Keyphrases

Aspirin hydrolysis—tablets
Fatty acids, effect—aspirin hydrolysis
Column chromatography—separation
UV spectrophotometry—analysis
GLC—analysis

Pharmaceutical Heterogeneous Systems III

Inhibition of Stearate Lubricant Induced Degradation of Aspirin by the Use of Certain Organic Acids

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The acceleration of aspirin degradation in capsule formulations where an alkali stearate is employed as a lubricant can be inhibited by the inclusion of malic, hexamic, or maleic acid. The acids when included at a level of 20 percent by weight of the complete mixture achieve a level of inhibition at which it could be said that the preparations are stable with respect to salicylic acid content. The mechanisms operative in these systems and the factors contributing to successful inhibition are described. Moisture content of the capsule mix and in the gelatin capsule shell is studied in regard to effects on the stability of aspirin and the dissolution rate of aspirin from the capsule formulations considered.

THE ASPIRIN MOLECULE is subject to instability whenever moisture is present in appreciable amounts in an aspirin formulation (1). Excipients as well as physiologically active substances which influence the pH of the moisture in the solid dosage form can influence the rate of degradation. Aspirin hydrolysis is accelerated at both low and moderately high pH values (2). Substances, such as antacids, have been cited as being detrimental to aspirin stability (3). In a recent study the acceleration of aspirin hydrolysis by alkali stearate lubricants was demonstrated (4). The physicochemical mechanism leading to this effect was explained on the basis of a reaction between the lubricant and aspirin. The reaction leads to formation of a soluble alkali salt of aspirin which maintains the moisture in the formulations at a hydroxyl ion concentration and greatly accelerates the breakdown of aspirin. The object of the present study was to investigate the feasibility of including organic acids of comparable or lower pKa values and greater solubility than aspirin to compete for the magnesium cation creating an environment buffered close to the optimum pH for aspirin stability. Factors influencing the amount of acid and/or alkali salt present in the moisture in the system would, of course, determine the effectiveness of the individual acids. The study was carried out using capsule formulations. A second phase of the study was concerned with the humid microatmosphere very often existing within the capsule shell. The effect of reducing the moisture content in the gelatin shell on aspirin stability and the dissolution rate of aspirin from aspirin-stearate lubricant-organic acid capsule formulations is demonstrated.

EXPERIMENTAL

Capsules[1] containing a mixture of 20 parts aspirin USP (40 mesh), 1 part magnesium stearate USP, and 1, 2, 5, 10, and 20 parts, respectively, of organic acid by weight were prepared. Control capsules containing aspirin alone and aspirin plus magnesium stearate (20:1) were also prepared. The acids chosen for the study were hexamic,[2] maleic,[3] malic,[4] and tartaric acid NF. Maleic anhydride[5]

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[1] Parke Davis No. 3, clear gelatin capsules, Parke Davis and Co., Detroit, Mich.
[2] Abbott Laboratories, North Chicago, Ill.
[3] Practical Grade, Matheson Coleman & Bell, East Rutherford, N. J.
[4] Practical Grade, Eastman Organic Chemicals, Distillation Products Inc., Rochester, N. Y.
[5] Monsanto EMA Grade 31, Monsanto Co., St. Louis, Mo.

was also included in the study and employed in the same parts by weight as the acids.

Two sets of capsules and corresponding capsule mixes, independently prepared, were stored at 22° (±0.5°), 40° (±0.25°), and 50° (±0.25°) for 30 days at which time salicylic acid analysis, dissolution rate, and moisture determinations, as previously described, were performed.

A third and fourth set of capsules identical with the first two, except that tartaric acid and maleic anhydride were eliminated from this phase of the study, were prepared and subjected to vacuum drying for 24 hr. at 40° (±0.1°) and 0.1 mm. Dissolution rates, moisture, and salicylic acid determinations were performed initially (after drying) and after 1 month's storage, as described for the first sets of samples. Nondried capsules and powder mixes were run as controls with the dried samples. The results reported in Tables I and II, and Figs. 1–6 are average results from two separate experiments. The error of reproducibility between experiments was less than 5%. To determine loss of moisture from the gelatin on drying, 10 g. (weighed exactly) of empty gelatin capsules[1] were dried under the conditions described for the filled capsules and moisture loss determined by weight loss. In addition, a Karl Fisher moisture analysis was performed on the same batch of empty gelatin capsules before and after drying. The gelatin was ground to a fine particle size in an electric blender (Waring) before analysis. Samples equivalent to 200 mg. of aspirin were analyzed according to the method of Levine (5). Moisture determinations were performed on all capsules and powder mixes immediately after preparation by Karl Fischer titration.

