its use is described by Kelly (1961). The reviews of Gershenfeld and Witlin (1950a) and Gershenfeld (1957) describe the wide range of the applications of iodine's antiseptic properties and also its action.

Problems involved in formulating antiseptic iodine preparations are presented by its low water solubility (0.285 g./litre at 20° (Seidell, 1953), the irritant properties of certain solutions and the instability of some formulations. Solvents used in official formulae have included ethanol alone or with an alkali iodide, alkali iodides themselves, chloroform, ether, phenol, castor oil, oleic acid, liquid paraffin, glycerol and collodion. Of these, the ethanolic, ethanol/iodide and iodide solutions are in common use today, but their irritant and staining properties leave them open to criticism. MacDonald and Peck (1928) suggested the use of isopropanol as a solvent when iodine was to be used as a skin antiseptic. Gershenfeld and Witlin (1950b) found that propylene glycol was not entirely satisfactory, while Osol and Pines (1952) found that high proportions of glycols were required to include useful amounts of iodine. Cantor and Shelanski (1951) and Terry and Shelanski (1952a, b) reported that iodine dissolved in surface-active agents had antibacterial properties whilst Allawala and Riegelman (1953a, b) provided studies of iodine/non-ionic surface-active agent complexes. The complexes which form between iodine and surface-active agents have been termed "iodophors" and

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Terry and Shelanski (1952b) defined them as "a mixture of iodine and a carrier which greatly increases the solubility of and tends to stabilise iodine in aqueous systems to reactants other than micro-organisms." The term "carrier" is used to include polymeric materials which can also be used to form iodophors.

Reviews of the properties of iodophors have been published by Wetzler (1959), Wilson, Mizuno and Bloomberg (1960, 1961), Connor (1961) and Davies (1962). From these it would appear that iodophors possess over conventional formulations certain advantages, such as increased stability, especially in dilute solutions; reduction in staining, irritant properties and corrosion of metals; low oral toxicity and a reduction in general chemical reactivity without loss of antibacterial activity. Unfortunately many of the published works lack experimental evidence for the claims made and there are few comparisons between iodophors and conventional formulae.

By analogy with the ability of various non-ionic surface active agents to produce iodophors (Allawala and Riegelman, 1953a, b; Bartlett and Schmidt, 1957; Brost and Krupin, 1957), the possible use of Cetomacrogol 1000 B.P.C. and the properties of such a system have been investigated.

EXPERIMENTAL

Materials and Methods

The iodine used was of analytical reagent grade. Three batches of Cetomacrogol 1000, hereafter referred to as cetomacrogol were supplied by Boots Pure Drug Company. The specifications as required by the B.P.C. of these three samples, designated A, B and C, are in Table I,

TABLE I
ANALYTICAL DATA OF SAMPLES OF CETOMACROGOL

	B.P.C. requirements	Samples		
		A	B	C
Identification		+	+	+
Acetyl value	40.0-52.5	50.9*	49.3*	52.2†
Acid value	Not more than 0.5	0.0	0.0	0.0
Alkalinity	Neutral	0.0	0.0	0.0
Melting-point	Not lower than 38°	40.5°	39.5°	39.5°
Refractive index at 60°	1.448-1.452	1.4520	1.4517	1.4570
Saponification value	Not more than 0.5	0.0	0.4	0.5
Water content	Not more than 1.0 per cent	0.6	1.1 per cent	0.7

* By method of B.P.C. 1954. † By method of B.P.C. 1959.

from which it may be seen that neither B, nor C, comply with the B.P.C. requirements. The samples of polyethylene 1540 were kindly supplied by Union Carbide Company, whilst those of the polyoxyethylene mono-alkyl ethers by Glovers Chemicals Ltd.

The critical micelle concentration (CMC) of the three batches of cetomacrogol were determined in duplicate by measurements of surface tension, using a Du Nouy tensiometer, dye solubilisation, employing dimethylaminoazobenzene (Koltoff and Stricks, 1948) and iodine solubilisation (Ross and Olivier, 1959), the results being given in Table II.

