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SOLUBILIZATION OF CHLORHEXIDINE DIACETATE AND DICHLORIDE IN AQUEOUS DECAOXYETHYLENE OLEIC ETHER SYSTEMS

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SUMMARY

An investigation of the solubilizing effect that the surfactants decaoxyethylene oleic ether and polyoxyethylene sorbitan monooleate have on chlorhexidine disalts has shown that (a) the species that dissolves in the micelle is the disalt (ion pair), (b) that the site of solution is the hydrocarbon core of the micelle, and (c) that the system undergoes an abrupt change at about 10% surfactant, presumably due to size or shape change of the micelle.

INTRODUCTION

Chlorhexidine is a well known bactericidal agent (Richards and Macbride, 1973; Warner et al., 1973). Surfactive properties of the diacetate salt have been investigated by Heard and Ashworth (1968) who reported a critical micelle concentration (CMC) of the diacetate of 0.009 M and by Perrin and Witzke (1971) who reported a CMC for the gluconate of about 0.004 M. Interactions with micellar systems have also been reported in the literature (e.g., Senior, 1972).

It is the purpose of this study to report findings which shed light on the site of absorption of chlorhexidine salts in the decaoxyethylene oleic ether (Brij 96) micelle, to elucidate which ionic species is absorbed, and to estimate the effect of the state (shape and size) of the micelle of decaoxyethylene oleic ether on the solubility of chlorhexidine diacetate and dichloride.

MATERIALS AND METHODS

The solubility of the chlorhexidine salts [1,2] (S g/100 g) was determined in decaoxy-

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[1] Chlorhexidine diacetate was obtained from I.C.I. Pharma, 6 rue Blanche, 95880 Enghein, France.

[2] Chlorhexidine dihydrochloride was obtained from Atlas Chemical Industries, N.V., Everslaan 45, B. 3078 Everberg, Belgium.

ethylene oleic ether[3] water systems of the following surfactant concentrations (percent weight by weight, C): 1, 3, 5, 6, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13 and 14%. Excess chlorhexidine was added to these systems, and they were agitated in a circularly rotating shaker[4] for 96 h at 21°C. The supernatant was then assayed for chlorhexidine in the manner described by Gautier and Malangeau (1968): the sample to be assayed was added to a 1 : 3 mixture of chloroform and water. An indicator consisting of methyl yellow and aminoanthraquinone was added and the system then titrated with dioctylsulfosuccinate. Results from this assay method compare favorably with other methods of analysis, for instance that of Pinzauti et al. (1976).

Solubilities of chlorhexidine salts in polyoxyethylene sorbitan monooleate[5] (Tween 80) systems was similarly determined.

The viscosity of the various systems was determined by means of a recording rheometric viscometer[6] at 25°C. All the systems were Newtonian. All solutions were prepared by adjusting to volume *and* weighing added amounts so that the above weight concentrations could easily be converted to volume concentrations.

RESULTS AND DISCUSSION

The solubilities of chlorhexidine diacetate and dihydrochloride as a function of the concentration of decaoxyethylene oleic ether are shown in Fig. 1. The solubilities of chlorhexidine diacetate and dihydrochloride in polyoxyethylene sorbitan monooleate are shown in Fig. 2. It is apparent that the graphs represent the typical solubilization curve for a micellar system, where the solubility increases linearly with concentration beyond the CMC (Carstensen, 1972), but it also appears that there is a further break in this curve. This slope change, in the case of the chlorhexidine–decaoxyethylene oleic ether system occurs at a concentration of about 10% of surfactant and will be the subject of discussion at a later point. The comments will first concentrate on the first linear portion beyond the CMC.

As shown in Table 1, addition of decaoxyethylene oleic ether to solutions of chlorhexidine does not cause a lowering of the pH. If the dissolved species were the base (R) or the monosalt (RHM), then the disalt (RH_2M_2) when partitioning would liberate acid (HM):

$$RH_2M_2(\text{solution}) \rightarrow RHM(\text{micelle}) + HM$$

or

$$RH_2M_2(\text{solution}) \rightarrow R(\text{micelle}) + 2\ HM$$

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[3] Decaoxyethylene oleic ether (Brij 96) was obtained as Simulsol 96, from Seppic Montanoir, 60 rue Pierre Charon, 75008 Paris, France.

