

only 3% in the monozygotic twins; in fact, it was virtually negligible in four of five pairs. Intrapair variation with respect to predicted availability in the dizygotic twins averaged about 14%. The mean predicted availability was essentially identical in both groups. The predicted availabilities in all subjects ranged between 45 and 85%, which is consistent with the range of 56–70% observed in a study with three subjects (1). The mean predicted availability of 65% was in perfect agreement with the previously observed mean (1).

This retrospective study provides greater confidence in the reliability of Eq. 1 as a predictor of average bioavailability for drugs undergoing first-pass metabolism.

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Effects of Acids and Bases on Salicylic Acid-Cetrimide Systems

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Abstract □ The effects of acids and bases on the viscosity of salicylic acid-cetrimide systems were investigated. A viscosity reduction was produced by the addition of acids and was independent of the degree of saturation of the cetrimide solution with salicylic acid. The incorporation of base followed by that of acid increased and decreased the viscosity, respectively. This viscosity behavior was demonstrated in undersaturated systems and was not governed by the relative amounts of base or acid used. In oversaturated systems, only a lowering of viscosity was observed.

Keyphrases □ Salicylic acid-cetrimide systems—effects of various acids and bases on viscosity □ Cetrimide-salicylic acid systems—effects of various acids and bases on viscosity □ Viscosity—salicylic acid-cetrimide systems, effects of various acids and bases

Since solutions of alkaline sodium salts have been shown to effect different changes in the viscosity of salicylic acid-cetrimide systems (1), a study of the reaction of the viscosity of the systems to acid additives was considered desirable. It was also the purpose of this investigation to determine whether the viscosity change arising from the addition of either acid or base is retained when these additives are added alternately to the same system. This approach is an attempt to test the sensitivity of the viscous property to these additives. A literature survey did not reveal information on this particular area of research.

EXPERIMENTAL

Recrystallized salicylic acid, mp 158–159°, and cetrimide¹ BP were the same as those described earlier (2). The acids were citric

acid², tartaric acid³, phosphoric acid⁴, acetic acid⁵, lactic acid⁶, 1 N hydrochloric acid², and dilute hydrochloric acid BP. The alkalis were 1 N sodium hydroxide³ and 1 N potassium hydroxide³. These additives were selected because they are representative of relatively weak acids, strong acids, and alkalis and are likely to be included in suspension formulation studies in which salicylic acid-cetrimide systems are involved.

The viscosity was measured at 25° as reported previously (2) and the pH⁷ was determined.

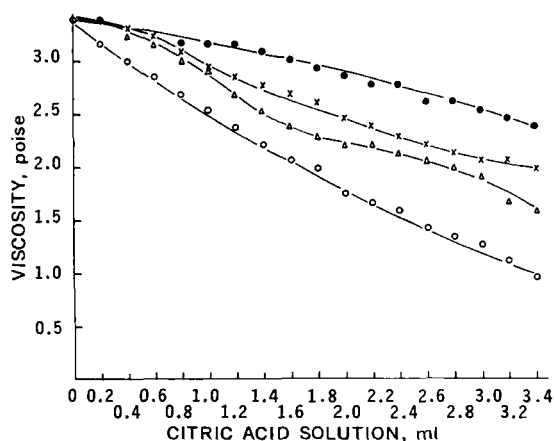


Figure 1—Decrease in viscosity on addition of citric acid solutions of different concentrations to systems (50 g) containing 5% cetrimide and 1.4% salicylic acid at 25°. Key (citric acid, % w/v): ●, 1; ×, 4; Δ, 6; and ○, 10. Shear rate is 78.56 sec⁻¹.

² May and Baker, Dagenham, England.

³ E. Merck, Darmstadt, Germany.

⁴ Hopkin and Williams Ltd., England.

⁵ British Drug Houses, Ltd., England.

⁶ Larporte Industries Ltd., Ilford, Essex, England.

⁷ Beckman pH expandometer, Fullerton, CA 92634

¹ Glovers Chemicals Ltd., Leeds 12, England.

