far greater cosolvency effect of ethanol–water on aminopyrine is seen in the smaller ratios in this solvent mixture.

SUMMARY

It can be observed from Fig. 1 that in both cases the polarity of antipyrine is greater than aminopyrine by virtue of possessing both higher DR's and magnitude to solubility. Furthermore, the solubility curve for aminopyrine moves closer with respect to both DR and magnitude in the solvent mixture of higher polarity. It would be interesting to note how these differences in DR and magnitude would change by the use of more polar binaries such as methanol–water mixtures and less polar binaries such as propanol–water mixtures.

It may be assumed for this particular pair of solutes in the systems studied that from the differences in the position of the DR's and the concomitant magnitude that antipyrine is inherently more polar than aminopyrine. This is further substantiated by the characterization of solute polarity from dielectric constant studies of saturated solutions.

The rather obvious noncorrelation of DR in the 2 solvent systems for aminopyrine and the vague correlation in the case of antipyrine may imply that the concept of DR agreement, irrespective of the solvent system, is suspect.

Although previous publications (4, 5) had assumed that this concept was true, and at times tenuously true, it is now reasonable to postulate that the solubility profiles and respective DR(s) may be considered unique unto themselves in any given solvent system, a situation previously reported (6–9).

It is felt that this does not obviate either the usefulness or application of this knowledge, and that the cosolvency phenomena relative to dielectric constants has been amply illustrated. It is hoped that continuing studies on solutes of pharmaceutical interest relative to the above points will allow amplification and reinterpretation of past experiences in this area.

Presently, the author's research interests are concerned with the parabens and barbiturates, and these will be the subject of future communications.

REFERENCES

(1) Paruta, A. N., and Irani, S. A., *J. Pharm. Sci.*, **54**, 1334(1965).
(2) Paruta, A. N., and Sheth, B. B., *ibid.*, **55**, 896(1966).
(3) Paruta, A. N., *Am. J. Pharm.*, **137**, 138(1966).
(4) Paruta, A. N., Sciarrone, B. J., and Lordi, N. G., *J. Pharm. Sci.*, **53**, 1349(1964).
(5) *Ibid.*, **54**, 1325(1965).
(6) Krause, G. M., and Cross, J. M., *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 137(1951).
(7) Peterson, C., and Hopponen, R. E., *ibid.*, **42**, 541 (1953).
(8) Moore, W. E., *ibid.*, **47**, 855(1958).
(9) Gorman, W. G., and Hall, G. D., *J. Pharm. Sci.*, **53**, 1017(1964).

Pharmaceutical Heterogeneous Systems I

Hydrolysis of Aspirin in Combination with Tablet Lubricants in an Aqueous Suspension

By S. S. KORNBLUM and M. A. ZOGLIO

The chemical mechanism that explains the accelerated hydrolysis demonstrated by aspirin when in combination with an alkali stearate, *i.e.*, calcium stearate, in a solid dosage form has been elucidated by employing a suspension technique. The mechanism primarily involves a reaction of the alkali cation with aspirin in a solution to form a salt of aspirin which, in the presence of solvated aspirin, comprises a buffer system at a pH detrimental to the stability of aspirin. Using the kinetic data obtained from the suspension study, an attempt was made to predict aspirin stability in a solid dosage form. There is evidence presented to support the concept that stearic acid will serve as a medium for aspirin degradation at temperatures slightly above room temperature.

PREVIOUS RESEARCHERS (1–4) studying the hydrolysis of aspirin in either a homogeneous or heterogeneous aqueous system have demonstrated that decomposition is a function of water content, pH, and temperature. An aspirin tablet can be identified as a heterogeneous system. One may compare an aspirin tablet with an aqueous aspirin suspension in order to facilitate an explicit definition of the hydrolysis phenomena. The effect of antacids in mixtures with aspirin has been studied in the presence of moisture and has been demonstrated to increase decomposition rate (5, 6). Some substances employed as tablet lubricants can effectively act as antacids, *e.g.*, stearate salts. The purpose of this study was to evaluate the commonly used tablet lu-

Received April 14, 1967, from the Pharmacy Research and Development Department, Sandoz Pharmaceuticals, Hanover, NJ 07936
Accepted for publication August 8, 1967.
Presented to the Industrial Pharmaceutical Technology Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.
The technical assistance of D. Murdock and A. Dilatush is gratefully acknowledged.

bricants as to their effect on the stability of aspirin and define the chemical mechanisms that lead to an accelerated hydrolysis in mixtures of aspirin and alkali stearates.