Dissolution rates of aspirin from the capsules were in all instances performed in duplicate. In some cases a third experiment was added to fortify data. The experiments were carried out in the following manner.

One capsule was placed in a bottle containing 100 ml. of distilled water, the bottle sealed, and rotated at 60 r.p.m. in a water bath at 37° (±0.1°). Two-milliliter samples were taken at 5, 10, 15, 20, 45, and 60 min. using pipets with filters attached. Two milliliters of distilled water was added to the bottle after sampling to maintain volume. One milliliter of the sample was quickly (within 2 min.) brought to 50 ml. volume with water and a reading taken at 280 mμ on a spectrophotometer (Perkin-Elmer 202) to determine aspirin in solution.

TABLE I—HYDROLYSIS OF ASPIRIN IN CAPSULES CONTAINING ASPIRIN PLUS MAGNESIUM STEARATE (20:1 WEIGHT TO WEIGHT RATIO)

	Salicylic Acid Formation/200 mg. Aspirin[a]		
	R.T. (22°C. ±0.5°), mg.	40°C. (±0.25°), mg.	50°C. (±0.25°), mg.
Aspirin-magnesium stearate capsules[b]	1.02	3.22	15.81
Aspirin-magnesium stearate powder mix[b]	1.00	2.68	5.56
Aspirin capsules, control[b]	0.0429	0.262	0.348
Aspirin USP, control[b]	0.0362	0.0719	0.2623

[a] Storage time = 30 days. [b] All samples contained less than 0.1% moisture.

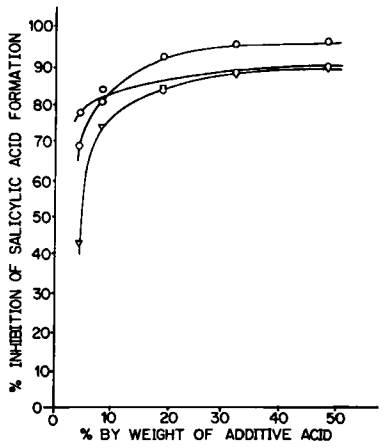

Fig. 1—Inhibition of salicylic acid formation in aspirin-magnesium stearate-maleic acid capsules. Percentage inhibition is compared to aspirin-magnesium stearate capsules (Table I). Time of storage is 30 days. Key: ○, R.T. (22 ± 0.5°); ▽, 40° (± 0.25°); ○, 50° (± 0.25°).

RESULTS AND DISCUSSION

The acceleration of the hydrolysis of aspirin by inclusion of magnesium stearate as a lubricant in a capsule formulation is shown in Table I.

Figures 1, 2, and 3 indicate that malic, maleic, and hexamic acids successfully inhibit the stearate-induced degradation of aspirin at the three storage conditions. A minimum of 20% by weight of these acids is needed for successful inhibition. The 40° curves for these acids show less effect than the room temperature and 50° curves. This could possibly be due to the following explanation. At lower temperatures the additive acid is most likely operating through pH effects. The amount of solubilized

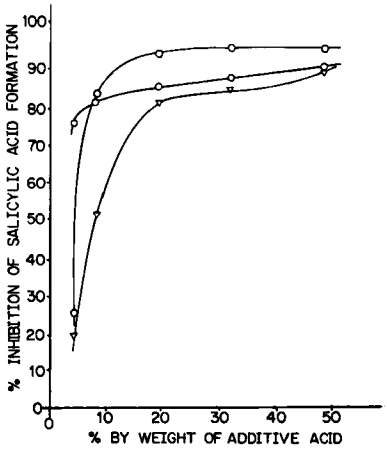

Fig. 2—Inhibition of salicylic acid formation in aspirin-magnesium stearate-malic acid capsules. Percentage inhibition compared to aspirin-magnesium stearate capsules (Table I). Time of storage is 30 days. Key: ○, R.T. (22 ± 0.5°); ▽, 40° (±0.25°); ○, 50° (± 0.25°).