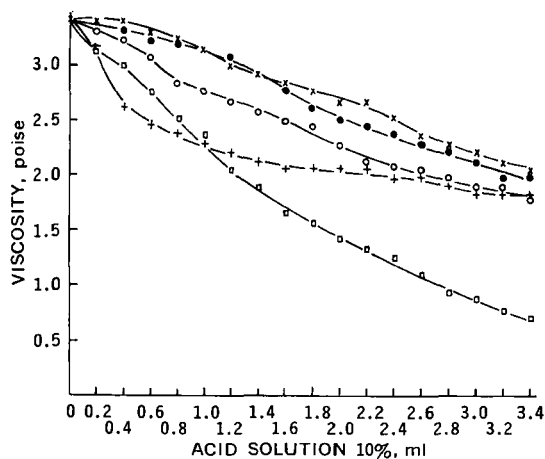


Figure 2—Effect of 10% acid solutions on the viscosity of systems (50 g) containing 5% cetrimide and 1.4% salicylic acid at 25°. Key: ×, tartaric acid; ○, phosphoric acid; ●, acetic acid; +, dilute hydrochloric acid BP; and □, lactic acid. Shear rate is 78.56 sec⁻¹.

RESULTS AND DISCUSSION

Figure 1 shows that the viscosity of salicylic acid–cetrimide systems was lowered in the presence of citric acid; a higher concentration of citric acid resulted in a greater lowering. Similarly, tartaric, acetic, phosphoric, lactic, and hydrochloric acids decreased viscosity (Fig. 2). The viscosity reduction was unrelated to the degree of saturation of the surfactant solution with salicylic acid, as can be seen in the action of an acetic acid solution on undersaturated and oversaturated systems (Fig. 3). This behavior also applied to the other acids employed. However, when the quantity of salicylic acid present in the system was low, no appreciable alteration in the viscosity was recorded (Fig. 3). Table I shows that the pH remained practically constant with increasing volumes of acid solution, with the exception of hydrochloric acid where a decrease in pH was observed. Therefore, it appears that the presence of most of these acids led to the formation of buffer systems.

Salicylic acid was found to interact with cetrimide to form a viscous product (3). It is believed that macromolecules resulting from this interaction are responsible for the high viscosity obtained. In the presence of other additives, the viscosity of salicylic acid–cetrimide systems was shown to vary according to the compounds added and the state of saturation of the system (2, 4, 5).

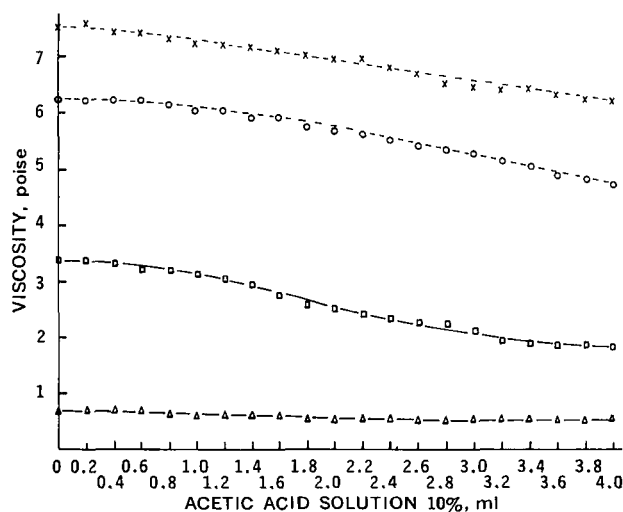


Figure 3—Viscosity reduction by 10% acetic acid solution in dispersions (50 g) containing 5% cetrimide and such amounts of salicylic acid to form undersaturated and oversaturated systems at 25°. Key (salicylic acid, % w/v): ×, 1.8; ○, 1.6; □, 1.4; Δ, 1.2; —, undersaturated; and ----, oversaturated. Shear rate is 78.56 sec⁻¹.