EXPERIMENTAL

Aqueous Aspirin Suspensions—Mixtures of equal quantities (200 mg.) of aspirin crystals (USP) and various tablet lubricants: talc, stearic acid, hydrogenated vegetable oil,[1] calcium stearate, magnesium stearate, and aluminum stearate were prepared. Excess lubricant was employed in an attempt to insure saturation throughout the experiment. The weighed powders were transferred into glass vials of 18.5 ml. capacity and exactly 10 ml. distilled water was added to form a suspension. To prevent leakage the vials were sealed with aluminum foil before securing with Bakelite caps. The vials were then attached to a rotating circular disk in a constant-temperature bath which permitted continuous agitation at 30°. Appropriate aliquots were withdrawn at various time intervals for pH and free salicylic acid determinations. The amount of free salicylic acid formed was determined by adding to an exact volume of the suspension filtrate 4 ml. of 2% ferric chloride solution with subsequent dilution to 100 ml. with distilled water. Exactly 3 min. was permitted for the color development before reading at 540 mμ employing the Perkin-Elmer 202 spectrophotometer. The validity of the salicylic acid assay was demonstrated by adherence to the Beer-Lambert law over the concentration range studied. pH values were obtained by using a Metrohm E 300.

Determination of Aspirin Species in Suspension Filtrate—Total aspirin content was determined by withdrawing a 1-ml. aliquot of the suspension filtrate and diluting to 100 ml. with a 0.2 *M* sodium acetate–acetic acid buffer solution (pH 6.09). The spectrophotometric reading was taken at 268 mμ.

Calcium aspirin content was determined by withdrawing a 5-ml. aliquot of the suspension filtrate and diluting with distilled water to 150 ml. The pH of this solution was adjusted to 12.0–12.5 using 1 *N* sodium hydroxide solution. Hydroxynaphthol blue A.R. was employed as the indicator in a 0.2–0.3 Gm. quantity. The solution was titrated with 0.05 *M* disodium EDTA solution to a clear blue color. Each milliliter of 0.05 *M* disodium EDTA solution is equivalent to 2.0064 mg. of calcium ion.

Free aspirin contained in the suspension filtrate was calculated from the following equation:

$$\text{free aspirin} = \text{total aspirin} - \text{aspirin as calcium aspirin}$$

Effect of Reducing the Water Content in an Aqueous Aspirin–Calcium Stearate Suspension—A study was performed in order to establish the effect of decreasing the water content of the suspension from 10 to 0.1 ml. Below 1 ml. glass beads were placed in the reaction vials to insure uniform agitation. When less than 5 ml. was employed, the suspension was diluted at the time of withdrawal for analysis to contain 10 ml. of water.

Effect of Stearic Acid on Aspirin Degradation in a Solid Mixture Study—Aspirin crystals were dissolved in molten stearic acid USP in a 1:80 ratio at 75°. Equal quantities of the melt were transferred into glass vials and tightly sealed. The melt was quickly cooled by immersion in an ice bath. Samples were then kept in an oven at 40 ± 0.5° and routinely assayed after exact weighing of approximately 800 mg. of the solidified melt. The solidified melt was dissolved and diluted with chloroform to a volume of 200 ml. The solution was spectrophotometrically read in the UV at 310 mμ.

Aspirin crystals containing approximately the same amount of moisture as the stearic acid melt were stored at 40° and used as a control. Moisture present in the samples was determined by Karl Fischer titration. The analytical method employed for the aspirin crystals is outlined in the next section.