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The concentration at which aqueous solutions of the cetomacrogols gelled, was determined approximately by dissolving known weights of cetomacrogol in 25 ml. of distilled water and observing the lowest weight to form a gel at 20°. For batches A, B and C, the weights were 8.4 g., 11.4 g. and 10.1 g. respectively.

TABLE II

VALUES OF THE CMC OF THE THREE BATCHES OF CETOMACROGOL IN AQUEOUS SOLUTION

Batch of cetomacrogol	Concentration of cetomacrogol in g./litre			Average value
	Surface tension	Dye solubilisation	Iodine solubilisation	
A	0.0119	0.0122	0.0141	0.0137
	0.0133	0.0180	0.0127	
B	0.0085	0.0160	0.0086	0.0111
	0.0097	0.0140	0.0095	
C	0.0175	0.0170	0.0188	0.0174
	0.0160	0.0170	0.0192	

Solubility determinations were made by placing finely powdered iodine in wide neck ampoules and adding the required solution. The ampoules were sealed and then agitated in a water-bath at the required temperature for the required time. They were then placed upright for 24 hr. to allow

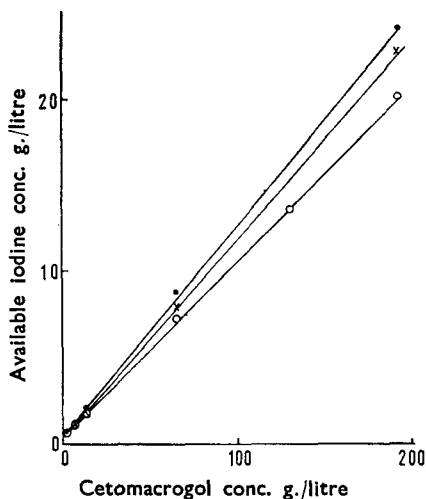


FIG. 1. The solubility of iodine in aqueous solutions of cetomacrogol at 20° C. X Batch A. O Batch B. • Batch C.

the solid iodine to settle before samples were removed. The iodine content of known weights or volumes of these solutions was determined with standard sodium thiosulphate solution, the end-point being determined by an amperometric method. For temperatures up to 40° solutions reached equilibrium within 24 hr. but above this temperature 72 hr. were required.

RESULTS

The Solubility of Iodine in Aqueous Solutions of Cetomacrogol

The solubility of iodine in aqueous solutions of the three batches of cetomacrogol at 20° is shown in Fig. 1. Dilutions of all these solutions remained clear. The effect of temperature on the solubility is shown in Fig. 2. In the region of the CMC, solutions did not clear on standing for

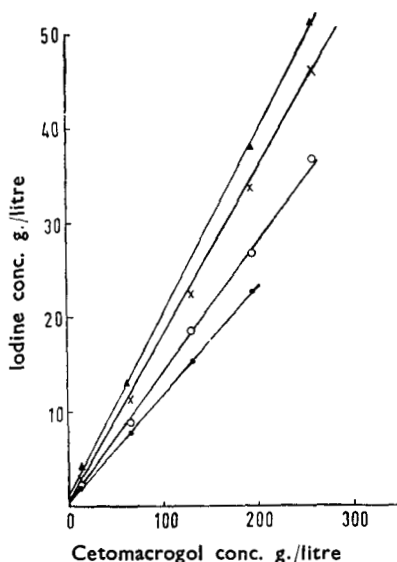


FIG. 2. The effect of temperature on the solubility of iodine in aqueous solutions of Batch A, cetomacrogol. • 20° C. ○ 30° C. X 40° C. ▲ 50° C.

