presumably because these changes are inconsequential in relation to the high concentration of serum cholesterol.

It should be noted that the above assay procedure is unsuitable for the screening of compounds that lower serum cholesterol by interfering with cholesterol biosynthesis, since this process is markedly reduced in rats fed high cholesterol diets (28, 29).

## REFERENCES


(1) Marshal, N. B., in "Lipid Pharmacology," Paoletti, R., ed., Academic Press Inc., New York, N. Y., 1964, p. 325.
(2) Hess, R., in "Advances in Lipid Research," Paoletti, R., and Kritchevsky, E., eds., Academic Press Inc., New York, N. Y., 1964, p. 295.
(3) Zlatkis, A., Zak, B., and Boyle, A. J., *J. Lab. Clin. Med.*, **41**, 486(1953).
(4) Technicon Corp., Method File, 24, 1961.
(5) van Handel, E., and Zilversmit, D. B., *J. Lab. Clin. Med.*, **50**, 152(1957).
(6) Whitley, R., and Alburn, H. E., *Ann. N. Y. Acad. Sci.*, **130**, 634(1965).
(7) Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J., *J. Biol. Chem.*, **193**, 265(1951).
(8) Searcy, R. L., Bergquist, L. M., Jung, R. C., Craig, R., and Korotzer, J., *Clin. Chem.*, **6**, 585(1960).
(9) Nath, N., Wiener, R., Harper, A. E., and Elvehjem, C. A., *J. Nutr.*, **67**, 289(1959).
(10) Tomarelli, R. M., Hartz, R., and Bernhart, F. W., *ibid.*, **71**, 221(1960).
(11) Meites, J., *Am. J. Physiol.*, **159**, 281(1949).
(12) Hughes, G. A., and Smith, H., Brit. pat. 991, 593 (priority from February 29, 1960).
(13) Edgren, R. E., unpublished data.
(14) Gaddum, J. H., *J. Pharm. Pharmacol.*, **6**, 345(1953).
(15) Merola, A. J., and Arnold, A., *Science*, **144**, 301(1964).
(16) Gordon, S., Cantrall, E. W., Cekleniak, W. P., Albers, H. J., Mauer, S., Stolar, S. M., and Bernstein, S., *Steroids*, **4**, 267(1964).
(17) Uchida, K., Kadowaki, M., and Miyake, T., *Shionogi Kenkyusho Nempo*, **13**, 112(1963); through *Chem. Abstr.*, **60**, 2006c(1964).
(18) van der Vies, J., *Acta Endocrinol. Suppl.*, **67**, 163 (1962).
(19) Boyd, G. S., in "Biochemical Society Symposium No. 24," Popjack, G., and Grant, V. K., eds., Academic Press Inc., New York, N. Y., 1963, p. 296.
(20) Abel, L. L., and Mosbach, E. H., *Lipid Res.*, **3**, 88 (1962).
(21) Smith, H., Hughes, G. A., Douglas, G. H., Hartley, D., McLoughlin, B. J., Siddall, J. B., Wendt, G. R., Buzby, G. C., Jr., Herbst, D. R., Ledig, K. W., McMenamin, J. R., Pattison, T. W., Suida, J., Tokolics, J., Edgren, R. A., Jansen, A. B. A., Gadsby, B., Watson, D. H. R., and Phillips, P. C., *Experientia*, **19**, 394(1963).
(22) Smith, H., Hughes, G. A., Douglas, G. H., Wendt, G. R., Buzby, G. C., Jr., Edgren, R. A., Fisher, J., Foell, T., Gadsby, B., Hartley, D., Herbst, D., Jansen, A. B. A., Ledig, K., McLoughlin, B. J., McMenamin, J., Pattison, T. W., Phillips, P. C., Rees, R., Siddall, J., Suida, J., Smith, L. L., Tokolics, J., and Watson, D. H. P., *J. Chem. Soc.*, **1964**, 4472.
(23) Smith, H., Douglas, G. H., and Walk, C. R., *Experientia*, **20**, 418(1964).
(24) Thorp, J. M., and Waring, W. S., *Nature*, **194**, 948 (1962).
(25) Blohm, T. R., Kariya, T., and Laughlin, M. W., *Arch. Biochem. Biophys.*, **85**, 250(1959).
(26) Feiser, L., and Feiser, M., "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p. 477.
(27) Edgren, R. A., *J. Atheroscler. Res.*, **3**, 206(1963).
(28) Siperstein, M. D., and Guest, M. J., *J. Clin. Invest.*, **39**, 642(1960).
(29) Morris, M. D., Chaikoff, I. L., Felts, J. M., Abraham, S., and Fansah, N. O., *J. Biol. Chem.*, **224**, 039(1957).


