

# Hydrolytic Stability of Calcium Acetylsalicylate Carbamide in the Presence of High Concentrations of Additives

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The hydrolysis of calcium acetylsalicylate carbamide in aqueous solution at 25, 40, and 50° in the pH range from 1 to 9 has been studied. The effect of high concentrations of several additives, commonly used in pharmaceutical formulation, on the rate of hydrolysis was determined.

NUMEROUS studies (1-5) of the stability of acetylsalicylic acid and its derivatives have been made over a wide range of pH and temperature; however, few reports have been quantitatively concerned with their hydrolytic stability in the presence of high concentrations of additives commonly used in pharmaceutical formulation.

In the development of dosage forms, not only the pH effect but other effects of the ingredients on the stability of a drug must be considered. The kinetics of degradation of many drugs have been studied as a function of pH or in the presence of a low concentration of additives. A limited number of studies have been conducted with additives utilized as stabilizers by virtue of complex formation; yet, even these studies have employed low concentrations of complexing agents (6-8). Practical formulations often contain large amounts of additives beyond the concentration range at which the laws of dilute solutions apply.

The purpose of this investigation was to study the kinetics of hydrolysis of calcium acetylsalicylate carbamide in the presence of a high concentration of several pharmaceutical additives.

Calcium acetylsalicylate carbamide,<sup>1</sup> a complex salt of urea, is an amorphous, white powder with a melting point of 243-245°, at which decomposition occurs. It has a molecular weight of 458. Its solubility made it particularly suitable for this work. At 37° it is soluble to the extent of 231 mg./ml. of solution, yielding a solution with a pH 4.8.

## EXPERIMENTAL

**Apparatus and Reagents.**—Unless specified otherwise all chemicals were reagent grade. Aminoacetic

acid N. F.; calcium acetylsalicylate carbamide (Calurin), Dorsey Laboratories; gelatin U. S. P.; glycerin, U. S. P.; polyethylene glycol (Carbowax 6000), Union Carbide and Carbon Co.; polyvinylpyrrolidone (Plasdone K 30), Antara Chemicals; sodium lauryl sulfate U. S. P.; sorbitol; 0.2 *M* ammonium chloride; 0.2 *M* ammonium hydroxide; 0.2 *M* boric acid; 0.1 *M* citric acid; 0.2 *M* disodium phosphate; 0.1 *N* hydrochloric acid; 0.5 *M* sodium borate; constant temperature bath; thermometer calibrated to 0.1°; Beckman pH meter; Beckman model DU spectrophotometer; silica cells.

**Procedure.**—Calcium acetylsalicylate carbamide, 0.250 Gm., was accurately weighed into a 250-ml. volumetric flask and dissolved in a sufficient amount of buffer to bring to a volume of 250 ml. of solution. The buffer solutions, ranging from pH 1 to 9, were preheated to the temperature at which the particular determinations were to be made. The flask was placed in the constant temperature bath and a 10-ml. sample, representing the zero-time sample, was withdrawn by pipet, transferred to a 100-ml. volumetric flask, and the volume was made to 100 ml. with 0.1 *N* hydrochloric acid. Absorbance of this solution was determined at 302 m $\mu$ , using a spectrophotometer with a blank of an identical system not containing calcium acetylsalicylate carbamide but diluted in the same manner. By means of a standard absorption curve, the amount of salicylic acid formed was measured and the concentration of calcium acetylsalicylate carbamide was calculated. Samples were removed at definite intervals of time and analyzed by this procedure. The method used is essentially that of Edwards (1).

McIlvaine's buffer was used from pH 3 to 6; Palitzsch's buffer was used from pH 7 to 9. At less than pH 3, Sorensen's citrate-hydrochloric acid buffer was employed. In the presence of polyhydric alcohols, an ammonium hydroxide-ammonium chloride buffer was used instead of Palitzsch's buffer to avoid the formation of a strongly ionized, complex acid (9). The additives were dissolved in the buffer and equilibrated to 40°. Any adjustments in pH were made using a Beckman pH meter model H. All concentrations are expressed in terms of per cent weight in volume.