Aspirin–Stearic Acid Capsule Study—The following samples were prepared and stored at room temperature, 40°, and 50°: (*a*) aspirin–stearic acid powder blend (20:1 ratio), aspirin–stearic acid capsules[2] (20:1 ratio), (*c*) aspirin crystals, 40 mesh, (*d*) aspirin capsules.[2]

The samples were assayed for salicylic acid after dissolving a quantity equivalent to 200 mg. of aspirin in 10 ml. of chloroform. The solution was transferred to a diatomaceous earth[3] column which had been previously moistened with 2% ferric chloride solution. The column was washed with chloroform until the purple zone migrated to the lower portion of the column. These washings were discarded. Subsequently the column was washed with 10 ml. of 10% acetic acid–chloroform followed by 1% acetic acid–chloroform until the purple zone was eluted. These washings were concentrated to 50 ml. and read spectrophotometrically at 310 mμ. Moisture content of the samples studied was determined by Karl Fischer titration.

Aspirin Degradation in Aspirin–Calcium Stearate Tablets—Tablets were manufactured containing aspirin crystals and calcium stearate (1:1 ratio). The tablets were stored at 30° for 60 days. At the time of assay the tablets were comminuted and a quantity of 400 mg. of the powder was dissolved in 20 ml. chloroform and mixed for less than 1 min. This was rapidly passed through a Millipore membrane into a separator and aqueous washings followed to remove any calcium aspirin. The chloroform solution was passed through a diatomaceous earth column. From this point the analysis proceeds as described under *Aspirin–Stearic Acid Capsule Study*.

RESULTS AND DISCUSSION

The kinetics observed for the hydrolysis of aspirin in the presence of tablet lubricants is depicted in Fig. 1. The reaction rates appear to follow a zero-order reaction law with the exception of the initial rates for the aspirin–calcium stearate and the aspirin–magnesium stearate suspensions. The linear portion of the decomposition curves for each of the aspirin–lubricant combinations was accompanied by a relatively static hydrogen ion concentration for the 30-hr. period studied. A summary of pH values and reaction rate constants for the apparent zero-

[1] Sterotex. Capitol City Products, Columbus, Ohio.

[2] No. 3 Parke-Davis pink capsules were used.

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

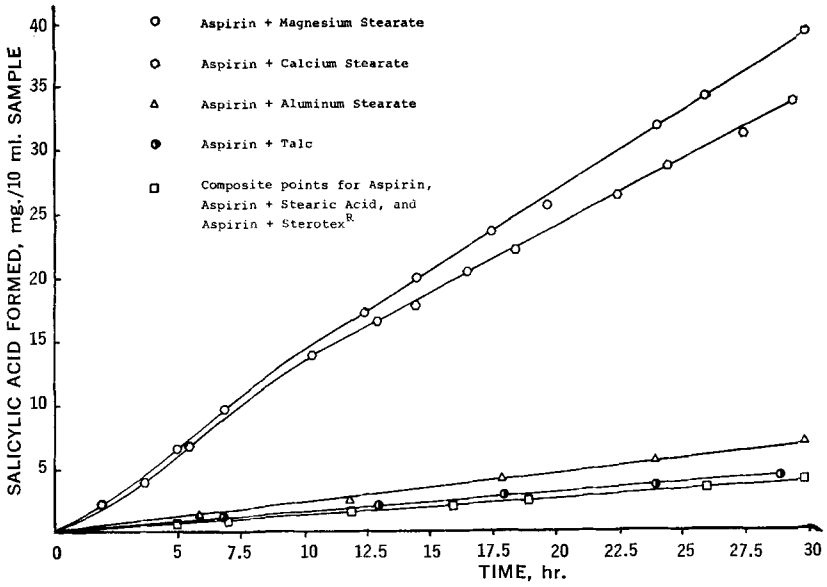

Fig. 1—Aspirin hydrolysis at 30° in aqueous suspensions containing tablet lubricants.