# Interaction of Substituted Benzoic Acids with Cationic Surfactants

By LUCY S. C. WAN

**The interaction of benzoic acid and a series of hydroxy, amino, chloro, and nitrobenzoic acids with surfactants of the quaternary ammonium type was studied by means of viscosity measurements. Only salicylic acid was found to interact with the surfactants leading to an increase in viscosity which reached a maximum at approximately the concentration at which the surfactant solution became saturated with salicylic acid. Apparently the interaction is specific and is limited to the *ortho* hydroxy substitution of benzoic acid, as no viscosity effect was observed with the *ortho, meta,* and *para* isomers of amino, chloro, and nitro substituted benzoic acids. In addition, sodium lauryl sulfate and cetomacrogol 1000 did not exhibit viscosity changes in the presence of salicylic acid. The viscosity effect was not related to pH.**

BENZOIC ACID and its substituted isomers have been found to interact with a varied number of pharmaceutical compounds. Salicylic acid, *meta*, and *para* hydroxybenzoic acids have been shown to complex with polyethylene glycols (1) and with polyvinylpyrrolidone (2). In addition, the hydroxybenzoic acids have been found to interact with caffeine (3) and with theophylline and theobromine (4). Goodhart and Martin (5) reported that the solubilities of benzoic acid and its substituted isomers were greatest in the least hydrophilic of the polyethylene stearates. The solubilities of benzoic acid, salicylic acid, and *p*-hydroxybenzoic acid have also been found to increase in the presence of their sodium salts and the addition of a hydroxy group to the acid led to the formation of complexes (6).

Chelation of ferric and aluminum ions with salicylic acid and its amino, chloro, and nitro derivatives have been demonstrated by Foye and Turcotte (7). Results from the investigation of the action of Schardinger dextrins on benzoic acid and hydroxybenzoic acids did not seem to indicate a clear cut mechanism of the complexation involved. Apparently hydrogen bonding is an important factor in the cyclodextrin–hydroxybenzoic acid interaction (8). Schlenk and Sand (9) showed that the molecular ratio of cyclodextrin to certain benzoic acid derivatives was a function of the physical state of the complex. Monohalogenated benzoic acids and

Received May 23, 1966, from the School of Pharmacy, University of Singapore, Singapore.
Accepted for publication September 13, 1966.

aminobenzoic acids have been reported to interact with cyclodextrins. The resultant complexes were considered to be due to inclusion formation and other attractive forces existing between host and guest molecules (10).

Higuchi and Drubulis (11) have attributed the interaction of hydroxyaromatic acids and their salts to a donor–acceptor type of mechanism. Urea has been shown to form complexes of low stability with benzoic acid while with salicylic acid it forms insoluble interaction products (12). Goudah and Guth (13) demonstrated that benzoic acid and its substituted compounds complexed with potato and arrowroot starch and postulated that attractive forces and inclusion formation were responsible for the interaction observed. Salicylic acid has been reported to exhibit the greatest binding tendency for polysorbate 80, followed by the *meta* and *para* isomers (14). This was identical with the findings of Blaug and Ebersman (15) for the behavior of hydroxybenzoic acids toward hyprose ester. Chakravarty, Lach, and Blaug (16) studied the interaction of hydroxybenzoic acids with polyoxyl 40 stearates based on solubility measurements.

