

295  $m\mu$ . The same experiment repeated with sodium 2-chlorobenzoate produced a similar band at 295  $m\mu$ . The above procedure repeated with the hydrochloride salt of 2-dimethylaminomethyl-4-methylphenol instead of the benzoates revealed a peak at approximately 307  $m\mu$  very similar in its sharpness to that obtained with the procaine hydrochloride-caffeine system.

These results indicate that theophylline appears to participate in charge-transfer complexation. The observed spectra with both the benzoates and the protonated Mannich base suggest theophylline's ability to share electrons with both positively and negatively charged aromatic compounds. It is evident, however, that further investigation of a more quantitative nature would be required to determine whether these charge-transfer interactions account for the total interaction by theophylline in aqueous solutions.

### CONCLUSIONS

Solubility studies on the interactions of theophylline, prednisolone, and phenacetin with substituted benzoates, phthalates, and naphthoates produced the following observations.

Complex formation between aromatic carboxylate salts and the above drugs occurred in every instance, but with varying extents.

Introduction of substituents on the aromatic ring appears to have a marked effect on the binding tendencies.

There is a surprising absence of any significant "lock and key" specificity, particularly among the complexes of the aromatic acid salts with prednisolone and phenacetin.

The results suggest that both hydrophobic bonding and donor-acceptor interactions involving the nucleus of the aromatic carboxylates contribute to formation of the complexes.

The binding with theophylline appears to be at least partially due to specific charge-transfer interactions.

The extent of complex formation of the aromatic carboxylate salts with theophylline, phenacetin, and prednisolone is increased by (a) substitution of halo groups *meta* and *para* to the carboxylate, the enhancement increasing in the order chloro, bromo, and iodo; (b) methyl, nitro, and hydroxyl groups substituted *meta* and *para* to the carboxylate; (c) placement of carboxylic acid and hydroxy groups *ortho* to the carboxylate ion; (d) further substitution of the above substituents on the aromatic carboxylates; (e) expansion of a benzenoid system to a naphthalene structure and by generally increasing the planar surface of the substituted acid salts.

The extent of interaction of these systems is decreased by halogen substitution on the ring *ortho* to the carboxylate group and by substitution of carboxylate ion.

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## Emulsifying Effects of Some Nonionic Surfactants on a Nonaqueous Immiscible System

By R. V. PETERSEN, R. D. HAMILL, and J. D. MCMAHON

Representative members of seven classes of nonionic surfactants and combinations of these agents were tested by hand methods of trituration for their ability to induce emulsification of glycerin and olive oil. No relation between HLB values and emulsifying capacity, method of mixing, or emulsion type was apparent. On the other hand, the chemical nature of the surfactant appeared to have an effect on the method of mixing and emulsion type. Only stearate ester surfactants induced emulsification when the surfactant was first added to olive oil. In addition, only stearate ester surfactants induced glycerin-in-oil emulsification.

**I**N A SEPARATE publication (1), the emulsifying effects of several anionic and cationic surfactants on the immiscible system, glycerin and olive oil, were reported. The present report describes the emulsifying effects of some *nonionic* surfactants on this system.

Various nonionic surfactants have been used in formulations which have been administered orally to humans (2). Ester type products are hydrolyzed in the digestive tract in a manner similar to edible fats and oils. The fatty acid portions are available for nutrition like those from natural fats, while the polyol moieties are eliminated (3). The glyceryl monostearate products (GMS 165,<sup>1</sup> glyceryl monostearate, self-

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<sup>1</sup> Marketed as Arlacel 165 by Atlas Chemical Industries, Inc., Wilmington, Del.

emulsifying, and GMS 169,<sup>2</sup> glyceryl mono-stearate, nonself-emulsifying) are types of partial ester emulsifiers long accepted for use as ingestible ingredients (3). Various sucrose derivatives, particularly the esters, have been found to be quite nontoxic; hence, their use as emulsifying agents in pharmaceuticals has been suggested (4-7).

