Keyphrases

Differential scanning calorimetry—analysis
Purity determination, drugs—differential scanning calorimetry
Solid solution effect—purity determination
TLC—analysis confirmation
NMR spectroscopy—analysis confirmation

Pharmaceutical Heterogeneous Systems II

Study of Hydrolysis of Aspirin in Combination with Fatty Acid Tablet Lubricants

By H. V. MAULDING, M. A. ZOGLIO, and E. J. JOHNSTON

Stearic acid USP, in combination with aspirin in tablets, capsules, and powder mixes increases the rate of salicylic acid formation over pure aspirin controls. The breakdown of aspirin in combination with stearic acid USP and reagent grade stearic and palmitic acids has been studied with regard to the relative suitability of the fatty acids in question as tablet lubricants. Commercial stearic acid was found to have a marked effect on acceleration of salicylic acid formation as compared to reagent palmitic and stearic acids which were 95% + pure (gas chromatography). In powders and tablets with a constant aspirin:fatty acid ratio (20:1) the degree of aspirin degradation reaches a maximum when the two reagent acids are mixed together at approximately the same molar ratio as found in stearic acid USP. This maximum closely parallels the minimum on the melting point curve for mixtures of stearic and palmitic acids.

IT HAS BEEN observed that the commonly used tablet lubricant, stearic acid USP, accelerates aspirin decomposition and salicylic acid formation upon combination with pure aspirin in tablets, powders, and capsules (1). This deleterious effect has been well documented in this laboratory (2). It was thought that by varying the purity of the stearic acids used, one might note a difference in the degree of acetylsalicylic acid degradation as a result of either chemical and/or physical effects of the fatty acid lubricants. For this comparison aspirin powder mixes and tablets containing food grade stearic acid[1] USP and reagent grade stearic and palmitic acids (Fisher Chemical Co.) were compared.

EXPERIMENTAL

Free Salicylic Acid Determination (3)—A sample of powder or tablet (crushed in a mortar) equivalent to 200 mg. of aspirin was dissolved in 10 ml. of water-saturated chloroform with agitation (1 min.). This solution was then poured onto a column containing 8 g. of acid-washed diatomaceous earth[2] previously mixed with 8 ml. of 2% ferric chloride. The column was eluted with water-saturated chloroform (about 50 ml.) to remove the aspirin. The purple complex was eluted into a volumetric flask with 10% acetic acid in chloroform (10 ml.) followed by 1% acetic acid in water-saturated chloroform to remove the complex. The concentration of salicylic acid was determined by measuring the absorbance of the solution at 310 mμ.

Melting Point Determination—Exactly weighed quantities of reagent steric and palmitic acids (Fisher) were mixed and heated to melting on a water bath. The mixtures were stirred and allowed to cool overnight. The congealed mixtures were crushed, mixed intimately, and melting points run on a Thomas-Hoover melting point apparatus with a temperature increase of 1°/min.[3]

Gas Chromatography—*Esterification Procedure*—One gram of fatty acid was transferred to a 125-ml. conical flask, and 30 ml. of BF_3-methanol reagent, 14% w/v (Applied Science Laboratories, Inc., State College, Pa.) added. The flask was fitted with an air condenser and the reactants refluxed on a steam bath for at least 0.5 hr. The reactants were cooled at room temperature, 20 ml. of petroleum ether added, the flask swirled, and the mixture

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[1] Emeresol 6332, Emery Ind. Inc.

[2] Celite 545, Johns-Manville, New York, N. Y.

[3] All melting points are uncorrected.

quantitatively transferred to a 125-ml. separator fitted with a Teflon stopcock. Twenty milliliters of water was added to the mixture, extracted with petroleum ether, and two additional extractions performed with 20-ml. portions of petroleum ether. The extract was filtered through anhydrous sodium sulfate into a tared 100-ml. beaker. The petroleum ether was evaporated and the residue weighed, then redissolved in 50 ml. of chloroform. The solution was chromatographed and the fatty acid distribution calculated.