It is the purpose of this investigation to study the interaction of hydroxybenzoic acids and the amino, chloro, and nitro derivatives of benzoic acid with cationic surfactants of the quaternary ammonium type as previous work has dealt with the interaction of pharmaceutical drugs with nonionic surfactants.

## EXPERIMENTAL

**Materials.**—Recrystallized benzoic acid, m.p. 122–122.5° (Monsanto Chemicals Ltd.); recrystallized salicylic acid, m.p. 158–159°, recrystallized *m*-hydroxybenzoic acid, m.p. 205–205.5°, recrystallized *p*-hydroxybenzoic acid, m.p. 215–216°, recrystallized acetylsalicylic acid, m.p. 137–138°, recrystallized *o*-aminobenzoic acid, m.p. 145.5–146° (British Drug Houses Ltd.); recrystallized *m*-aminobenzoic acid, m.p. 174–175°, recrystallized *p*-aminobenzoic acid m.p. 187–188°, recrystallized *o*-chlorobenzoic acid, m.p. 140–141°, recrystallized *m*-chlorobenzoic acid, m.p. 155–156°, recrystallized *p*-chlorobenzoic acid, m.p. 240–241°, recrystallized *o*-nitrobenzoic acid, m.p. 146–147°, recrystallized *m*-nitrobenzoic acid, m.p. 140–141°, recrystallized *p*-nitrobenzoic acid, m.p. 241–242° (Hopkin and Williams Ltd.). The cationic surfactants were dodecyltrimethylammonium bromide,[1] tetradecyltrimethylammonium bromide,[1] and cetyltrimethylammonium bromide.[2] The anionic surfactant was sodium lauryl sulfate (Sipon Products Ltd.) and the nonionic surfactant was cetomacrogol 1000 B.P.C.[3] The melting points and the critical micelle concentrations of the surfactants are listed in Table I.

[1] Marketed as Morphan D and Morphan T, respectively, by Glovers Chemicals Ltd.
[2] Marketed as Cetrimide by Imperial Chemical Industries.
[3] Marketed as Texofor AIP by Glovers Chemicals Ltd.

Table I.—Physical Constants of Surfactants

| Surfactant | M.p.[a] | CMC 25°[b] %w/v |
|---|---|---|
| Dodecyltrimethylammonium bromide | 244–245 | 0.041 |
| Tetradecyltrimethylammonium bromide | 246–247 | 0,082 |
| Cetyltrimethylammonium bromide | 262–263 | 0.051 |
| Sodium lauryl sulfate | 204–206 | 0.014 |
| Cetomacrogol 1000 | 37–38 | 0.0021 |

[a] Micro melting apparatus. [b] From surface tension measurements using the Du Nouy tensiometer.

**Apparatus.**—Portable Ferranti viscometer, model VL; Pye Tropical universal pH meter.

**Measurement of the Solubilities of the Isomers of Hydroxy, Amino, Chloro, and Nitrobenzoic Acids in Surfactant Solutions.**—Varying amounts of the organic acid were weighed into a series of 25-ml. graduated glass-stoppered cylinders containing the required concentration of surfactant. The cylinders were rotated in a thermostatically controlled water bath at 25 ± 0.1° for 24 hr. The end point was taken as the mean between a clear solution and one in which a slight excess of acid was present.

**Measurement of Viscosity.**—The required amounts of the organic acid were weighed into a series of 100-ml. volumetric flasks containing the required concentration of the surfactant. The flasks were rotated in a thermostatically controlled water bath at 25 ± 0.1° for 24 hr. The viscosities of the dispersions were measured using the portable Ferranti viscometer placed in a thermostatically controlled water bath at 25 ± 0.5°. The shear rates employed ranged from 483.0 to 78.56 sec. An interval of 30 sec. was allowed between any two readings.

