Interaction of Sucrose and Propoxylated Sucrose Esters with Some Pharmaceuticals

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The interaction between either fatty acid mono or diesters of sucrose or fatty acid monoesters of propoxylated sucrose and benzoic acid or a series of hydroxy and amino substituted benzoic acids is reported. The sugar esters, because of their lack of long polyether chains, have been proposed for use in formulations in which association between a nonionic emulsifier and preservative is a problem. A dialysis method was used to study the interactions. The degree of interaction appears to be dependent upon the type of functional group present and its position in the complexed molecule. In the case of the surfactant the esters of the propoxylated sucrose appear to associate more than those of sucrose. The fatty acid moiety influences the extent of interaction; of the series studied, the laurate esters generally undergo interaction to the greatest extent, while the stearate esters exhibit only slight interaction. The results obtained differ to some degree from work previously reported with other nonionic surfactants. A possible mechanism of interaction based upon the binding of drug within the palisade layer of the micelles of the surfactant solution is proposed.

THE LAST DECADE has witnessed the appearance of a multitude of surface-active agents. These agents can roughly be classified into groups which describe the charge of the major portion of the molecule upon dissociation in water, *i.e.*, anionics, cationics, amphoterics, and those which do not dissociate—the nonionics.

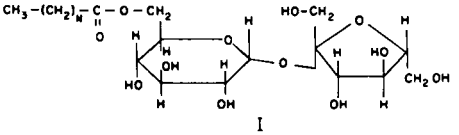
A group of nonionic surfactants were introduced in 1956, the fatty acid esters I and II of sucrose (1, 2). Members of this group have been proposed for use (3–5) in the petroleum industry, the textile industry, and for agricultural use. In England, the sugar esters have been given wide attention for possible use as laundry detergents (6, 7). Pollution of rivers and streams (from which drinking water is taken) by synthetic detergents is becoming a widespread problem. Sucrose esters do not constitute a threat to the purity of drinking water since they can be metabolized by microorganisms.

In the pharmaceutical and cosmetic fields the sucrose esters can be widely used in forming emulsion bases and as dispersing agents in suspensions. They have the advantage of being tasteless and odorless, a factor which gives them a decided advantage over competitive products. Some of the esters are solids, resulting in easier handling than with the liquid surfactants.

Attempts to synthesize fatty acid esters of sucrose date back to the work of Berthelot in 1860 (8). Other methods have been attempted (9–16), but none have received the wide acceptance accorded the method developed by Snell, Osipow, and Marra (1). Their method involves a transesterification, using as the reactants the methyl ester of a fatty acid, and potassium carbonate dissolved in N,N-dimethyl formamide. The raw materials involved are relatively inexpensive; as soon as the manufacturing method can be accomplished efficiently and cheaply it is apparent that there will be a very large market for these surfactants.

Initially it was thought (5) that these agents were completely nontoxic; however, a recent work (17) has provided evidence that while these surfactants are nontoxic orally, they are toxic upon injection. This prevents their proposed use in the formulation of intravenous emulsions.

Another group of related surfactants was introduced a few years after the sucrose esters (18, 19). These are the fatty acid esters (III)



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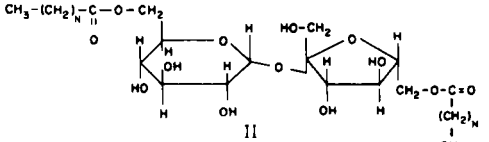

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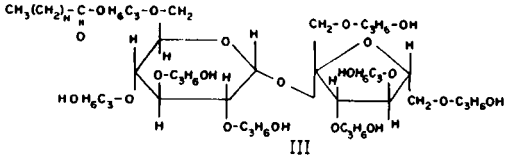