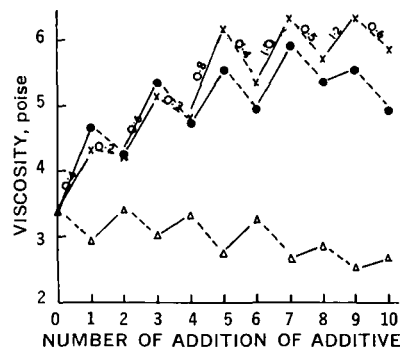


Figure 4—Effect of various methods of adding base and acid to the viscosity of systems (50 g) containing 5% cetrimide and 1.4% salicylic acid at 25°. Key: ●, 0.6 ml of 1 N NaOH–0.3 ml of 1 N HCl; ×, 1 N NaOH–1 N HCl fixed at 2:1 but volume of additive varies as indicated in milliliters on graph; Δ, 0.6 ml of 1 N HCl–0.3 ml of 1 N NaOH; —, 1 N NaOH; and ---, 1 N HCl. Shear rate is 78.56 sec⁻¹.

In preliminary experiments, it was observed that when the acid solutions were added to cetrimide solutions in the absence of salicylic acid, they had no effect on the viscosity. Hence, it was unlikely for this viscosity reduction to be brought about by a reaction between acid solutions and the surfactant. The viscosity decrease could not be attributed to a simple dilution effect, because the inclusion of water as an additive did not give a marked change in viscosity (4).

In the current investigation, the reduction in viscosity in both types of systems due to the added acids might arise from a break-up of the mesh-like structure of the system, the macromolecules becoming unstable in the presence of the acids. This condition indicates a high sensitivity of the macromolecules to these additives and the weakness of the links in the macromolecular network. The acid effect on viscosity is essentially the opposite to that of the sodium salts for undersaturated systems (1) but similar for oversaturated systems.

Instead of the usual method of adding the additive solution directly to the salicylic acid–cetrimide system, other procedures were adopted to ensure that the technique employed was not a contributing factor to the viscosity response obtained. First, the acid solution was added to the cetrimide solution and then the salicylic acid solution was added. Second, salicylic acid was added to the acid solution and this step was followed by the cetrimide solution addition. In both cases, a decrease in viscosity resulted. This finding suggests that the viscosity effect is not influenced by the manner of addition of the additive.

To examine further the mechanism of acid additive effect, a base was selected and, from preliminary studies, it was found that sodium hydroxide increased the viscosity of undersaturated systems but decreased that of oversaturated systems in the same way

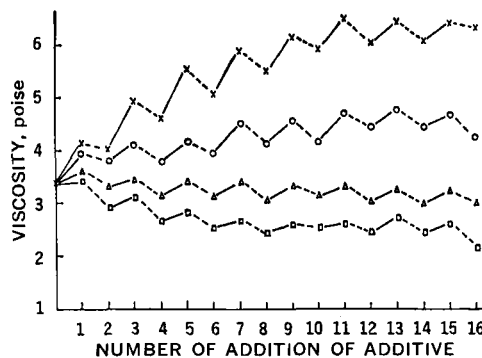


Figure 5—Viscosity variation produced by different ratios of sodium hydroxide to citric acid in systems containing 5% cetrimide and 1.4% salicylic acid (50 g) at 25°. Key (1 N sodium hydroxide–7% citric acid): ×, 1:1; ○, 1:2; Δ, 1:4; □, 1:6; —, 1 N sodium hydroxide; and ---, 7% citric acid. Shear rate is 78.56 sec⁻¹.

Table I—pH of Systems Containing 5% Cetrimide and 1.4% Salicylic Acid^a in the Presence of Varying Volumes of 10% Acid Solutions

Acid Solution	Volume of Acid Solution, ml							
	0.2	0.4	0.8	1.2	1.6	2.2	2.8	3.4
Citric acid	2.45	2.45	2.45	2.45	2.45	2.40	2.40	2.35
Tartaric acid	2.45	2.45	2.45	2.45	2.45	2.45	2.45	2.45
Acetic acid	2.45	2.45	2.45	2.45	2.45	2.45	2.45	2.45
Lactic acid	2.35	2.35	2.35	2.35	2.35	2.35	2.35	2.35
Phosphoric acid	2.35	2.35	2.35	2.30	2.30	2.25	2.25	2.25
Dilute hydrochloric acid BP	2.35	2.25	2.15	2.10	2.05	1.95	1.90	1.85