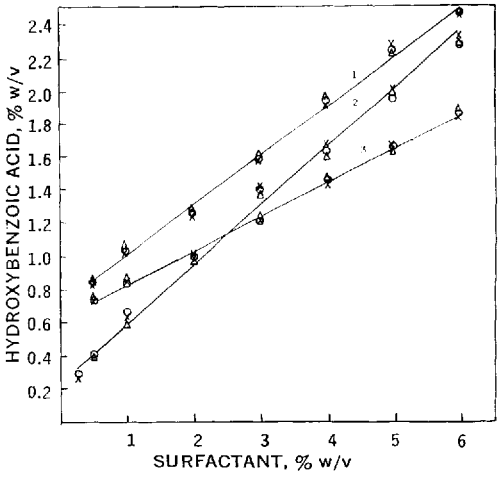


Fig. 1.—Solubilities of hydroxybenzoic acids in aqueous solutions of alkyltrimethylammonium bromide surfactants of varying chain length at 25°. Key: ×, dodecyltrimethylammonium bromide; O, tetradecyltrimethylammonium bromide; △, cetyltrimethylammonium bromide; *1*, *m*-hydroxybenzoic acid; *2*, salicylic acid; *3*, *p*-hydroxybenzoic acid.

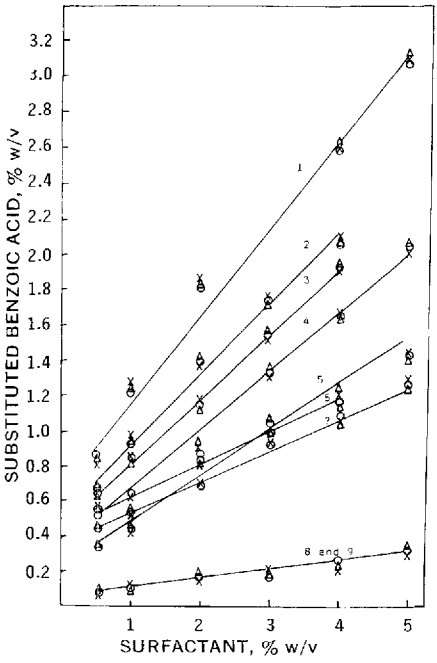


Fig. 2.—Solubilities of substituted benzoic acids in aqueous solutions of alkyltrimethylammonium bromide surfactants of varying chain length at 25°. Key: ×, dodecyltrimethylammonium bromide; O, tetradecyltrimethylammonium bromide; △, cetyltrimethylammonium bromide; *1*, *o*-nitrobenzoic acid; *2*, *m*-nitrobenzoic acid; *3*, *o*-aminobenzoic acid; *4*, *o*-chlorobenzoic acid; *5*, *m*-chlorobenzoic acid; *6*, *m*-aminobenzoic acid; *7*, *p*-aminobenzoic acid; *8*, *p*-nitrobenzoic acid; *9*, *o*-chlorobenzoic acid.

The shear rate was increased and then decreased for all viscosity measurements.

## RESULTS AND DISCUSSION

**Solubilities of Substituted Benzoic Acids in Surfactant Solutions.**—Figures 1 and 2 show the solubilities of the isomers of hydroxy, amino, chloro, and nitrobenzoic acids in surfactant solutions. In all cases the solubilities of the acids are proportional to surfactant concentration. There is, however, no appreciable difference in the solubilities of the acids in the three surfactants. These solubility graphs seem to indicate that variation of the chain length of the lipophilic portion of the surfactant molecule has no effect on the solubilities of the acids suggesting that the solubilities of the various substituted benzoic acids studied are independent of the chain length of the surfactant molecule. Except for the hydroxy derivatives, the other acids show a decrease in solubility in the order of *ortho*, *meta*, and *para* isomers.

