Binding of Organic Electrolytes by a Nonionic Surface-Active Agent

By ARTHUR R. HURWITZ†, PATRICK P. DELUCA‡, and H. B. KOSTENBAUDER

Although possible consequences of combining ionic pharmaceuticals with surface-active agents of opposite charge are generally recognized, there has been little or no consideration of possible interactions between drug ions and nonionic surface-active agents. In the present study, cations such as chlorpromazine, promethazine, tetracaine, methylrosaniline, and dodecylpyridinium, and anions such as naphthalenesulfonate and methyl orange were bound to the nonionic surface-active agent polysorbate 80. The degree of interaction in some cases is sufficient to suggest that polysorbate 80 might have considerable influence on the stability and availability of ionic drugs in pharmaceutical formulations.

THE USE OF nonionic surface-active agents in the formulation of various pharmaceutical dosage forms is often a routine procedure. Their presence in pharmaceuticals sometimes results in incompatibilities—notably, the inactivation of some antimicrobial agents which are commonly used in pharmaceuticals for their preservative activity (1–16). In the majority of examples of incompatibility which have previously been described, the agent which is bound to the surfactant is primarily in molecular or nonionized form; interaction with the surfactant has generally been explained on the basis of either the formation of specific molecular complexes or the preferential solubility in the surfactant micelle. Persons engaged in pharmaceutical formulation are generally cognizant of possible incompatibilities of this nature.

Although textbooks devote considerable discussion to incompatibilities which might arise from the combination of an ionic surfactant with a drug or germicide of opposite charge, there is usually no suggestion of possible incompatibility or inactivation which might arise from the combination of an ionic drug or germicide with a nonionic surfactant. Recent observations in these laboratories indicated that organic ions, such as quaternary ammonium germicides, can be strongly bound by nonionic surfactants (16). These observations suggest that such generally unrecognized incompatibilities might exist in many pharmaceutical systems and might markedly influence the release of a drug from a dosage form or might alter the stability of a drug. The present study was designed to investigate the possible association of various cations and anions with a typical nonionic surface-active agent, polysorbate 80.[1] The existence of a significant degree of interaction between ionic drugs and nonionic surfactants might require a re-evaluation of the routine use of nonionic surface-active agents in pharmaceutical formulation.

EXPERIMENTAL

Reagents.—Ephedrine hydrochloride N.F.; sulfathiazole sodium N.F.; methylrosaniline chloride U.S.P.; promethazine hydrochloride U.S.P.[2]; methapyriline hydrochloride N.F.[3]; diphenhydramine hydrochloride U.S.P.[4]; chlorpromazine hydrochloride U.S.P.[5]; tetracaine hydrochloride U.S.P.[6]; cetylpyridinium chloride U.S.P.[7]; polysorbate 80, a commercial sample; sodium salt of 2-naphthalene sulfonic acid, recrystallized from water; dodecylpyridinium bromide, laboratory prepared; were used. All other chemicals were reagent grade.

Method for Detecting Interaction.—Equilibrium dialysis was employed to detect possible drug–nonionic surface-active agent interaction. The technique was similar to that described previously by Patel and Kostenbauder (17) in their study of the interaction of methyl and propyl *p*-hydroxybenzoate with polysorbate 80. This method involves equilibration of two solutions across a semipermeable membrane, one solution containing the surface-active agent and the other solution containing only the drug. Nylon membranes were used in this study, these membranes being selected to permit the drug to come to equilibrium in both solutions but to prevent passage of the nonionic surface-active agent.

The nylon membranes were cut to give bags which held 20 ml. of solution. The bags, when filled with the solution of the ionic agent being studied, were tied and placed in wide mouth,

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† Fellow of the American Foundation for Pharmaceutical Education, 1959–1960. Present address: School of Pharmacy, The University of Wisconsin, Madison.
‡ Walter G. Karr Fellow, Smith Kline and French Laboratories, Philadelphia, Pa. Present address: Ciba Pharmaceutical Co., Summit, N. J.