Nonaqueous emulsions, such as those described in this report, may be of pharmaceutical or cosmetic value since they are composed primarily of edible, nontoxic ingredients and can be formulated to exhibit a wide range of physical properties. Some possible uses might be as topical application bases for dermatologicals, particularly for hydrolyzable drugs, as emollient bases for cosmetic preparations, or as nutrient preparations.

In 1949, Griffin (8) devised a method of classification of nonionic surfactants based on the ratio of hydrophilic to lipophilic (polar to non-polar) properties. Subsequently, other investigators have proposed various ways of expressing polar-nonpolar relations of surfactants (9, 10). The values used throughout this report are based on the Griffin proposals.

Although the emulsifying effects of nonionic surfactants on water-oil systems and the validity of the HLB scale as a guide to the estimation of the effects of these agents on aqueous systems have been extensively studied, very little is known regarding the emulsifying effects of nonionic surfactants on nonaqueous systems or regarding the utility of established HLB values as predictive tools for their effects in such systems. For these reasons, this study was undertaken. The results obtained serve as a basis for this report.

## EXPERIMENTAL

The methods employed throughout this study were the same as reported in a previous paper which described the emulsifying effects of *ionic* surfactants on glycerin and olive oil (1). Briefly, in *Method I* the surfactant was added to the requisite weight of glycerin. An equal weight of olive oil was added in small portions, with vigorous trituration after each addition. The quantities of reagents and procedure in *Method II* were the same as in *Method I*, except for the order of mixing. In *Method II*, the surfactant was first added to the olive oil. The glycerin was then added in small portions, with rapid trituration after each addition. Heat was applied when necessary to effect solution or dispersion of the surfactant in the glycerin or olive oil, but all reagents were returned to room temperature before emulsification was attempted. Commercial grades of surfactants were used without further

purification. The glycerin and olive oil were U.S.P. grade.

To study the influence of the hydrophile-lipophile-balance (HLB) value on emulsifying capacity, order of mixing, and emulsion type, blends of Arlacels and polysorbates were prepared. Solid surfactants required heating in a water bath to effect blending. The proportion of each surfactant in a blend was calculated by alligation methods or by reference to the Atlas HLB computing graph.<sup>3</sup> These methods depend on a linear relation of the HLB value of a mixture with that of the pure components.

The criteria used to evaluate the products were based on three observations: emulsifying capacity, miscibility of emulsions with added olive oil or glycerin, and microscopic examination. Emulsifying capacity was evaluated on the basis of the appearance of the preparation after standing for 7 days. If any degree of separation into layers occurred within this period of time, the preparation was considered unstable. If no separation was detectable, the product was considered an emulsion. Figure 1 illustrates six representative preparations as they appear after standing 7 days. These preparations served as standards for evaluation of all other preparations. Bottle 1 contains 2% polyoxyethylene lauryl ether (POL 35)<sup>4</sup> in equal weights of glycerin and olive oil and is representative of preparations classified as *separations*. Bottle 2 contains 2% GMS 165. This, and similar preparations, are classified as *partial separations*. In most instances, preparations classified as partial separations appeared emulsified when first made, but exhibited some degree of separation on standing for 1 week. Bottles 3 to 6 contain a clear emulsion, an opaque emulsion, a creamy, white emulsion, and a semisolid, white emulsion, respectively. No. 3 was induced by 2% POL 30<sup>5</sup> by *Method I*; No. 4 by 5% GMS 165 by *Method I*; No. 5 by 4% of a combination of sorbitan monostearate (S-60)<sup>6</sup> and polyoxyethylene sorbitan monostearate (PS-60)<sup>7</sup> at HLB 6 by *Method I*; and No. 6 by 4% S-60 by *Method II*. These four and similar preparations are classified as *emulsions*.

Miscibility of emulsions with added olive oil or glycerin was used for determining emulsion type. This observation was based on the usual assumption that emulsions mix readily with additional liquid corresponding to the external phase, but not the internal phase.

Microscopic examination of emulsions prepared from olive oil which contained 1.0% dissolved D&C Red No. 18 dye was employed to confirm emulsification and to verify emulsion type.