**Viscosity Measurements.**—Figures 3, 4, and 5 show the viscosities of dispersions containing varying amounts of salicylic acid. In general, there is an increase in viscosity with increasing concentration of salicylic acid in the surfactant solution up to approximately when the system becomes saturated with the acid, after which the viscosity remains constant or decreases. This behavior is seen with all the concentrations of surfactants studied, 2%, 3%, 4%, 5%, and 6% and in the range of shear rates used, the viscosity being greater at low rates of shear than at high rates of shear. These observations can be attributed to interaction of salicylic acid with the surfactants, particularly the tetradecyltrimethylammonium and cetyltrimethylammonium bromides. In the case of dodecyltrimethylammonium bromide a lesser degree of interaction with salicylic acid is apparent as no marked changes in viscosity have been observed. Probably it is due to the shorter chain length of the lipophilic portion of the surfactant molecule which may tend to discourage interaction, or it may be due to the resultant complex being smaller in size and hence is unable to produce the relatively higher viscosity seen with the longer chain surfactants. When the system becomes saturated with salicylic acid, the viscosity tends to remain constant with further additions of the acid and this is particularly noticeable at low surfactant concentration. These observations suggest that once interaction is complete the excess salicylic acid has no effect on the viscosity of the system. However, at high surfactant concentration the viscosity decreases at about the concentration at which the system becomes saturated with salicylic acid. This may be due to the unstable nature of the complex and which may manifest itself more predominantly in the presence of a large number of complexes which follows from an increased concentration of the surfactant.

When the concentration of salicylic acid in the surfactant solution is low, the system behaves like a Newtonian liquid. As the salicylic acid content is increased the system changes to a non-Newtonian liquid producing large differences in viscosities with varying rates of shear (Figs. 3, 4, and 5). It would appear that adequate salicylic acid must be present for interaction to take place to produce the viscosity effect. With a higher concentration of the surfac-

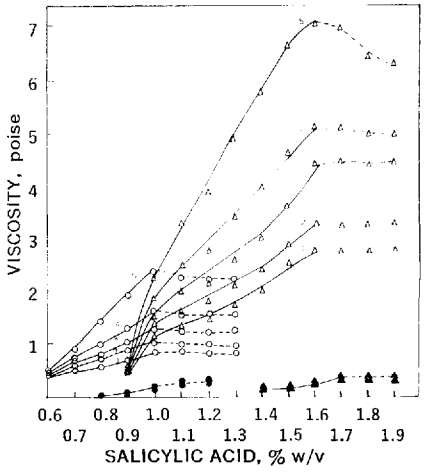


Fig. 3.—Effect of salicylic acid on the viscosity of alkyltrimethylammonium bromide solutions at 25°. Dodecyltrimethylammonium bromide: ●, 2%; ▲, 4%; tetradecyltrimethylammonium bromide: O, 2%; △, 4%; ——, below saturation; - - - -, above saturation. Shear rate: *1*, 234.6 sec.$^{-1}$; *2*, 195.9 sec.$^{-1}$; *3*, 155.1 sec.$^{-1}$; *4*, 117.35 sec.$^{-1}$; *5*, 78.56 sec.$^{-1}$.