[1] Polyoxyethylene 20 sorbitan monooleate is marketed as Tween 80 by Atlas Powder Co., Wilmington, Del.
[2] Marketed as Phenergan Hydrochloride by Wyeth Laboratories, Philadelphia, Pa.
[3] Marketed as Histadyl Hydrochloride by Eli Lilly and Co., Indianapolis, Ind.
[4] Marketed as Benadryl Hydrochloride by Parke, Davis and Co., Detroit, Mich.
[5] Marketed as Thorazine Hydrochloride by Smith Kline and French Laboratories, Philadelphia, Pa.
[6] Marketed as Pontocaine Hydrochloride by Winthrop Laboratories, New York, N. Y.
[7] Marketed as Ceepryn by The William S. Merrell Co., Cincinnati, Ohio.

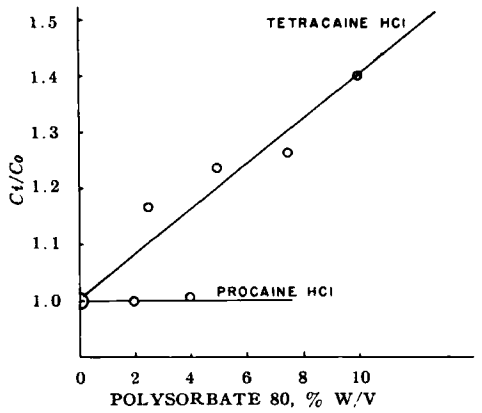

Fig. 1.—Binding of tetracaine hydrochloride by polysorbate 80 at 30°.

screw-cap, glass bottles containing 60 ml. of a polysorbate 80 solution with a concentration of ionic agent equal to that in the internal phase. By starting with equal concentrations of drug in both phases, the equilibration or agitation time could be greatly reduced. Also, shorter agitation time decreased the possibility of membrane breakage. The bottles were then tightly closed, using a piece of polyethylene film between the cap and the bottle top to prevent leakage. The bottles were agitated in a constant temperature water bath at 30° for 2 to 6 days. Aliquot portions were then taken from both the internal and external phases and assayed spectrophotometrically for the ionic agent, using a Beckman DU spectrophotometer and an appropriate blank solution in each case. A few agents were studied in the presence of potassium chloride to determine the effect of salt on the interaction, and sodium bisulfite was added to solutions of promethazine and chlorpromazine to retard oxidation. The spectrophotometric assays of methyl orange and methylrosaniline chloride were performed on the Beckman model B spectrophotometer. The addition of polysorbate 80 (2% w/v) caused a shift in the absorption maximum of methyl orange from 465 mμ to 425 mμ, and the maximum for methylrosaniline chloride was shifted from 595 mμ to 600 mμ. The polysorbate-containing solutions of these agents were always assayed by adjusting the final polysorbate concentration to 2%, then determining the absorbance at the shifted maximum.

The extent of binding is represented as C_i/C_o, where C_i represents the total concentration of organic electrolyte on the polymer-containing side of the membrane, and C_o is the concentration on the nonpolymer-containing side. For calculation of the apparent degree of binding, the ratio total/free is taken as equal to the ratio C_i/C_o. Actually, as a result of a Donnan effect, the free concentration on the polymer-containing side of the membrane is less than C_o and the actual ratio total/free $> C_i/C_o$. The complexity of the systems prevents calculation of the Donnan correction for most of the examples of binding considered in this report but, if applied, such a correction would indicate even greater binding than the apparent ratios reported here.

RESULTS

Tetracaine Hydrochloride and Procaine Hydrochloride.—The relative affinity of tetracaine hydrochloride and procaine hydrochloride for polysorbate 80 is shown in Fig. 1. At a concentration of 5% polysorbate 80, approximately 20% of the total tetracaine is bound to the surfactant; at a concentration of 10% polysorbate 80, approximately 30% of the tetracaine is bound. The procaine ion does not appear to interact significantly with the polysorbate under the conditions of this study.

Chlorpromazine Hydrochloride.—Figure 2 illustrates interaction of chlorpromazine hydrochloride with polysorbate 80 in aqueous solution. The addition of electrolyte appears to enhance the interaction considerably. In an aqueous solution of 2% polysorbate 80, approximately 50% of the total chlorpromazine present is bound to the surfactant; when 0.1% $NaHSO_3$ is present in this system (to retard oxidation), approximately 75% of the chlorpromazine is bound; when the system consists of 2% polysorbate 80, 0.1% $NaHSO_3$, and 0.5 *M* KCl, approximately 90% of the chlorpromazine is bound to the surfactant.

