Effect of Inorganic Additives on Solutions of Nonionic Surfactants VI: Further Cloud Point Relations

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Abstract □ Disperse dosage forms stabilized with nonionic surfactants frequently contain electrolytes as active ingredients or adjuvants. Salting out of the surfactants by these electrolytes may cause breakdown of the dosage forms. The cloud point of an aqueous solution of octoxynol 9 was used to measure the salt effects. Electrolytes which salt octoxynol 9 out lower its cloud point, while salting-in electrolytes raise it. The observed cloud point effects are discussed according to the mechanisms involved. Salting out by dehydration in competition with octoxynol 9 for the available water was observed with sulfate and phosphate anions, sodium, potassium, and ammonium tribasic cations, and the nonelectrolyte sorbitol. The extensive self-association of water by hydrogen bonds at and below room temperature weakens its solvent power. Ions which reduce this self-association, breaking the structure of water, increased the cloud point of octoxynol 9. Among them were the iodide, thiocyanate, and nitroprusside anions. Ions which tighten the structure of water and enhance its self-association salted the surfactant out, lowering its cloud point. Among these were the fluoride and hydroxide anions. Complex formation between the ether linkages of octoxynol 9 and the following cations increased its cloud point: hydrogen (from strong acids), silver, magnesium, and zinc. Including published data, the only cations which do not form complexes with polyoxyethylated surfactants (and are, therefore, unable to salt them in) were the alkali metal ions sodium, potassium, and cesium and the ammonium ion. The cloud point increases produced by a weak organic base and acids are ascribed to the formation of mixed solvents with water. The hydrotropes sodium salicylate, phenobarbital sodium, and sodium benzoate raised the cloud point appreciably even at low concentrations. The most efficient cloud point boosters were the three surfactants studied, namely, two ionic and a nonionic surfactant with an elevated cloud point. They formed mixed micelles with octoxynol 9. The changes in cloud point caused by electrolytes having a common ion were compared at equal values of a concentration parameter chosen to produce cloud point additivity. By using the nitrate ion as a reference and arbitrarily equating its change in cloud point to zero, cloud point shift values could be assigned to other individual ions. For the anions, these cloud point shift values were related by a smooth function to the lyotropic numbers in the Hofmeister series. There was no correlation between the cloud point shift values and the lyotropic numbers of cations, presumably because of complexation between the ether groups of octoxynol 9 and many of the cations.

Keyphrases □ Surfactants, nonionic—octoxynol 9, effect of inorganic additives, cloud point relations □ Octoxynol 9—effect of inorganic additives on nonionic surfactants, cloud point relations □ Cloud point relations—effect of inorganic additives on nonionic surfactants, octoxynol 9

The influence of electrolytes on the solubility of nonionic polyoxyethylated surfactants can be assessed by their effect on the cloud point (1–5). The present work extends cloud point measurements of a representative nonionic surfactant to solutions containing electrolytes with anions and/or cations used in dosage forms. It also presents a numerical system for rating the capacity of various ions to salt the polyoxyethylated surfactant in or out.

BACKGROUND

Dosage forms consisting of micellar solutions and of disperse systems—suspensions, emulsions, ointments, and aerosols—are commonly stabilized with surfactants. Electrolytes may be present as active ingredients, adjuvants, or impurities. They frequently have an adverse effect on stability. Salting out of the surfactants by the electrolytes may cause breakdown of the dosage form.

The method generally used to study the effect of electrolytes on the solubility of nonelectrolytes is to determine that solubility in water (S_n^0) and in aqueous solutions containing C_e mol/L of electrolyte (S_n). These parameters are related by the Setschenow equation (6):

$$\log (S_n^0/S_n) = K \cdot C_e \qquad (Eq. 1)$$

where the magnitude and sign of the salt parameter, K, indicate the extent of salting in or out.

Solubility measurements of nonionic surfactants in water or aqueous salt solutions are difficult to perform because of the high values and the appearance, in concentrated systems, of viscous mesomorphic phases (7). The cloud point of these surfactants is sensitive to electrolytes (1–5), but insensitive to surfactant concentration within rather wide limits (8, 9). It can be measured readily and reproducibly and serves, therefore, as a convenient parameter for salt effects.

Electrolytes that raise the cloud point expand the region in the surfactant–water phase diagram between the upper consolute temperature, represented by the cloud point curve, and either the Krafft point curve or the freezing point curve. In this region (Region II of Fig. 1 in Ref. 10), which contains a single phase, the surfactant exists in an undersaturated isotropic solution. Such electrolytes increase the solubility of the surfactant, salting it in ($K < 0$). Electrolytes that depress the cloud point reduce the region in which the surfactant is soluble, *i.e.*, they salt it out ($K > 0$).

Information on the effect of electrolytes on the cloud point of nonionic surfactants also has practical uses. Dosage forms stabilized with nonionic surfactants frequently break down when heated above the cloud point, *e.g.*, during thermal sterilization.

EXPERIMENTAL

Materials—The surfactant, octoxynol 9 NF[1], was an anhydrous, viscous liquid. The following reagents were USP/NF grade: boric acid, citric acid, light magnesium carbonate, phenobarbital sodium, sodium benzoate, sodium fluoride, sorbitol, and trolamine (2,2′,2″-nitrilotriethanol). Sodium bromide was purified[2], tribasic sodium phosphate was technical grade[2], and sodium salicylate was certified[3]. Sodium dodecyl sulfate, triethanolamine hydrochloride, hexadecane, and xylenes were research chemical grade[4]. Another nonionic surfactant, polyoxyl 20 oleyl ether[5] (oleyl alcohol with 20 ethylene oxide units), was solid at room temperature. All other chemicals were ACS reagent grade.