order degradation is given in Table I. The order of magnitude of the reaction rates for aspirin–calcium stearate and aspirin–magnesium stearate suspensions suggested that something other than saturation solubility had manifested the relatively high pH during decomposition. The possibility existed that perhaps a reaction between aspirin and the stearate salt had taken place. If so, then a high concentration of magnesium or calcium aspirin could be expected in solution. The aspirin salt would exert a buffering effect in combination with aspirin in the solvate portion of the suspension. In order that this theory could be verified the quantity of calcium transferring into solution was followed as a function of time during the 30-hr. reaction period. Figure 2 demonstrates that the quantity of calcium ion in solution very quickly exceeds its aqueous saturation solubility (0.02 mg./ml.) in the presence of aspirin and rises radically during the initial 3-hr. period. The period of constant pH is established

TABLE I—PERTINENT DATA FOR ASPIRIN SUSPENSIONS STUDIED[a]

Compn.	Constant pH (Arithmetic Mean)[b]	Apparent Zero-Order Rate Constant, mg. of Free Salicylic Acid/hr.
Aspirin	2.60	0.123
Aspirin + stearic acid	2.62	0.133
Aspirin + hydrogenated vegetable oil	2.68	0.123
Aspirin + talc	2.71	0.133
Aspirin + aluminum stearate	3.16	0.281
Aspirin + calcium stearate	3.75	0.986
Aspirin + magnesium stearate	4.14	1.314

[a] All aspirin suspensions contained exactly 10 ml. distilled water. [b] The arithmetic mean has been determined from a minimum of 6 pH values.

during the first 10 hr. in the aspirin–calcium stearate suspension studied and is thereafter followed by a relatively unchanging calcium ion concentration. The information obtained supports the existence of a buffer system composed of calcium aspirin and aspirin which appears to be controlling the pH from the 10th to 30th hr. of the reaction. Figure 3 establishes the fact that there does exist approximately a 2:1 ratio of calcium aspirin to aspirin in the buffer system. The amount of aspirin shown in Fig. 3 at the 5th hr. is representative of the saturation solubility for aspirin at 30° in the suspension system. This concentration of aspirin is henceforth maintained throughout the 30-hr. time interval studied.

The initial S-shaped portion of Fig. 1 for the aspirin–calcium stearate and aspirin–magnesium stearate systems can be explained by analyzing the data for pH (Fig. 4) and species of aspirin in solution (Fig. 3) *versus* time. Figure 4 depicts a sharp increase in pH for the aspirin–calcium stearate system which then rises to a peak after about 3 hr. and then reverses to establish a constant pH. Observation of Fig. 3 makes it possible to explain the initial rise in pH as a result of the rapid formation of the calcium salt of aspirin. However, the dissolution rate of aspirin falls short of maintaining the saturation of aspirin during the initial stage of the salt-forming reaction. After 1.5 hr. the concentration of aspirin diminishes thus allowing the pH of the solution to be further elevated by the predominance of calcium aspirin. When the reaction has progressed for 3.5 hr., the dissolution rate of aspirin catches up with the utilization of aspirin in the salt formation. By virtue of the lower saturation pH of aspirin in solution (pH = 2.66), as compared with calcium aspirin in solution (pH = 4.2), the system stabilized to a buffer pH at 3.75 and remained constant over the 30-hr. period studied.

Experiments were performed where the amount of water employed in the suspensions was reduced in order to approach that found in a solid dosage