## RESULTS

Several of the nonionic surfactants tested and blends of these agents were effective in producing emulsions of glycerin and olive oil. A summary of the results is given in Table I.

<sup>3</sup> Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>4</sup> Marketed as Brij 35 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>5</sup> Marketed as Brij 30 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>6</sup> Marketed as Arlacel 60 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>7</sup> Marketed as Tween 60 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>2</sup> Marketed as Arlacel 169 by Atlas Chemical Industries, Inc., Wilmington, Del.

Fig. 1.—Physical appearance of representative preparations. Key: 1, a separation; 2, a partial separation; 3, a clear emulsion containing 2% POL 30; 4, an opaque emulsion containing 5% GMS 165; 5, a creamy, white emulsion containing 4% of a combination S-60 and PS-60 at HLB 6; 6, a semisolid, white emulsion containing 4% S-60.

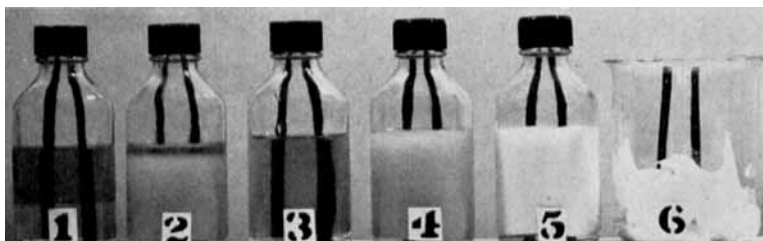


TABLE I.—EMULSIFYING EFFECTS OF SOME NONIONIC SURFACTANTS AND COMBINATIONS ON EQUAL WEIGHT OF GLYCERIN AND OLIVE OIL OBSERVED 7 DAYS FOLLOWING PREPARATION

