Dissolution of Aspirin from Tablets Containing Various Buffering Agents

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Abstract □ Eleven different compounds representing various classes of buffering agents were studied with respect to their effect on the dissolution of aspirin from tablet formulations. In general, carbon dioxide-producing buffering agents (sodium bicarbonate, magnesium carbonate, and calcium carbonate) gave more rapid dissolution than the readily water-soluble buffering agents (sodium ascorbate and sodium citrate), and both of the preceding classes of buffering agents gave much faster dissolution than water-insoluble buffering agents such as magnesium and aluminum compounds.

Keyphrases □ Aspirin dissolution from tablets—effect of 11 buffering agents □ Buffering agents—effect on aspirin dissolution from tablets □ Tablet dissolution, aspirin—buffering agent effect □ Dissolution of aspirin tablets—effect of 11 buffering agents

Buffering agents are used in tablet formulations to increase the dissolution and absorption of weak acid drugs such as salicylic acid, aspirin, and *p*-aminosalicylic acid as well as to decrease gastric irritation of active ingredients. Scattered reports in the literature (1–5) have discussed the effects of some buffering agents on the disintegration times, dissolution, and gastric irritation of aspirin formulations. The buffering agents usually utilized in buffered tablets and associated with these reports have been antacid compounds such as dihydroxyaluminum aminoacetate, magnesium carbonate, sodium bicarbonate, sodium citrate, or some combination thereof. Although numerous buffering agents are available for tablet formulations, little effort has been made to study and compare their effects on dissolution of active ingredients from solid dosage forms.

Buffering agents can be classified according to their physical behavior in water and dilute hydrochloric acid as follows: (*a*) no reaction in water but a reaction in dilute acid with evolution of carbon dioxide gas, (*b*) readily soluble in water and dilute acid, and (*c*) insoluble in water but soluble to some extent in dilute acid. The purpose of this investigation was to investigate the effect of different buffering agents representative of these classes on the dissolution of aspirin from tablets.

EXPERIMENTAL

Materials—The aspirin[1] and starch[1] used in the study were USP grade. The aspirin used was separated into 60–80-mesh size particles using U. S. standard sieves. Sodium bicarbonate reagent[2], magnesium carbonate reagent[1], calcium carbonate USP[1], sodium citrate reagent[3], sodium ascorbate[4], magnesium hydroxide NF[1], magnesium oxide (light) USP[5], magnesium trisilicate USP[5], dihydroxyaluminum aminoacetate NF[6], dihydroxyaluminum sodium carbonate NF[6], and aluminum hydroxide CP[7] were used after passing through a 40-mesh screen.

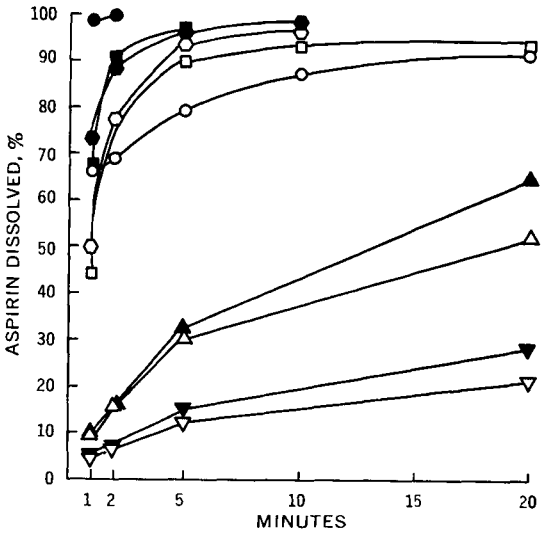

Figure 1—*Percent aspirin dissolved from tablets containing buffering agents (equivalent to 5 meq. of hydrochloric acid) which produce carbon dioxide in dilute acid and from starch control and lactose control tablets. Key: in 0.1* N *HCl*—○, *sodium bicarbonate;* □, *magnesium carbonate;* ○, *calcium carbonate;* △, *142.5 mg. lactose; and* ▽, *starch; in distilled water*—●, *sodium bicarbonate;* ■, *magnesium carbonate,* ●, *calcium carbonate;* ▲, *142.5 mg. lactose; and* ▼, *starch.*