A stock solution of dibasic magnesium citrate, $MgH(C_6H_5O_7)$, was made by dissolving light magnesium carbonate in a citric acid solution. Stock solutions of the sodium citrates were made by neutralizing citric acid solutions
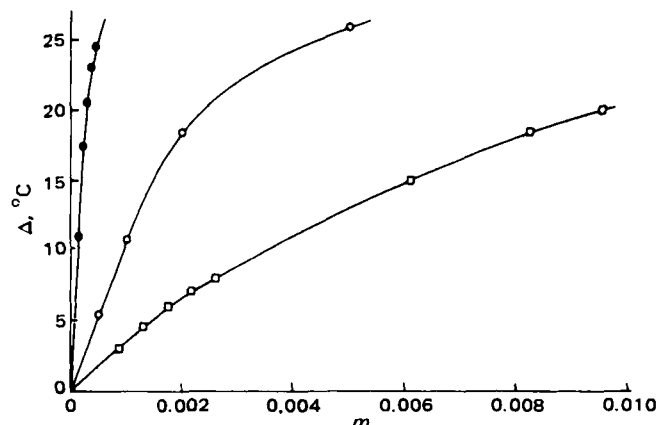

Figure 1—*Cloud point increases by surfactants as a function of their molal concentrations. Key: (●) sodium lauryl sulfate; (○) decylammonium chloride; (□) polyoxyl 20 oleyl ether.*

Table I—Effect of Surfactants and Hydrotropes on the Cloud Point of Octoxynol 9

Rank No.	Additive	Concentration to Produce Δ = 10°C, m	Δ at Molality, °C						
			0.0005	0.001	0.005	0.010	0.050	0.100	0.500
1	Sodium lauryl sulfate	0.00013	26						
2	Decylammonium chloride	0.00093	5.5	11	26				
3	Polyoxyl 20 oleyl ether	0.0035	2	3.5	13	20.5			
4	Sodium salicylate	0.023			3.5	6	13.5	20	
5	Phenobarbital sodium	0.065				2	8	14	
6	Sodium benzoate	0.128				2	5.5	8.5	24.5

Table II—Effect of Acids on the Cloud Point of Octoxynol 9

Rank No.	Additive	Concentration to Produce Δ = 10°C, m	Δ at Molality, °C			
			0.10	0.50	1.0	3.0
7	Citric acid	0.45	2.5[b]	11	23	
13	Acetic acid	1.13	0.5	4	9	27.5
15	Hydrochloric acid[a]	1.46	−1	2	5	28.5
16	Phosphoric acid	1.50		2	6	22.5
18	Sulfuric acid[a]	1.70	−2	0.2	3	28
—	Boric acid	—		2		

[a] Taken from Refs. 4 and 5 plus present data. [b] Taken from Ref. 1.

Table III—Effect of Various Salting-In Electrolytes on the Cloud Point of Octoxynol 9

Rank No.	Additive	Concentration to Produce Δ = 10°C, m	Δ at Molality, °C		
			0.50	1.0	2.0
7	NaSCN	0.32	14.5	21	
9	$Na_2[Fe(CN)_5NO]$	0.55	9.5	15	
11	NaI	0.87	6.5	11	16
10	$AgNO_3$	0.87	6.5	11	18
14	$Zn(NO_3)_2$	1.43	4.5	7.5	
17	$Mg(NO_3)_2$[a]	1.56	4.5	7.5	12.5
19	$Al(NO_3)_3$[a]	1.89	5	7.5	10

* Taken from Ref. 4.

with sodium hydroxide solutions to varying degrees. The water used was double distilled.

Methods—Concentrated stock solutions of the electrolytes were analyzed as reported (4, 5) or by the official USP methods. Octoxynol 9 solutions were aged for at least 48 h before mixing with the electrolyte solutions to permit complete hydration and breakdown of mesomorphic phases and large micelles.

Cloud points were determined at the 2.00% octoxynol 9 level (4, 5). All concentrations in the ternary mixtures are based on the weight of water.

An analysis of the errors incurred in weighing out stock solutions and water and in measuring cloud points indicates that the reported electrolyte molalities are accurate to three significant figures, resulting in an accuracy for the cloud points of ±0.5°C or better.

RESULTS AND DISCUSSION

Five lots of octoxynol 9 were used. Their cloud points ranged from 64.5°C to 67°C. Therefore, the changes in the cloud point of 2.00% octoxynol 9 solutions, Δ, were calculated as the difference between the cloud point of the solutions containing octoxynol 9 plus the additive and the cloud point of the corresponding blank octoxynol 9 solution. A positive Δ indicates salting in, and a negative Δ indicates salting out. The data are listed in Tables I–VI and plotted in Figs. 1–8.

Cloud points usually varied monotonically with increasing additive concentrations. The main exceptions were magnesium chloride and sulfuric acid. The plot of Δ versus molality for the former (Fig. 6) went through a minimum of −16°C at 2 m. However, at 3.4 m, Δ was only −11°C, the same value as at 0.7 m. The chloride ion probably acts as a ligand for magnesium in competition with the ether groups of octoxynol 9. The upturn in the curve is ascribed to increasing complexation with the latter at higher salt concentrations, either as a result of the law of mass action or because the coordination number of magnesium is increased to 6. Sulfuric acid depressed the cloud point of
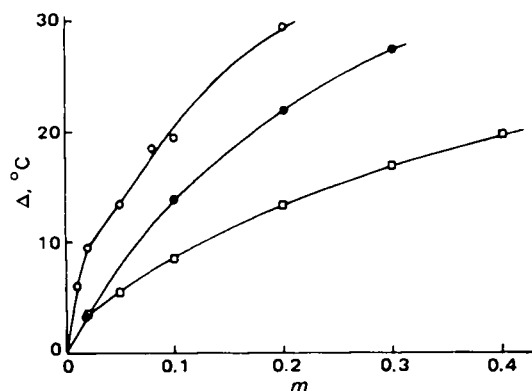
octoxynol 9 by 2°C at 0.10 m, but raised it considerably more at higher concentrations (4). The Δ values of ammonia cover the narrow interval from 2°C to −6°C in the broad concentration range extending to 10 m (Table IV, Fig. 5).