## RESULTS AND DISCUSSION

The rate of hydrolysis of calcium acetylsalicylate carbamide was followed over a pH range of 1 to 9 at 25, 40, and 50°. A plot of the logarithm of concentration against time produced a straight line

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<sup>1</sup> Marketed as Calurin by Dorsey Laboratories, a division of the Wander Co. and kindly supplied by them.

indicative of a pseudo first-order reaction with the net velocity being a function of several possible reactions (1, 3). Figure 1 is typical of the results obtained.

The observed velocity constants were determined

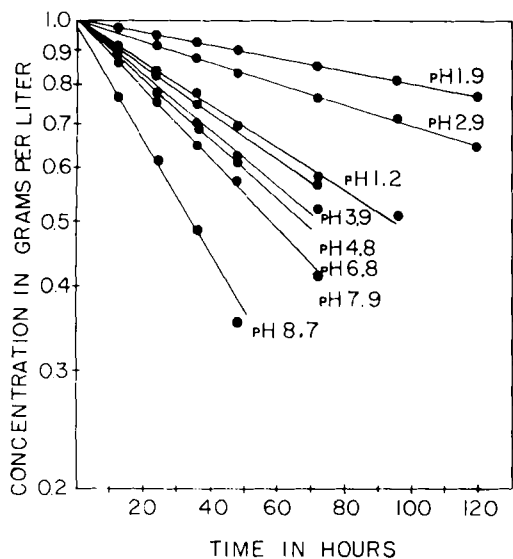


Fig. 1.—Pseudo first-order hydrolysis of calcium acetylsalicylate carbamide at 25°.

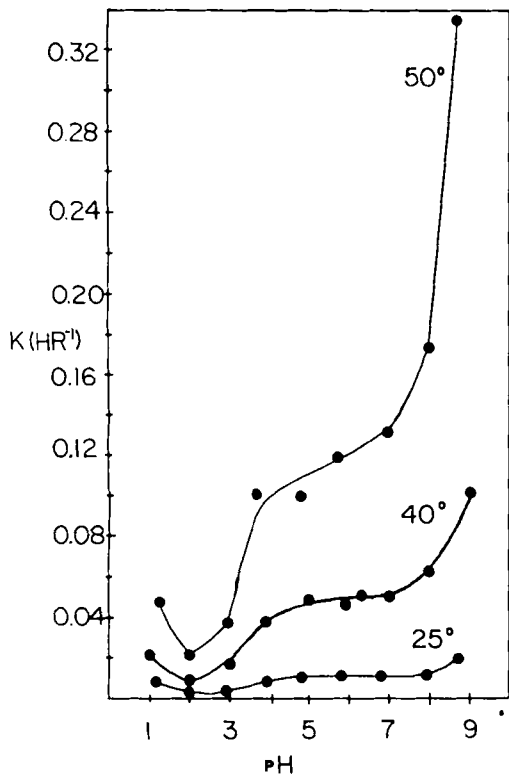


Fig. 2.—Observed velocity constants for calcium acetylsalicylate carbamide hydrolysis as a function of pH.

and are plotted in Fig. 2. The velocity constants are expressed in reciprocal hours.

It was thought desirable to compare the stability of calcium acetylsalicylate carbamide under these conditions with the stability of acetylsalicylic acid.

