Heterogeneous Catalysis of Aspirin Degradation in Chloroformic Solution and Its Relationship to the Determination of Salicylic Acid in Buffered Aspirin Products

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Difficulties and spurious results were encountered when buffered aspirin tablets were subjected to the official test for salicylic acid. The present investigation was concerned with this problem and with a characterization of the behaviors of aspirin and salicylic acid in chloroformic solution in contact with chloroform-insoluble agents which are commonly used as buffering agents in buffered aspirin tablets. Two phenomena were studied which can have manifestations of analytical importance. Both aspirin and salicylic acid were found to be adsorbed by solids such as magnesium carbonate, aluminum glycinate, aluminum hydroxide, and magnesium trisilicate. Rate studies showed that chloroformic solutions of aspirin in contact with solid buffers were unstable and generated at a relatively rapid rate a compound with the chromatographic characteristics of salicylic acid. The rate of generation was shown to be due neither to the water or ethanol content of the chloroform nor to the presence of dissolved buffer. Rather, it was demonstrated that catalysis was due to solid surfaces. The addition of citric acid monohydrate to such systems resulted in an almost complete abolition of adsorption and catalysis.

A LIMIT TEST for free salicylic acid in aspirin tablets is described in the USP XVII (1) and is based on the procedure which was developed and described by Weber and Levine (2). A sample preparation is formulated by treating powdered tablets with chloroform and introducing the resulting mixture to a partition chromatographic column. The aqueous stationary phase of the column contains urea and ferric chloride. Salicylic acid is retained on the column in the form of a urea–iron–salicylate complex while other components are eluted with chloroform. Salicylic acid is finally removed by elution with an ethereal solution of acetic acid which decomposes the complex and releases salicylic acid. The absorbance of the salicylic acid fraction is subsequently determined at 306 mμ.

Special problems exist with buffered aspirin tablets, and a modified procedure is recommended by the compendium. During the course of studying this latter procedure, interesting and unusual behaviors were observed which can be of analytical importance. As it will be shown, two effects are operant in systems encountered in this test which, depending on conditions, can result in apparent salicylic acid contents which are significantly lower or higher than the true content.

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RESULTS

Spurious and nonreproducible results were obtained when a synthetic mixture[1] formulated to simulate an analytical sample prepared from buffered aspirin tablets was subjected to the USP limit test for free salicylic acid. Usually low recoveries were obtained. However, it was found that if the chloroformic sample preparation was allowed to stand prior to the chromatographic procedure, a recovery which was significantly higher than theory was obtained.

Low recoveries can be explained by an adsorption phenomenon. Experiments designed to evaluate this possibility are summarized by Fig. 1. It is apparent that significant adsorption of salicylic acid occurred when chloroformic solutions were contacted with chloroform-insoluble agents which are commonly employed as buffers in aspirin tablets. It is interesting to observe that the affinity of salicylic acid for magnesium carbonate and aluminum glycinate is high but that the capacity of these solids for the acid is rather low. That salicylic acid is tenaciously held by magnesium carbonate and aluminum glycinate is indicated by the fact that it was impossible to completely elute adsorbed material by repeated contacts with fresh solvent.

Further experimentation showed that high recoveries of salicylic acid from samples of the synthetic mixture resulted from a surprisingly rapid transformation of aspirin to a product having the chromatographic characteristics of salicylic acid. The nature of this phenomenon is shown in Fig. 2 which depicts kinetic studies which were conducted on various chloroform–aspirin systems. It is seen that the rate of production of salicylic acid in a one-

[1] Aspirin, 3 g.; magnesium carbonate, 0.9 g.; aluminum glycinate, 0.45 g.; salicylic acid, 0.03 g.

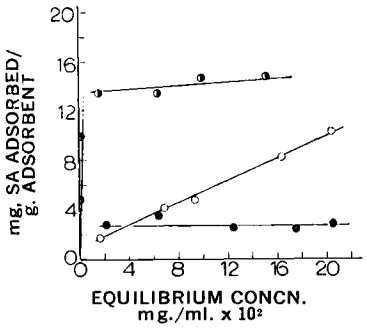


Fig. 1—Adsorption of salicylic acid (SA) from chloroformic solution by various solids. Key: ◐, magnesium carbonate, 10 mg./ml.; ●, aluminum glycinate, 10 mg./ml.; ○, aluminum hydroxide and magnesium trisilicate mixture obtained by powdering antacid tablets, 20 mg./ml. The studies were conducted at room temperature, 25 ± 2°.