Some of the plots of Δ versus concentration were curved, indicating that the tendency towards salting octoxynol 9 in or out increased less than proportionally with the additive concentration. Linear plots of Δ versus concentration were observed for the following additives in the entire concentration range investigated: trolamine, acetic acid, dibasic sodium citrate, and tribasic sodium phosphate. Linearity for most of the plots was observed for citric acid (Fig. 3) and sodium nitrate (4). Sodium, ammonium, and magnesium sulfates had linear plots over 50-67% of the concentration ranges investigated (Fig. 7).

The numbers in the first columns of Tables I–VI rank the salting-in or salting-out efficiency of the additives. Increasing numbers from 1 to 19 indicate that progressively higher additive molalities were required to boost the cloud point of octoxynol 9 by 10°C. These numbers thus rank the additives in order of decreasing salting-in capacity. Increasing numbers from 20 to 40 indicate that progressively lower additive concentrations were required to reduce the cloud point of octoxynol 9 by 10°C. These numbers rank the additives in order of increasing salting-out capacity. Thus, additive no. 1 is the most efficient salting-in agent, and additive no. 40 is the most efficient salting-out agent on a molal basis. Boric acid was not assigned a number because its solubility was too low to produce a Δ value of 10°C. The tabulated Δ values at the listed additive molalities were either measured directly or interpolated. No extrapolated values were used.

Mechanisms of Electrolyte–Octoxynol 9 Interaction—Polyoxyethylated surfactants are soluble in water because of the hydration of their ether linkages. Studies with model ethers have shown that a maximum of two water molecules are bound directly to each oxygen by hydrogen bonding (11). The hydration
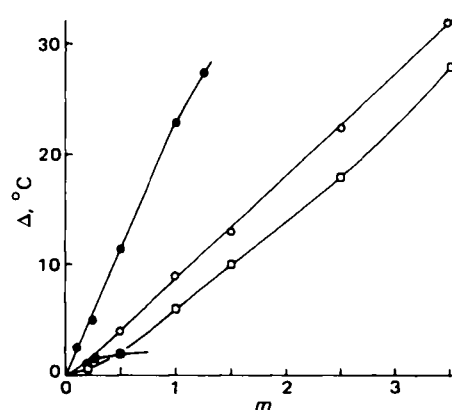
Figure 2—Cloud point increases by hydrotropes as a function of their molal concentrations. Key: (O) sodium salicylate; (●) phenobarbital sodium; (□) sodium benzoate.

Figure 3—Cloud point increases by acids as a function of their molal concentrations. Key: (●) citric; (O) acetic; (□) phosphoric; (■) boric.

Table IV—Effect of Various Additives on the Cloud Point of Octoxynol 9

Rank No.	Additive	Concentration to Produce Δ = ±10°C, m	Δ at Molality, °C				
			0.50	1.0	3.0	6.0	10.0
20	NH₃	~12		1	2	-0.5	-6
21	NH₄NO₃	3.0	-1	-1	-10		
24	NH₄Cl	0.96	-6	-10.5	-20.5		
35	(NH₄)₂SO₄	0.16	-28	-52			
12	Trolamine	0.98[a]	6	10			
26	Trolamine hydrochloride	0.80	-7.5	-12			
30	Tetramethylammonium chloride[b]	0.45	-11	-19			
25	Sorbitol	0.93	-4.5	-11	-38.5		

[a] Δ = 10°C. For the other additives, Δ = -10°C. [b] Taken from Ref. 18.

Table V—Effect of Various Salting-Out Electrolytes on the Cloud Point of Octoxynol 9

Rank No.	Additive	Concentration to Produce Δ = -10°C, m	Δ at Molality, °C				
			0.10	0.50	1.0	2.5	5.0
22	NaBr	1.90		-3.5	-6	-12.5	
23	NaNO₃[a]	1.59	-1	-2	-6	-13	
29	NaCl	0.50	-2	-10	-16.5	-33	-50
32	NaOH	0.28	-4	-16.5	-30.5		
33	NaF	0.24	-4.5	-19			
27	MgCl₂	0.59		-9	-13	-15	
36	MgSO₄	0.16	-6.5	-29.5	-68		
37	Na₂SO₄	0.12	-8.5	-37			
39	Na₃PO₄	0.093	-11				
40	Al₂(SO₄)₃	0.063	-16				

[a] Taken from Ref. 4.

of small and nearly spherical nonionic micelles varies between 0.4 and 6.3 water molecules per micellar ether linkage (12). Water solubility and cloud point increase with the number of ether groups and the hydrophilic-lipophilic balance (HLB) of the surfactants. The various mechanisms by which electrolytes affect hydration, cloud point, and solubility of octoxynol 9 are discussed below and used to interpret present and previously published data.

Salting Out by Dehydration—Many cloud point-depressing electrolytes act through water binding or dehydration, reducing the amount of water available for the hydration of the polyoxyethylene moiety of the surfactant by tying up water through their own hydration. The sulfate and phosphate anions are examples of ions that salt out octoxynol 9 by competing with the surfactant for water of hydration (see Table V, Figs. 4 and 7) (1-4).

Dehydration is probably the most important salting-out mechanism for nonelectrolytes. Additional mechanisms include dielectric effects and electrostriction. Their application to nonionic surfactants has been discussed (5).
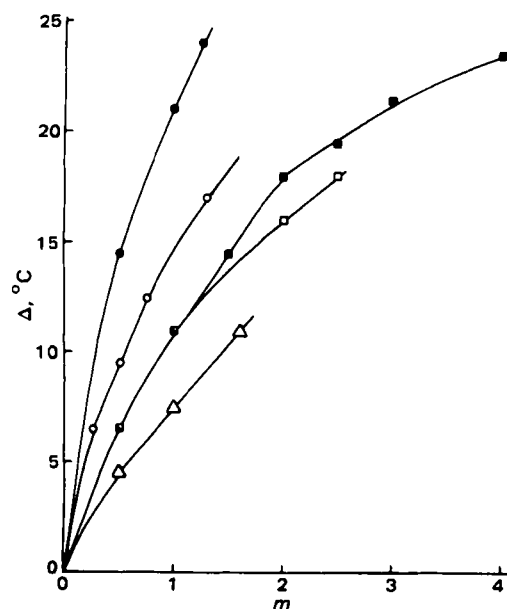

Figure 4—*Cloud point increases by salting-in electrolytes as a function of their molal concentrations. Key: (●) NaSCN; (○) Na₂[Fe(CCN)₅NO]; (■) AgNO₃; (□) NaI; (△) Zn(NO₃)₂.*

Sorbitol also depresses the cloud point through water binding or dehydration (Table IV, Fig. 6). Although not an electrolyte, it was included among the additives because it is so hygroscopic that it is used as a humectant.