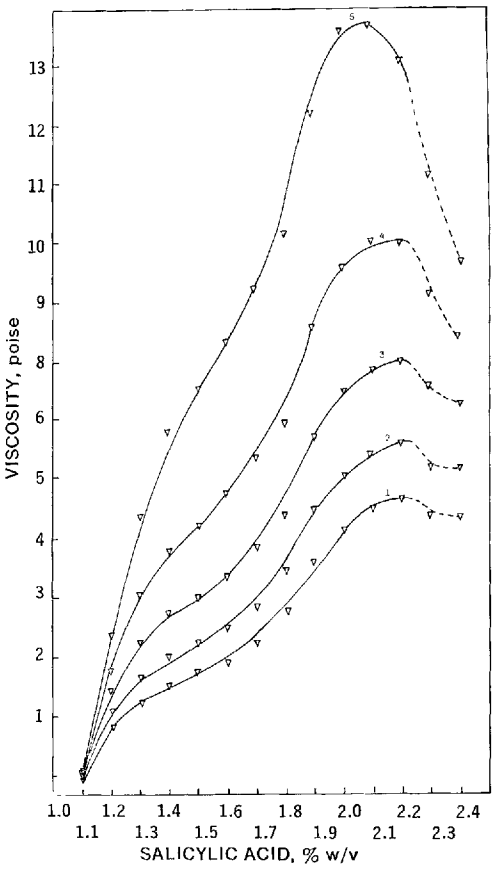


Fig. 4.—Effect of salicylic acid on the viscosity of tetradecyltrimethylammonium bromide solution (6%) at 25°. Key: ——, below saturation; - - - -, above saturation. Shear rate: *1*, 234.6 sec.$^{-1}$; *2*, 195.9 sec.$^{-1}$; *3*, 155.1 sec.$^{-1}$; *4*, 117.35 sec.$^{-1}$; *5*, 78.56 sec.$^{-1}$.

tant, more salicylic acid is required to initiate the non-Newtonian flow and this amount increases proportionately (Fig. 6). However, the ratio of salicylic acid concentration to surfactant concentration at which non-Newtonian flow commences decreases with the surfactant concentration as shown in Table II. As the ratio is probably linked up with the degree of interaction it may mean that a smaller degree of interaction is necessary for the system to exhibit non-Newtonian flow in the presence of a high concentration of the surfactant. At a low concentration of surfactant where there are less molecules of the surfactant a greater degree of interaction is required to initiate the non-Newtonian flow. In the case of dodecyltrimethylammonium bromide the viscosity effect is less marked, and the change to non-Newtonian flow is therefore less obvious.

The amounts of salicylic acid that have to be added to the tetradecyltrimethylammonium bromide solutions to produce the non-Newtonian flow initially are slightly lower than for the corresponding cetyltrimethylammonium bromide solutions as seen in Fig. 6. Furthermore, the viscosity of a tetradecyltrimethylammonium bromide solution containing the same amount of salicylic acid as in a cetyltrimethylammonium bromide solution is much higher (Figs. 3, 4, and 5) indicating that the chain length of tetradecyltrimethylammonium bromide is probably optimally favored for interaction. The maxi-

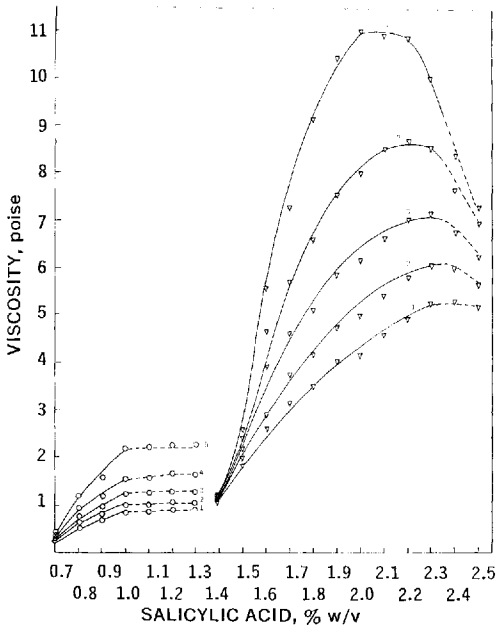


Fig. 5.—Effect of salicylic acid on the viscosity of cetyltrimethylammonium bromide solutions at 25°. Key: O, 2%; ▽, 6%; ——, below saturation; - - - -, above saturation. Shear rate: *1*, 234.6 sec.$^{-1}$; *2*, 195.9 sec.$^{-1}$; *3*, 155.1 sec.$^{-1}$; *4*, 117.35 sec.$^{-1}$; *5*, 78.56 sec.$^{-1}$.