Promethazine Hydrochloride.—The interaction of promethazine hydrochloride with polysorbate 80 is illustrated in Fig. 3. At a concentration of 2% polysorbate 80 and in the presence of 0.1% $NaHSO_3$ (to retard oxidation of the promethazine), approximately 38% of the total promethazine is bound to the surfactant; when KCl is added to this system to establish a total ionic strength of approximately 0.6, approximately 70% of the promethazine is bound to the polysorbate 80.

Dodecylpyridinium Chloride and Cetylpyridinium Chloride.—DeLuca and Kostenbauder previously presented data to illustrate the high degree of

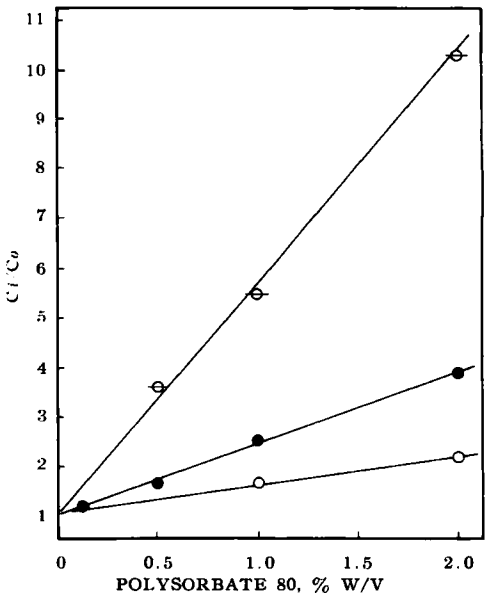

Fig. 2.—Influence of electrolyte on binding of chloropromazine hydrochloride by polysorbate 80 at 30°. Sodium bisulfite added as antoxidant. Key: O, in polysorbate 80; ●, in polysorbate 80 plus 0.1% $NaHSO_3$; ⊖, in polysorbate 80 plus 0.1% $NaHSO_3$ and 0.5*M* KCl.

interaction between cetylpyridinium chloride and polysorbate 80 (16). These data are reproduced in Fig. 4 to permit comparison with the interaction between dodecylpyridinium ion and polysorbate 80. At a concentration of 2% polysorbate 80 approximately 40% of the dodecylpyridinium ion is bound to the polysorbate; while at this concentration of polysorbate 80, approximately 97% of the cetylpyridinium ion is bound.

Methylrosaniline Chloride.—Figure 5 illustrates the interaction of the cationic dye methylrosaniline chloride with polysorbate 80. These adsorption isotherms indicate that the nature of the binding may change markedly with concentration of free methylrosaniline ion, and it is not possible to apply the relatively simple description of the binding used previously; *i.e.*, it is not sufficient to describe the binding in terms of a definite percentage of the methylrosaniline chloride bound to the polysorbate at any specific polysorbate concentration. For example, at a concentration of 0.25% polysorbate 80, the percentage of dye bound to the surfactant varied from approximately 70% at the lower dye concentrations to 40% at the higher dye concentrations. At a concentration of 5% polysorbate 80, approximately 90% of the dye was bound throughout the concentration range studied.

Sodium Naphthalene Sulfonate.—Sodium naphthalene sulfonate was included in this study to demonstrate that anionic as well as cationic agents might be bound to nonionic surface-active agents. The interaction of the naphthalene sulfonate anion with polysorbate 80 is illustrated in Fig. 6. In the presence of a 2% aqueous solution of polysorbate 80, approximately 7% of the total naphthalene sulfonate ion is bound to the polysorbate; however, when 0.1 *M* KCl was added to this system, approximately 17% of the naphthalene sulfonate was bound to the polysorbate. The naphthalene sulfonate ion was selected for study because of the absence of functional groups, other than sulfonate, which might permit hydrogen bonding to the polyether portion of the polysorbate, and because this ion is essentially in the completely dissociated form in aqueous solution, thereby eliminating the possibility of an interaction being attributed to binding of undissociated molecules to the polysorbate.

Methyl Orange.—The interaction of the anionic dye methyl orange with polysorbate 80 is shown in Fig. 7. As with methylrosaniline chloride, the fraction of dye bound to the surfactant at any polysorbate concentration changes markedly with the concentration of unbound dye; in the presence of 5% polysorbate 80, the percentage of bound dye ranged from 96% at low dye concentrations to 83% at higher dye concentrations.