[4] Agitateur rectilignealternatif, Ateliers A. Baudard, 2 bis rue de l'Ermitage, 75020 Paris, France.

[5] Tween 80, Atlas Chemical Company, Wilmington, Delaware. The data referring to this originate from an unpublished thesis, DEPS, at the Faculté de Pharmacie, l'Université de Paris-Sud, 92290 Châtenay-Malabry, France, By Jean Pierre Paris.

[6] Rheomat 30, Contraves, A.G., Zurich, Schaffhauserstrasse 580, CH 8052, Zurich, Switzerland.

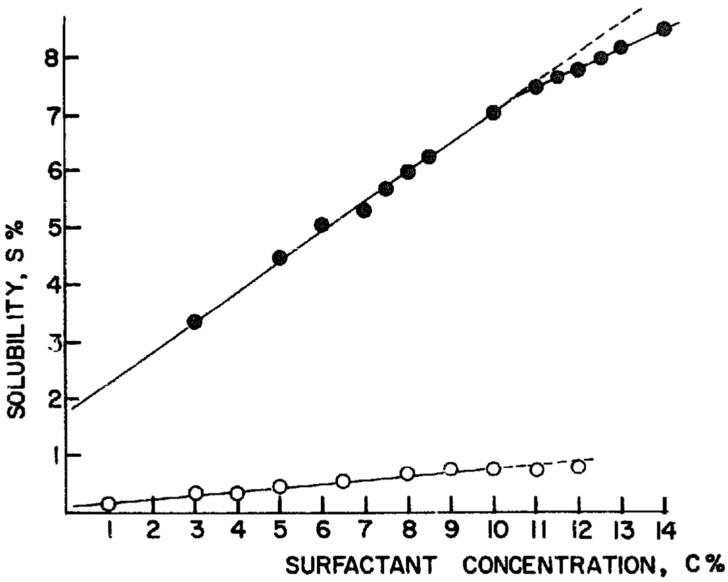

Fig. 1. Solubility of chlorhexidine diacetate (●) and dihydrochloride (○) as a function of concentration of decaoxyethylene oleic ether. Each point is the average of two or three independent determinations. CMC break omitted because of graphical limitations.

hence the pH should be lower upon addition of decaoxyethylene oleic ether to solutions of chlorhexidine salts. Since this is not the case (Table 1), the dissolving species is either the disalt or a higher salt. The latter is unlikely and the conclusion is tentatively reached that the dissoving species is the diacetate or dihydrochloride. Ordinarily it is to be expected that ionic species do not dissolve in the micelle cores, since these latter are lyophilic and the salts are hydrophilic. However, as shown in Table 2, chlorhexidine *increases* in solubility in solvents with decreasing polarity. This may explain why a salt or ion-pair, not the base, enters the micelle. It could be visualized that the salt would be located not in the core, but at the exterior (polar) part of the micelle. However, as shown

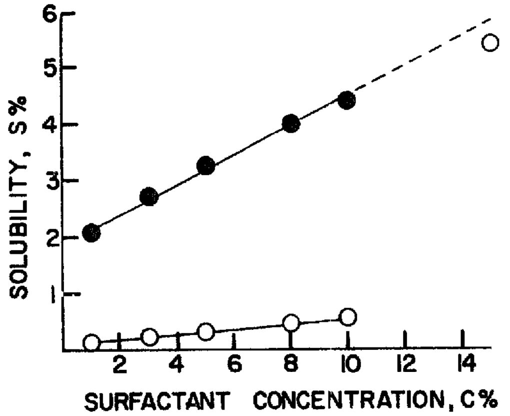

Fig. 2. Solubility (S) of chlorhexidine diacetate (●) and dihydrochloride (○) as a function of concentration of decaoxyethylene oleic ether. CMC break omitted because of graphical limitations.