phase system of aspirin in chloroform or in chloroform which had been saturated by prolonged contact with magnesium carbonate was slow. In contrast, a rapid rate of production was observed when solid magnesium carbonate was suspended in the aspirin solution. It is apparent that a transformation of aspirin occurred which was surface catalyzed. The curves indicate that, in the solid-containing systems, an equilibration reaction occurred which was first-order with respect to the aspirin concentration. That the plateauing of the curves was due to an approach to equilibrium and not to depletion of catalyst is suggested by the observation that addition of fresh magnesium carbonate to a system which had attained the plateau concentration of salicylic acid did not result in further generation of salicylic acid. Addition of more aspirin to such a system was, however, followed by the appearance of a substantial additional amount of salicylic acid. It was further found that no difference in behavior could be detected between systems prepared with reagent grade chloroform, water-saturated chloroform, or

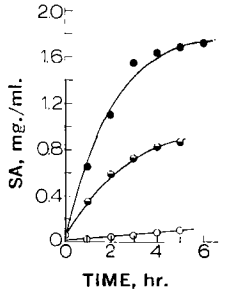


Fig. 2—Generation of salicylic acid (SA) with time in chloroformic solution. Key: ○, a one-phase system containing aspirin at an initial concentration of 20 mg./ml. prepared with reagent grade chloroform or reagent grade chloroform which was saturated by prolonged shaking with magnesium carbonate; ◒, a two-phase system containing aspirin at an initial concentration of 10 mg./ml. and magnesium carbonate at a concentration of 10 mg./ml.; ●, a two-phase system containing aspirin at an initial concentration of 20 mg./ml. and magnesium carbonate at a concentration of 10 mg./ml. The studies were conducted at room temperature, 25 ± 2°.

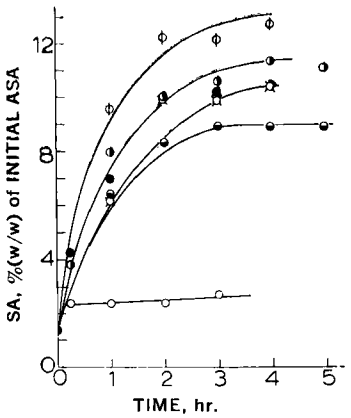


Fig. 3—Generation of salicylic acid (SA) with time in chloroformic solution in contact with suspended solids. The systems were prepared with buffered aspirin tablets to contain an initial concentration of aspirin of 20 mg./ml. Key: ϕ, tablets containing aluminum and magnesium hydroxides; ◑, tablets containing magnesium carbonate and calcium carbonate; ⧖ ●, tablets containing aluminum hydroxide, glycine, and magnesium carbonate; ◒, tablets containing magnesium carbonate and aluminum glycinate; ○, tablets containing calcium phosphate, sodium bicarbonate, and citric acid. The studies were conducted at room temperature, 25 ± 2°.

freshly distilled reagent grade chloroform. Similarly no significant difference in behavior was found between such systems and one prepared with a 5% (v/v) solution of ethanol in chloroform.

Figure 3 illustrates similar rate studies conducted with aspirin–buffer–chloroform systems prepared from commercially available buffered aspirin products. A number of different buffering components were encountered in this study. With one exception, rapid generation of salicylic acid with time was observed in these systems. The exception was a system prepared from tablets which contained, in addition to alkalinizing agents, citric acid. This observation motivated further studies on the influence of citric acid on the kinetics of salicylic acid

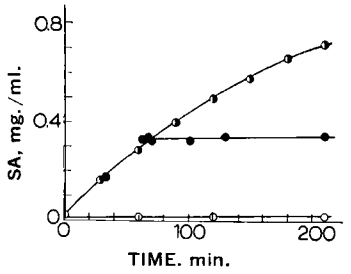


Fig. 4—Influence of citric acid on the rate of generation of salicylic acid (SA) in chloroformic solution in contact with magnesium carbonate. The magnesium carbonate was at a concentration of 5 mg./ml. and aspirin at an initial concentration of 10 mg./ml. Key: ◑, no citric acid added; ○, citric acid added at 0 time to yield a concentration of 5 mg./ml.; ●, citric acid added at 60 min. to yield a concentration of 5 mg./ml. The studies were conducted at room temperature, 25 ± 2°.