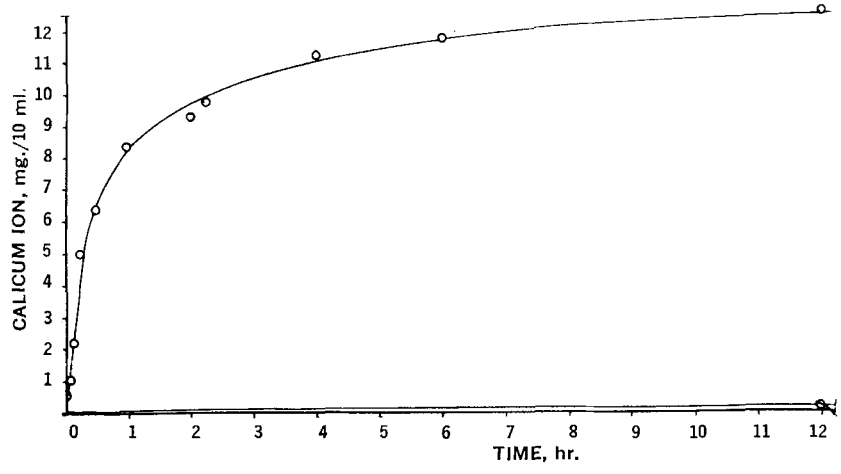

Fig. 2—Calcium ion concentration in solution during the initial segment of the aspirin–calcium stearate suspension study.

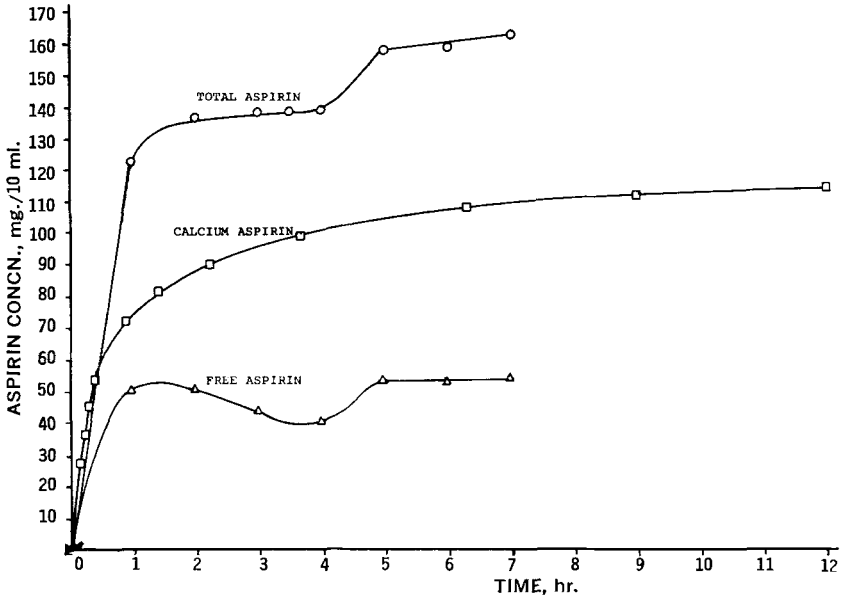

Fig. 3—Species of aspirin in solution during the initial segment of the aspirin–calcium stearate suspension study.

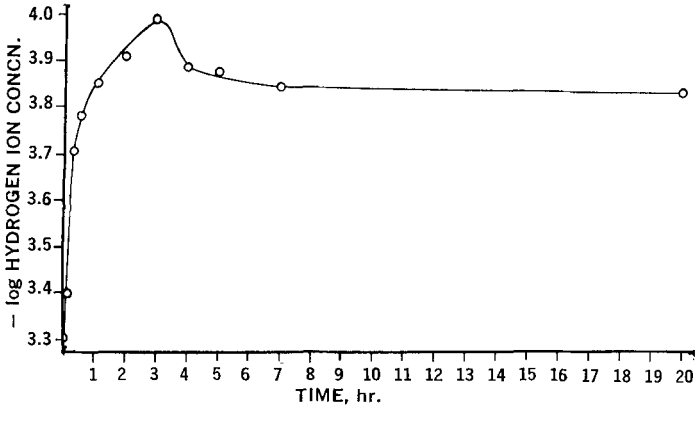

Fig. 4—pH changes occurring during the aspirin–calcium stearate suspension study (each sample contained 10 ml. water).

form. The ultimate aim was the achievement of data that would permit subsequent extrapolation to the tablet or capsule dosage form. Zero-order rate constants for the aspirin-calcium stearate aqueous suspensions were determined as a function of water content, and the data have been plotted in Fig. 5. The curve fortunately appears to be linear in the region of low water content enabling

