

placed on the agar after drying up the ethanol. After an incubation period of 36 hr., the zones of inhibition around the disks were measured. The organisms included in this study were: *Escherichia coli*, *Salmonella typhosa*, *Aerobacter aerogenes*, and *Staphylococcus aureus*.

DISCUSSION

Eight compounds, obtained by varying the substituents at the 3- and 5-positions of benzothiazoline-2-thione, were evaluated for their inhibitory effects on four organisms. The results of this study are recorded in Table I. The substituents at position 3 were: 3-methylpiperidinomethyl, 4-methylpiperidinomethyl, 4-phenylpiperidinomethyl, 4-phenylpropylpiperidinomethyl, 2,6-dimethylmorpholinomethyl, hexamethyleneiminomethyl, anilinomethyl, 4-fluoroanilinomethyl, acetoxymethyl, 3,4,5-trimethoxybenzoxymethyl, and hydroxymethyl groups. Position 5 was occupied by a chlorine atom in certain compounds, and others were without any substituents. Compounds 3 and 13 were devoid of any inhibition. Activity was considerably reduced when the heterocyclicamino function was replaced by the arylamino, acetoxy, or 3,4,5-trimethoxybenzoxymethyl groups. Five compounds (2, 8, 10, 17, and 18) were active against all four organisms.

REFERENCES

- (1) A. Moys, G. Bloeckinger, and E. Schwartz, *Cesk. Dermatol.*,

39, 269(1964); through *Chem. Abstr.*, **61**, 15068(1964).

(2) M. G. Chatterjee, S. K. Ranganathan, B. B. L. Saxena, and S. R. Sengupta, *Def. Sci. J.*, **11**, 70(1961); through *Chem. Abstr.*, **61**, 3631(1964).

(3) E. A. Kuznetsova, S. V. Zhuravlev, T. N. Steianova, V. N. Solovev, and V. S. Zueva, *Khim. Farm. Zh.*, **1**, 7(1967); through *Chem. Abstr.*, **67**, 90708(1968).

(4) H. D. Cossey, R. N. Gartside, and F. F. Stephens, *Arzneim.-Forsch.*, **16**, 33(1966).

(5) V. G. Zapadnyuk, *Farm. Zh. (Kiev)*, **17**, 36(1962); through *Chem. Abstr.*, **57**, 2341(1962).

(6) A. Moys, E. Schwartz, and G. Bloeckinger, *Lek. Listy*, **43-II**, 325(1963); through *Chem. Abstr.*, **60**, 7351(1964).

(7) W. Logenmann, S. Galimberti, G. Tosolini, I. Decarneri, and G. Coppi, *Farmaco Ed. Sci.*, **16**, 795(1961).

(8) R. S. Varma and W. L. Nobles, *J. Pharm. Sci.*, **58**, 497(1969).

(9) *Ibid.*, **57**, 1801(1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 17, 1972, from the *Chemistry Department, Lucknow University, Lucknow, India*, and the *School of Pharmacy, University of Mississippi, University, MS 38677*

Accepted for publication August 1, 1972.

The authors thank Professor Ram Gopal for his interest in this work.

* Present address: Division of Microbiology, Central Drug Research Institute, Lucknow, India.

▲ To whom inquiries should be directed. Present address: Office of the President, Mississippi College, Clinton, MS 39058

Viscosity Change in Salicylic Acid-Cetrimide System by Surfactants

LUCY S. C. WAN

Abstract □ The series of cationic and nonionic surfactants studied were found to decrease the viscosity of the salicylic acid-cetrimide system. This viscosity decrease varied with the surfactant concentration and with the volume of additive solution. With cationic surfactants, the fall in viscosity could be attributed to a dilution of the system, with the same type of surfactant resulting in a decrease of saturation; with nonionic surfactants, the fall in viscosity could be attributed to a penetration of the additive into the mesh structure of the macromolecules, bringing about a separation of the macromolecules from each other.

Keyphrases □ Viscosity—effect of surfactants on salicylic acid-cetrimide system □ Surfactants, cationic and nonionic—effect on viscosity of salicylic acid-cetrimide system □ Salicylic acid cetrimide system—effect of surfactants on viscosity □ Cetrimide-salicylic acid system—effect of surfactants on viscosity

As stated in an earlier paper (1), the anionic surfactants studied caused an increase in viscosity followed by a decrease in similar salicylic acid-cetrimide systems. It was considered logical as a follow-up to investigate the other two common types of surfactants as additives to these systems. Hence, some cationic and nonionic surfactants were selected on the basis that they could be used in pharmaceutical practice. Studies of this nature

have not apparently been undertaken, although some related work has been carried out on the interaction of pharmaceutical compounds such as starch, amylopectin, and chondroitin with quaternary ammonium compounds (2-4).