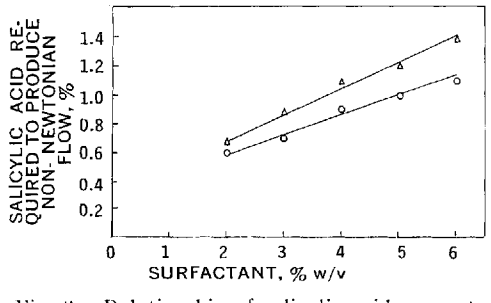


Fig. 6.—Relationship of salicylic acid concentration required to initiate non-Newtonian flow and surfactant concentration. Key: O, tetradecyltrimethylammonium bromide; △, cetyltrimethylammonium bromide.

Table II.—Ratios of Salicylic Acid Concentration to Surfactant Concentration at Which Non-Newtonian Flow is Initiated

| Surfactant, %w/v | Salicylic Acid TTAB[a] | Salicylic Acid CTAB[b] |
|---|---|---|
| 2.0 | 0.300 | 0.350 |
| 3.0 | 0.230 | 0.300 |
| 4.0 | 0.225 | 0.275 |
| 5.0 | 0.200 | 0.260 |
| 6.0 | 0.183 | 0.233 |

[a] TTAB, tetradecyltrimethylammonium bromide.
[b] CTAB, cetyltrimethylammonium bromide.

TABLE III.—pH OF SURFACTANT SOLUTIONS CONTAINING HYDROXYBENZOIC ACIDS

| Salicylic Acid % in 2% DTAB[a] | pH | *m*-Hydroxybenzoic Acid % in 2% DTAB | pH | *p*-Hydroxybenzoic Acid % in 2% DTAB | pH |
|---|---|---|---|---|---|
| 0.6 | 1.9 | 0.6 | 2.25 | 0.6 | 2.45 |
| 0.7 | 1.85 | 0.7 | 2.2 | 0.7 | 2.4 |
| 0.8 | 1.8 | 0.8 | 2.15 | 0.8 | 2.35 |
| 0.9 | 1.8 | 0.9 | 2.15 | 0.9 | 2.3 |
| 1.0 | 1.6 | 1.0 | 2.1 | 1.0 | 2.3 |
| Salicylic Acid % in 2% TTAB[b] | | *m*-Hydroxybenzoic Acid % in 2% TTAB | | *p*-Hydroxybenzoic Acid % in 2% TTAB | |
| 0.6 | 1.85 | 0.6 | 2.2 | 0.6 | 2.4 |
| 0.7 | 1.8 | 0.7 | 2.15 | 0.7 | 2.4 |
| 0.8 | 1.8 | 0.8 | 2.1 | 0.8 | 2.35 |
| 0.9 | 1.75 | 0.9 | 2.1 | 0.9 | 2.35 |
| 1.0 | 1.65 | 1.0 | 2.05 | 1.0 | 2.3 |
| Salicylic Acid % in 2% CTAB[c] | | *m*-Hydroxybenzoic Acid % in 2% CTAB | | *p*-Hydroxybenzoic Acid % in 2% CTAB | |
| 0.6 | 1.8 | 0.6 | 2.25 | 0.6 | 2.35 |
| 0.7 | 1.8 | 0.7 | 2.2 | 0.7 | 2.3 |
| 0.8 | 1.75 | 0.8 | 2.15 | 0.8 | 2.25 |
| 0.9 | 1.7 | 0.9 | 2.1 | 0.9 | 2.2 |
| 1.0 | 1.7 | 1.0 | 2.1 | 1.0 | 2.2 |

[a] DTAB, dodecyltrimethylammonium bromide. [b] TTAB, tetradecyltrimethylammonium bromide. [c] CTAB, cetyltrimethylammonium bromide.

mum viscosity of salicylic acid in the tetradecyltrimethyl and cetyltrimethylammonium bromide solutions occurs in about the same concentration due to the fact that the solubility of the acid in both the surfactants are practically identical. In dodecyltrimethylammonium bromide solutions containing salicylic acid this is not clear as the viscosity effect is not marked.