Drug Ions Not Bound to Polysorbate 80.—No significant interaction was observed for the following drug ions in the presence of aqueous solutions of polysorbate 80: ephedrine hydrochloride, sulfathiazole sodium, methapyrilene hydrochloride, and diphenhydramine hydrochloride.

DISCUSSION

Nature of Interaction with Polysorbate 80.—The interaction of drug ions with polysorbate 80 appears to be similar to the interaction of cetylpyridinium ion with polysorbate 80 as described by DeLuca and Kostenbauder (16). It appears that ions having a large hydrophobic group can undergo association with the polysorbate micelle to form a type of mixed-micelle. Binding of ions such as dodecylpyridinium and naphthalene sulfonate, which exist entirely in dissociated form in aqueous solution and have no other functional groups which might be expected to hydrogen bond to the ethylene oxide portion of the polysorbate, indicates that the necessary structural feature for an organic ion to interact with a nonionic surface-active agent is that of a relatively large hydrophobic portion.

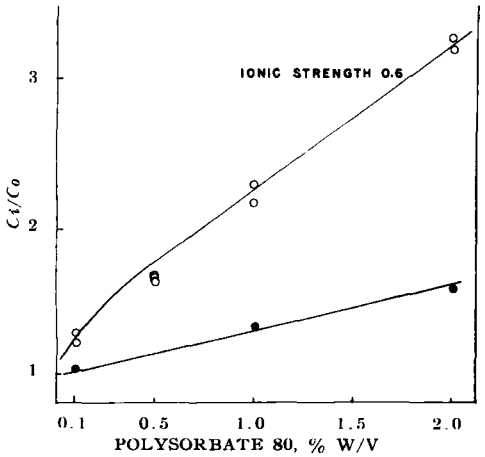

Fig. 3.—Binding of promethazine hydrochloride by polysorbate 80 at 30°. Solid symbols correspond to systems containing 0.1% $NaHSO_3$ as antoxidant; open symbols represent systems containing 0.1% $NaHSO_3$ plus sufficient KCl to produce an ionic strength of 0.6.

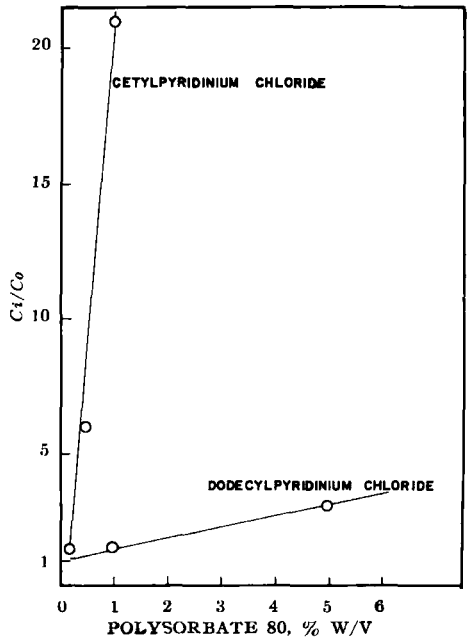

Fig. 4.—Relative binding by polysorbate 80 of dodecylpyridinium chloride and cetylpyridinium chloride at 30°. Binding data for cetylpyridinium chloride reproduced from DeLuca and Kostenbauder (16).

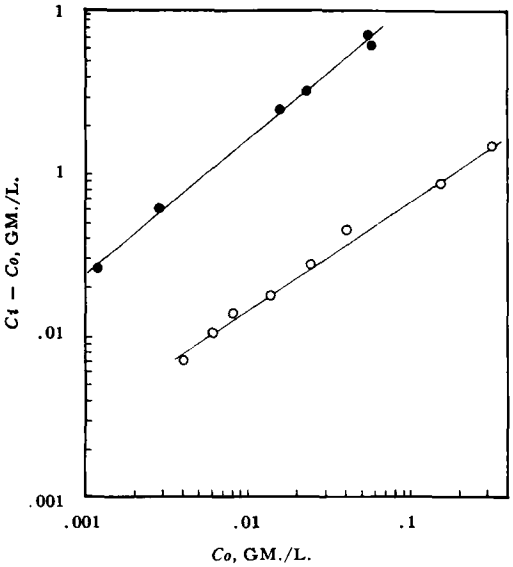

Fig. 5.—Binding of methylrosaniline chloride by polysorbate 80 at 30°. Open symbols represent solutions containing 0.25% polysorbate 80; solid symbols represent 5% polysorbate 80.