EXPERIMENTAL

Materials—The cationic surfactants used were dodecyltrimethylammonium bromide¹, alkyl aryl trimethylammonium chloride¹, and cetrimide BP²; the nonionic surfactants were polysorbate 20³, polysorbate 40³, polysorbate 60³, polysorbate 80³, polysorbate 85³, and polyoxyethylene ether of cetyl alcohol⁴. The recrystallized salicylic acid, m.p. 158–159°, was the same as that stated in a previous paper (5).

Measurement of Viscosity at 25°—A system containing 1.4% salicylic acid and 5% cetrimide in water was prepared, and its viscosity in the presence of an added solution of surfactants was

¹ Marketed as Morphan D and Gloquat C, respectively, by Grovers Chemicals Ltd., Leeds 12, England. The active ingredient content of Gloquat C is 50% w/w.

² Grovers Chemicals Ltd., Leeds 12, England.

³ Marketed as Tween 20, 40, 60, 80, and 85, respectively, by Honeywell-Atlas Ltd., London, England.

⁴ Marketed as Texofor A24 by Grovers Chemicals Ltd., Leeds 12, England.

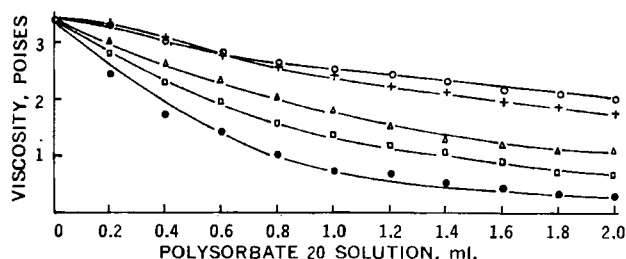


Figure 1—Effect of various concentrations of polysorbate 20 on the viscosity of the salicylic acid-cetrimide system. Key (percent polysorbate 20 concentration): ○, 1; +, 2; △, 4; □, 6; and ●, 10.

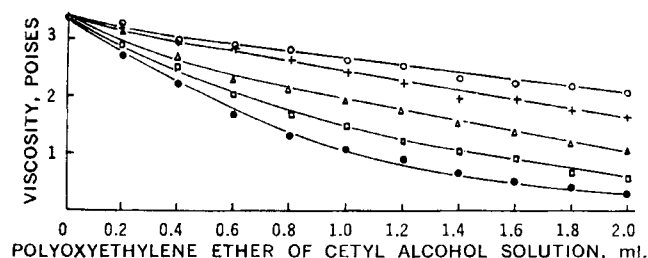


Figure 2—Effect of various concentrations of polyoxyethylene ether of cetyl alcohol on the viscosity of the salicylic acid-cetrimide system. Key (percent polyoxyethylene ether of cetyl alcohol concentration): ○, 1; +, 2; △, 4; □, 6; and ●, 10.

measured⁵ at a shear rate of 78.56 sec.⁻¹ in the same manner as described before (5). The additive solution was delivered from a graduated pipet to a sample of 50 g. (about 51 ml.) of the salicylic acid-cetrimide system and dispersed in the sample without removing the viscometer cylinders (6).

RESULTS AND DISCUSSION

Figures 1 and 2 show that the viscosity of the salicylic acid-cetrimide system decreased in the presence of solutions of some nonionic surfactants. The viscosity became lower when a higher concentration and a larger volume of the additive solution were added. This was also true with the other surfactants, polysorbate 40, polysorbate 60, polysorbate 80, and polysorbate 85. However, the amount of viscosity lowering due to the addition of a solution of greater additive concentration was slightly less than that produced by a larger volume of more dilute concentration such that both volumes contained an equivalent quantity of additive. This may be attributed to the effect of the increase in volume of the total system. Evidence in support of this can be seen in the small decrease in viscosity resulting from the addition of water to such a system (6).

It is believed that the interaction of cetrimide and salicylic acid leads to the formation of macromolecules which are responsible for the high viscosity achieved in the system. Molecules are considered to

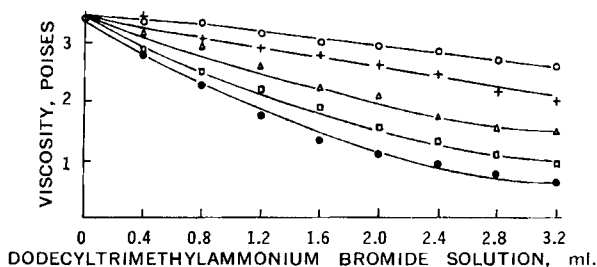


Figure 3—Effect of dodecyltrimethylammonium bromide of varying concentration on the viscosity of the salicylic acid-cetrimide system. Key (percent dodecyltrimethylammonium bromide concentration): ○, 1; +, 2; △, 4; □, 6; and ●, 10.