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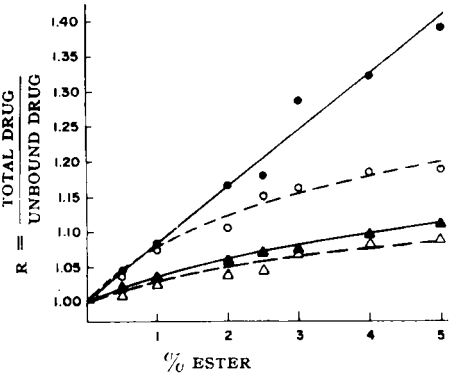

Fig. 1.—Binding of benzoic acid and three hydroxybenzoic acids by sucrose monolaurate in water at 30°. Key: ●——●, benzoic acid; O— — —O, *o*-hydroxybenzoic acid; ▲——▲, *m*-hydroxybenzoic acid; Δ— — —Δ, *p*-hydroxybenzoic acid.

of propoxylated sucrose which are chemically described as octakis (2-hydroxypropyl) sucrose. This agent has also been proposed as an emulsifying agent for cosmetics and pharmaceuticals. A recent work (20) describes a series of emulsions prepared with the aid of the propoxylated sucrose esters.

Because of their lack of long polyether chains, the sucrose esters have been recommended (4) for use in formulations to replace other nonionic surfactants such as the Tweens[1] Myrj 52,[2] and polyethylene glycols which have been shown (21–23) to interact with materials—such as preservatives incorporated in the formulation. It was the purpose of this investigation to observe whether and to what extent the esters of sucrose and/or propoxylated sucrose, which do not have as part of their molecule long polyether chains, would associate with a series of hydroxy and amino substituted benzoic acids.

EXPERIMENTAL

The interaction of benzoic acid and the substituted benzoic acids was studied using a dialysis method similar to those previously described in the literature (24–26). The method consisted of bringing two solutions into equilibrium across a semipermeable membrane. The membrane, Fisher cellulose casing,[3] permitted the low molecular weight compound in the solution outside of the dialysis sack to pass freely through the membrane; at the same time it did not permit the passage of the sucrose ester contained in the sack. Therefore, if the compound studied did not interact with the sucrose ester and was not bound by the membrane itself, the concentration of compound inside and outside of the dialysis sack was equal. If interaction did occur, the concentration of the compound on the ester side of the semipermeable membrane increased.

[1] Marketed by the Atlas Powder Co., Wilmington, Del.
[2] Polyoxyl 40 stearate. Marketed by the Atlas Powder Co., Wilmington, Del.
[3] Product of Fisher Scientific Co., Catalog No. 8-667.

The data obtained during the study were plotted to show the value *R*, the ratio of total drug in solution to the unbound drug, as a function of the concentration of the sucrose or hyprose ester. With the method used it was not possible to determine the stoichiometric ratio in which the reactants unite and thus accurately determine the formation constants. However, by use of the phase diagrams (Figs. 1–4) the degree of association between the various reactants can be readily seen.

Reagents.—Recrystallized benzoic acid, m.p. 122°, *o*-hydroxybenzoic acid, m.p. 157–159°, *m*-hydroxybenzoic acid, m.p. 200°, *p*-hydroxybenzoic acid, m.p. 212–213°, *o*-aminobenzoic acid, m.p. 145°, *m*-aminobenzoic acid, m.p. 174°, *p*-aminobenzoic acid, m.p. 186–187°, sucrose monostearate, sucrose monolaurate, sucrose dioleate, hyprose monostearate, hyprose monolaureate, hyprose monooleate, 0.001 *N* sulfuric acid were employed.