Modification of Water Structure—At and below room temperature, water molecules are extensively self-associated by hydrogen bonding into "icebergs" or "flickering clusters" (13). Ions that reduce the self-association among water molecules, depolymerizing water and reducing its viscosity, are designated as structure breakers (13, 14). Only monomeric or nonassociated water molecules can hydrate the ether linkages of octoxynol 9 effectively. Therefore, structure-breaking ions increase the solubility of octoxynol 9 (raising its cloud point) by increasing the hydrogen bonding between ether groups and nonassociated water molecules at the expense of the hydrogen bonding among water molecules.

Examples of structure breakers are the large and polarizable iodide, thiocyanate, and nitroprusside anions (13). These anions were also efficient cloud point boosters (Table III, Fig. 4). The nonelectrolyte urea has also been found effective in breaking the structure of water and in raising the cloud point of nonionic surfactants (5).

The mucolytic action of potassium iodide and sodium thiocyanate (15, 16) is probably due to the same mechanism as their salting-in of octoxynol 9. By breaking the structure of water and making the aqueous environment a better solvent, the gel structure and viscoelasticity of mucus are reduced.

Ions that tighten the structure of water and increase its viscosity are designated as structure promoters. They include the fluoride and hydroxide ions (13). These anions salt octoxynol 9 out by enhancing the self-association of water molecules, thereby reducing the association of water molecules with the ether linkages of the surfactant (Table V, Figs. 6 and 7). The tetramethylammonium cation, which enhances the hydrogen bonding among water

Table VI—Effect of Various Citrates on the Cloud Point of Octoxynol 9

Rank No.	Additive	Concentration to Produce Δ = -10°C, m	Δ at Molality, °C		
			0.10	0.50	1.0
31	Dibasic magnesium citrate	0.37	-3		
28	Monobasic sodium citrate	0.53	-2	-9.5	-17.5
34	Dibasic sodium citrate	0.17	-6	-29.5	-61
38	Trisodium citrate	0.10	-10	-45.5	

Table VII—Effect of Octoxynol 9 on the pH of Solutions of Weak Acids

Acid	Concentration, m	In Water	In 2.00% Octoxynol 9	Percent Ionized in Water
Citric	1.00	1.50	1.53	2
	0.216	1.95	1.95	6
	0.0515	2.28	2.30	12
Acetic	2.50	2.19	2.19	0.3
	0.554	2.55	2.58	0.6
	0.132	2.90	2.91	1.4

[a] At 26°C; pH of 2.00% (0.032 m) octoxynol 9 solution was 5.32.

molecules and the structure of water by hydrophobic bonding (17) also salts the surfactant out (18).

Complex Formation—The ether oxygen atoms of model ethers like dioxane, ethyl ether, and eucalyptol act as ligands for most cations, forming adducts similar to hydrates. Nonionic polyoxyethylated surfactants, with their multiplicity of ether groups, act as polydentate ligands and may, therefore, even displace water of hydration from these cations (4). Solid, water-soluble complexes with calcium chloride were isolated (19).

When octoxynol 9 solutions and silver nitrate solutions were combined to produce mixtures containing 2.00% octoxynol 9, a white precipitate formed when the silver nitrate concentration exceeded 1.50 m. Higher silver nitrate concentrations produced larger amounts of precipitate. This precipitate, which is probably a complex between the two compounds, dissolved when the mixture was heated for the cloud point determination. Mixtures containing 2.5 and 3.0 m AgNO$_3$ turned clear at ~38°C and 43°C, respectively. The precipitate reappeared on cooling.

Complex formation between octoxynol 9 and metal ions salts the octoxynol 9 in, raising its cloud point. The only cations unable to form complexes with model ethers and to raise the cloud point of nonionic surfactants were sodium, potassium, cesium, ammonium (Tables IV and V, Figs. 5 and 7) (4), and presumably rubidium. Among other monovalent cations, lithium, silver, and especially the hydrogen ion, which forms oxonium ions with ether linkages, as well as all di- and trivalent cations raised the cloud point of nonionic surfactants (Tables II and III, Fig. 3) (4, 5). Zinc and magnesium ions are in this category. Their nitrates raised the cloud point of octoxynol 9, while magnesium sulfate and citrate lowered it (Tables V and VI, Figs. 7 and 8). The nitrate anion has an intermediate lyotropic number (20); it has a slight tendency towards salting in. Unlike the chloride ion, it does not tend to act as a ligand for metal ions in competition with ether linkages. The cloud point-depressing effect of the citrate and sulfate anions, which have low lyotropic numbers, overcame the cloud point-raising effect of the magnesium cation.
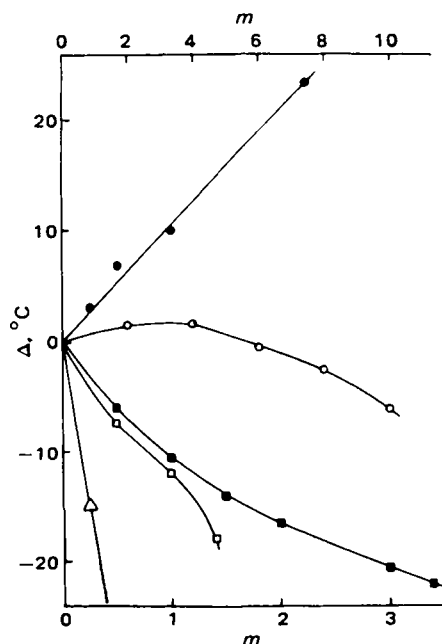