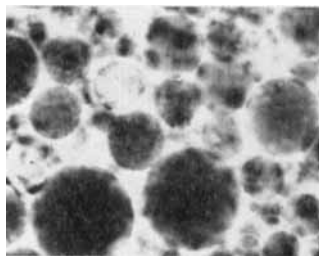
Surfactant or Blend	HLB <sup>a</sup>	%	Method I <sup>b</sup>	Method II <sup>b</sup>	Appearance of Emulsion	Type of Emulsion
S-20	8.6	4	Emulsion	Separation	Clear	o/g
PS-20	16.7	4	Emulsion	Separation	Clear	o/g
S-20 + PS-20 (83:17) <sup>c</sup>	10.0	4	Emulsion	Separation	Clear	o/g
S-20 + PS-20 (58:42)	12.0	4	Emulsion	Separation	Clear	o/g
S-20 + PS-20 (33:67)	14.0	4	Emulsion	Separation	Clear	o/g
S-20 + PS-20 (9:91)	16.0	4	Emulsion	Separation	Clear	o/g
S-40	6.7	4	Emulsion	Separation	Opaque	o/g
PS-40	15.6	4	Emulsion	Separation	Clear	o/g
S-40 + PS-40 (85:15)	8.0	4	Partial sep.	Separation	...	...
S-40 + PS-40 (63:37)	10.0	4	Partial sep.	Separation	...	...
S-40 + PS-40 (40:60)	12.0	4	Partial sep.	Separation	...	...
S-40 + PS-40 (18:82)	14.0	4	Partial sep.	Separation	...	...
S-60	4.7	4	Emulsion	Emulsion	Semisolid, white	o/g
PS-60	14.9	4	Emulsion	Separation	Clear	o/g
S-60 + PS-60 (87:13)	6.0	4	Emulsion	Emulsion	Creamy, white	o/g
S-60 + PS-60 (68:32)	8.0	4	Emulsion	Emulsion	Creamy, white	o/g
S-60 + PS-60 (48:52)	10.0	4	Emulsion	Partial sep.	Opaque	o/g
S-60 + PS-60 (29:71)	12.0	4	Emulsion	Partial sep.	Opaque	o/g
S-60 + PS-60 (9:91)	14.0	4	Emulsion	Separation	Clear	o/g
S-80	4.3	4	Emulsion	Separation	Clear	o/g
PS-80	15.0	4	Emulsion	Separation	Clear	o/g
S-80 + PS-80 (84:16)	6.0	4	Emulsion	Separation	Clear	o/g
S-80 + PS-80 (66:34)	8.0	4	Emulsion	Separation	Clear	o/g
S-80 + PS-80 (47:53)	10.0	4	Emulsion	Separation	Clear	o/g
S-80 + PS-80 (28:72)	12.0	4	Emulsion	Separation	Clear	o/g
S-80 + PS-80 (9:91)	14.0	4	Emulsion	Separation	Clear	o/g
S-83	3.7	4	Emulsion	Separation	Clear	o/g
S-85	1.8	4	Emulsion	Separation	Clear	o/g
GMS 165	11.0	2	Partial sep.	Partial sep.	...	...
GMS 165	11.0	5	Emulsion	Emulsion	Opaque	g/o
GMS 169	4.0	2	Partial sep.	Partial sep.	...	...
GMS 169	4.0	5	Emulsion	Emulsion	Opaque	g/o
POL 30	9.5	2	Emulsion	Separation	Clear	o/g
POL 30	9.5	5	Emulsion	Separation	Clear	o/g
POL 35	16.9	2	Separation	Separation	...	...
POL 35	16.9	5	Separation	Separation	...	...
POS 45	11.1	2	Separation	Separation	...	...
POS 45	11.1	5	Separation	Separation	...	...
POS 52	16.9	2	Partial sep.	Separation	...	...
POS 52	16.9	5	Partial sep.	Partial sep.	...	...
POS 52	16.9	10	Partial sep.	Partial sep.	...	...
DPM 600	...	2	Emulsion	Separation	Creamy, white	o/g
DPM 600	...	5	Emulsion	Separation	Creamy, white	o/g
OHS 80	...	2	Emulsion	Separation	Opaque	o/g
OHS 80	...	4	Emulsion	Separation	Opaque	o/g
PPO L-64 <sup>d</sup>	...	4	Separation	Separation	...	...
PPO L-64	...	8	Separation	Separation	...	...
PPO F-68 <sup>d</sup>	...	4	Separation	Separation	...	...
PPO F-68	...	8	Separation	Separation	...	...

<sup>a</sup> HLB values given in Atlas Catalog of "Products for Cosmetic Formulations," Atlas Powder Co., Wilmington, Del., 1957  
<sup>b</sup> See text. <sup>c</sup> Figures in parentheses indicate the ratio of Arlacel polysorbate in a blend. <sup>d</sup> Polyoxyethylene derivatives of polypropylene oxides. Marketed as Pluronic L-64 and Pluronic F-68 by the Wyandotte Chemical Corp., Wyandotte, Mich.

It should be emphasized that the results reported in the table were derived only from those preparations which contained equal weights of olive oil and glycerin. Indeed, on several occasions emulsification was apparent at lower concentrations of oil, but not the 50% level. For example, in the experiments using a blend of polyoxyethylene sorbitan monopalmitate (PS-40)<sup>8</sup> and sorbitan monopalmitate (S-40)<sup>9</sup> at HLB 10, an emulsion resulted when 43% oil was used, whereas partial separation occurred in the preparations containing 50% oil.

In a few instances, preparations listed as emulsions in Table I showed a partial separation after standing for 2 or 3 months. Preparations made from POL 30, sorbitan monolaurate (S-20)<sup>10</sup>-polyoxyethylene

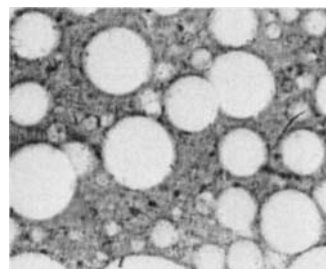
Fig. 2.—Photomicrograph of an emulsion containing 4% of a combination of S-60 and PS-60 (HLB 6) in equal weights of glycerin and olive oil, stained with D&C Red No. 18 dye. The emulsion was deaerated under reduced pressure prior to being photographed (520× magnification).