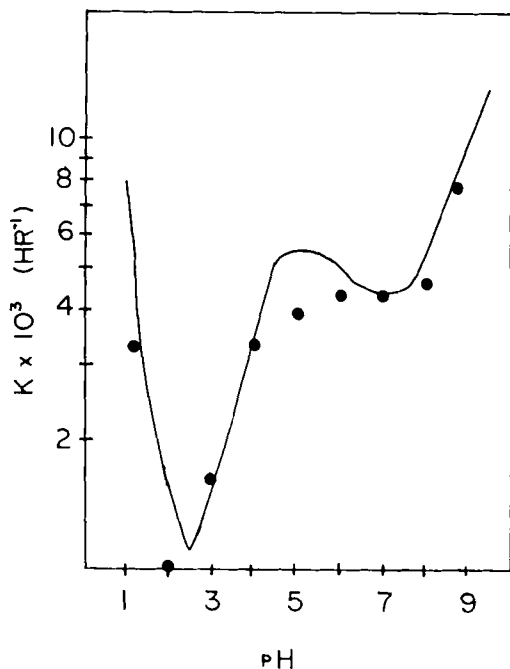


Fig. 3.—Observed velocity constants for aspirin and calcium acetylsalicylate carbamide hydrolysis at 17° as a function of pH. —, drawn from Edwards, L., *Trans. Faraday Soc.*, **46**, 730(1950); ●, calculate  $K$  at 17° for calcium acetylsalicylate carbamide.

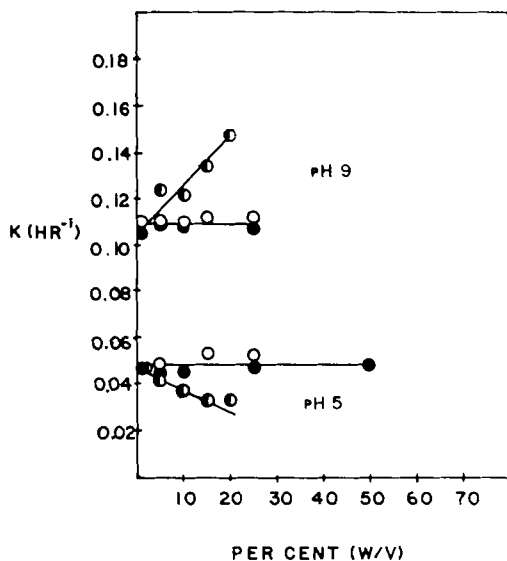


Fig. 4.—Observed velocity constants for calcium acetylsalicylate carbamide hydrolysis at 40° as a function of concentration of polyethylene glycol 6000, polyvinylpyrrolidone, and sodium lauryl sulfate. ●, Polyethylene glycol 6000; ○, polyvinylpyrrolidone; ◐, sodium lauryl sulfate.

By the use of the Arrhenius equation, the energy of activation was determined and the velocity constants for calcium acetylsalicylate carbamide at 17° were calculated for comparison with the work of Edwards. An examination of Fig. 3 shows that within experimental error, the hydrolytic stability of acetylsalicylic acid and calcium acetylsalicylate carbamide are identical. At 25° the velocity constant for the hydrolysis of calcium acetylsalicylate carbamide was the same as that of acetylsalicylic acid as determined by Garrett (3).

Bolton (4) has shown that although the pH of an acetylsalicylic acid solution is the major consideration in determining the rate of hydrolysis, certain additives, such as a solution of sodium citrate and phosphate, increase degradation. A similar effect was found at a pH 9 with a change of buffer in a solution of calcium acetylsalicylate carbamide. As shown in Figs. 4 and 6, at pH 9 the velocity constant is 0.11 hr.<sup>-1</sup> and 1.44 hr.<sup>-1</sup> in Palitzsch's buffer and ammonium hydroxide-ammonium chloride buffer, respectively. This variation presents another example of the necessity of considering the additives, *per se*, as well as the pH the additives maintain.