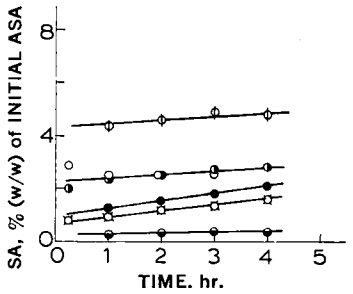


Fig. 5—Influence of citric acid on the rate of production of salicylic acid (SA) in chloroformic solution prepared from buffered aspirin tablets. Each system was prepared to contain aspirin at an initial concentration of 20 mg./ml. A weight of citric acid equal to the weight of sample was added to the powdered sample prior to the addition of chloroform. Key: same as Fig. 3. The studies were conducted at room temperature, 25 ± 2°.

formation. That the influence is dramatic is shown by Fig. 4. In contrast to the relatively rapid increase in salicylic acid content with time which was observed with magnesium carbonate-containing systems, a system formulated to contain equal concentrations of citric acid and magnesium carbonate was found to be essentially unreactive. Similarly, the addition of citric acid to a magnesium carbonate system after 1 hr. of reaction resulted in an almost immediate cessation of salicylic acid production. It was visually observed that the addition of citric acid had a pronounced effect on the nature of the suspension. Marked flocculation of particles was apparent immediately after the addition of citric acid. Citric acid which was oven-dried immediately before addition to a reaction medium had a much less marked effect in inhibiting salicylic acid production.

Citric acid treatment was established to be equally effective in inhibiting salicylic acid production in systems prepared from buffered aspirin tablets as shown by studies which are depicted in Fig. 5. Here, an aliquot of powdered tablet was triturated with an equal weight of citric acid and then treated with sufficient chloroform to obtain the desired aspirin concentration. A comparison of this figure with Fig. 3 shows that in all systems, citric acid was effective in markedly reducing the catalytic ability of suspended solids.

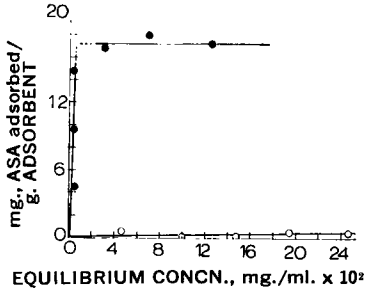


Fig. 6—Adsorption of aspirin (ASA) from chloroformic solution by magnesium carbonate and by a mixture of magnesium carbonate and citric acid. Key: ●, magnesium carbonate 10 mg./ml.; ○, magnesium carbonate 10 mg./ml. and citric acid 10 mg./ml. The studies were conducted at room temperature, 25 ± 2°.

An insight into the mechanism by which citric acid functioned to inhibit the surface-catalyzed transformation of aspirin is provided by adsorption studies which are summarized in Fig. 6. Aspirin, it is seen, was strongly adsorbed to magnesium carbonate. However, a mixture of citric acid and magnesium carbonate possessed little adsorptive capacity for aspirin. It is also of significance that treatment of solids with citric acid also significantly reduced their capacities for adsorbing salicylic acid. Experiments which illustrate this effect are summarized in Table I.

DISCUSSION

Instability of aspirin in chloroformic solution was noted by Levine (3) who reported that aspirin anhydride and salicylic acid were formed, and that anhydride formation was accelerated in the presence of weakly alkaline reagents. He did not, however, comment on the phenomenon of surface catalysis which was observed in this study. Davidson and Auerbach (4) investigated the behavior of aspirin in nonaqueous media and found that in the presence of dissolved base, the compound functioned as an effective acetylating agent. They postulated the existence of a cyclic intermediate which results from the intramolecular nucleophilic attack by the ionized carboxyl group on the ester carbonyl. The resulting intermediate decomposed to yield either aspirin or salicyloylacetic anhydride. Considerable discussion has appeared in the literature relative to the hydrolytic behavior of aspirin in aqueous solution and particularly concerned with the mechanism of intramolecular catalysis which is apparent in the pH region of approximately 4 to 8 (5–13). Recently, Fersht and Kirby (14, 15) have presented convincing evidence to suggest that intramolecular nucleophilic attack to form a cyclic intermediate and subsequent formation of the anhydride is not the most probable mechanism. Rather they concluded that the mechanism of hydrolysis is general base catalysis of attack by water by the carboxylate anion. They did state, however, that a few percent of hydrolysis could occur by the nucleophilic mechanism and their studies do not rule out the possibility that such a mechanism is operant in nonhydroxylic solvents.