24 hr., a fine suspension remaining. This suspension was however soluble on dilution with water and on estimation of such dilutions, Fig. 3a

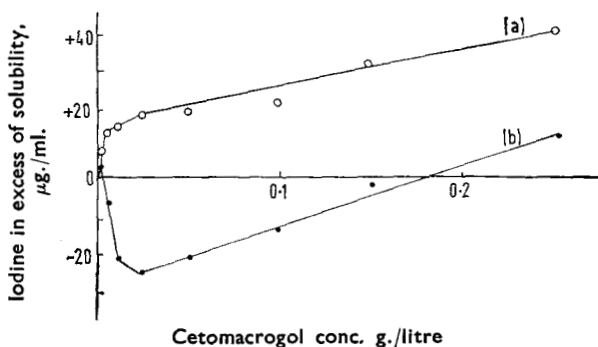


FIG. 3. The solubility of iodine in aqueous solutions of cetomacrogol Batch C, in the region of the CMC at 20° C. ○ Before centrifugation. • After centrifugation.

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was obtained. A clear solution could be produced by centrifuging the ampoules in 50 ml. centrifuge buckets, containing water of the required temperature, for 10 min. at 4000 rev./min. When this was carried out the data presented in Fig. 3b was obtained for batch C, at 20°, the solubility curves for the three batches obtained by this method being shown in Fig. 4.

Previous workers have reported that not all the iodine added to surface-active agents is available for titration with sodium thiosulphate. Allawala and Riegelman (1953b) claimed that half the iodine lost was organically bound, whilst the remaining half could be titrated with silver nitrate. Bartlett and Schmidt (1957) on unsubstantial evidence, claimed that the half not organically bound, appeared as hydrogen iodide. Brost and Krupin (1957), using non-ionic surface-active agents and Siggia (1957) using polyvinylpyrrolidone, reported that the sum of the iodine estimated with thiosulphate and iodide, estimated after removal of iodine with thiosulphate, could account for 99 per cent of the iodine added.

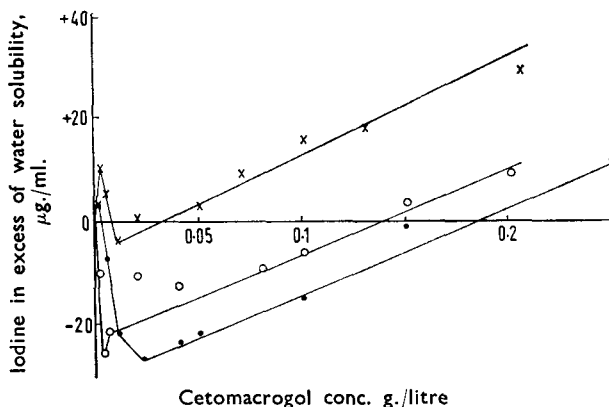


FIG. 4. The solubility of iodine in aqueous solutions of the three batches of cetomacrogol in the region of the CMC at 20° C. X Batch A. O Batch B. • Batch C.

To investigate this, the total amount of iodine present in the system was estimated for a series of aqueous solutions of iodine in cetomacrogol, by the sodium fusion method as described in the *British Pharmacopoeia* 1958 for Chiniophon Sodium. On adding known amounts of iodine to cetomacrogol solutions, the percentage of iodine found by this method ranged from 99.2 to 102.6 per cent. Results for a series of cetomacrogol, batch C, solutions are shown in Fig. 5.

In the next stage of the investigation, analysis of an aqueous solution of cetomacrogol to which a known amount of iodine had been added was made. After determinations with sodium thiosulphate, methyl red was added, and the acid present was titrated with sodium hydroxide. The total iodine was determined by the sodium fusion method. The iodide content was determined with potassium iodate, with the cyanide stabilisation of the end-point and potentiometrically with silver nitrate, with

calomel and silver electrodes connected by an agar salt bridge. The results are shown in Table III indicating that the iodine not available for titration with thiosulphate can be accounted for by the hydrogen iodide content, as reported by Brost and Krupin (1957).