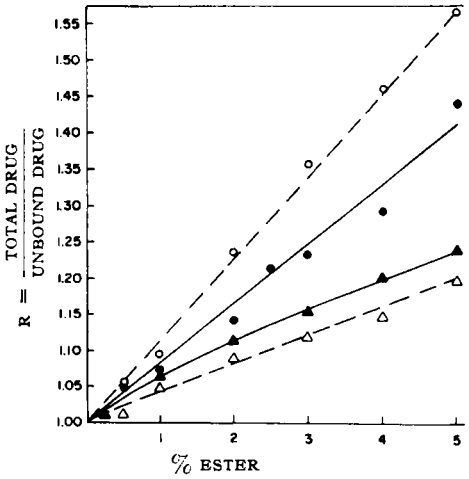

Fig. 2.—Binding of benzoic acid and three hydroxybenzoic acids by hyprose monolaurate. Key: ●——●, benzoic acid; O— — —O, *o*-hydroxybenzoic acid; ▲——▲, *m*-hydroxybenzoic acid; Δ— — —Δ, *p*-hydroxybenzoic acid.

Procedure.—Solutions of the aromatic acids in 0.001 *N* sulfuric acid were prepared. Amounts of acids used corresponded to half saturated solutions, *i.e.*, each solution contained in 50 ml. the following amount of acid: benzoic acid, 140 mg.; *o*-hydroxybenzoic acid, 460 mg.; *p*-hydroxybenzoic acid, 400 mg.; *o*-aminobenzoic acid, 180 mg.; *m*-aminobenzoic acid, 300 mg.; *p*-aminobenzoic acid, 170 mg. Fifty milliters of the solutions were pipetted into 125-ml. glass-stoppered bottles. Sacks were prepared from the Fisher cellulose casings and filled with 20 ml. of solutions containing varying concentrations of sucrose or propoxylated sucrose ester (0 to 5.0%). The sacks were tightly closed and immersed in a bottle containing a solution of the acid under study. The bottles were placed in a constant temperature water bath shaker at 30 ± 0.2° for 48 hours, after which time aliquots were pipetted from the external solution, diluted, and assayed for acid content using a Beckman model DU spectrophotometer and 1-cm. cells. For each series of determinations, a control bottle was prepared which differed from the other bottles since it contained no sucrose ester inside the sack. The internal and external solutions of each

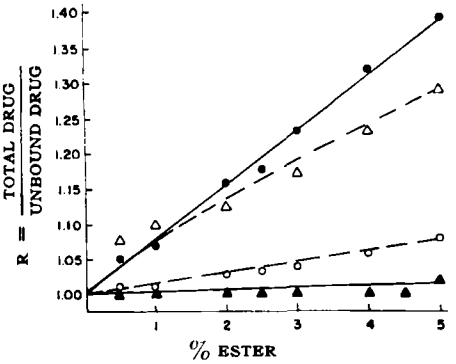

Fig. 3.—Binding of benzoic acid and three aminobenzoic acids by sucrose monolaurate in water at 30°. Key: ●——●, benzoic acid; O— — —O, *o*-aminobenzoic acid; ▲——▲, *m*-aminobenzoic acid; △——△, *p*-aminobenzoic acid.

blank were assayed for acid content to determine if equilibrium had been reached. Solutions were assayed for acid content at the following wavelengths: benzoic acid, 240 mμ; *o*-hydroxybenzoic acid, 240 mμ; *m*-hydroxybenzoic acid, 240 mμ; *p*-hydroxybenzoic acid, 240 mμ; *o*-aminobenzoic acid, 275 mμ; *m*-aminobenzoic acid, 267 mμ, and *p*-aminobenzoic acid, 275 mμ.