^a pH of system without additive is 2.45.

as the other sodium salts reported (1). Several approaches were made to determine whether the viscosity change brought about either by an acid or a base can be further influenced by a number of alternate additions of each additive. When the volumes of solutions of sodium hydroxide and of hydrochloric acid were kept constant so as to maintain a fixed ratio of base to acid, the viscosity increased and decreased with each addition of the basic and acidic solutions, respectively (Fig. 4). Keeping the same ratio but varying the additive volume did not alter the pattern of viscosity variation (Fig. 4). This behavior was not restricted either to a strong acid and a strong base or to one ratio.

By replacing hydrochloric acid with a weaker acid, citric acid (Fig. 5), each of the ratios used produced the typical viscosity reaction to sodium hydroxide and to citric acid. It was noted that the larger the ratio, the smaller the viscosity rise and the greater the viscosity fall. When the order of additive addition was reversed (Fig. 4), an increase and a decrease with respect to the additives were produced. From these results, it may be concluded that the changes in viscosity in these systems due to the added base and the acid can be predicted and that the viscosity effect exhibited by either additive can be reproduced in the presence of the other.

These procedures were applied to salicylic acid-cetrimide systems which were more than saturated with salicylic acid (Fig. 6).

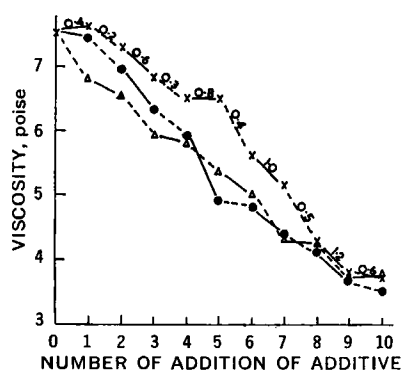


Figure 6—Effect of different methods of adding base and acid on the viscosity of oversaturated systems (50 g) which contain 5% cetrimide and 1.8% salicylic acid at 25°. Key: ●, 0.6 ml of 1 N NaOH-0.3 ml of 1 N HCl; ×, 1 N NaOH-1 N HCl fixed at 2:1 but volume of additive is varied as indicated in milliliters on graph; Δ, 0.6 ml of 1 N HCl-0.3 ml of 1 N NaOH; —, 1 N NaOH; and ---, 1 N HCl. Shear rate is 78.56 sec⁻¹.

The normal rise and fall in viscosity (Figs. 4 and 5) were absent and only a lowering of viscosity occurred. Thus, two additives with contrasting properties have the same effect on these dispersions. Apparently, the viscosity behavior resulting from both types of additives was maintained. By varying the concentration of cetrimide but keeping the amount of salicylic acid constant and vice versa, systems undersaturated or oversaturated with salicylic acid were obtained. The effects of potassium hydroxide and hydrochloric acid solutions on such systems were also studied to ascertain that the observed viscosity changes were not limited to the sodium salt. The results were similar to those with sodium hydroxide and the same acid in corresponding systems.

The data presented show that the macromolecules in both types of salicylic acid-cetrimide systems are unstable to the additives. Recovery from a lower viscosity after the addition of acid additive to a greater value following the subsequent addition of alkali additive in an undersaturated system suggests that these systems are sensitive to these additives and that the viscosity change can be altered readily. This rapid recovery illustrates the degree of sensitivity.

This finding also supports the view that the bonding links involved in the formation of macromolecules are probably not strong and that there may exist a preferential reaction between sodium hydroxide and salicylic acid to produce sodium salicylate, which then interacts with the free cetrimide molecules, rather than between salicylic acid and cetrimide molecules, notwithstanding the previous presence of acid additive. Both reactions lead to an increase in viscosity. The insensitivity of the oversaturated systems may be due to the lack of free cetrimide molecules. Hence, the mechanism of macromolecule formation is not likely to involve complex interactions of such a nature as to give rise to a rigid structural system that is not easily affected by additives.

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