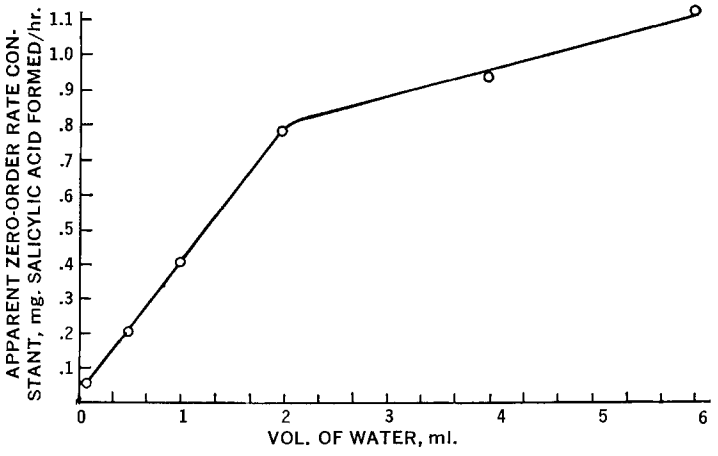

Fig. 5—Relationship of the rate of salicylic acid formation to the volume of water contained in the aspirin–calcium stearate suspension

a correlation with the solid dosage form data. The change of slope above 2 ml. is most likely due to insufficient amounts of calcium aspirin in the system to accomplish saturation. When the aqueous solubility of calcium–aspirin (0.165 Gm./ml.) is used to estimate the volume of water at this change in slope, 0.8 ml. would be indicated. The higher value in Fig. 5 indicates the solubility of calcium aspirin to be considerably lower in the system studied. Table II shows that the pH of the suspensions possessing minimal water content ascends until the pH reaches the saturation pH of calcium aspirin which is 4.2 at 2 ml. It is assumed that the linearity experienced at volumes less than 2 ml. is a result of the saturation of the water with calcium aspirin and the maintenance of the pH observed at 2 ml. The predictive aspects of the results are limited, since the reactions were only studied for a 30-hr. period. From observing Fig. 6, one can see that the pH for a period longer than 30 hr. is not a constant as was true in the suspensions studied. As the degradation products accumulate, the pH declines, until after 8 days a constant pH does exist. The data from Fig. 5 prove valuable in predicting maximum decomposition to be expected in a solid dosage form. This is true even though the reaction rate studies with the suspensions were conducted at pH values more detrimental to aspirin stability than those observed with an extended study (Fig. 6). Aspirin–calcium stearate (1:1 ratio) powder blend and tablets of the same composition were prepared. Both were stored for a 2-month period at 30°.

TABLE II—CONSTANT pH ESTABLISHED FOR ASPIRIN SUSPENSION CONTAINING CALCIUM STEARATE WHEN REDUCING THE WATER CONTENT

Compn.	Water Content, ml.	Constant pH (Arithmetic Mean)
Aspirin + calcium stearate (200 mg. each)	10	3.75
	6	3.91
	4	4.04
	2	4.19

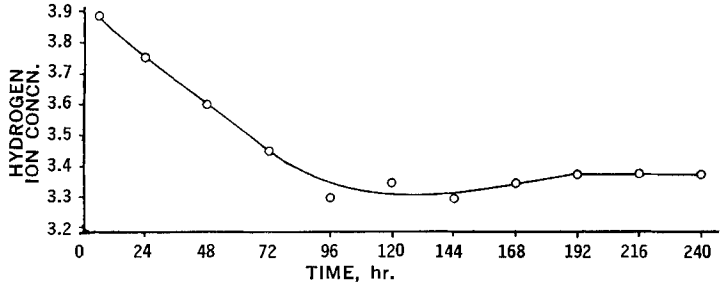

Fig. 6—pH changes occurring during an extended aspirin–calcium stearate suspension study (each sample contained 10 ml. water).