Figure 6—*Cloud point decreases by salting-out additives as a function of their molal concentrations. Key: (●) NaBr; (○) sorbitol; (□) NaCl; (■) MgCl$_2$; (△) NaF.*

On the other hand, in sulfuric acid, the cloud point-boosting effect of the two hydrogen ions overcame the cloud point-depressing effect of the sulfate ion. The cloud point-depressing action of the chloride anion when combined with the cloud point-raising lithium (1, 2), calcium (1–3), magnesium (2), or aluminum cation (1) is ascribed to its tendency to act as a ligand, displacing the ether group. This mechanism may also apply to the fluoride ion, which forms more stable complexes with some of these cations than the chloride ion.

Mixed Micelles and Micellar Solubilization—The two ionic and the nonionic surfactants listed in Table I were the most effective cloud point boosters (Fig. 1). Ionic surfactants exhibit no cloud points; their solubilities increase with temperature. The nonionic surfactant, polyoxyl 20 oleyl ether,

Figure 5—*Cloud point changes by weak bases and their salts as a function of their molal concentrations. Upper abscissa scale refers to molality of ammonia (○), lower abscissa scale refers to molality of trolamine (●), trolamine hydrochloride (□), ammonium chloride (■), and ammonium sulfate (△).*
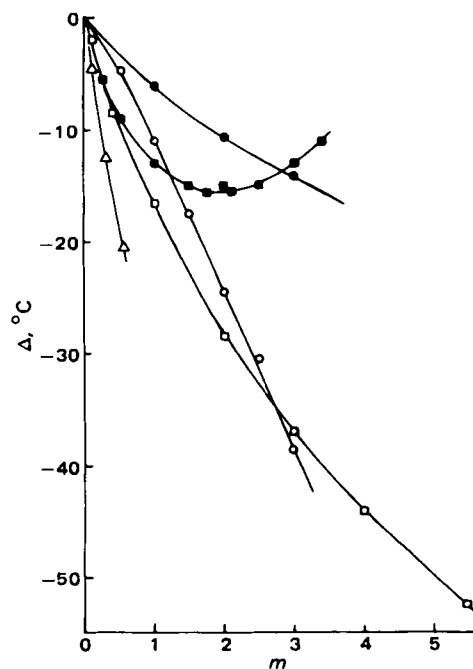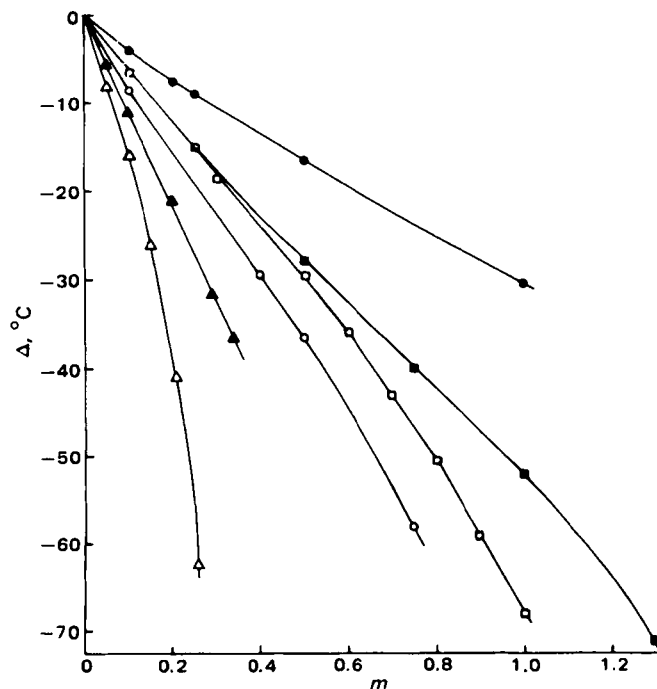

Figure 7—*Cloud point decreases by salting-out electrolytes as a function of their molal concentrations. Key: (●) NaOH; (■) (NH$_4$)$_2$SO$_4$; (□) MgSO$_4$; (○) Na$_2$SO$_4$; (▲) Na$_3$PO$_4$; (△) Al$_2$(SO$_4$)$_3$.*

Table VIII—Additivity of Cloud Point Effects Caused by Electrolytes and Solubilized Hydrocarbons

Hydrocarbon	Electrolyte	Conc., m	$\Delta_{obs}{}^{a}$, °C	$\Delta_{calc}{}^{b}$, °C
Hexadecane	None	—	14.5	—
	HCl	2.00	29.5	29.5
	Mg(NO₃)₂	2.00	25	27
	NaSCN	1.50	~33	41.5
	Na₂SO₄	0.40	−18	−15
	NaCl	2.00	−18	−14
Xylene	None	—	−42.5	—
	HCl	2.00	−17.5	−26
	Mg(NO₃)₂	2.00	−20	−30
	NaSCN	1.50	−9.5	−15.5
	Na₂SO₄	0.40	−60.5	−72
	NaCl	2.00	−58.5	−71

[a] In systems containing 2.00% octoxynol 9 + 0.50% hydrocarbon + electrolyte. *[b]* Calculated as the sum of the Δ values of the systems containing 2.00% octoxynol 9 + 0.50% hydrocarbon and 2.00% octoxynol 9 + electrolyte, respectively.

has an HLB of 15.3 and a cloud point above 100°C. The great salting-in effectiveness of surfactants has been ascribed to mixed micelles (1). The formation of mixed micelles between anionic and nonionic surfactants has been substantiated by various techniques (21, 22).