Conditions for Gas Chromatography—Chromatography was performed with an Aerograph model 1520 gas chromatograph equipped with a thermal conductivity detector, a Leeds & Northrup Speedmax "W" recorder, and a 1.5-m. stainless steel column, packed with 11.6% SE-30 on Anakrom ABS, 70/80 mesh (Analabs Inc., Hamden, Conn.). The temperatures were: column 215°, injector, 265°, and detector, 250°. The carrier gas was helium with a flow rate of 30 ml./min. The detector was calibrated with C_{14}, C_{16}, and C_{18} methyl ester standards (Mann Research Laboratories, New York, N. Y.). Peak areas were calculated with a Disc integrator.

Tablet Preparation—The reagent stearic and palmitic acids were chilled to −10° and passed through a 35-mesh screen while still cold. The commercial stearic acid was passed through a bolting cloth. The powders were then mixed in a Hobart mixer for 20 min. followed by compression of the tablets on a Stokes E machine to give 10-mm., 320-mg. tablets. The powders used were taken from these mixtures. Tablet hardness varied from 3 to 5 on Strong Cobb Arner Inc. tablet hardness tester.

Kinetic Studies—Aspirin (100 mg.) and the fatty acid (8 g.) were placed in a sealed ampul in an oil bath at 70° (±0.01°) and rotated at 60 r.p.m. Samples were taken out at intervals and quickly frozen. One gram of the mixture was crushed in a mortar and analyzed for free salicylic acid, as previously mentioned.

The lower concentrations of aspirin (30 mg.)/8 g. of fatty acid were analyzed in the same manner except a 2-g. sample was used.

The salicylic acid solution was eluted into a volumetric flask and the concentration determined by measuring the absorbance at 310 mμ.

The mineral oil study was carried out by diluting a sample containing 30 mg. aspirin in 10 ml. heavy mineral oil to 100 ml. with chloroform and reading in the UV for salicylic acid with correction for unreacted aspirin.

Table I—Salicylic Acid Formed from Aspirin in Powders and Capsules

Aspirin: Stearic Acid[a]	Final Salicylic Acid[b]	Initial Salicylic Acid[b]	Salicylic Acid Formed[b]
Aspirin-Stearic Acid Powders[c]			
1.0:0.0	0.25	0.23	0.02
0.9:0.1[d]	1.00	0.24	0.76
0.5:0.5[d]	3.80	0.25	3.55
0.9:0.1[e]	0.42	0.23	0.19
0.5:0.5[e]	0.93	0.23	0.70
Aspirin-Stearic Acid Tablets[c]			
1.0:0.0	0.28	0.23	0.05
0.9:0.1[d]	0.53	0.25	0.28
0.8:0.2[d]	1.13	0.23	0.90
0.5:0.5[d]	3.13	0.25	2.88
0.9:0.1[e]	0.30	0.23	0.07
0.8:0.2[e]	0.41	0.25	0.16
0.5:0.5[e]	0.59	0.25	0.34

[a] Ratios on mole fraction basis; time, 36 days, temperature, 50° (±0.25°). [b] Salicylic acid calculated in mg./200 mg. aspirin. [c] Stored in closed amber glass bottles. [d] Commercial triple pressed stearic acid (Emery Ind.). [e] Fisher reagent grade stearic acid.

Table II—Gas Chromatographic Analysis of Acids

	Mole, % C_{14}	C_{16}	C_{18}
Stearic acid USP	3.2	52.7	44.1
Reagent stearic acid	—	2.8	97.2
Reagent palmitic acid	—	97.0	3.0

RESULTS AND DISCUSSION

Powders and tablets composed of variable quantities of aspirin with the two grades of stearic acid were prepared and the following results were obtained (Table I) after allowing them to stand at 50° (±0.25°) for 36 days.

From the preceding data it can be seen that although both reagent and practical grades of acid increase salicylic acid formation over pure aspirin controls, the commercial product produces considerably greater decomposition than the reagent grade.

Stearic acid USP (4), is a mixture of acids consisting principally of palmitic and stearic. Upon gas chromatographic analysis of reagent palmitic and stearic as well as stearic acid USP, the data as shown in Table II were obtained.