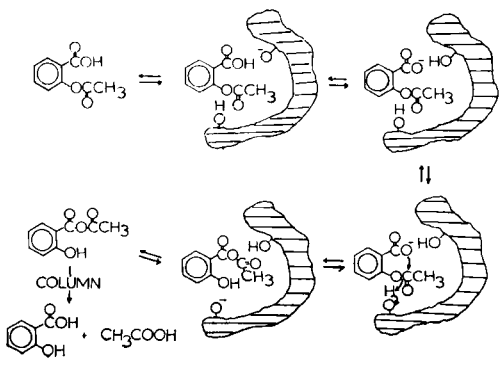
The present investigation has demonstrated that finely divided solids do catalyze a conversion of aspirin to a product which, by the analytical method employed, is determined as salicylic acid. The reaction occurred under essentially anhydrous conditions and adsorption of the aspirin is apparently a prerequisite for the transformation. Although insufficient data is available to definitively characterize the mechanism of reaction, the speculative scheme presented as Scheme I does appear to be consistent with the data. Aspirin is portrayed as being adsorbed to a negatively charged adsorption site where a protolytic reaction occurs to yield aspirin anion. Nucleophilic attack by carboxyl group on the ester carbonyl then occurs to form the cyclic intermediate. The intermediate decomposes

TABLE I—INFLUENCE OF CITRIC ACID ON THE ADSORPTION OF SALICYLIC ACID FROM CHLOROFORMIC SOLUTION BY VARIOUS SOLIDS

Concentration of Citric Acid, mg./ml.	Initial Concentration of Salicylic Acid, mg./ml. × 10^2	Equilibrium Concentration of Salicylic Acid, mg./ml. × 10^2
Magnesium Carbonate, 10 mg./ml.		
0	5	0.0282
0	10	0.018
0	15	1.65
0	20	6.56
0	25	10.2
0	30	15.3
10	5	5.2
10	10	9.7
10	15	15.3
10	20	19.8
10	25	24.5
10	30	30
Aluminum Glycinate, 10 mg./ml.		
0	5	2.25
0	10	6.54
0	15	12.5
0	20	17.6
0	25	22.6
0	30	27.2
10	5	4.18
10	10	8.43
10	15	14.4
10	20	19
10	25	23.7
10	30	29.4
Aluminum Hydroxide Magnesium Trisilicate,[a] 20 mg./ml.		
0	5	1.69
0	10	6.9
0	15	6.9
0	20	10.6
0	25	8.58
0	30	9.49
20	5	3.27
20	10	8.06
20	15	13
20	20	17
20	25	22
20	30	29

[a] Powdered antacid tablets.

to aspirin or to the anhydride with the involvement, in the latter case, of a grouping on the adsorption side functioning as a general acid. The salicyloylacetic anhydride so formed is retained on the chromatographic column by virtue of its phenolic hydroxyl group, and it is rapidly hydrolyzed on the column to acetic and salicylic acid.



Scheme I

It is possible that citric acid monohydrate, which is essentially chloroform insoluble, inhibits the reaction by releasing water of hydration to the surface of the adsorbent and undergoing a neutralization reaction in the hydrate layer which modifies the surface characteristics of the adsorbent so as to destroy adsorption sites.

Since citric acid monohydrate was shown to be effective in inhibiting the formation and adsorption of salicylic acid in the systems of interest, a logical extension of this study was to evaluate the possibility of incorporating a citric acid treatment in the analytical determination of salicylic acid in systems containing aspirin and chloroform-insoluble buffers. The results obtained by such a treatment, using a synthetic mixture, are shown in Table II. The citric acid treatment involved triturating an aliquot of the sample mixture with an equal weight of citric acid monohydrate prior to the addition of chloroform and subsequent chromatography. The results show that, in contrast to the official procedure, the citric acid procedure resulted in almost quantitative recovery of salicylic acid. It should be noted that additional experimentation demonstrated that citric acid treatment was not effective in displacing salicylic acid from metallic salts which are known to form in buffered aspirin products. A modification of this procedure is, however, quite effective in estimating the total nonaspirin salicylate content of buffered products and will be described in a subsequent communication.

EXPERIMENTAL

Materials—Aspirin, salicylic acid, magnesium carbonate (basic), citric acid monohydrate, reagent grade solvents were all obtained from the Fisher Scientific Co. The magnesium carbonate was dried at 120° for 72 hr. prior to use. All other chemicals were used as received. Aluminum glycinate was kindly provided by Dr. John H. Wood, Bristol-Myers Products. Magnesium trisilicate–aluminum hydroxide mixtures were obtained by powdering commercially available antacid tablets. All buffered aspirin tablets which were studied were obtained from local pharmacies.

