

If you don't believe this, try to remember, without looking it up, who supplied your kitchen calendar this year.

It should be remembered, too, that novelties chosen for direct advertising of a drug store should be appropriate and in keeping with the character of the business. If they are otherwise, they may attract attention, but the attention won't be favorable and the reaction thus produced upon customers and prospective customers will be decidedly negative. For example, there are many women, and men, too, who are violently opposed to the use of tobacco. There could thus be a needless risk of antagonizing a group of important customers. What applies to cigarettes may also apply to other items, pictures, reading matter, etc.; in other words the selection of advertising requires careful consideration and study.

ACETYLSALICYLIC ACID AND ITS SOLUTION IN POTASSIUM CITRATE SOLUTION.

BY A. H. CLARK.

Frequently we have seen published statements or heard discussions regarding the solubility of aspirin in potassium citrate and similar salts. For some time it was thought that such a solution was an ideal way to dispense acetylsalicylic acid. Leech¹ has shown very clearly that acetylsalicylic acid in such a solution hydrolyzes rapidly and that after about four days fifty per cent is broken down. Snidow and Langenhan² have reviewed the literature of this decomposition quite completely as well as the hydrolysis of the acid by water alone. All the evidence presented in connection with the hydrolysis of acetylsalicylic acid by water, either with or without alkaline citrate, is very easy of confirmation. All that one needs to do is to carefully titrate a given volume of a newly prepared solution with standard alkali, half normal preferred, using phenolphthalein as indicator. From time to time titrate the same volume in the same way and note the increased volume of alkali required. When this volume has doubled complete hydrolysis is indicated. Leech plotted a curve, volume of alkali used against time of standing, which is very interesting and a similar experiment is plotted below.

After listening to numerous discussions of this subject by pharmacists and physicians, I became much impressed with the insistence of many that such solutions were therapeutically effective for some time after preparation. Even though, as Leech points out, fifty per cent of the acid is decomposed at the end of four days, the decomposition is progressive and for this four-day period such a solution might be very effective. Several "favorite prescriptions" of doctors have been mentioned in the writer's presence in which acetylsalicylic acid is dissolved in potassium citrate solution and sugar or syrup and flavoring added. The often repeated statement that such solutions retained their therapeutic activity excited the writer's interest to such an extent that experiments were started to determine whether or not something had remained undiscovered in connection with this question.

It was surprising to note that some of the prescriptions containing flavored syrups did not show the rapid rate of hydrolysis that Leech found in his aqueous

¹ *Jour. A. M. A.*, 78 (1922), 275.

² "A Pharmaceutical Study of Acetylsalicylic Acid," *JOUR. A. PH. A.*, 14 (1925), 694.

mixture. This led to the very natural conclusion that sugar might decrease the rate of hydrolysis of acetylsalicylic acid in such solutions. Several solutions were made and the rate of hydrolysis noted. It was found that with increasing amounts of sugar the rate of hydrolysis decreased. For example, a solution which contained about 300 Gm. sugar in 500 cc. and 2.5 times as much potassium citrate as aspirin, was hydrolyzed to the extent of 41 per cent at the end of five days and remained thus for thirty days. Another solution, saturated with sugar, otherwise the same as above was 19.3 per cent hydrolyzed at the end of the second day. The maximum amount of hydrolysis, 34.5 per cent, was reached between the fifth and sixth day and at the end of thirty days no further hydrolysis had taken place. The graph below shows typical curves of a solution without sugar and two solutions with different amounts of sugar.

Glycerin also seems to inhibit the hydrolysis of solutions of acetylsalicylic acid in potassium citrate. Since glycerin dissolves potassium citrate freely there is no

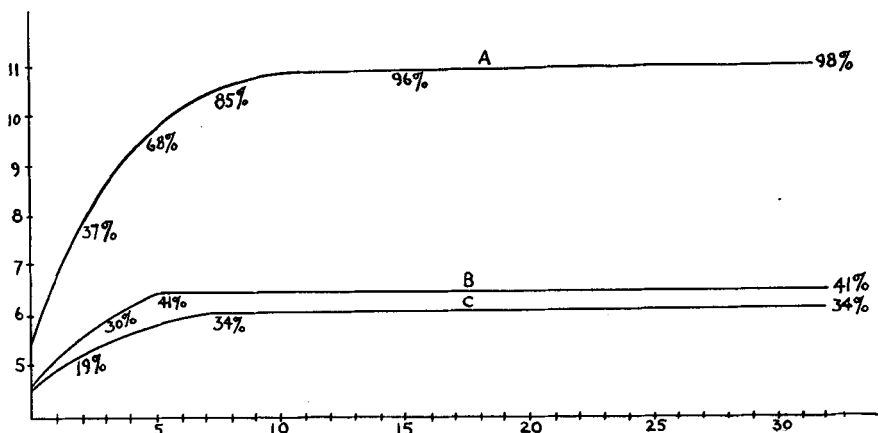


Fig. 1.—A, shows the curve for aqueous solution, no sugar or glycerin. B, curve for a solution containing 600 Gm. sugar per liter. C, curve for a solution saturated with sugar (about 850 Gm. per liter).