As the possibility of a liquid phase serving as a reaction media was suspected, a melting point curve was run on a binary system of reagent stearic and palmitic acids to determine the lowest temperature at which liquefaction might occur (Fig. 1). The curve shows a minimum at approximately 70 mole % of palmitic acid. This low point corresponds closely to that previously shown for mixtures of pure stearic and palmitic acids (5). It may also be noted that stearic acid USP falls quite close to this minimum (see Fig. 1).

Aspirin tablets and powders containing realistic ratios (20:1) of acetylsalicylic acid to lubricant were prepared. Various concentrations of reagent stearic and palmitic acids mixed together were used along with stearic acid USP and aspirin controls and their stability studied at room temperature, 20° (±0.5°), 40° (±0.25°), and 50° (±0.25°) (Figs. 2 and 3). Moisture determinations were run on the tablets and powders by the Karl Fischer method and all were found to be lower than 0.066% which is below the confidence limits of this procedure. Too large a weight of sample is necessary (not dissolvable in the medium used for the determination) to obtain meaningful data.

The results (Figs. 2 and 3) indicate maximum aspirin degradation occurs around the range of composition (with regard to stearic and palmitic acid content) of the commercial stearic acid.

The reagent palmitic and stearic acids were chilled to −10° prior to reduction of their particle size.

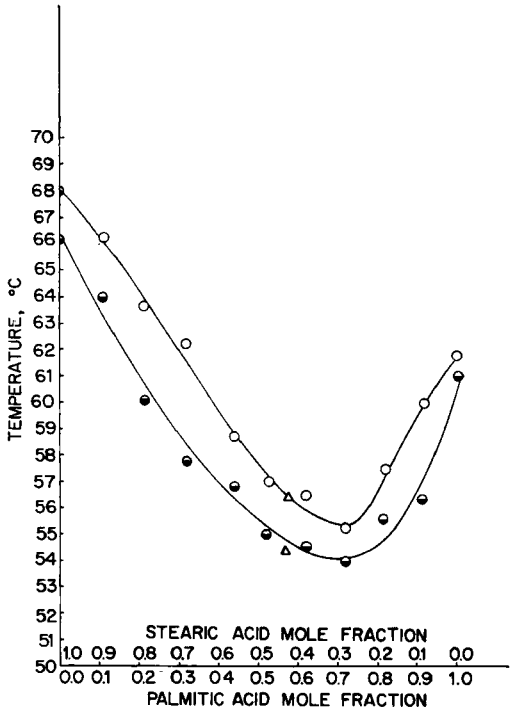

Fig. 1—Melting point curve for mixtures of reagent grade stearic and palmitic acids. Key: ○, complete melting; ◒, melting begins; △, stearic acid USP.

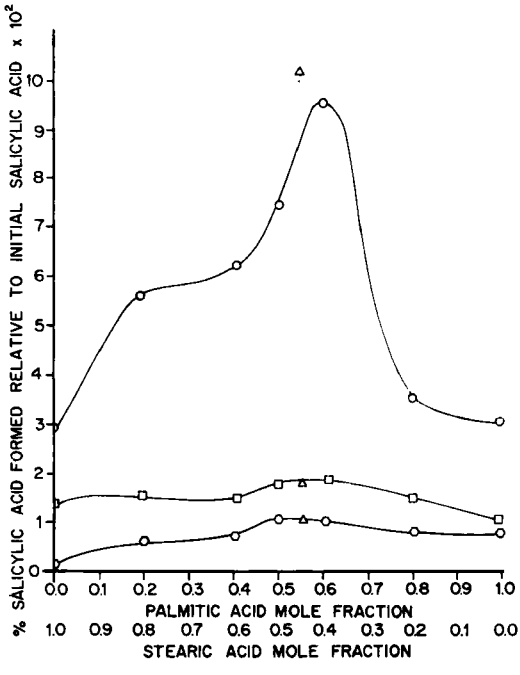

Fig. 2—Aspirin degradation in powder mixes (320 mg.) containing aspirin plus fatty acid lubricant (20:1 w/w ratio, time = 60 days). Pure aspirin controls formed less salicylic acid at all temperatures than aspirin lubricant combinations. Key: ○, 50° (±0.25°); □, 40° (±0.25°); ○, R.T. (±0.50°); △, stearic acid USP.