DISCUSSION

It can be noted that while the degree of association was not very great between the various reactants certain definite complexing tendencies can be discerned (Tables I–III). In the hydroxybenzoic acid series, *o*-hydroxybenzoic was the most reactive, the *m*-substituted compound less reactive, and the *p*-hydroxy less reactive. This order of reactivity varied from that of work previously reported with certain xanthines (27–29) and polymers (30–33). However, it is similar to some work reported (21) with the Tweens, which, in addition to the ethylene oxide polymer in the molecule, contains a hydrophobic moiety. Blaug and Ahsan (21) attributed the greater complexing ability of the Tweens, compared to polyethylene glycol, to the presence of a hydrophobic moiety in the molecule. The degree of reactivity of benzoic acid appears to depend on the nature of the ester. In the series of interactions with the esters of sucrose (Fig. 1), benzoic acid was more reactive than *o*-hydroxybenzoic acid. However, in the series of interactions with the propoxylated sucrose esters (Fig. 2), the benzoic acid was less reactive than the *o*-hydroxy compound but more reactive than the *m*-hydroxy acid. It is possible, in the case of the sucrose ester, that due to intramolecular bonding the *o*-hydroxy acid has less available sites for bonding than the benzoic acid molecule, making it less reactive. However, in the propoxylated sucrose ester molecule the availability of a greater number of bonding sites in close proximity to the acid molecule, partially fixed in place by a hydrophobic bond, allows the macromolecule to compete advantageously with the intramolecular bonding forces of the acid. Figures 1–4 are illustrative of the results obtained in these interaction studies.

The exact reason for the formation of molecular complexes is not completely known at the present time. A number of theories have been proposed (34–37) to account for the experimental data generally obtained. It was believed that hydrogen bonding was the major driving force of these interactions in the early work conducted with water soluble polymers (34). In a recent work (35) Higuchi and Drubulis stated that the degree of interaction shown by the hydroxy-aromatic acids and their salts was too great to be caused by hydrogen bonding or by hydrophobic bonding. They attributed the interaction to another donor-acceptor type of mechanism.

In the field of soap chemistry the solubilization of organic acids and phenols has been attributed (36) to micellar solubilization. Klevans (37), in

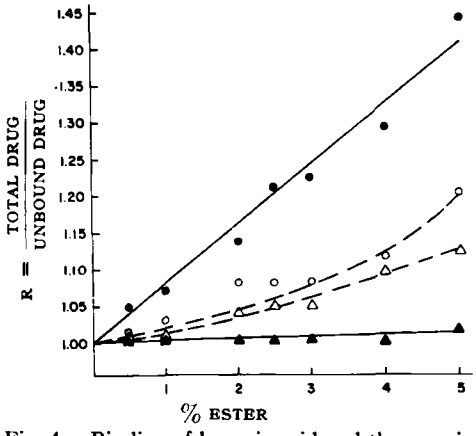

Fig. 4.—Binding of benzoic acid and three aminobenzoic acids by hyprose monolaurate in water at 30°. Key: ●——●, benzoic acid; O— — —O, *o*-aminobenzoic acid; ▲——▲, *m*-aminobenzoic acid; Δ— — —Δ, *p*-aminobenzoic acid.

his review of solubilization, stated that molecules can be solubilized by three possible mechanisms. The first was the adsorption of the added molecule on the surface of the micelle. The second was the dissolution of the added hydrocarbon in the lipophilic portion of the micelle. The third, thought to be the best explanation of the three, stated that the molecule becomes oriented in the palisade layer of the micelle. A group of English workers (36) studying soap interactions stated that the aromatic compounds studied appeared to orient themselves in the micelle in the same manner as the soap molecules. If this were the mechanism by which the compounds in the present study reacted, then a correlation based on the dipole moment should be valid. This was attempted by the authors but found unsuitable to explain the results obtained.

If we study the macromolecules in question, the sucrose, or the propoxylated sucrose esters, it can be seen that a fatty acid moiety is present which corresponds to the hydrophobic portion of a soap molecule. In contrast to the soap molecule, the hydrophilic portion of the sucrose or hyprose ester is nonionized. The hydrophilic portion does not possess the large number of binding sites found in the polyethers. Based on water solubility data,

TABLE I.—*R* VALUES FOR THE INTERACTION OF BENZOIC ACID AND SOME HYDROXY AND AMINO-SUBSTITUTED BENZOIC ACIDS WITH SOME SUCROSE AND PROPOXYLATED SUCROSE ESTERS (1% MACROMOLECULE CONCENTRATION)