TABLE III—ASPIRIN DEGRADATION IN ASPIRIN–CALCIUM STEARATE TABLETS

Sample	Actual Deg.	Deg. Predicted from Extrapolation of Results from Fig. 5
Aspirin–calcium stearate tablet, 1:1 wt. ratio (0.0843% water)	2.25 mg. of salicylic acid formed/ 200 mg. of aspirin	1.94 mg. of salicylic acid formed/ 200 mg. of aspirin
Aspirin–calcium stearate powder mixture, 1:1 wt. ratio (1.05% water)	2.49 mg. of salicylic acid formed/ 200 mg. of aspirin	2.42 mg. of salicylic acid formed/ 200 mg. of aspirin

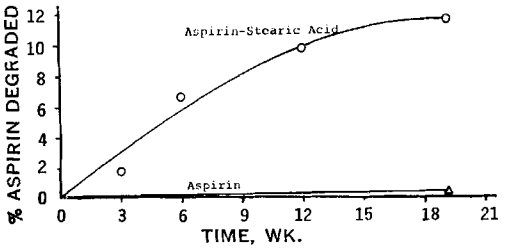

Fig. 7—Degradation of aspirin–stearic acid. Solid mixture (1:80 ratio) at 40°.

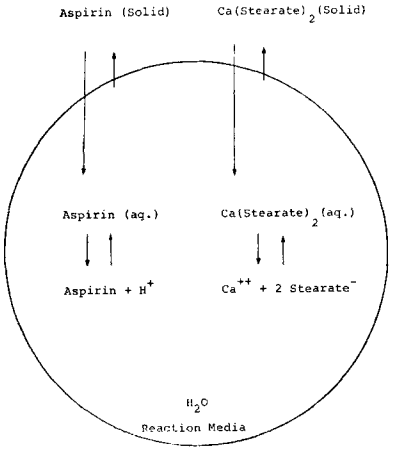

Fig. 8—Solution of aspirin and stearate salt.

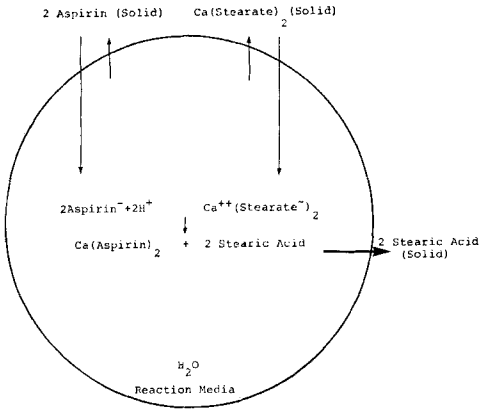

Fig. 9—Calcium aspirin formation.

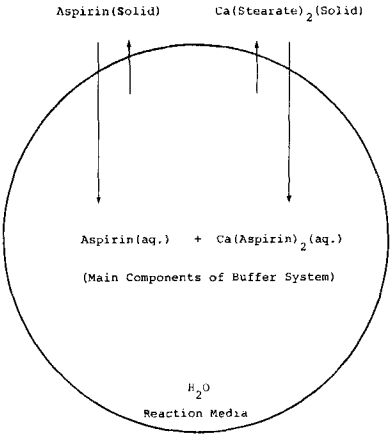

Fig. 10—Buffer system.

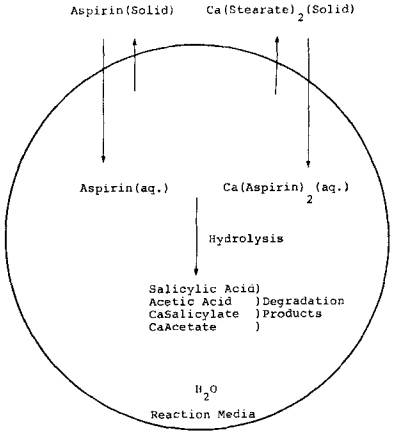

Fig. 11—Aspirin hydrolysis.

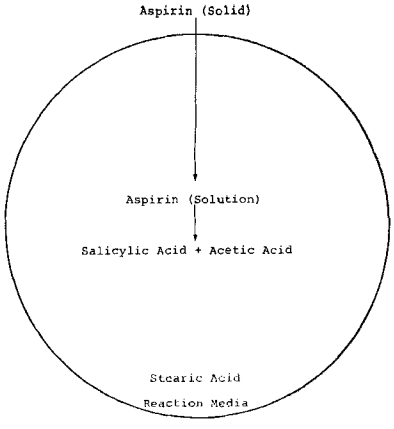

Fig. 12—Anhydrous aspirin degradation in the presence of stearic acid at 40°.