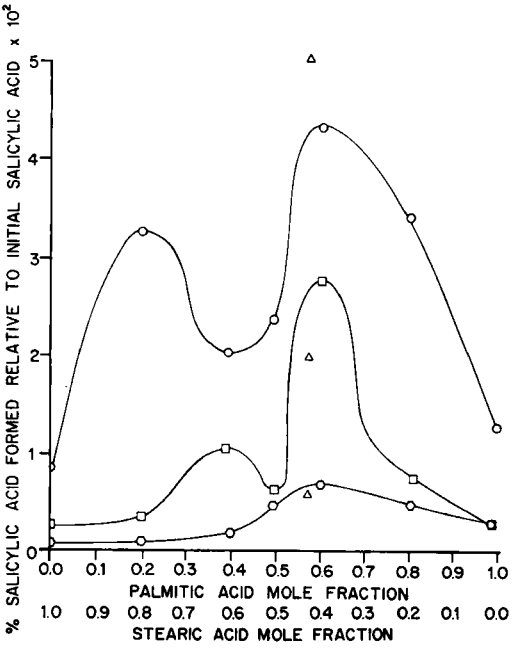

Fig. 3—Aspirin degradation in tablets containing aspirin plus fatty acid lubricant (20:1 w/w ratio, time = 60 days). (Pure aspirin controls formed less salicylic acid at all temperatures than aspirin lubricant combinations.) Key: ○, 50° (±0.25°); □, 40° (±0.25°); ○, R.T. (±0.50°); △, stearic acid USP.

This was necessary because of their consistency which caused difficulty in both their passage through a screen or a bolting cloth. After screening the material was allowed to warm up to room temperature.

It is apparent that in most cases there is a significant increase in aspirin degradation in powders over tablets of identical lubricant concentration.

Kinetic studies were run at 70° on solutions of aspirin in each of the 3 acids as well as in mineral oil to determine their role in increasing salicylic acid formation (Fig. 4). The graph indicates that stearic acid USP, shows the most aspirin decomposition at any given time interval up to 96 hr. Reagent grade palmitic acid gives less degradation with reagent stearic acid giving the least for the 96 hr.

Mineral oil shows little salicylic acid formation after the initial 12-hr. assay. The leveling effect is probably caused by consumption of the total water present in the system.

Kinetic studies on lower concentrations of aspirin (30 mg.) in stearic acid USP (8 g.) give the predictable first-order picture at 70° for 96 hr. (Fig. 5). This may be a result of the lesser concentration of aspirin relative to the water in the system.

Moisture determinations (Karl Fischer) again failed to produce any conclusive evidence of the amount of water present in the aspirin-fatty acid system due to the same reasons previously stated.

Although the concentration of water in any of these fatty acids is exceptionally small, one must bear in mind that only 10 mg. of water is required

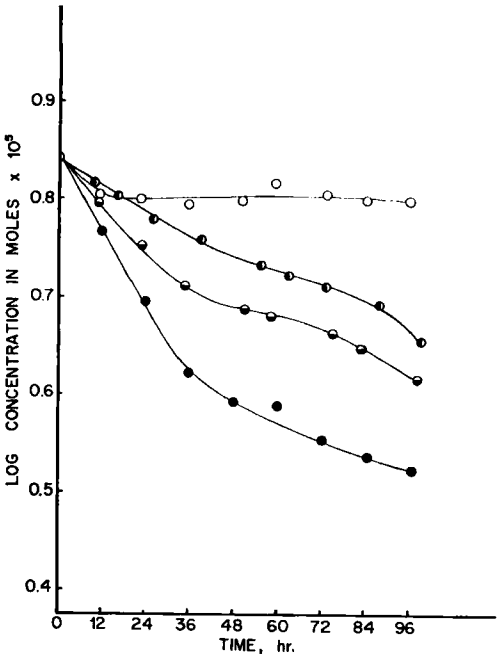

Fig. 4—Kinetic studies at 70° (±0.01°) of aspirin degradation in fatty acid lubricants and mineral oil (100 mg. aspirin/8.100 g. sample). Key: ○, mineral oil; ◐, reagent stearic acid; ◒, reagent palmitic acid; ●, stearic acid USP.