TABLE III
ANALYSIS OF AN IODINE/CETOMACROGOL/WATER SYSTEM

		Sum of available iodine and iodide g./litre
Iodine added g./litre	23.690	
Available iodine g./litre	20.320	
Total iodine g./litre (sodium fusion)	23.700	
Hydrogen iodide g./litre		
(a) Sodium hydroxide	3.365	23.685
(b) Potassium iodate	4.210	24.530
(c) Silver nitrate	3.320	23.640

The Interaction of Iodine and Cetomacrogol

Methods used industrially to produce iodophors have, as their first stage, a process of heating iodine with the carrier, e.g., U.S. Patent (1961). The effect of heating varying amounts of iodine and cetomacrogol together was investigated by placing known proportions of each into

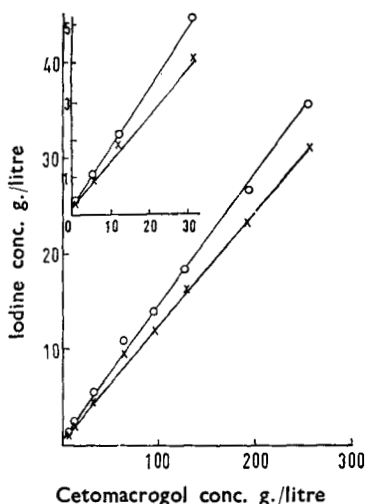


FIG. 5. The total and available iodine content of iodine/cetomacrogol/water systems at 20° C. Insert represents values at lower cetomacrogol concentrations. ○ Total iodine g./litre. × Available iodine g./litre.

stoppered containers and agitating for known times in a water-bath at either 50 or 60°. Samples containing no iodine crystals were removed and placed in a tared beaker, reweighed, and the available iodine content determined as before. The hydrogen iodide content was determined,

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after titration of the iodine, with sodium hydroxide and methyl red as indicator. The results for the 40/60 per cent iodine cetomacrogol system at 60° showed an available iodine content varying from 0.03 to 0.02 g./g. mixture while the hydrogen iodide content varied between 0 and 0.009 g./g. For a 20/80 per cent mixture at 50 and 60°, the available iodine varied from 0.017–0.012 g./g. and the hydrogen iodide from 0–0.005 g./g. For a 10/90 per cent mixture the figures were 0.009–0.007 and 0.003–0.002 respectively.

The effect of heat on aqueous solutions of iodine in cetomacrogol was investigated by agitation of excess iodine in a 20 per cent solution cetomacrogol, batch C, for known times at 60°. The iodine was allowed to settle and the solution to cool at 20° for 48 hr. The available iodine and hydrogen iodide contents were determined as before. The available iodine concentration rose to 0.035 g./g. mixture in 10 hr. and then

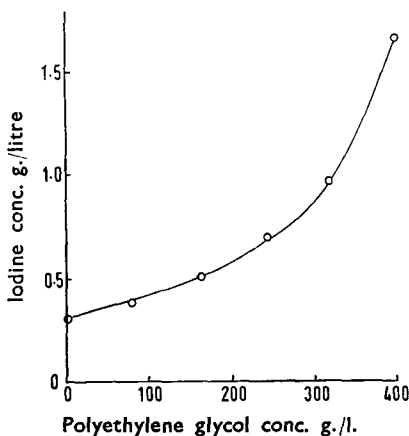


FIG. 6. The solubility of iodine in aqueous solutions of polyethylene glycol 1540 at 20° C.

increased very slowly to 0.04 g./g. after 60 hr. The hydrogen iodide content varied from 0.002–0.003 g./g. over the same period. The figures are below the iodine content determined at 60° (0.055 g./g.) but are above that determined at 20° (0.022 g./g.).

The Solubility of Iodine in Polyethylene Glycol and Polyoxyethylene Ethers

The solubility of iodine in aqueous solutions of polyethylene glycol 1540 at 20° is shown in Fig. 6. Solutions containing more than 300 g./litre polyethylene glycol gave a precipitate on dilution with water above 1 in 10, but cleared on dilutions above 1 in 100.