TABLE 1

pH OF SYSTEMS OF CHLORHEXIDINE SALTS IN VARIOUS CONCENTRATIONS OF DECAOXYETHYLENE OLEIC ETHER

Chlorhexidine salt	Concentration of decaoxyethylene oleic ether						
	0%	1%	3%	5%	8%	10%	12%
None (surfactant alone)		6.86	6.97	7.38	7.83	8.15	8.05
Diacetate	6.80	6.75	6.89	6.86	6.99	7.07	7.25
Dihydrochloride	6.00	6.24	6.96	7.05	7.22	7.23	7.58
Monohydrochloride	10.0						

in Fig. 3, polyoxyethylene glycol does not greatly increase the solubility of the salts in water.

A further piece of evidence that points to the plausibility of the site of solubilization being the core is the following. The solubilities of the salts in decaoxyethylene oleic ether and polyoxyethylene sorbitan monooleate can be calculated from the slopes of the lines in Figs. 1 and 2. These are shown in Table 3, and are expressed as solubility per weight unit of surfactant. Since the surfactants contain a certain percentage of hydrocarbon (oleic chain) and a certain percentage of polyoxyethylene the solubilities may be expressed on a weight (or mol) basis in terms of these fractions as well. It is seen that when the solubility is expressed as weight fraction based on hydrocarbon, the solubility is the same in decaoxyethylene oleic ether as in polyoxyethylene sorbitan monooleate both for the diacetate and for the dihydrochloride. It would hence appear that the process is akin to a partitioning into the hydrocarbon portion of the surfactant, regardless of the surfactant, and thus that the core of the micelle is the site of solubilization.

As mentioned, Fig. 1 implies a change in slope of the solubility curve at 10% surfactant concentration. This change into two linear segments is statistically significant in the case of the diacetate, whereas for the dihydrochloride it would seem to be so, although the data do not suffice to show whether it is a case of two line segments or whether it is

TABLE 2

SOLUBILITY OF CHLORHEXIDINE SALTS IN SOLVENTS LISTED IN ORDER OF DECREASING POLARITY

Solvent	Solubility in g/100 g of solvent	
	Dihydrochloride	Diacetate
Water	0.09	1.9
Ethanol	0.22	6.6
Polyoxyethylene glycol 400	0.085	9
Propylene glycol	8	Very soluble

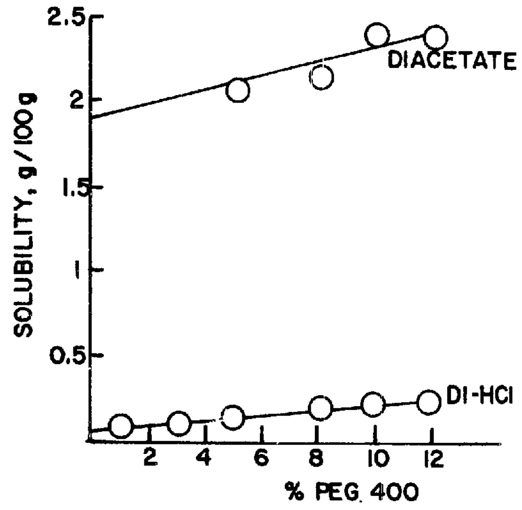

Fig. 3. Solubility of chlorhexidine salts in aqueous solutions of polyethyleneglycol 400.

simply curvature starting. The following comments will, therefore, be confined to the diacetate system.

Abrupt changes in slopes of properties of micellar systems plotted versus surfactant concentration were first reported by Prasad et al. (1979), who observed an extra slope change in surface tension plots of polyoxytheylene–polyoxypropylene glycol–water systems. In the case in Fig. 1, the least squares fit for the two line segments are given below. At low surfactant concentration:

$$S = 1.779 + 0.530\,C\ (r = 0.96, N = 14) \qquad (1A)$$

and at high surfactant concentration:

$$S = 3.613 + 0.350\,C\ (r = 0.94, N = 8) \qquad (1B)$$

r is here the correlation coefficient, N is the number of points, S is the solubility of

TABLE 3

SOLUBILITY OF CHLORHEXIDINE DIACETATE AND DIHYDROCHLORIDE IN DECAOXYETHYLENE OLEIC ETHER AND IN POLYOXYETHYLENE SORBITAN MONOOLEATE

Values are expressed as solubility per mol of surfactant, per g of hydrocarbon and per mol of polyoxyethylene.