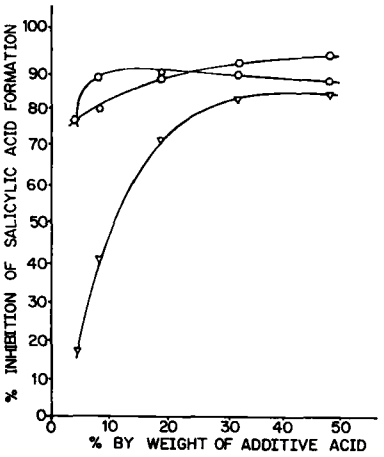

Fig. 3—Inhibition of salicylic acid formation in aspirin-magnesium stearate-hexamic acid capsules. Percentage inhibition is compared to aspirin-magnesium stearate capsules (Table I). Time of storage is 30 days. Key: ○, R.T. (22° ± 0.5°); ▽, 40° (± 0.25°); ○, 50° (±0.25°).

aspirin is decreased by the lower pH. The small amount in solution should not be degraded rapidly unless the pH of the moisture in the system is below 2.0 (2). At moderately high temperatures (40°) the additive acid concentration is apparently increased to a point where the pH slightly accelerates degradation. At 50° the salt-forming reaction between the additive acid and magnesium ion becomes quite significant and a buffer system composed of the additive acid and its magnesium salt raises the pH to a safe level for aspirin stability. All three effects, that is, inherent pH, solubility, and the salt-forming reaction are most likely operating to some degree at all of the conditions of storage. Malic, hexamic, and maleic acids appear to possess a good balance with regard to their ability to dominate the pH picture through solubility and reactivity

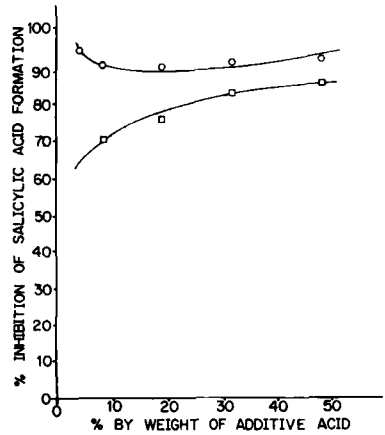

Fig. 4—Inhibition of salicylic acid formation in aspirin-magnesium stearate-tartaric acid and aspirin magnesium stearate-maleic anhydride capsules. Percentage inhibition is compared to aspirin-magnesium stearate capsules control (Table I). Storage condition is 22° (±0.5°). Time of storage is 30 days. Key: ○, tartaric acid formulations; □, maleic anhydride formulations.

with magnesium stearate. The formation of the relatively alkaline aspirin:magnesium-aspirin buffer system described in a previous report (4) is apparently successfully inhibited by these acids.

Figure 4 demonstrates the inhibition of aspirin-stearate lubricant degradation employing tartaric acid and maleic anhydride. The effects at room temperature are shown only since at 40° and 50° there was no significant inhibition by tartaric acid and maleic anhydride accelerated salicylic acid formation above the magnesium stearate-aspirin control. Maleic anhydride was apparently effective at room temperature through a pH effect, but introduced an additional 1.3% (average) moisture into the samples which supported enough hydrolysis to offset any pH or buffer system effects at the higher temperatures. (In general, samples in this study ranged from 0.1 to 0.5% moisture content, whereas the maleic anhydride formulations averaged 1.7%.) The ineffectiveness of tartaric acid at the higher temperatures was due to a relatively high pKa and the poor solubility of its magnesium salt.

TABLE II—HYDROLYSIS OF ASPIRIN IN CAPSULES CONTAINING ASPIRIN ALONE AND ASPIRIN PLUS MAGNESIUM STEARATE (20:1 WEIGHT TO WEIGHT RATIO)[a]

	Salicylic Acid Formation/200 mg. Aspirin[b]		
	R.T. (22° ± 0.5°C.), mg.	40° (± 0.25°C.), mg.	50° (±0.25°C.) mg.
Aspirin capsules control[c]	0.036	0.053	0.091
Aspirin-magnesium stearate capsules, control[c]	0.10	1.68	4.5

[a] The filled capsules were dried at 40°, 0.1 mm. pressure for 24 hr. [b] Storage time = 30 days. [c] Capsule ingredients contained less than 0.1% moisture after drying.

Table I illustrates an important point with regard to the role of the gelatin capsule in aspirin breakdown. Moisture present within the gelatin appears to set up a humid microatmosphere which accelerates aspirin breakdown in both plain aspirin and aspirin-magnesium stearate capsules. Moisture was removed from the gelatin by vacuum drying the filled capsules, and its effect on aspirin stability, moisture content of the capsule mix, and dissolution rate studied. The moisture loss from the gelatin was calculated as 10.1% by the two methods described. Malic, maleic, and hexamic were used in this phase of the study, since they presented the most successful inhibition in the initial study. Table II demonstrates the effect on aspirin stability with and without stearate lubricant.