Preparation of Tablets—Compressed tablets were made by double compression with a hydraulic press[8], using 2.86-cm. diameter test cylinders. Slugs were compressed at 1207 kg./cm. using a thoroughly mixed powder containing 9.75 g. of aspirin and 0.975 g. of starch and the desired amount of buffering agent. The slugs were subsequently broken into granules with a mortar and pestle, and a 20–40-mesh fraction of the granules was separated by sieving. An amount of granules containing 325 mg. of aspirin and 32.5 mg. of starch and an appropriate amount of buffering agent (equivalent to 2 or 5 meq. of hydrochloric acid) was accurately weighed and compressed at 947 kg./cm. using a 1.1-cm. (0.43-in.) shallow concave punch and die set. The finished tablets weighed between 357.5 and 1347.5 mg., depending on the weight of buffering agent in the formulation.

Two tablet formulations were used as controls. One formulation was a tablet containing 325.0 mg. of aspirin and 32.5 mg. of starch. The second control tablet contained, in addition to these ingredients, 142.5 mg. of lactose[3] to give a 500-mg. finished tablet. The hardness of all tablets when tested with a hardness tester[9] ranged between 9 and 15 kg. Disintegration tests on tablets were performed in 0.1 *N* HCl using a USP XVIII disintegration apparatus without disks (6).

Dissolution Studies—The modified beaker method consisted of a 500-ml., three-necked round-bottom flask, with a 6-cm. hole cut in the center to accommodate the entrance of a 5-cm. propeller. A 250-ml. quantity of dissolution medium (distilled water or 0.1 *N* HCl) preheated to 37° was added to the flask immersed in a water

[1] Fisher Scientific Co.
[2] Allied Chemicals.
[3] Mallinckrodt Chemical Works.
[4] K & K Laboratories.
[5] Merck & Co.
[6] Chattem Chemicals.
[7] J. T. Baker Chemical Co.
[8] Carver, model B.
[9] Pfizer.

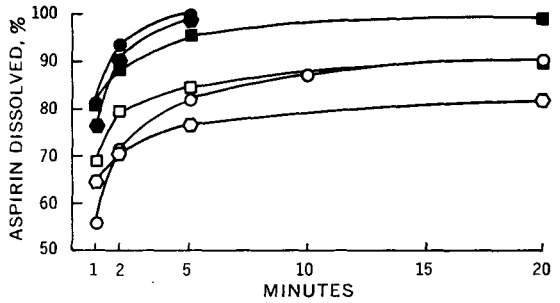

Figure 2—*Percent aspirin dissolved from tablets containing buffering agents (equivalent to 2 meq. of hydrochloric acid) which produce carbon dioxide in dilute acid. Key: in 0.1 N HCl—○, sodium bicarbonate; ○, magnesium carbonate; and □, calcium carbonate; in distilled water—●, sodium bicarbonate; ●, magnesium carbonate; and ■, calcium carbonate.*

bath maintained at 37 ± 0.5°. A three-blade, stainless steel, 5-cm. diameter propeller was centered and immersed in the dissolution medium up to a depth of 2.7 cm. The stirrer was rotated at 55 r.p.m. by an electronic motor and monitored by a constant-speed torque control unit[10]. The tablet was dropped into the dissolution medium through the side opening of the flask and came to rest on the bottom of the flask directly under the propeller. Two-milliliter samples were withdrawn at appropriate time intervals and filtered through a Millipore filter unit containing a 0.45-μ filter. A 2-ml. portion of dissolution medium was immediately added to replace the sample withdrawn. A correction factor was used in the calculations to account for the drug lost during sampling. A minimum of four runs was carried out on each experimental tablet and on control tablets.

Assay Procedure—A 1.0-ml. sample was transferred to a 50-ml. volumetric flask containing 3 ml. of distilled water. A 0.5-ml. quantity of 50% w/v solution of sodium hydroxide was added to each flask and mixed throughly. After 15 min., 1.5 ml. of concentrated hydrochloric acid was added and the volume was brought to the mark with 0.1 *N* HCl. The solutions were read on a spectrophotometer[11] for salicylic acid at 302 nm. using an appropriate blank. The amount of aspirin dissolved at any time interval was calculated by comparison with a standard reference obtained by treating known solutions as the samples.