The solubility of iodine in 20 per cent aqueous solutions of cetyl and lauryl ethers of polyoxyethylene are shown in Fig. 7a and the molecular ratio of available iodine to ether, assuming the manufacturer's value for the number of ethylene oxide units are given in Table IV. The effect of preheating these systems for 72 hr. at 60° is shown in Fig. 7b and the molecular ratios given in Table IV.

DISCUSSION

The Table of B.P.C. specifications, the gel point and the CMC values indicate that the three batches of cetomacrogol have different characteristics. It is interesting to note the surface tension/concentration curves

TABLE IV
RATIO OF MOLECULES OF IODINE TO MOLECULES OF POLYOXYETHYLENE GLYCOL ETHERS

Ether and number of ethylene oxide units	Ratio of molecules of available iodine to molecules of polyoxyethylene glycol ether	
	When dissolved at 20°	When preheated for 72 hr. at 60° and cooled to 20°
Cetomacrogol, batch C	0.627	1.055
Cetyl alcohol ether		
16	0.608	0.733
18	0.580	0.765
24	0.676	0.863
30	0.736	0.923
45	0.863	1.191
60	0.882	1.371
Lauryl alcohol ether		
9	0.263	0.383
16	0.355	0.769
23	0.401	0.854

gave no noticeable minima which characterise impure surface-active agents. Each batch of cetomacrogol also varied in its ability to dissolve iodine (Fig. 1), but the source of this variation cannot be stated from the information available.

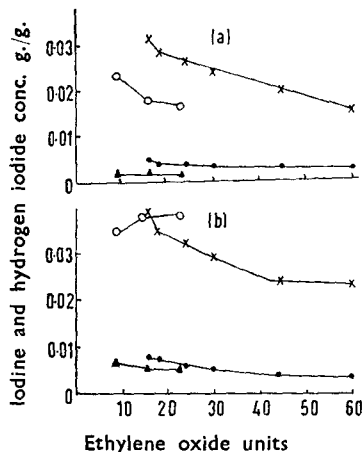


FIG. 7. The Solubility of iodine in 20 per cent aqueous solutions of polyoxyethylene cetyl and lauryl ethers (a) at 20° C. and (b) at 20° C., after preheating at 60° C. for 72 hr. X Available iodine content of cetyl ethers g./g. O Available iodine content of lauryl ethers g./g. • Hydrogen iodide content of cetyl ethers g./g. ▲ Hydrogen iodide content of lauryl ethers g./g.

Terry and Shelanski (1952a) and Allawala and Riegelman (1953a, b) considered the solubility of iodine in non-ionic surface-active agents to be due to the presence of micelles in solution, although Lazarus (1954) was

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not fully convinced that this was so. The phenomenon of micellar solubilisation as described fully by McBain and Hutchinson (1954), was shown by McBain and McBain (1936) to be reproducible and independent of the system's previous history. The iodine/cetomacrogol complex described here is not reproducible in that, when heated in the presence of excess iodine, and then cooled to a lower temperature, the iodine content does not return to that of a saturated solution at the lower temperature. We have, therefore, evidence that micellar solubilisation cannot provide the complete answer. Considering the solubility curve in the region of the CMC, Fig. 3a shows that, where the water-soluble suspension was not removed, the solubility of iodine increased more rapidly with cetomacrogol concentration, below the CMC. When the suspension was removed (Fig. 4) there was an increase in the solubility of iodine, below the CMC of batches A and C, followed by a decrease in solubility in the region of the CMC. A similar decrease has been noted for benzene (McBain and Lissant, 1951; Mulley and Metcalf, 1962), chloroxyleneol (Mulley and Metcalf, 1962) and possibly octanol (Mulley and Metcalf, 1962) in low concentrations of non-ionic surface-active agents. Above the CMC there was a linear relationship between the amount of available iodine and the cetomacrogol concentration (Fig. 1), the available iodine in solution at a given cetomacrogol concentration increasing with temperature (Fig. 2).