Ions such as ephedrine, sulfathiazole, methapyrilene, diphenhydramine, and procaine apparently are not sufficiently hydrophobic to associate with polysorbate 80 micelles. The presence of the *n*-butyl substituent on the *p*-amino group of tetracaine apparently confers sufficient hydrophobic character for this ion to associate with the polysorbate. The importance of the hydrophobic character of the ion is further illustrated in the comparative binding of cetylpyridinium ion and dodecylpyridinium ion.

Salt Effects.—For a weakly bound electrolyte such as sodium naphthalene sulfonate, enhanced binding to polysorbate 80 in the presence of added electrolyte might be accounted for on the basis of swamping of a Donnan effect. Adsorption of hydrophobic ions would, in effect, cause the polysorbate 80 to act as an ionic polymer and necessitate a Donnan correction for the binding studies. If the adsorbed hydrophobic ion binds few counter ions, and if it is assumed that the hydrophobic ion under study does not form micelles at the concentrations considered, then a Donnan correction can be applied in the following manner

Let

C_o = concentration of hydrophobic ion in the outside or nonpolymer containing compartment.

C_i = concentration of total hydrophobic ion in the inside compartment and consists of bound plus free.

$C_{i,\,free}$ = concentration of free hydrophobic ion in inside compartment.

Donnan equilibrium:

$$(C_o)^2 = C_i \times C_{i,\,free}$$

$C_{i,\,free}$ is therefore less than C_o and actual ratios of total/free drug are greater than the observed ratio C_i/C_o.

This Donnan correction was applied to the naphthalene sulfonate–polysorbate 80 data. As

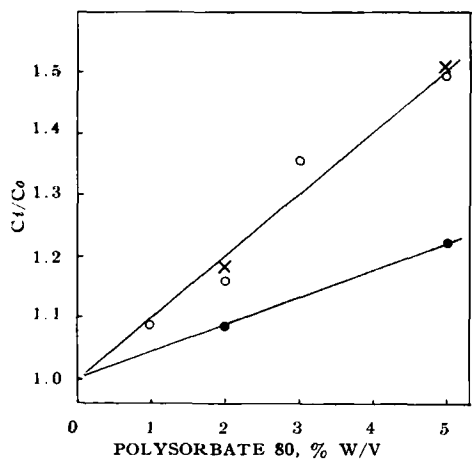

Fig. 6.—Binding of sodium naphthalene sulfonate by polysorbate 80 at 30°. Key: O, with 0.1 *M* KCl; ●, without KCl; ×, points obtained by applying a Donnan correction to the binding data obtained in absence of KCl.

shown in Fig. 7, the binding data in absence of salt, when corrected for the Donnan effect, are in excellent agreement with the degree of binding observed in the presence of 0.1 *M* swamping electrolyte. The effect of electrolyte on the apparent degree of binding of naphthalene sulfonate to polysorbate 80 can therefore be attributed almost entirely to elimination of the Donnan effect.

Other systems studied are not amenable to correction for this Donnan effect. Where there is a high degree of interaction with the polysorbate 80, it is almost a certainty that there is considerable counter-ion retention, just as there would be in micelles of ionic surfactants. While it is not feasible to apply a Donnan correction, it can be predicted that any correction for a Donnan effect could only lead to an even greater degree of interaction than that indicated by the ratio C_i/C_o; therefore, total/free $\geqq C_i/C_o$ in all cases.

Where there is considerable counter-ion retention by bound hydrophobic ions, added electrolyte may have a further effect as indicated by application of the law of mass action to micelle formation. Where A^+ represents the hydrophobic ion and B^- the counter-ion, the interaction with polysorbate may be represented as

$$aA^+ + bB^- + Tw \rightleftarrows (A_a^+ B_b^- \, Tw) \qquad a > b$$

$$K = \frac{(A_a^+ B_b^- \, Tw)}{(A^+)^a \, (B^-)^b \, Tw}$$

The concentration of bound hydrophobic ion, (A^+), is

$$\frac{K \, (A^+)^a \, (B^-)^b \, (Tw)}{a}$$

and an increase in the concentration of the counter-ion (B^-), on addition of an electrolyte such as KCl, would be expected to increase markedly the binding of the hydrophobic ion, A^+.