Acid	Sucrose			Hyprose		
	Monostearate	Monolaurate	Dioleate	Monostearate	Monooleate	Monolaurate
Benzoic	1.03	1.08	1.08	1.03	1.05	1.09
o-Hydroxybenzoic	1.01	1.08	1.01	1.11	1.05	1.11
m-Hydroxybenzoic	1.01	1.03	1.01	1.03	1.03	1.07
p-Hydroxybenzoic	1.01	1.03	1.02	1.05	1.04	1.05
o-Aminobenzoic	1.01	1.01	1.01	1.06	1.04	1.02
m-Aminobenzoic	1.00	1.00	1.00	1.00	1.00	1.00
p-Aminobenzoic	1.00	1.08	1.01	1.03	1.07	1.01

TABLE II.—*R* VALUES FOR THE INTERACTION OF BENZOIC ACID AND SOME HYDROXY AND AMINO-SUBSTITUTED BENZOIC ACIDS WITH SOME SUCROSE AND PROPOXYLATED SUCROSE ESTERS (2.5% MACROMOLECULE CONCENTRATION)

Acid	Sucrose			Hyprose		
	Monostearate	Monolaurate	Dioleate	Monostearate	Monooleate	Monolaurate
Benzoic	1.07	1.20	1.21	1.07	1.15	1.20
o-Hydroxybenzoic	1.03	1.10	1.02	1.32	1.22	1.32
m-Hydroxybenzoic	1.01	1.07	1.02	1.07	1.06	1.13
p-Hydroxybenzoic	1.02	1.05	1.02	1.08	1.05	1.10
o-Aminobenzoic	1.02	1.03	1.02	1.09	1.07	1.06
m-Aminobenzoic	1.00	1.00	1.00	1.00	1.01	1.01
p-Aminobenzoic	1.00	1.05	1.00	1.05	1.10	1.05

TABLE III.—*R* VALUES FOR THE INTERACTION OF BENZOIC ACID AND SOME HYDROXY AND AMINO-SUBSTITUTED BENZOIC ACIDS WITH SOME SUCROSE AND PROPOXYLATED SUCROSE ESTERS (5% MACROMOLECULE CONCENTRATION)

Acid	Sucrose			Hyprose		
	Monostearate	Monolaurate	Dioleate	Monostearate	Monooleate	Monolaurate
Benzoic	1.10	1.40	1.34	1.30	1.17	1.44
o-Hydroxybenzoic	1.04	1.19	1.05	1.47	1.41	1.56
m-Hydroxybenzoic	1.01	1.11	1.05	1.15	1.13	1.25
p-Hydroxybenzoic	1.04	1.09	1.03	1.12	1.10	1.20
o-Aminobenzoic	1.03	1.28	1.05	1.13	1.14	1.20
m-Aminobenzoic	1.00	1.01	1.00	1.01	1.01	1.01
p-Aminobenzoic	1.01	1.07	1.01	1.07	1.12	1.12

it has been stated (5) that the oxygen atoms present in the sucrose portion or the molecule are equivalent to a minimum of ten ethylene oxide groups. This would make these esters more reactive than the Tweens. The results obtained indicated that the macromolecules in question were appreciably less reactive than those of the Tween series because of the lack of ethylene oxide groups in the sucrose or hyprose molecule.

The authors noted differences in the degree of reactivity between esters of the various fatty acids and between the esters of sucrose and those of hyprose. In most instances the esters of hyprose interacted to a greater degree than those of sucrose. The observed differences were probably due to the greater number of binding sites in the propoxylated sucrose molecule. The fatty acid portion of the ester molecule appeared to exert some effect on the degree of interaction. The laurate esters generally were the most reactive, while the stearate esters generally were least reactive. This latter effect was probably due, in part, to greater solubility of the laurate ester—hence greater availability of the molecule for interaction.