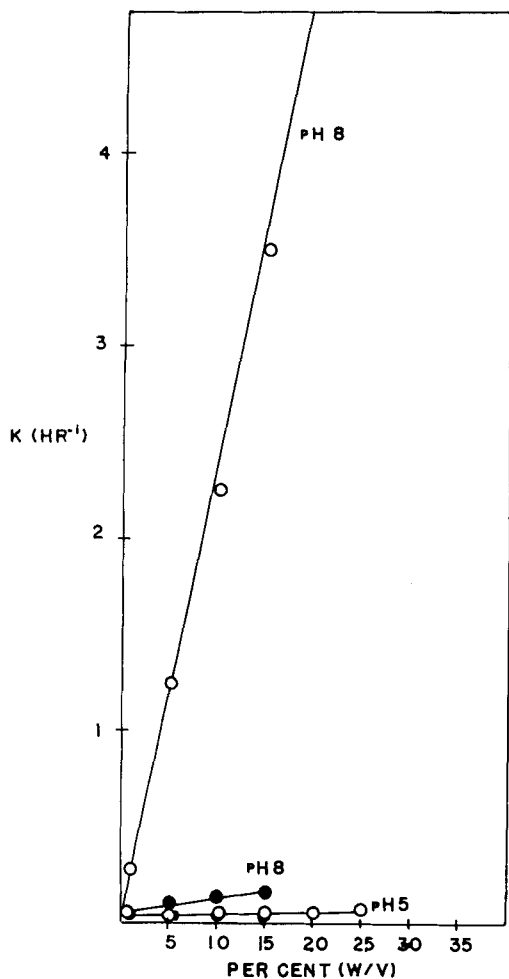


Fig. 5.—Observed velocity constants for calcium acetylsalicylate carbamide hydrolysis at 40° as a function of concentration of glycine and gelatin. O, Aminoacetic acid; ●, gelatin.

Also, it is shown in Fig. 5 that aminoacetic acid increased the rate of hydrolysis of calcium acetylsalicylate carbamide. Thus, if one attempted to buffer a calcium acetylsalicylate carbamide solution at an acidic pH using Sorensen's glycochloric acid buffer, the resulting formulation would be less stable than a similar product buffered to the same pH, using McIlvaine's buffer.

It is the purpose of this work to observe, at an acidic and an alkaline pH, the rate of hydrolysis as a function of the concentration of common pharmaceutical ingredients; therefore, no attempt has been made to maintain a given ionic strength but the additives were added as they might be in actual developmental procedures.

**Nonionic Polymers.**—Polyethylene glycol 6000 and polyvinylpyrrolidone were chosen as examples of polymers frequently used in compounding pharmaceuticals. From 0.1 to 50% polyethylene glycol 6000 was added to calcium acetylsalicylate carbamide solutions buffered at pH 5 and 9 at 40°. The observed velocity constants were determined at each concentration and plotted in Fig. 4. Polyethylene glycol 6000 in concentrations up to 50% had no effect on the hydrolytic rate of calcium acetylsalicylate carbamide at pH 5 and 9 at 40°.

Similar experimentation with polyvinylpyrrolidone in concentrations from 1 to 25% showed no effect on the rate of hydrolysis of calcium acetylsalicylate carbamide.

It has been reported that polyethylene glycols retard the hydrolysis of acetylsalicylic acid solutions (10). Although the concentrations of these polymers were high, the mole fractions of the polymers were small. It may be for this reason that no stabilization was observed in this work and it would appear that to have any value as a stabilizer of solutions of acetylsalicylic acid or its derivatives, the polymers should completely replace water in a liquid preparation.

**Polyols.**—The use of sugar and glycerin has been suggested as a means of retarding the hydrolysis of solutions of aspirin (11, 12). The wide-spread use

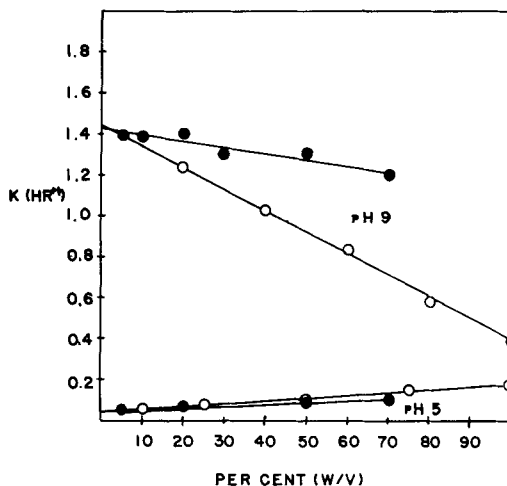


Fig. 6.—Observed velocity constant for calcium acetylsalicylate carbamide hydrolysis at 40° as a function of concentration of polyols. ●, Glycerin; ○, sorbitol.