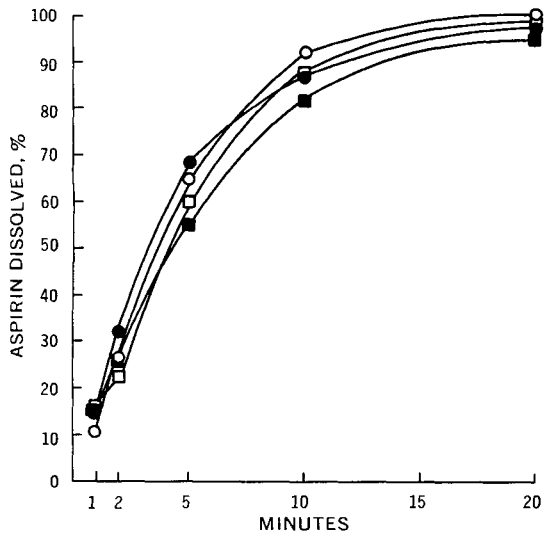

Figure 3—*Percent aspirin dissolved from tablets containing readily water-soluble and dilute acid-soluble buffering agents equivalent to 5 meq. of hydrochloric acid. Key: in 0.1 N HCl—○, sodium citrate; and □, sodium ascorbate; in distilled water—●, sodium citrate; and ■, sodium ascorbate.*

[10] Master Servodyne Laboratory Drive System, Cole-Parmer Instrument Co.
[11] Beckman DU-2.

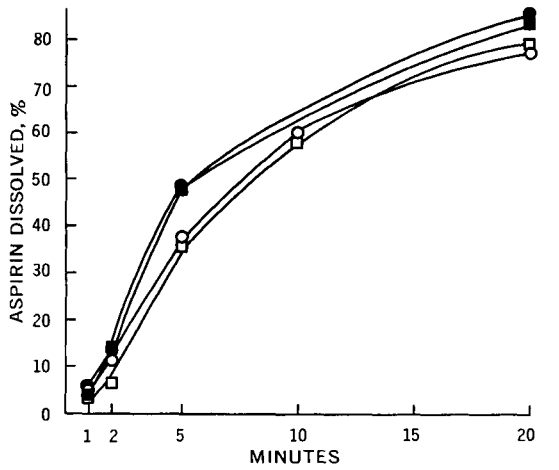

Figure 4—*Percent aspirin dissolved from tablets containing readily water-soluble and dilute acid-soluble buffering agents equivalent to 2 meq. of hydrochloric acid. Key: in 0.1 N HCl—○, sodium citrate; and □, sodium ascorbate; in distilled water—●, sodium citrate; and ■, sodium ascorbate.*

RESULTS AND DISCUSSION

In the present studies, 11 different buffering agents were investigated to determine their effects on the dissolution of aspirin from tablets. The dissolution profiles of aspirin from tablets containing the various buffering agents are shown in Figs. 1–8. The data reported are the average of at least four experimental runs on each tablet formulation, and the variations in the amount of drug dissolved from one run to another were between ±5 and 16% during the first 20 min., after which the variations ranged between ±1 and 8%

Buffering Agents Giving No Reaction in Water but a Reaction in Dilute Acid with Evolution of Carbon Dioxide—As seen in Figs. 1 and 2, dissolution of aspirin observed in 0.1 *N* HCl and distilled water from sodium bicarbonate, magnesium carbonate, and calcium carbonate formulations was very rapid. The amount of aspirin dissolved from tablets containing these buffering agents was generally 80% or more in the first 5 min. both in 0.1 *N* HCl and distilled water, with the exception of magnesium carbonate (2 meq.) in 0.1 *N* HCl.

Somewhat lower aspirin dissolution was observed in 0.1 *N* HCl than in distilled water with the carbon dioxide-producing formula-