*m*-Hydroxybenzoic and *p*-hydroxybenzoic acids were included in the investigation, but both failed to show the viscosity effect observed with salicylic acid. The viscosities of both these acids remain unchanged when compared with the corresponding concentrations of surfactant in the absence of the acid. Benzoic acid and acetylsalicylic acid also failed to show any viscosity changes. The interaction of salicylic acid with the quaternary type of surfactants is highly specific as further investigations with the *ortho*, *meta*, and *para* substituted aminobenzoic, chlorobenzoic, and nitrobenzoic acids produced no viscosity change. In addition, salicylic acid did not exhibit this viscosity effect when dispersed with an anionic surfactant such as sodium lauryl sulfate or with a nonionic surfactant such as cetomacrogol 1000. The viscosities of dodecyltrimethylammonium, tetradecyltrimethylammonium, and cetyltrimethylammonium bromide solutions are independent of the concentration of the surfactant and practically independent of each other.

The viscosity effect is not related to pH. Table III shows the pH of surfactant solutions containing hydroxybenzoic acids. There is a small change in pH with increasing concentration of the acid. The viscosity of a surfactant solution whose pH is adjusted to that of a corresponding surfactant solution containing salicylic acid remains unaffected. This is true for all the three surfactants.

The mechanism of interaction is complicated and perhaps not yet fully understood. Suggestions for interactions of compounds with surfactants of the polyether type have been made by Higuchi and Lach (1) as due to the formation of molecular complexes and by Goodhart and Martin (5), Blaug and Ebersman (15), and Autian and Shaikh (17) as due to micellar solubilization. The results from this investigation indicate that the interaction of salicylic acid with surfactants of the quaternary type involves complex formation which leads to a marked change in viscosity and is only possible with the *ortho* substituted hydroxybenzoic acid while the *meta* and *para* compounds possess structures which are unfavorable to interaction. Besides, other attractive forces are likely to play a part as it is not only the *ortho* substituent that effects a viscosity change; a hydroxy group is essential, since the amino, chloro, and nitrobenzoic acids do not exhibit this viscosity effect.

The above-mentioned complexation is of importance to pharmaceutical formulation. It can be made to stabilize emulsified preparations such as creams, ointments containing the quaternary ammonium type of surfactants, and salicylic acid due to the high viscosity resulting from the interaction.

## REFERENCES


(1) Higuchi, T., and Lach, J. L., *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 465(1954).
(2) Higuchi, T., and Kuramoto, R., *ibid.*, **43**, 398(1954).
(3) Higuchi, T., and Lach, J. L., *ibid.*, **42**, 138(1953).
(4) *Ibid.*, **43**, 527(1954).
(5) Goodhart, F. W., and Martin, A. N., *J. Pharm. Sci.*, **51**, 50(1962).
(6) Valinoti, M. R., and Bolton, S., *ibid.*, **51**, 201(1962).
(7) Foye, W. O., and Turcotte, J. G., *ibid.*, **51**, 329(1962).
(8) Cohen, J., and Lach, J. L., *ibid.*, **52**, 132(1963).
(9) Schlenk, H., and Sand, D., *J. Am. Chem. Soc.*, **83**, 2312(1961).
(10) Lach, J. L., and Chin, T. F., *J. Pharm. Sci.*, **53**, 69 (1964).
(11) Higuchi, T., and Drubulis, A., *ibid.*, **50**, 905(1961).
(12) Bolton, S., *ibid.*, **52**, 1071(1963).
(13) Goudah, M. W., and Guth, E. P., *ibid.*, **54**, 298 (1965).
(14) Patel, N. K., and Foss, N. E., *ibid.*, **54**, 1495(1965).
(15) Blaug, S. M., and Ebersman, D. S., *ibid.*, **53**, 35 (1964).
(16) Chakravarty, D., Lach, J. L., and Blaug, S. M., *Drug Std.*, **25**, 137(1957).
(17) Autian, J., and Shaikh, Z. J., *ibid.*, **28**, 103(1960).