Procedures—*Adsorption Studies*—Stock solutions of salicylic acid or aspirin in chloroform were prepared to obtain a range of concentrations. Ten-milliliter aliquots of such solutions were placed in 3-

TABLE II—DETERMINATION OF THE SALICYLIC ACID CONTENT OF A SYNTHETIC MIXTURE CONTAINING ASPIRIN, SALICYLIC ACID, MAGNESIUM CARBONATE, AND ALUMINUM GLYCINATE (ASPIRIN 3 g.; SALICYLIC ACID 0.03 g.; MAGNESIUM CARBONATE 0.9 g.; ALUMINUM GLYCINATE 0.45 g.)

Salicylic Acid Theory, %	Salicylic Acid Found, %	
	USP Procedure	Citric Acid Procedure
1.0	0.215	0.975
	0.365	0.975
		1.09
		0.984

dr. glass prescription vials. A weight of adsorbent, usually 100 mg., was added to each vial which was then stoppered. The stoppers were firmly taped and the vials were agitated on a rotating device for 1 hr. Solids were allowed to sediment and an aliquot from each vial was removed and filtered using a Swinney adaptor to a hypodermic syringe. An accurately measured volume of the clear filtrate was appropriately diluted and assayed spectrophotometrically. A Beckman DU spectrophotometer was used throughout. A wavelength of 306 mμ was used for salicylic acid studies while 278 mμ was employed in the case of aspirin solutions. In the citric acid experiments, the citric acid and solid buffer were added as a powdered mixture. These studies were conducted at room temperature, 25 ± 2°.

Rate Studies with Magnesium Carbonate—A solution of aspirin in chloroform was prepared in a 100-ml. volumetric flask by dissolving the required amount of aspirin in sufficient chloroform to make 100 ml. The required weight of magnesium carbonate was then added. A magnetic stirring bar was introduced to the flask, and the mixture was stirred continually by use of a magnetic stirrer. At various time intervals aliquots were removed and filtered. Preliminary experiments showed that filtration resulted in an immediate cessation of salicylic acid production. An accurately measured volume of the filtrate was assayed for salicylic acid by the chromatographic method described under free salicylic acid in the monograph for aspirin tablets in the 17th revision of the USP (1) beginning with the phrase, under *Procedure*, "Pass 50 ml. of chloroform in several portions...." In the citric acid experiments, a weight of citric acid equivalent to the weight of magnesium carbonate was added when the magnesium carbonate was added to the aspirin solution. These and all other rate studies were conducted at room temperature, 25 ± 2°.

Rate Studies with Systems Formulated from Buffered Aspirin Tablets—Buffered aspirin tablets were powdered and a weight equivalent to 2 g. of aspirin was placed in a 100-ml. volumetric flask. Chloroform was added to volume and a stirring bar was placed in the flask. Sampling and assay were conducted as described above. In the citric acid experiments, a weight of citric acid equivalent to the weight of powdered tablets was triturated with the powdered tablets and the mixture was placed in the volumetric flask.

Salicylic Acid Content of the Synthetic Mixture—A synthetic mixture was prepared by intimately mixing 3 g. of aspirin, 0.03 g. of salicylic acid, 0.9 g. of magnesium carbonate, and 0.450 g. of aluminum glycinate. An aliquot of the mixture was assayed for salicylic acid content by the procedure specified for free salicylic acid, for tablets which are coated or contain buffers, in the 17th revision of the USP (1). The citric acid method consisted of accurately weighing a portion of the mixture which was equivalent to 400 mg. of aspirin. The portion was placed in a glass mortar and triturated with 200 mg. of citric acid monohydrate using a glass pestle. Twenty milliliters of chloroform was added to the mixture and it was stirred by means of a stirring bar and magnetic stirrer for 15 min. The mixture was filtered and the filtrate was collected in a 50-ml. volumetric flask. The mortar and pestle were washed with two 10-ml. portions of chloroform which were passed through the filter and collected in the volumetric flask. Chloroform was added to volume. Exactly 10 ml. of the resulting solution was used as a sample and assayed by the free salicylic acid test procedure described in the aspirin tablet monograph in the 17th revision of the USP (1) beginning with the phrase, under *Procedure*, "Pass 50 ml. of chloroform in several portions...."

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Keyphrases

Aspirin, buffered—heterogeneous catalysis of degradation
Chloroform—aspirin-catalyzed degradation
Salicylic acid, free—analysis
Citric acid effect—aspirin stability, buffered
Adsorbents, effect—free salicylic acid analysis