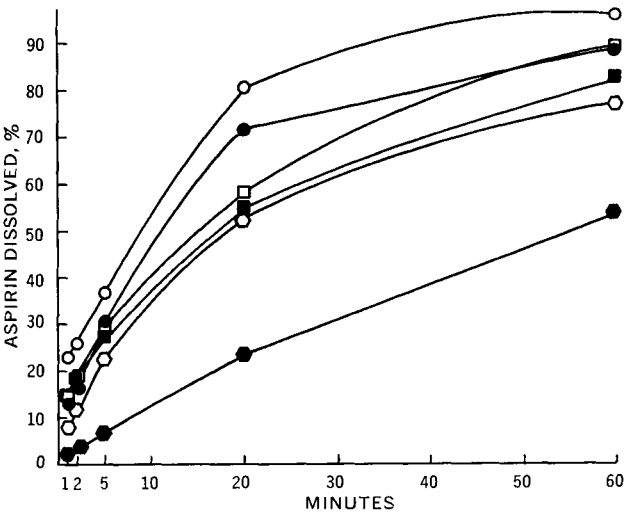

Figure 5—*Percent aspirin dissolved from tablets containing buffering agents (equivalent to 5 meq. of hydrochloric acid) insoluble in water but soluble to some extent in dilute acid. Key: in 0.1 N HCl—○, magnesium hydroxide; □, magnesium oxide; and ○, magnesium trisilicate; in distilled water—●, magnesium hydroxide; ■, magnesium oxide; and ●, magnesium trisilicate.*

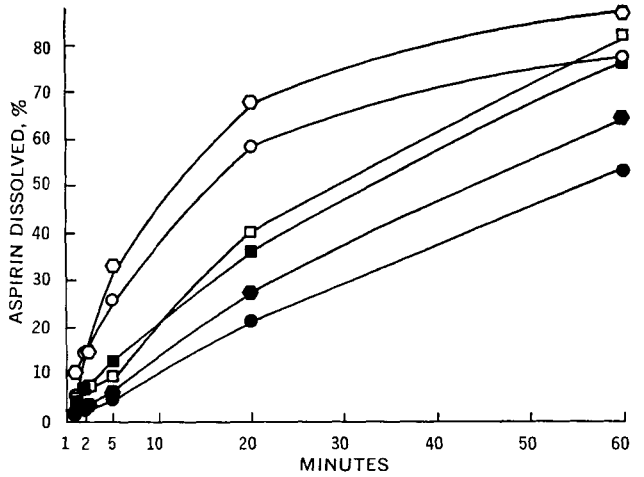

Figure 6—*Percent aspirin dissolved from tablets containing buffering agents (equivalent to 2 meq. of hydrochloric acid) insoluble in water but soluble to some extent in dilute acid. Key: in 0.1* N *HCl—○, magnesium hydroxide; □, magnesium oxide; and ○, magnesium trisilicate; in distilled water—●, magnesium hydroxide; ■, magnesium oxide; and ●, magnesium trisilicate.*

tions. A probable explanation is that the buffering agents react and are neutralized by the hydrochloric acid and, consequently, there is little or no reaction with the aspirin in solution. However, the same buffering agents in distilled water react with the aspirin and thereby increase the dissolution of the acid drug.

The dissolution of aspirin in dilute hydrochloric acid and water from all three buffering agent formulations was much faster than that of the control tablets.

Buffering Agents Readily Soluble in Water and Dilute Acid—The dissolution curves for tablets containing sodium ascorbate and sodium citrate (equivalent to 5 and 2 meq. of hydrochloric acid) in 0.1 *N* HCl and water are depicted in Figs. 3 and 4. The dissolution of aspirin from both these buffering agent formulations was much faster than the control tablets. This can be attributed to the rapid increase in pH in the immediate vicinity of the aspirin particles brought about by the rapid and complete solubility of these buffering agents.

It has been reported in the literature (7–11) that solution rates of sodium and calcium salts of aspirin are much greater than the acid.

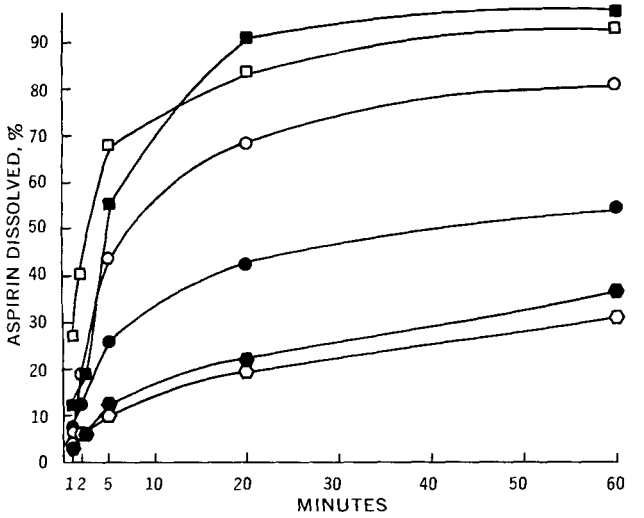

Figure 7—*Percent aspirin dissolved from tablets containing buffering agents (equivalent to 5 meq. of hydrochloric acid) insoluble in water but soluble to some extent in dilute acid. Key: in 0.1* N *HCl—○, dihydroxyaluminum aminoacetate; □, dihydroxyaluminum sodium carbonate; and ○, aluminum hydroxide; in distilled water—●, dihydroxyaluminum aminoacetate; ■, dihydroxyaluminum sodium carbonate; and ●, aluminum hydroxide.*