sorbitan monolaurate (PS-20)<sup>11</sup> combinations, S-40-PS-40 combinations, sorbitan monooleate (S-80)<sup>12</sup>-polyoxyethylene sorbitan monooleate (PS-80)<sup>13</sup> combinations, or from sorbitan trioleate (S-85)<sup>14</sup> showed a layer of oil on top with a gradual lightening of color on the bottom after 90 days. Products thus separated could not be restored to their original emulsified state by simple shaking. Emulsions made from S-60, PS-60, combinations of S-60 and PS-60, sorbitan sesquioleate (S-83),<sup>15</sup> GMS 165, GMS 169, or sucrose dipalmitate (DPM 600)<sup>16</sup> showed little or no tendency to separate and were considered the most stable products.

As shown in Table I, *Method I* was effective in all systems which contained Arlacels, polysorbates, combinations of Arlacels and polysorbates (except combinations of S-40 and PS-40), POL 30, DPM 600, or octakis(2-hydroxypropyl)sucrose OHS 80<sup>17</sup>; whereas *Method II* was effective only in those preparations which contained GMS 165, GMS 169, S-60, or combinations of the latter with PS-60. Table I shows also that all of the emulsions were of the oil-in-glycerin (o/g) type, except for those

Fig. 3.—Photomicrograph of an emulsion containing 5% GMS 165 in equal weights of glycerin and olive oil, stained with D&C Red No. 18 dye (260× magnification).



prepared from GMS 165 or GMS 169. Figure 2 is a photomicrograph of an o/g emulsion containing 4% of a combination of S-60 and PS-60 at HLB 6. Figure 3 is a photomicrograph of a glycerin-in-oil (g/o) emulsion containing 5% GMS 165. Mixed emulsification can be detected in the latter figure. Some degree of mixed emulsification was observed also in many other preparations.

All of the preparations which contained GMS 165, GMS 169, or high proportions of S-60 were opaque, creamy, or semisolid preparations. The incorporation of large amounts of air was characteristic of preparations containing relatively high proportions of S-60, but not of the other opaque emulsions. Trituration of glycerin and S-60, in the absence of olive oil, produced foams which retained the entrapped air for several days. Deaeration under reduced pressure of small portions of S-60-containing emulsions resulted in almost complete clarification. In all other instances where opaque emulsions formed, the opacity was not due to entrapped air, and clarification could not be achieved by application of reduced pressures. Incomplete solubility of the surfactant may have contributed to their appearance in such cases.

Preparations made from S-60 or its blends, by *Method II*, required heavy trituration for long periods of time (20-40 minutes) after addition of all glycerin before emulsification was effected.

## DISCUSSION

The results of these studies indicate that neither the capacity to produce an emulsion of glycerin and olive oil, the comparative efficacy of *Methods I* and *II*, nor the type of emulsion formed can be related to the HLB value of the surfactant used.

Evidence for the lack of correlation between the capacity to produce an emulsion and the HLB value of the surfactant is shown by the fact that emulsification resulted from the use of agents with HLB values from 1.8 (S-85) to 16.7 (PS-20), and by the fact that separations and partial separations occurred also within this range. To cite a specific example—at HLB 10, combinations of S-20 and PS-20, S-60 and PS-60, or S-80 and PS-80 produced emulsions, whereas a combination of S-40 and PS-40 at the same HLB value failed to produce an emulsion. Immediately after manipulation it appeared that emulsification of the latter was effected, but partial separation occurred within 7 days.

Emulsions were obtained by *Method I* from surfactants having HLB values from 1.8 (S-85) to 16.7 (PS-20) and by *Method II* from agents having HLB values from 4.0 (GMS 165) to 11.0 (GMS 169). In one series of experiments it appeared originally that emulsification had been induced by an agent with an HLB value of 16.9 (polyoxyethylene

<sup>8</sup> Marketed as Tween 40 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>9</sup> Marketed as Arlacel 40 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>10</sup> Marketed as Arlacel 20 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>11</sup> Marketed as Tween 20 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>12</sup> Marketed as Arlacel 80 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>13</sup> Marketed as Tween 80 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>14</sup> Marketed as Arlacel 85 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>15</sup> Marketed as Arlacel 83 by Atlas Chemical Industries, Inc., Wilmington, Del.