Vertical divisions represent cc. $N/2$ KOH used to titrate. Horizontal divisions represent the age of the solution in days. Percentage figures show approximate decomposition on the days titrated.

difficulty in preparing such solutions with glycerin. One solution of the acid in glycerin saturated with potassium citrate showed very little hydrolysis in a month's time. This solution was very viscous and hard to handle. It would hardly be practical to make or use such a solution on this account unless it would be for use as a stock solution for the preparation of small amounts of solutions of acetylsalicylic acid to be used over a short period of time.

Solutions containing less glycerin seemed to behave much like the sugar solutions although a very thorough examination of these was not carried out.

The solutions examined were made by dissolving the potassium citrate in water, using about fifteen times as much water as acetylsalicylic acid, and about three times as much potassium citrate as acid. The acid was then added to this solution and shaken rapidly until dissolved. The sugar (or glycerin) was then added and the mixture made up to a definite volume with water and shaken

frequently until the sugar was dissolved. If the solution of sugar and potassium citrate is first made and the acid added to this, solution takes place very slowly, from one to three days being required, depending upon the density of the sugar solution. During this time appreciable hydrolysis of the acid takes place. If glycerin is saturated with potassium citrate the solution is very viscous and several days are required for solution of the acid although, in this mixture, hydrolysis of the acid is not great during the process of solution.

Two very interesting problems were brought forcefully to mind during this work. The first one is that of the relative quantities of the acid, the potassium citrate, and water most advantageous to use in making such solutions. Very little was done in this connection but it was shown by one series of experiments that in a one part aspirin, three parts potassium citrate, ten parts water mixture, more aspirin dissolved than in a 1, 1, 10 or 1, 2, 10 or 1, 4, 10 or 1, 5, 10 proportion. By doubling the proportion of water, solution was very promptly completed in the 1, 3, 20 combination, while the others were but little affected by the increased amount of water.

The second and most interesting question is—What is the nature of the combination, if any, of acetylsalicylic acid and potassium citrate that makes the acid more soluble? This latter question is still open for study.

SUMMARY.

The experiments described show that in a solution of acetylsalicylic acid in potassium citrate the hydrolysis of the acid, which is complete in about two weeks, can be reduced to about thirty per cent in four to six days by the addition of sugar and that thereafter no further hydrolysis takes place within thirty days. This is assuming that the rate of hydrolysis of the acid is accurately shown by the increase in acidity.

It is also evident that an acetylsalicylic acid-glycerin-potassium citrate solution behaves in much the same manner.

The best proportions of acid, potassium citrate and water seem to be about one of acid, three of potassium citrate and fifteen to twenty of water. Such a solution saturated with sugar seems to undergo the least change.

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CANADIAN MEETINGS.

The AMERICAN PHARMACEUTICAL ASSOCIATION met in Toronto, September 4, 1877; William Saunders, of London, Ontario, was elected president. The second meeting in Canada was held at Montreal, August 12, 1896, and Joseph E. Morrison was elected president of the ASSOCIATION. Since the meetings mentioned the Canadian Pharmaceutical Association has been organized, so that the convention in Toronto in August will be a joint meeting with our sister organization, to which many A. PH. A. members are looking forward with happy anticipations. This will be the 25th anniversary of the Canadian Pharmaceutical Association and the 80th annual meeting of the AMERICAN PHARMACEUTICAL

ASSOCIATION; the Ontario Retail Druggists will also be in session, thus the convention will be international, and it is hoped the Associations of a number of countries other than those named will be represented by delegates.

Sir Henry S. Wellcome, Honorary President of the AMERICAN PHARMACEUTICAL ASSOCIATION, has been elected fellow of the Royal College of Surgeons. This is the second time that a person, not holding a medical degree aside from members of the Royal Family, has been thus honored; the other recipient was Field Marshall, Lord Roberts; Hon. Lord Dawson, Physician to His Majesty was given the same distinction by the Council of the Royal College of Surgeons of England.