of sorbitol in liquid pharmaceuticals suggested that sorbitol be investigated in regard to its effect on the hydrolysis of calcium acetylsalicylate carbamide. As shown in Fig. 6, at pH 9 an increase in the concentration of glycerin or sorbitol decreased the rate of hydrolysis. With 70% sorbitol, the half-life was increased approximately 15%; with 100% glycerin, the half-life was increased almost threefold. This is in agreement with other workers who suggested that sorbitol and glycerin may bind water tenaciously so the water is less available for chemical interaction, thus enhancing the stability of the preparation (13).

At pH 5 the rate of hydrolysis increased as the concentration of glycerin or sorbitol increased. At pH 5, the half-life of calcium acetylsalicylate carbamide in 70% sorbitol decreased approximately one-half; in 100% glycerin, the half-life decreased to roughly one-third. It is difficult to rationalize this behavior in view of the above statement. According to the available water theory, a given concentration of sorbitol or glycerin should bind the same amount of water in both alkaline and acidic medium. The fact that this is not actually the case suggests that some other mechanism is operative.

**Amphoteric Amines.**—Aminoacetic acid and gelatin were chosen as typical amphoteric substances that might be used in pharmaceutical formulation. As shown in Fig. 5, an increase in aminoacetic acid concentration in both alkaline and acidic medium increased the rate of hydrolysis. At pH 5, the addition of 25% aminoacetic acid decreased the half-life of calcium acetylsalicylate carbamide approximately 40%; at pH 8, the addition of 25% aminoacetic acid decreased the half-life almost tenfold.

At pH 5, there was little significant change in the stability of calcium acetylsalicylate carbamide upon the addition of up to 15% gelatin. At a pH 8, the increase in gelatin concentration caused an increase in the rate of hydrolysis; 15% gelatin produced approximately a 60% decrease in the half-life.

It appears that protein-type additives decrease the hydrolytic stability of calcium acetylsalicylate carbamide in both alkaline and acidic solutions.

**Surfactant.**—Anionic surface-active agents are occasionally used as aids to facilitate tablet disintegration, as wetting agents, and as dispersing agents. Although the amounts employed are small, it seemed advisable to determine the effect of a typical anionic surfactant, such as sodium lauryl sulfate, on the hydrolysis of calcium acetylsalicylate carbamide. At pH 5, it was found that an increase in the concentration of sodium lauryl sulfate retarded hydrolysis; 20% sodium lauryl sulfate increased the half-life approximately one-third. At pH 9, 20% sodium lauryl sulfate produced approximately 30% reduction in half-life.

One might postulate that in acidic medium the surfactant is in the highly polar form of a sulfuric acid derivative. This strong dipole may decrease the activity of the water, thus slowing the rate of hydrolysis. In alkaline medium, the salt form of the surfactant may have less affinity for water, resulting in a greater activity for water and a more rapid hydrolysis in alkaline solution.

## SUMMARY

1. The hydrolytic kinetics of calcium acetylsalicylate carbamide were studied over a pH range from 1 to 9 at 25, 40, and 50°.

2. In evaluating the stability of a solution, the effect of the constituents *per se* should be evaluated as well as the pH effect.

3. In acidic solution, aminoacetic acid, glycerin, and sorbitol increased the rate of hydrolysis of calcium acetylsalicylate carbamide solutions.

4. In alkaline solution, aminoacetic acid, gelatin, and sodium lauryl sulfate increased the rate of hydrolysis of calcium acetylsalicylate carbamide solutions.

5. In alkaline solution, glycerin and sorbitol decreased the rate of hydrolysis of calcium acetylsalicylate carbamide solutions.

6. In acidic solutions, sodium lauryl sulfate decreased the rate of hydrolysis of calcium acetylsalicylate carbamide solutions.

7. In both acidic and alkaline solution, polyethylene glycol and polyvinylpyrrolidone had no effect on the rate of hydrolysis of calcium acetylsalicylate carbamide solutions.

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