An alternate mechanism for the increase in cloud point of octoxynol 9 by other surfactants is the following. At temperatures well above its cloud point, the nonionic surfactant precipitates from its aqueous solution due to insufficient hydration. The precipitated octoxynol 9 is then solubilized by micelles of the more soluble surfactants. The two mechanisms are related because micelles of the soluble surfactant containing solubilized octoxynol 9 molecules are, in effect, mixed micelles.

A third mechanism, compatible with the previous two, to explain the increase in cloud point of octoxynol 9 by the other surfactants is complex formation. Anionic surfactants are bound far more extensively to polyethylene oxide and to its low molecular weight analogue, polyethylene glycol, than cationic surfactants (23–25). The strong interaction of sodium lauryl sulfate with polyethylene oxide has been investigated by various techniques (26–28). Presumably, the binding or complexation of one nonionic surfactant by another is the weakest of the three classes of surfactants. Accordingly, sodium lauryl sulfate was 5–7 times more efficient in raising the cloud point of octoxynol 9 than decylammonium chloride and 13–27 times more efficient than polyoxyl 20 oleyl ether.

Hydrotropy—The pronounced increases in cloud point produced by sodium salicylate, sodium benzoate, and phenobarbital sodium (Table I, Fig. 2) are ascribed to hydrotropy (18). The first two of these compounds are recognized as typical hydrotropes (29).

Mixed Solvents—As the temperature of nonionic surfactant solutions is increased, the critical micelle concentrations decrease and the micellar molecular weights increase. The cloud point can be regarded as the temperature at which the micelles have become infinitely large, resulting in macroscopic phase separation. The addition of increasing amounts of ethanol, dioxane, methanol, or propanol to aqueous solutions of nonionic surfactants at constant temperature progressively increased the critical micelle concentration and decreased the micellar size (30–34), thereby lowering the cloud point (30, 33, 34). For instance, 5% (v/v) or 0.90 m ethanol decreased the micellar molecular weight of nonoxynol 10 by 18% and increased its cloud point by 12°C (33). These reductions in cloud point are analogous to the effect of several water-miscible solvents, whose addition to water increases the solubility of compounds poorly soluble in water but appreciably soluble in the solvent. Mixed solvents act through reductions in the dielectric constant, solubility parameter, or structure of water. The cloud point-boosting action of acetic acid, trolamine, and possibly also of citric acid (Table II, Fig. 3) is attributed to the formation of such mixed solvent systems with water. At the pH values prevailing in their solutions, these compounds exist mainly in the un-ionized form (see Table VII for the two acids).

Alternate salting-in mechanisms for the two acids are discussed below. Less soluble carboxylic acids, such as benzoic, p-hydroxybenzoic, and salicylic acids, formed complexes with polyethylene glycol (35) and were solubilized in micelles of nonionic surfactants (36). The extent to which citric and acetic acids are distributed between the polyoxyethylene shell of octoxynol 9 micelles and water will be the subject of future investigations. Table VII shows only insignificant increases in the pH of citric and acetic acid solutions on the addition of 2.00% or 0.032 m octoxynol 9. Since the bulk of the two acids exists in the un-ionized form, the hydrogen ion activity is not a sensitive indicator for their binding to micellar octoxynol 9.

Increasing ionization of citric acid converted it progressively from an effective cloud point booster to an effective cloud point depressant (Table VI, Fig. 8). The tribasic citrate ion was the third most powerful salting-out additive. Tribasic magnesium citrate was not investigated because of its low

solubility. In the dibasic magnesium citrate, the salting-out capacity of the $C_6H_6O_7{}^{2-}$ anion outweighed the salting-in capacity of the magnesium cation, making the salt a cloud point depressant.

Whereas ammonia exerted only a weak action on the cloud point of octoxynol 9, trolamine boosted it substantially. This observation is in keeping with the pronounced salting-in capacity of ethanol for polyoxyethylated surfactants and the similarity in structure between trolamine and ethanol. The hydrochlorides of both bases reduced the cloud point of octoxynol 9 substantially (Table IV, Fig. 5).

Additivity of Cloud Point Effects of Electrolytes and Hydrocarbons—Organic liquids of low water solubility either lowered or raised the cloud points of nonionic surfactants (1, 9). The additivity of these effects with the cloud point-lowering or -boosting effects of electrolytes is examined below.

The effect of solubilized hexadecane and xylene on the cloud point of octoxynol 9 is shown in Fig. 9. The onset of turbidity on heating and the disappearance of turbidity on cooling were more gradual in the presence of the two hydrocarbons, especially at higher levels. The recorded cloud points, corresponding to the temperatures at which the solutions turned substantially cloudy on heating or cleared appreciably on cooling, were as much as 3–4°C above the temperatures at which the first cloudiness appeared or at which the last cloudiness disappeared. The arrow in Fig. 9 indicates the solubility limit of hexadecane in 2.00% octoxynol 9 solution at room temperature. Systems with higher hexadecane concentration separated visible oil droplets at room temperature. On heating, these droplets largely dissolved before the systems became cloudy due to octoxynol 9 separation. The solubility limit of xylene in 2.00% octoxynol 9 was over twice as large as that of hexadecane.

The solvent systems in Table VIII contained either 0.5 g of hexadecane/100 g of octoxynol 9 solution (0.023 m) or 0.5 g of xylene/100 g of octoxynol 9 solution (0.048 m). The table compares the Δ values produced by the joint addition of hydrocarbon plus electrolyte (Δ_{obs}) with the sum of the Δ values
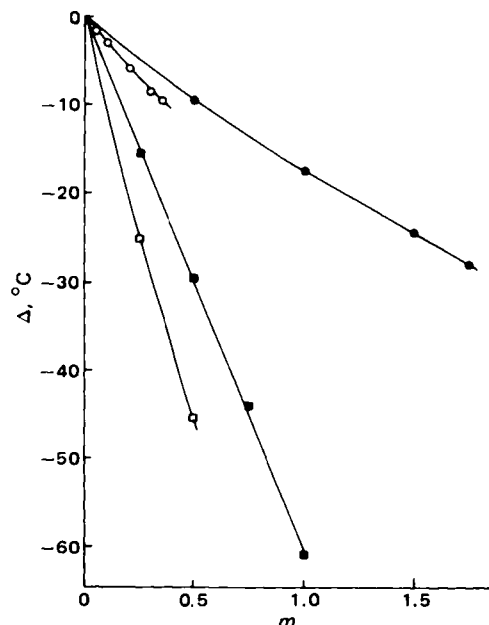