<sup>16</sup> Marketed as Sucrodet D-600 by the Millmaster Chemical Corp., New York, N. Y.

<sup>17</sup> Marketed as Hyprose SP-80 by the Dow Chemical Co., Midland, Mich.

stearate, POS 52<sup>18</sup>) by *Method II*; however, these preparations failed to remain stable for 7 days and are thus shown in Table I as partial separations. These data indicate that no correlations can be drawn between HLB values and the relative efficacy of *Methods I* and *II*.

Based on the fact that glycerin is considered to be a polar substance, it was expected that surfactants having high HLB values would favor o/g emulsification and those having low HLB values would favor g/o emulsification. This, however, did not result. Oil-in-glycerin emulsions were produced from agents ranging in HLB values from 1.8 (S-85) to 16.7 (PS-20), and glycerin-in-oil emulsions resulted from the use of agents having HLB values of 4.0 (GMS 165) and 11.0 (GMS 169). The fact that the HLB value of a surfactant could not be correlated with emulsion type in oil-glycerin systems is in direct conflict with the fact that there is a close correlation between HLB values and emulsion type in oil-water systems.

The chemical nature of the surfactant appears to influence the efficacy of the methods employed and the resulting emulsion type. Thus, the stearate ester surfactants, such as GMS 165 (glyceryl monostearate, self-emulsifying), GMS 169 (glyceryl monostearate, nonself-emulsifying), S-60 (stearate ester of sorbitol anhydride), and combinations of the latter with PS-60 (stearate ester of polyoxyethylene sorbitol anhydride), all produced emulsions by both methods and, except for S-60 and its combinations with PS-60, resulted in emulsions of the glycerin-in-oil type. It should be emphasized that these are the only emulsions produced by *Method II* and are the only g/o emulsions produced by either *Method I* or *Method II*. To test this interpretation, another stearate surfactant was used in an attempt to emulsify this system. Preparations containing POS 52 were made by both *Methods I* and *II*. These preparations, as shown in Table I, exhibited partial separation within 7 days. They did, however, remain stable for at least 24 hours. Microscopic observation of the dye-containing emulsions made from POS 52 revealed that they were of the g/o type. This was further substantiated by the fact that they mixed readily with added olive oil, but not with glycerin.

<sup>18</sup> Marketed as Myrj 52 by Atlas Chemical Industries, Inc., Wilmington, Del.

The above observations regarding stearates are in accord with previous work reported from our laboratories (1) which demonstrated that the only ionic surfactants tested which produced g/o emulsions were sodium stearate and stearyltrimethylammonium chloride. Thus, it might be concluded that the chemical nature, more than the HLB value, influenced the method of mixing and the type of emulsion produced.

## SUMMARY

Several nonionic agents, including S-20, S-40, S-60, S-80, S-83, S-85, GMS 165, GMS 169, PS-20, PS-40, PS-60, and PS-80, POL 30 and 35, POS 45 and 52, DPM 600, OHS 80, PPO L-64 and F-68 were tested for their capacity to emulsify the non-aqueous system, glycerin and olive oil. Blends of Arlacels and polysorbates at various HLB values also were prepared and tested. Stable emulsions resulted from the use of several of these agents and combinations. The HLB value of a given surfactant, or blends of two surfactants, could not be correlated either with its ability to induce emulsification, its effect on emulsion type, or its influence on method of mixing the emulsion components. It was shown that the chemical nature of the surfactant may be somewhat determinant in the type of emulsion formed and on the order of mixing of the components. In all cases where g/o emulsions formed and/or emulsification was successful by first incorporating the surfactant into the oil (*Method II*), the surfactant was a derivative of stearic acid.

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