⁵ Using a portable Ferranti viscometer, model VL, Ferranti Ltd., Moston, Manchester 10, England.

Table I—Viscosity of Salicylic Acid-Cetrimide Systems Containing 5% Cetrimide and Varying Amounts of Salicylic Acid at 25° (Shear Rate is 78.56 sec.⁻¹)

Salicylic Acid Concentration, %	Viscosity, poises
1.2	0.71
1.3	1.82
1.4	3.41
1.5	4.59
1.6	6.26
1.8	7.52
1.9	7.92

move more or less individually as in an ordinary liquid. Macromolecules, however, may be dispersed in the medium in the form of a network. The greater the degree of proximity of the macromolecules, the higher is the viscosity. The surfactant additives incorporated in this system are likely to penetrate the mesh structure. Since the high viscosity of the system is essentially due to the presence of the macromolecules produced by the interaction of the acid with cetrimide molecules and to the compactness of the network, the intermacromolecular penetration by the nonionic surfactant additives causes the macromolecules to move further apart from neighboring macromolecules, thereby reducing the viscosity. It was found previously (5) that cetomacrogol 1000 did not interact with salicylic acid in the absence of cetrimide.

The effect produced by the inclusion of cationic surfactants as additives to the system (Figs. 3 and 4) was the same as that produced by the nonionic surfactants. The viscosity reduction is probably due to the fact that the system has become diluted with the same type of surfactant. In addition, since the acid content remains the same, there is a decrease in saturation. This would lower the viscosity; it was found that when the amount of salicylic acid present was less and the system was not saturated to the same degree, there was a fall in viscosity (Table I). The penetration of the added cationic additive into the mesh structure exerts negligible effect because of the immediate dilution effect by a surfactant of a similar charge.

When salicylic acid was added to sodium lauryl sulfate solutions, no change in viscosity was observed. Even after adding graded

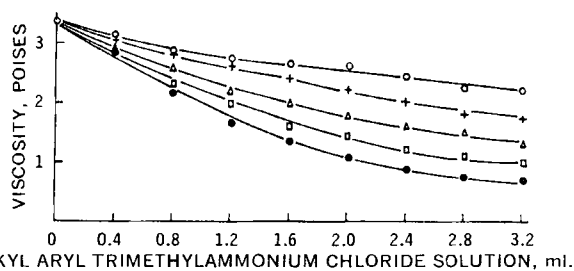


Figure 4—Effect of alkyl aryl trimethylammonium chloride of varying concentration on the viscosity of the salicylic acid-cetrimide system. Key (percent alkyl aryl trimethylammonium chloride concentration): ○, 1; +, 2; △, 4; □, 6; and ●, 10.

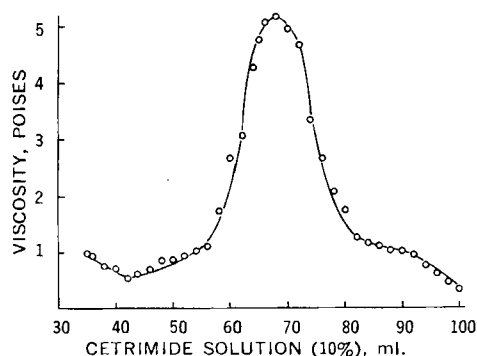


Figure 5—Viscosity of salicylic acid-sodium lauryl sulfate system on addition of a 10% cetrimide solution.

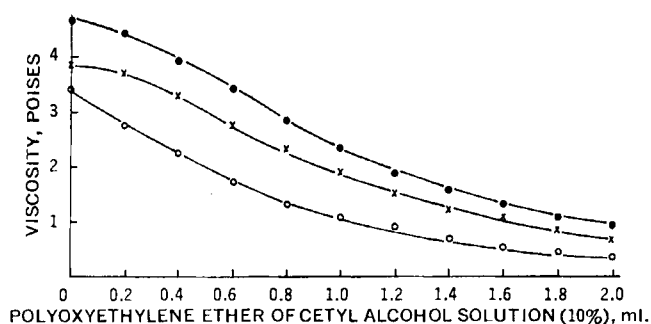


Figure 6—Viscosities of systems containing fixed salicylic acid concentration (1.4%) and varying cetrimide concentration on addition of a solution of polyoxyethylene ether of cetyl alcohol. Key (percent cetrimide concentration): ×, 3; ●, 4; and ○, 5.

volumes of a 10% cetrimide solution to an aqueous system containing 4% sodium lauryl sulfate and 2% salicylic acid, there was still no change. Eventually, when a much larger amount was incorporated, the viscosity decreased slightly and then increased markedly, rising to a maximum after which it decreased again (Fig. 5). The viscosity values could not be determined accurately in the presence of less than 35 ml. of a 10% cetrimide solution that was added to the system, because the precipitate formed by the neutralization of sodium lauryl sulfate with cetrimide interfered with the rotation of the viscometer cylinders.