Figure 8—*Cloud point decreases by various citrates as a function of their molal concentrations. Key: (●) NaH₂; (○) MgH; (■) Na₂H; (□) Na₃.*
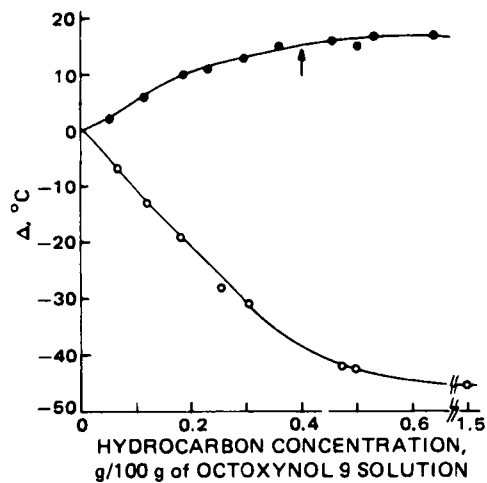
Figure 9—*Cloud point changes by two solubilized hydrocarbons as a function of their concentrations. Arrow indicates solubilization limit of hexadecane at 25°C. Key: (●) hexadecane; (○) xylene.*

produced when the hydrocarbon and the electrolyte were added to separate octoxynol 9 solutions (Δ_{calc}). All systems contained 2.00% (w/w) octoxynol 9 based on the weight of water.

Table VIII indicates that the cloud point-raising effect of hexadecane was approximately additive with the cloud point-raising or -lowering effects of salting-in and salting-out electrolytes. However, the cloud point lowering by xylene was between 6°C and 12.5°C smaller in the presence of salting-in as well as salting-out electrolytes than in their absence.

Additivity of Cloud Point Effects of Electrolyte Mixtures and Ionic Cloud Point Shifts—The effects of mixtures of electrolytes on the cloud point of octoxynol 9 were approximately additive. For instance, $\Delta MgSO_4$ at 0.25 m was −15°C, ΔNa_2SO_4 at 0.25 m was −19°C. A solution containing both 0.25 m $MgSO_4$ and 0.25 m Na_2SO_4 had Δ = −33°C compared with the additive value of −34°C. Similarly, a mixture containing 0.5 m NaCl and 0.5 m NH_4Cl has a Δ value of −16°C, identical to the sum of the Δ values of the two salts at 0.5 m concentrations. The Δ value of a mixture of 1.0 m NaCl and 1.0 m NaBr was −21°C compared with an additive Δ value of −22.5°C.

The only discrepancies arose when one component was hydrochloric or sulfuric acid, presumably because they had slightly negative Δ values at low concentrations which became large and positive at higher concentrations. A solution containing 1.0 m NaCl and 1.0 m HCl had a Δ value of −8°C compared with an additive value of −11°C. A solution containing 0.25 m $MgSO_4$ and 0.25 m H_2SO_4 had a Δ value of −11°C compared with an additive Δ of −16°C.

Since the effects of individual ions on the cloud point are approximately additive, it is possible to assign a "cloud point shift" or Δ value to each ion.
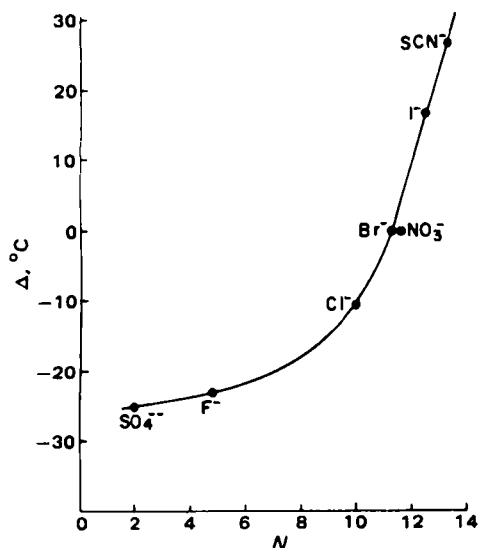

Figure 10—*Ionic cloud point shift values, Δ, of various anions at W = 2 as a function of their lyotropic numbers, N.*

Table IX—Effect of Various Ions on the Cloud Point of Octoxynol 9 at W = 2

	Cloud Point Shift Δ, °C		
Ion	From Sodium Salt	From Ammonium Salt	From Magnesium Salt
PO_4^{3-}	−18		
Cl^-	−10.5	−9.5	−7[a]
SO_4^{2-}	−25	−26	−34
OH^-	−24.5		
F^-	−23		
Br^-	0		
I^-	17	17.5	
SCN^-	27	26	
	From Nitrate	From Chloride	From Bromide
Na^+	−6		
NH_4^+	−1	1	−2
Al^{3+}	4		
Mg^{2+}	4.5		
Zn^{2+}	4.5		
Ag^+	11		
	From H_2SO_4	From HCl	From HNO_3
H^+	13	15	15

[a] Probably low due to complexation, see text.

To do this, the Δ values of different electrolytes must be compared at identical values of some concentration parameter. Various parameters, including ionic strength, were investigated by trial and error. The following two criteria must be satisfied when comparisons of Δ values are made at equal values of a concentration parameter that is suitable:

1. The cloud point shift values calculated for various individual ions must add up to the changes in cloud point observed for the electrolytes containing these ions.
2. Different electrolytes containing a common ion must furnish the same cloud point shift value for that ion. A self-consistent set of ionic cloud point shift values can then be calculated.