In studying the data obtained the possibility becomes apparent that more than one mechanism is responsible for the degree and order of reactivity of the acids studied. The theory proposed by Hyde, *et al.* (36), appears to explain best the results obtained. The aromatic acid is incorporated into the palisade layer of the sucrose or hyprose micelle in the same manner as the sugar ester molecules in the micelle. The stability of the complex can be attributed to two different types of binding. As represented in Fig. 5, the carboxyl and hydroxyl

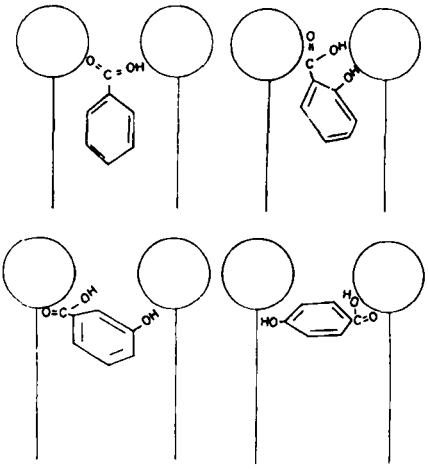

Fig. 5.—A schematic representation of the proposed mechanism of interaction between sucrose and hyprose ester, and benzoic acid and three hydroxybenzoic acids.

groups of the aromatic acids are associated with the hydroxyl groups and/or ether linkages present in the sucrose or hyprose molecule. The less polar portion of the interacting acid molecule associates with or becomes dissolved in the hydrocarbon tail of the ester in its micellar orientation. The greater degree of reactivity demonstrated by one acid molecule over another can be attributed to the ability of that molecule to make a better "fit," *i.e.*, the combination of hydrophilic bonding (hydrogen bonding or donor-acceptor type bonding) and hydrophobic bonding forming a more stable complex.

In the second series, the amino-substituted benzoic acids, Figs. 3 and 4, the orders of reactivity differed from those observed with the hydroxybenzoic acids. In most cases the *o*-substituted amino compound appeared to be most reactive, behaving similarly to the hydroxy counterpart. On the other hand, the *p*-aminobenzoic acid was next most reactive, instead of the *meta* compound showing opposite behavior from their hydroxy counterparts.

Since the studies were conducted in relatively strong acidic media, the amino compounds were present as the protonated species. Benzoic acid interacted to a greater degree than any of the aminobenzoic acids. This was expected as the protonated ion would not become involved in hydrogen bonding and would serve to inhibit any form of hydrophobic association. The phase diagrams presented indicate that the amino compounds, in general, were not as reactive as the hydroxybenzoic acids. The lack of reactivity of the *m*-aminobenzoic acid can be attributed, perhaps, to the steric configuration of the molecule, *i.e.*, the combination of hydrophilic and hydrophobic bonds forming a very weak complex.

TABLE IV.—RELATIVE COMPLEXING TENDENCIES OF SUCROSE AND HYPROSE ESTERS[a]

Sucrose Esters	Hyprose Esters
o-Hydroxybenzoic acid	Benzoic acid
Benzoic acid	*o*-Hydroxybenzoic acid
m-Hydroxybenzoic acid	*o*-Aminobenzoic acid
o-Aminobenzoic acid	*m*-Hydroxybenzoic acid
p-Hydroxybenzoic acid	*p*-Hydroxybenzoic acid
p-Aminobenzoic acid	*p*-Aminobenzoic acid
m-Aminobenzoic acid	*m*-Aminobenzoic acid

[a] Decreasing order of reactivity.

SUMMARY

A study was conducted to determine whether association would occur between a series of aromatic acids and some fatty acid esters of sucrose and a propoxylated sucrose.

Evidence of reactivity between the molecules studied was presented in addition to the degree to which this association occurred.

A mechanism was proposed to explain, to some degree, why association had occurred.

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