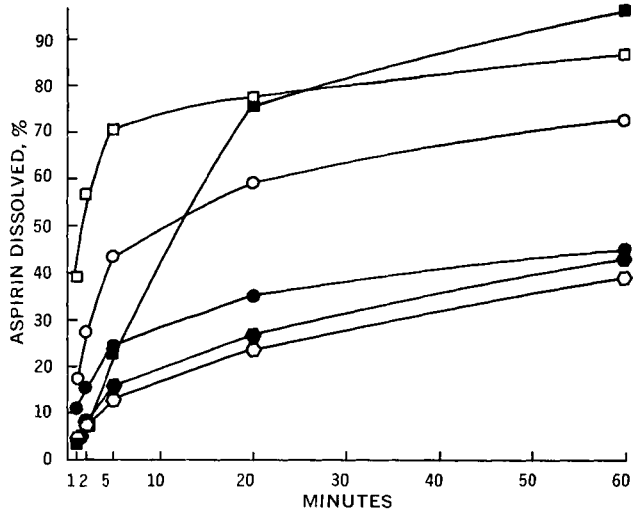

Figure 8—*Percent aspirin dissolved from tablets containing buffering agents (equivalent to 2 meq. of hydrochloric acid) insoluble in water but soluble to some extent in dilute acid. Key: in 0.1* N *HCl—○, dihydroxyaluminum aminoacetate; □, dihydroxyaluminum sodium carbonate; and ○, aluminum hydroxide; in distilled water—●, dihydroxyaluminum aminoacetate; ■, dihydroxyaluminum sodium carbonate; and ●, aluminum hydroxide.*

The results of aspirin dissolution from tablets containing sodium ascorbate and sodium citrate as buffering agents are in agreement with these findings. These buffering agents increase the solution rate of aspirin by raising the pH of the medium around the site of dissolution. In the stomach these buffering agents help to solubilize aspirin by making a soluble salt, which in the acidic environment would change into the acid form and be precipitated in the form of very small particles, exposing a large surface area. The well-dispersed particles have a tendency to redissolve quickly, resulting in rapid absorption and reduced gastric irritation (4).

Buffering Agents Insoluble in Water but Soluble to Some Extent in Dilute Acid—Dissolution profiles for magnesium hydroxide, magnesium oxide, and magnesium trisilicate are presented in Figs. 5 and 6. Faster dissolution of aspirin was observed in 0.1 *N* HCl than in distilled water from tablets containing these magnesium compounds. This is probably due to the fact that magnesium compounds are water insoluble but are soluble to some extent in dilute acid. The dissolution of aspirin from tablets containing the magnesium compounds was greater than the control tablets containing lactose. With the exception of magnesium hydroxide (at the 5-meq. level), the dissolution in distilled water of aspirin from magnesium compound formulations was slower than the lactose control tablets.

An interesting phenomenon was observed for magnesium trisilicate formulations. More rapid dissolution of aspirin was observed at the 2-meq. level than the 5-meq. level in both dilute hydrochloric acid and distilled water. A possible explanation might be the fact that some of the trisilicate compound forms a gelatinous mass (probably silicic acid) in aqueous media and thereby hinders dissolution of the aspirin. The amount of gelatinous material formed would be greater at the 5-meq. level than the 2-meq. level.

The dissolution profiles of aspirin from formulations containing aluminum compounds are given in Figs. 7 and 8. Of all the aluminum compounds studied, the fastest dissolution of aspirin was observed for the dihydroxyaluminum sodium carbonate formulation. Slight effervescence was observed when the tablets containing dihydroxyaluminum sodium carbonate were tested in dilute hydrochloric acid and distilled water, and this phenomenon may account for the more rapid dissolution of the active ingredient. Formulations containing dihydroxyaluminum aminoacetate gave faster aspirin dissolution in dilute hydrochloric acid than in distilled water. The use of aluminum hydroxide in formulations resulted in a slightly lower aspirin dissolution in 0.1 *N* HCl than in distilled water.