The simplest concentration parameter that satisfied these conditions, designated molal strength (W), is defined by:

$$W = \Sigma mz \qquad \text{(Eq. 2)}$$

where m is the molality and z is the valence of the ions that constitute the electrolyte. According to this equation, a molal strength value of W = 2 corresponds to the following molalities: for sodium chloride (a 1:1 electrolyte), 1.0; for sodium sulfate (a 1:2 electrolyte) and magnesium nitrate (a 2:1 electrolyte), 0.50; for magnesium sulfate (a 2:2 electrolyte), 0.50; and for tribasic sodium phosphate (a 1:3 electrolyte) and aluminum nitrate (a 3:1 electrolyte), 0.33. It is necessary to assign an arbitrary Δ value to one given ion to serve as reference. Accordingly, the cloud point shift value for the nitrate anion, ΔNO_3^-, was set equal to zero.

The following calculations illustrate how the data in Table IX were obtained. At W = 2, sodium nitrate (no. 23, Table V) has a molality of 1.0. A solution containing 1.0 m $NaNO_3$ and 2.00% octoxynol 9 had a cloud point of 59°C, while a 2.00% solution of octoxynol 9 from the same batch had a cloud point of 65°C. Hence, $\Delta NaNO_3 = 59 − 65 = −6°C$. Since $\Delta NaNO_3 = \Delta Na^+ + \Delta NO_3^-$ and ΔNO_3^- was arbitrarily set equal to zero, $\Delta Na^+ = −6°C$. The molality for sodium sulfate at W = 2 is 0.50 according to Eq. 2. The Δ value of 0.50 m Na_2SO_4 was −37°C (no. 37, Table V). Therefore, $\Delta SO_4^{2-} = \Delta Na_2SO_4 − 2\Delta Na^+ = −37 − (2)(−6) = −25°C$. Since the Δ value of 0.50 m H_2SO_4 was 1°C, $\Delta H^+ = \frac{1}{2}(\Delta H_2SO_4 − \Delta SO_4^{2-}) = \frac{1}{2}[1 − (−25)] = 13°C$.

Data at W = 1 and 4 were also calculated. To conserve space, they were not included in Table IX, but they showed trends comparable with the data at W = 2. As expected from the shape of the Δ versus m plots and Eq. 2, as the W values increase, the absolute values of the ionic cloud point shifts increase commensurately.

The ΔCl^- values obtained from magnesium chloride were consistently lower than those obtained from sodium chloride or ammonium chloride. This discrepancy is ascribed to the fact that the chloride ion acts as a ligand for magnesium, in competition with the ether groups of octoxynol 9, whereas the nitrate and sulfate ions do not.

The ionic cloud point shift values of the anions are related by a smooth function to their lyotropic numbers in the Hofmeister series (20), shown in Fig. 10. As the lyotropic numbers of the anions decrease, the negative values of the standard free energies of formation of the aqueous anions at 25°C increase (37). A plot of the ionic cloud point shift values versus the standard free energies of formation of the anions in water has a shape similar to Fig. 10 and can almost be superimposed on it.

For cations, the points of ionic cloud point shift values *versus* either lyotropic numbers or standard free energies of formation in water are scattered and do not fall on a single curve. This lack of correlation is ascribed to the fact that all cations except sodium, potassium, ammonium, rubidium, and cesium form complexes with the ether groups of octoxynol 9. The cloud points of polyoxyethylated surfactants are thus affected by cations in two ways. First, all cations tend to become hydrated, binding water and altering its structure. Second, there is a specific interaction by complexation between the ether groups of the surfactants and most cations, which predominates over their dehydrating effect to various degrees, resulting in net salting in or positive Δ values (4, 5). The ionic cloud point shift values for the complexing cations are probably related to the stability constants of the complexes they form with the ether linkages of the polyoxyethylated surfactants and the standard free energy changes of complexation.

Anions do not form complexes with the ether groups. Therefore, their effect on the cloud points of nonionic surfactants depends entirely on their interaction with water, which is also the dominant factor in ranking the anions in the Hofmeister series.

The ionic cloud point shift values of Table IX refer to octoxynol 9. They are higher than the corresponding absolute Δ values for polyoxyethylated surfactants having practically the same average number of ethylene oxide units per molecule and the same HLB but lacking an aromatic ring. Calculating the ionic cloud point shift values with the aid of Eq. 2 from the data of Ref. 5, it was found that polyoxyl 10 cetyl ether and polyoxyl 10 stearyl ether had the lowest absolute Δ values. Those of polyoxyl 10 oleyl ether were somewhat higher, but still well below the corresponding values for octoxynol 9. As the polarity of the hydrocarbon moiety of the surfactants decreased, the ionic cloud point shift values at a given W also decreased. Since the HLB values of the four surfactants were the same within one unit, this observation points up the major shortcoming of the HLB system, namely, that it does not take into account the nature of the hydrophobic moiety of the surfactants (8, 38).

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Dissolution Profile Determination of a Multicomponent Product Using a Rapid Liquid Chromatographic Analysis

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Abstract □ A system was developed which is capable of monitoring the dissolution profiles of each of the active components in a two-component combination product. The UV spectra of the two drugs (metoprolol and hydrochlorothiazide) overlap considerably, making conventional UV analysis of either component unrealistic. By resolving the two drugs on a high-performance liquid chromatographic (HPLC) system both can be quantitated after separation. The analysis is sufficiently short to allow for the use of a six-station dissolution tester in tandem with an HPLC for determination of dissolution profiles. The HPLC system and equipment, can monitor six samples of this product at 5-min intervals in real analysis time.

Keyphrases □ Dissolution—multicomponent product, rapid HPLC, metoprolol, hydrochlorothiazide □ Metoprolol—dissolution profile, multicomponent product with hydrochlorothiazide, rapid HPLC □ Hydrochlorothiazide—dissolution profile, multicomponent product with metoprolol rapid HPLC.

The determination of the release rate of an active drug from pharmaceutical dosage forms has become a standard technique in pharmaceutical development, research, and quality control testing laboratories. This information is valuable to formulators in selecting an optimum solid dosage formulation. *In vivo-in vitro* correlations can often be established which are