The results can be explained in terms of neutralization occurring in the system during the continuous addition of the cetrimide solution as the additive. The initial incorporation of the cetrimide solution brings about the precipitation of a complex between the anionic and cationic surface-active ions. When an adequate amount of cetrimide solution is present (*i.e.*, about 35 ml.), most of the sodium lauryl sulfate ions are attracted to the positively charged molecules of the additive. It was observed that at about this stage the precipitate became more uniformly dispersed and the viscosity values could be measured. Subsequent additions of cetrimide solutions allow the cationic surfactant to interact with the salicylic acid and thus produce a rise in viscosity. This viscosity increase continues until most of the acid molecules interact with the cetrimide molecules and then the viscosity begins to fall. Then the effect is similar to that obtained by the addition of a cationic surfactant solution directly to the salicylic acid-cetrimide systems (Figs. 3 and 4).

When the concentration of salicylic acid was fixed (1.4%) and the concentration of cetrimide was varied, the viscosity was reduced by solutions (10%) of polyoxyethylene ether of cetyl alcohol (Fig. 6). This also occurred with the other nonionic surfactants investigated. Figure 7 shows that similar results were obtained with systems in which the acid content was different and the cetrimide content was kept constant (5%). This was true when the cetrimide solution was employed as the additive. The system containing 3% cetrimide and 1.4% salicylic acid is above saturation because excess acid is found after the system is allowed to equilibrate in a thermostatically controlled water bath for 24 hr. (1). In such a system, there will be a minimal amount of free cetrimide molecules; in the other two systems containing 4 and 5% cetrimide, a rela-

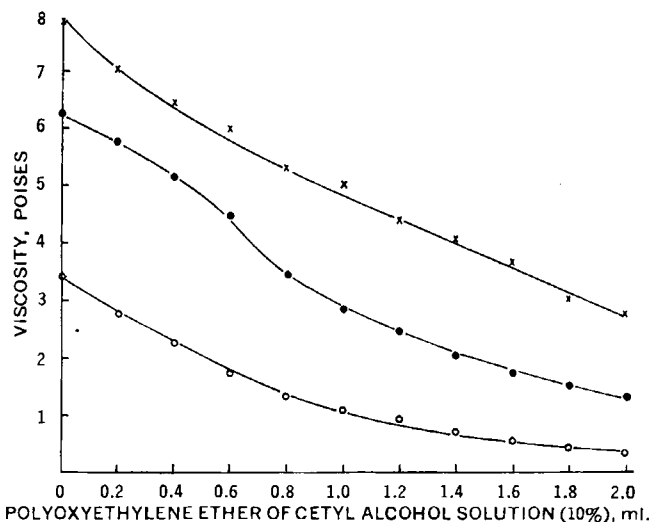


Figure 7—Viscosities of systems containing fixed cetrimide concentration (5%) and varying salicylic acid concentration on addition of a solution of polyoxyethylene ether of cetyl alcohol. Key (percent salicylic acid concentration): ×, 1.9; ●, 1.6; and ○, 1.4.

tively larger number of free cetrimide molecules will be present (Fig. 6). It appears, therefore, that irrespective of whether free cetrimide molecules were present or absent, the added solution of polyoxyethylene ether of cetyl alcohol did not increase the viscosity but decreased it. This finding is in contrast to that obtained with the anionic surfactants as additives (1). There is no neutralization taking place in these systems since the added surfactant is compatible with cetrimide.

These findings, together with those described previously (1), demonstrate the effects of different types of surfactant additives and provide knowledge that is useful when attempting to combine surfactants of the quaternary ammonium type in the formulation of products involving salicylic acid. This is particularly so in those preparations where the viscous property influences the physical stability of the presentation form of the preparation.

REFERENCES

- (1) L. S. C. Wan, *J. Pharm. Sci.*, **61**, 642(1972).
- (2) M. M. Fishman and R. S. Miller, *J. Colloid Sci.*, **15**, 232 (1960).
- (3) M. M. Fishman and I. Freund, *ibid.*, **16**, 392(1961).
- (4) S. Ehrenpreis and M. M. Fishman, *Biochim. Biophys. Acta*, **44**, 577(1960).
- (5) L. S. C. Wan, *J. Pharm. Sci.*, **55**, 1395(1966).
- (6) *Ibid.*, **60**, 939(1971).

ACKNOWLEDGMENTS AND ADDRESSES

Received February 22, 1972, from the *School of Pharmacy, University of Singapore, Sepoy Lines, Singapore 3.*
Accepted for publication July 24, 1972.