Tablets containing dihydroxyaluminum aminoacetate gave faster dissolution in 0.1 *N* HCl than did control tablets, while the same tablets in distilled water resulted in significantly slower dissolution than control tablets. Similarly, faster dissolution was observed by

Levy (2) in 0.1 *N* HCl at the end of 10 min. from tablets containing dihydroxyaluminum aminoacetate and magnesium carbonate than from plain tablets. Slower aspirin dissolution was observed in dilute hydrochloric acid and water from formulations containing aluminum hydroxide than from control tablets. In general, the slower dissolution of aspirin with aluminum compounds observed during this investigation substantiates the results of Cummings *et al.* (12), who reported that solution rates of aspirin from aluminum aspirin in buffer solutions of pH 2–8 were lower than that of aspirin. Levy (13) explained incomplete and slow absorption of aspirin from orally administered aluminum aspirin on the basis of very slow dissolution in the GI tract.

The effect of different concentrations of aluminum hydroxide on the dissolution of aspirin was similar to that of magnesium trisilicate. Faster dissolution was observed at the 2-meq. level than at the 5-meq. level in both dilute hydrochloric acid and water. This might be due to the formation of a larger amount of aluminum hydroxide gel at the 5-meq. level which might have impeded the dissolution of aspirin.

Comparison of Classes of Buffering Agents—In general, carbon dioxide-producing buffering agents such as sodium bicarbonate, magnesium carbonate, and calcium carbonate gave more rapid dissolution of aspirin that the readily soluble buffering agents such as sodium citrate and sodium ascorbate and the water-insoluble buffering agents such as magnesium and aluminum compounds. This might be explained by the fact that effervescence probably produces rapid and complete release of the active ingredient into its primary particles, allowing rapid dissolution of the aspirin.

Buffering agents readily soluble in water and dilute acid gave more rapid aspirin dissolution as compared to those of magnesium and aluminum compounds. The amount of aspirin dissolved from tablets containing magnesium compounds was generally higher than the amount of aspirin dissolved from tablets containing aluminum compounds, with the exception of dihydroxyaluminum sodium carbonate. The dissolution of aspirin from tablets containing aluminum hydroxide was the slowest observed of all the buffering agent formulations studied. Based on the observations of this study, it is evident that not all of the buffering agents would enhance the dissolution of aspirin from tablets. Care must be taken in the selection of a suitable buffering agent in appropriate quantities to achieve maximum dissolution effect.

SUMMARY

1. Eleven different compounds representing various classes of buffering agents were studied with respect to their effects on the dissolution of aspirin from tablet formulations.

2. The descending order of aspirin dissolution in 0.1 *N* HCl from tablets containing 5 meq. of buffering agent was found to be: calcium carbonate = magnesium carbonate > sodium bicarbonate > sodium citrate = sodium ascorbate > dihydroxyaluminum sodium carbonate > magnesium hydroxide > magnesium oxide > dihydroxyaluminum aminoacetate > magnesium trisilicate > aluminum hydroxide.

3. The descending order of aspirin dissolution in 0.1 *N* HCl from tablets containing 2 meq. of buffering agent was found to be: calcium carbonate > sodium bicarbonate > magnesium carbonate > sodium citrate > sodium ascorbate > dihydroxyaluminum sodium carbonate > magnesium trisilicate > dihydroxyaluminum aminoacetate > magnesium hydroxide > magnesium oxide > aluminum hydroxide.

4. The descending order of aspirin dissolution in distilled water from tablets containing 5 meq. of buffering agent was found to be: sodium bicarbonate > calcium carbonate = magnesium carbonate > sodium citrate > sodium ascorbate > dihydroxyaluminum sodium carbonate > magnesium hydroxide > magnesium oxide > magnesium trisilicate > dihydroxyaluminum aminoacetate > aluminum hydroxide.

5. The descending order of aspirin dissolution in distilled water from tablets containing 2 meq. of buffering agent was found to be: calcium carbonate = sodium bicarbonate > magnesium carbonate > sodium citrate > sodium ascorbate > dihydroxyaluminum sodium carbonate > magnesium oxide > magnesium trisilicate > magnesium hydroxide > dihydroxyaluminum aminoacetate > aluminum hydroxide.

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