Salt	Solubility					
	$\frac{\text{mol salt}}{\text{mol surfactant}}$		$\frac{\text{g salt}}{\text{g } C_{18}H_{33}}$		$\frac{\text{mol salt}}{\text{mol } (OC_2H_5)}$	
	Brij 96	Tween 80	Brij 96	Tween 80	Brij 96	Tween 80
Diacetate	0.58	0.57	1.42	1.40	0.057	0.028
Dihydrochloride	0.086	0.106	0.20	0.24	0.0085	0.0053

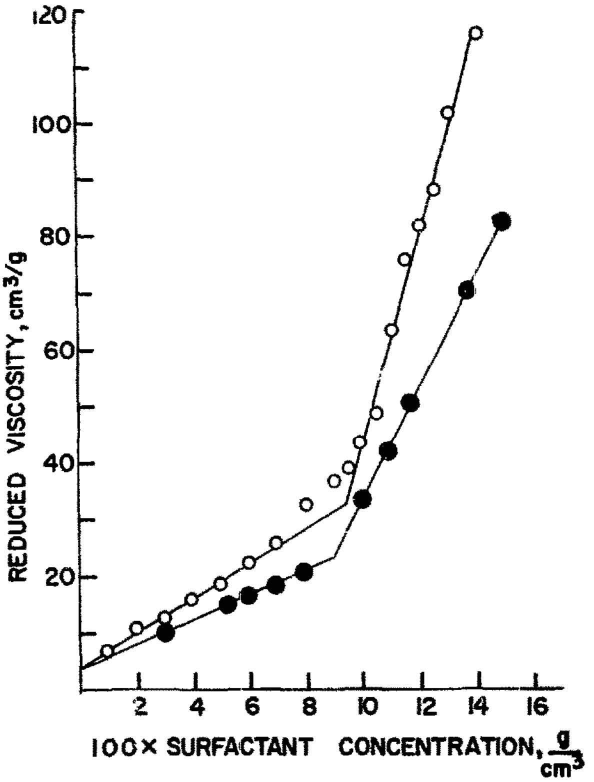

Fig. 4. Reduced viscity (cm^3/g) of aqueous decaoxyethylene oleic ether solution without (○) and with (●) chlorhexidine diacetate. In the latter case the systems are saturated in chlorhexidine diacetate.

chlorhexidine and C is concentration of decaoxyethylene oleic ether. The intersection of the two lines (i.e. where the S values are identical) was found arithmetically to be C = 10.2%.

The question why there is a change in slope in Fig. 1 at about 10% can, a priori, be visualized as being due to a change in the character (the size or the shape) of the micelle. If this is so then other properties connected with micelle shape and size should

TABLE 4

LEAST SQUARES PARAMETERS OF THE LINE SEGMENTS IN FIG. 4

Concentrations are in g/g and the reduced viscosities are in cm^3/g

Concentration range of decaoxyethylene oleic ether	Correlation coefficient r^2	10^{-2} × slope	Intersect
Less than 9% [a]	0.996	3.08	3.60
More than 10% [a]	0.985	18.64	−142.3
Less than 9% [b]	0.994	2.16	4.38
More than 10% [b]	0.976	10.4	−75.1

[a] With chlorhexidine.

[b] Without chlorhexidine.

also change at this concentration. It is for this reason that the viscosities of the system were determined. Fig. 4 shows the reduced viscosities of the chlorhexidine diacetate–water–decaoxyethylene oleic ether system, and the water–decaoxyethylene oleic ether system without chlorhexidine. It is noted, again, that there are breaks in these curves. The least square fits parameters are shown in Table 4, and it is seen that the intersections occur at concentrations of 9.6% and 9.4% respectively. This is in good agreement with the break in the solubility curve. The data in Fig. 4 are, at the lower concentration range, in good argreement with the data reported by Florence et al. (1975) on the intrinsic viscosity of nonyl-phenol polyoxyethylene ethers.

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