For a strongly bound electrolyte such as chlorpromazine hydrochloride, the effect of added electrolyte on the observed ratio C_i/C_o might therefore be attributed in part to swamping of the Donnan

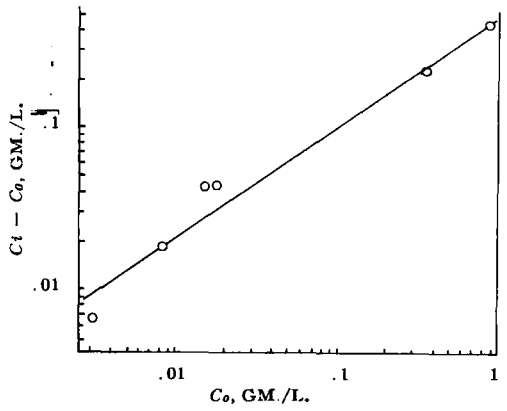

Fig. 7.—Binding of methyl orange by 5% polysorbate 80 at 30°.

effect and in part to the effect of increasing concentration of counter-ion on the equilibrium as predicted by the law of mass action.

Pharmaceutical Significance of These Interactions.—Perhaps the most obvious consequence of interactions such as those described in this paper is the influence of the binding on the release of a drug from a formulation containing a nonionic surfactant or the availability or activity of a germicidal agent in such a formulation. Interactions in which a large percentage of the drug is bound to a component in the formulation would be expected to modify greatly the release of the drug and subsequent absorption or access to the site of action. This might be particularly true in topical formulations where nonionic surface-active agents may be employed in concentrations of 5% or more in the aqueous phase. Of course absorption of drugs or release of drugs from formulations is an extremely complex process, and binding of drug to surfactant is only one aspect of the problem; it may well be that other factors to be considered make it highly desirable that the surfactant be employed in a large concentration in spite of possible interactions with the drug. Nevertheless, it is important to recognize that nonionic surfactants can interact with ionic drugs and that this interaction might be expected to exert considerable influence on the release of some drug ions from such systems.

The very pronounced effect of interaction between nonionic surfactants and quaternary ammonium compounds on the availability and antimicrobial activity of the quaternary ammonium compounds has been demonstrated previously (16). Such interactions between nonionic agents and quaternary ammonium compounds, or other materials having antimicrobial activity, are not always undesirable; the inactivation of quaternary ammonium compounds by addition of a nonionic agent is a common procedure in carrying out sterility tests where there normally would be interference from the antimicrobial agent present in the formulation.

A second important consequence of drug-surfactant interactions is the effect of such interaction on the stability of the drug. Although no data can be cited for systems discussed in this paper, Riegelman (18) has demonstrated the very significant effects on drug stability which might arise from association of drugs with surfactant micelles. Riegelman (18), Nogami, *et al.* (19, 20), and Nakajima (21) have shown that a number of drugs with labile ester linkages can be significantly stabilized against ester hydrolysis when solubilized in aqueous solutions of micellar nonionic surface-active agents. On the other hand, Motsavage and Kostenbauder (22) have recently demonstrated that binding of alkyl sulfates to nonionic micelle-forming agents may increase the rate of the hydronium ion catalyzed hydrolysis of the sulfate ester as much as 60-fold. Whether a drug is more or less stable when associated with the nonionic surfactant micelle will depend on the positioning of the labile group in or on the micelle and on the nature of the decomposition to which it is subject.

SUMMARY

Data have been presented to show that drug ions can interact in aqueous solution with a nonionic surface-active agent to an extent which might markedly influence the stability of the drug or the release of the drug from a formulation.

Only those drug ions having a relatively large hydrophobic group were found to interact with polysorbate 80. The mechanism of the interaction appears to be similar to the mixed micelle formation which occurs on interaction of cetylpyridinium ion with polysorbate 80. Addition of electrolyte appears to enhance the interaction considerably.

The following ions were found to bind to polysorbate 80 in aqueous solution: cetylpyridinium, methylrosaniline, methyl orange, chlorpromazine, dodecylpyridinium, promethazine, tetracaine, and naphthalene sulfonate.

The following ions did not appear to interact with polysorbate 80 to a significant extent: ephedrine, sulfathiazole, diphenhydramine, methapyriline, and procaine.

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