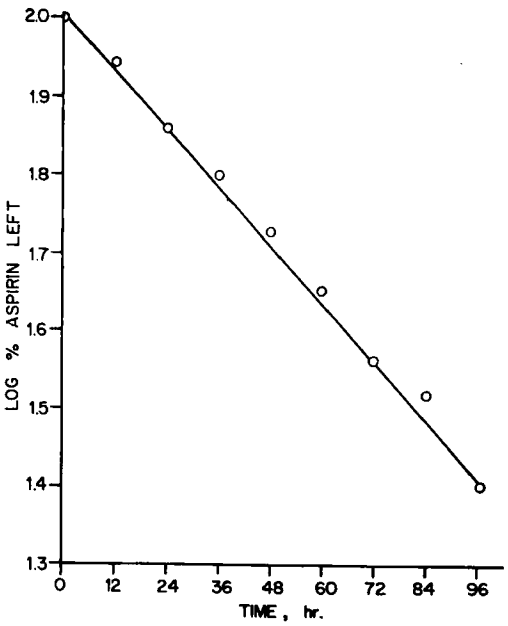

Fig. 5—Kinetic studies at 70° (±0.01°) of aspirin degradation in stearic acid USP (30 mg. aspirin/8.000 g. stearic acid).

to hydrolyze 100 mg. of aspirin. This would represent only a 0.12% moisture content/8 g. of acid.

From a practicality viewpoint, the reagent palmitic and stearic acids appear to be efficient lubricants, however, the cost differential is appreciable between them and stearic acid USP.

CONCLUSIONS AND DISCUSSION

Stearic acid USP, in combination with aspirin tablets and powders increases salicylic acid formation over pure aspirin controls.

Reagent grade stearic and palmitic acids (Fisher Chemical Co.) are found to retard aspirin degradation relative to the commercial "triple pressed stearic acid," stearic acid USP.

The effect of myristic acid was not evaluated due to its low concentration in the two fatty acids examined although the same basic situation with regard to aspirin stability would be expected to exist.

From the results presented it appears there are better fatty acid lubricants from a stability standpoint for use with aspirin than the standard commercial stearic acid.

Powders and tablets of the same composition (20:1, aspirin:fatty acid) show a significant difference in decomposition for a given period of time. As moisture content of the two should be equal, this anomaly could be partially due to the greater surface area and looser consistency of a given weight of powder when compared to tablets. It may be that the driving force of the reaction is sublimation and removal of salicylic acid from the system which should be much easier in the case of the loose powder than in the relatively hard-surfaced tablet. There will be a later report on this phenomenon.

The decomposition of aspirin powders and tablets (20:1) made of different ratios of reagent stearic and palmitic acids reach a maximum near the same point where the two acids reach a minimum in the melting point curve with stearic acid USP, being the worst of the group.

The kinetics of aspirin (100 mg.) solutions in the fatty acids (8 g.) show no definite order of reaction at 70° although, if the total amount of water in the system were known, the reaction would probably prove to be second order. In the lower aspirin concentrations (30 mg.)/8 g. acid a first-order plot is demonstrable, probably due to excess water in the system strengthening the case for a second-order mechanism.

The kinetic results with mineral oil indicate that little thermal degradation of aspirin takes place at 70° and thus is not a factor with the principal reaction in all cases being simple hydrolysis by the water present in the system.

The possibility exists of liquid or semiliquid being present in the system as a result of the low melting stearic acid which serves as the media for aspirin hydrolysis.

REFERENCES

(1) Ribeiro, D., Stephenson, D., Samyn, J., Milosovich, G., and Mattocks, A., *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 226(1955).

(2) Zoglio, M. A., and Korublum, S. S., *J. Pharm. Sci.*, **56**, 1569(1967).

(3) Levine, J., *ibid.*, **50**, 506(1961).

(4) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965, p. 667.

(5) Smith, J. C., *J. Chem. Soc.*, **1936**, 625.

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

By M. A. ZOGLIO, H. V. MAULDING, R. M. HALLER, and S. BRIGGEN

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.