Table II illustrates that decreasing moisture content of gelatin has a stabilizing effect on the aspirin. This effect was not so dramatic in the capsules containing aspirin-magnesium stearate-organic acid. Figures 5 and 6 demonstrate an inhibition of degradation, but not significantly greater on a percentage basis than had been observed with the nondried capsules. Maleic acid capsules showed no inhibition of degradation. The removal of the moisture from the system resulted in complete saturation of available moisture by the magnesium maleate-maleic acid buffer. This leads to pH of

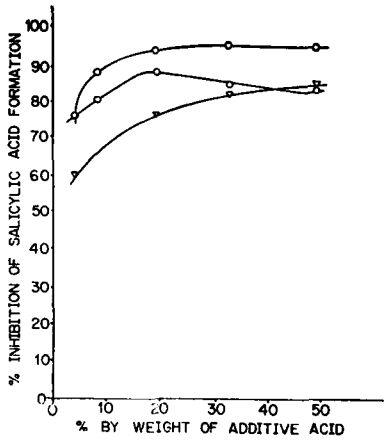

Fig. 5—Inhibition of salicylic acid formation in aspirin-magnesium stearate-hexamic acid capsules (dried in vacuo). *Percentage inhibition is compared to aspirin-magnesium stearate capsules (dried* in vacuo, *Table II), Time of storage is 30 days. Key:* ○, *R.T. (22 ± 0.50°);* ▽, *40° (±0.25°);* ○, *50° (±0.25°).*

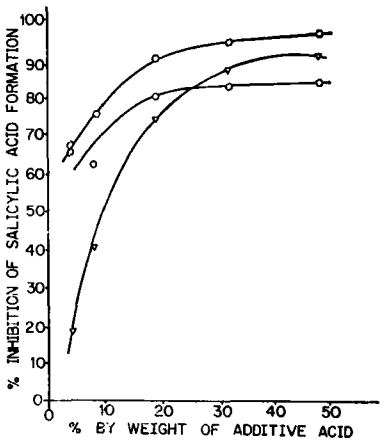

Fig. 6—Inhibition of salicylic acid formation in aspirin-magnesium stearate-malic acid capsules (dried in vacuo). *Percentage inhibition is compared to aspirin-magnesium stearate capsules (dried* in vacuo, *Table II). Time of storage is 30 days. Key:* ○, *R.T. (22 ± 0.5°);* ▽, *40° (±0.25°);* ○, *50° (±0.25°).*

approximately 1.3 of the saturated aqueous suspension, magnesium maleate, and maleic acid.

The decrease in moisture in this system was not only due to the decrease in the gelatin moisture, but also to a significant decrease in the capsule mix after drying. The initial moisture content of the samples was 0.4% (average) and was reduced to 0.2% (average) after drying. All other capsules showed insignificant loss of moisture from the ingredients after the drying process. In general, the drying effect on dissolution rate was negligible when measured immediately after drying. If an appreciable amount of salicylic acid was formed after storage, the dissolution rate appeared to be slightly decreased. The capsule ingredients set up when a significant amount of salicylic acid was formed causing the decreased dissolution rates.

The acceleration of aspirin degradation in capsule formulations where an alkali stearate is employed as a lubricant can be inhibited by the inclusion of malic, maleic, and hexamic acid. To achieve a level of inhibition at which it could be said that the preparation is stable with respect to salicylic acid content, approximately 20% by weight of the acid must be included in the formulation. In addition to pH effects contributed by the acids the mechanism operative in inhibiting degradation involves a competition for the lubricant cation between aspirin and the additive acid. The important factors when considering this type of inhibition are as follows.

(*a*) The pKa of the additive acid should be in the range of aspirin or lower.

(*b*) The solubility of the additive acid and alkali salt formed should be sufficient so as not to fix the acid–acid salt ratio through saturation at a pH value detrimental to aspirin stability.

(*c*) The moisture content of the capsule mix should be between 0.4 and 0.6%. If maleic acid is used, the lower limit is critical since very low moisture shifts the acid–acid salt ratio to the acid side accelerating degradation.

Decreasing the amount of moisture in the gelatin capsule shell was successful in decreasing degradation in capsules containing aspirin and aspirin plus magnesium stearate. The extent of aspirin hydrolysis inhibited in dried aspirin-lubricant-additive acid capsules was improved only in the hexamic acid formulation. The removal of moisture from the gelatin improves aspirin stability except when this lowering of available moisture creates a high concentration of substance detrimental to stability through a pH effect. This was apparently the case with maleic acid. The dissolution rates were not affected to any great extent by the drying process. A slight decrease was noted after storage with samples containing higher levels of salicylic acid.

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Keyphases

Heterogeneous systems—pharmaceutical
Aspirin degradation, stearate-induced—inhibition
Organic acids effect—stearate degradation, aspirin
Moisture effect—aspirin degradation
UV spectrophotometry—analysis