Further evidence against micellar solubilisation is the occurrence of a chemical interaction between iodine and the surface-active agent. That this reaction results in the production of an equivalent amount of hydrogen iodide is indicative of an oxidation/reduction reaction, a substitution reaction would yield half the amount of hydrogen iodide whilst in an additional reaction no hydrogen iodide would be produced. There does not appear to be any reports of such a reaction between iodine and polyoxyethylene ethers in the chemical literature, but Johnson and others (1951) report that halogens form loose addition compounds with ethers. With thioethers Hickinbottom (1957) reports that such an addition occurs readily, forming compounds of the R_2SBr_2 type, but these are unstable tending to lose the halogen in water to yield sulphoxides, e.g.,



A similar type of reaction possibly occurs between iodine and cetomacrogol, the oxygen atoms of the ether groups of cetomacrogol providing a mechanism of solubilisation and a source of the hydrogen iodide. Osol and Pines (1952) suggested that a bond of the Lewis acid-base type was responsible for the solubility of iodine in glycols and glycerol. Thus the iodine functions as an electron pair acceptor (presumably by the formation of I^+I^-), whilst the oxygen atoms function as electron donors.

The molecular ratios of iodine to ethers given in Table V, show however that neither an ethylene oxide unit, nor a molecule of ether, holds one molecule of iodine, and therefore the association would appear to be more complex than postulated above. However, the molecular ratios of iodine to surface-active agent do show a noticeable increase as the

number of ethylene oxide units increases, providing evidence of an association between iodine and the ethylene oxide units. Further evidence of the formation of a complex between iodine and the surface-active agent is obtained from a consideration of the absorption spectra of such systems. The occurrence of complexes between iodine and solvent are characterised by the appearance of a new absorption maximum at a value lower than that obtained for non-complex forming solvents (540 $m\mu$), e.g., 353 $m\mu$ for iodine in acetone (Benesi and Hilderbrand, 1950). Allawala and Riegelman (1953b) show the maximum for iodine/surface-active agents in solution as 370 $m\mu$, while Ross and Olivier (1959) report a value of 360 $m\mu$ in aqueous and non-aqueous solutions. Elworthy (1960) found a value of 390 $m\mu$ and this same value was obtained for the ethers used in this work. A recent investigation of an iodine/cationic surface-active agent complex (Cohen, Economou and Libackyj, 1962), shows that it had an absorption maximum of 360 $m\mu$ in chloroform solution. With iodine/polyvinylpyrrolidone complexes, Oster and Immergut (1954) suggested, from observation of absorption spectra, that iodine induces polyvinylpyrrolidone to assume a helical form, the centre of which is occupied by iodine. This explanation provides a mechanism similar to that for starch and cyclodextran complexes, the form of which is described by Brown (1962), and could be also involved in the solubilisation of iodine by non-ionic surface-active agents.

The concept that the mechanism which caused the binding of a solubilise to a non-ionic surface-active agent was also responsible for solubilisation has been postulated by Patel and Kostenbauder (1958) for *p*-hydroxybenzoates/polyoxyethylene glycol ethers. Blaug and Ashen (1961) noted that esters of *p*-hydroxybenzoic acids had a low solubility in polyethylene glycol but were soluble in polyethylene ethers, thus being analogous with the instance of iodine. They also found small amounts of binding between *p*-hydroxybenzoates and polyethylene glycol but greater binding with the ethers. They explained this difference on the suggestion of Higuchi and Lack (1954), that the presence of hydrophilic and hydrophobic moieties in the interacting molecules rendered the replacement of water molecules hydrogen bonded to the basic ether oxygen groups more favourable.

The foregoing work and explanations do not provide a complete elucidation of the means whereby cetomacrogol and similar compounds can bring iodine into homogeneous aqueous systems. Nevertheless, cetomacrogol can be employed to provide an aqueous iodine system and the properties of such a system will be described.

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