Table III reveals that data obtained from suspension studies can be satisfactorily compared with solid state information, thus enabling one to predict the extent of decomposition in the solid state from suspension data.

The data provided in Figs. 1 through 6 and Tables I and II substantiate the explanation, (Figs. 8–11), of the mechanism involved for the aspirin–calcium stearate system. The presence of moisture in the dosage form results in a solution of the aspirin and the stearate salt as illustrated in Fig. 8 (Figs. 2 and 3). In Fig. 9 calcium stearate and aspirin are shown reacting to form calcium aspirin and stearic acid (Figs. 2 and 3). Initially the buffer system (Fig. 10)

TABLE IV—ASPIRIN–STEARIC ACID CAPSULE STUDY

Aspirin + Stearic Acid (20:1) Moisture Content: 0.10%					
Powder			Capsules		
Free Salicylic Acid Content			Free Salicylic Acid Content		
22°C.	0.092%	(83 days)	22°C.	0.093%	(83 days)
40°C.	0.130%	(30 days)	40°C.	0.170%	(30 days)
50°C.	0.409%	(30 days)	50°C.	1.035%	(30 days)
Aspirin (Pure) Moisture Content: 0.10%					
Powder			Capsules		
Free Acid Salicylic Content			Free Salicylic Acid Content		
22°C.	0.082%	(86 days)	22°C.	0.092%	(86 days)
40°C.	0.068%	(30 days)	40°C.	0.158%	(30 days)
50°C.	0.160%	(30 days)	50°C.	0.200%	(30 days)

is mainly composed of calcium aspirin and aspirin which establishes a pH value detrimental to aspirin stability. In Fig. 11 the calcium–aspirin and aspirin in solution are shown undergoing hydrolysis (Fig. 1). The decomposition products being more acidic in nature than the aspirin–calcium aspirin system eventually overcome the capacity of the buffer system and lower the pH (Fig. 6). Again the pH levels at a lower value than the initial buffer pH but is still detrimental to aspirin stability.

The evaluation of the lubricants from the results in Fig. 1 indicate stearic acid and hydrogenated vegetable oil to be suitable for use in aspirin tablets. Although stearic acid does not demonstrate a pH effect, it apparently can serve as a medium for aspirin decomposition (Fig. 12). This can be demonstrated by comparing the stability of aspirin with aspirin–stearic acid in powder and capsule forms that have been stored at 22°, 40°, and 50° (Table IV).

Free salicylic acid content is significantly higher in the capsules than in the powder, most likely as a result of the water content in the gelatin. Figure 7 shows the degradation effect more dramatically when aspirin is suspended in molten stearic acid and stored at 40°.

CONCLUSION

From the kinetic data obtained with the aspirin–lubricant combinations it appears feasible that the suspension technique employed may be useful in solid dosage form stability predictions, lubricant evaluation, and as a basic method for elucidation of the chemical mechanism for other solid state decomposition.

Figure 1 illustrates the relative acceptability from a stability standpoint of tablet lubricants for combination with aspirin. The order is as follows: hydrogenated vegetable oil, stearic acid, talc, and aluminum stearate. This study has revealed that stearate salts should be avoided as tablet lubricants, if the active component is subject to hydroxyl-ion catalyzed degradation and if there is contained in the dosage form an ingredient which can react with the stearate salt to form a soluble basic species. Aluminum stearate appears to be the most suitable of the alkali stearate salts for combination with aspirin. This seems to be a result of the poor water solubility of aluminum aspirin thus limiting the total aspirin present in solution. Aside from the pH effect, the major factor influencing degradation when aspirin is combined with calcium or magnesium stearate in suspension is the high solubility of calcium aspirin and magnesium aspirin in an aqueous medium.

Talc possesses trace amounts of oxide impurities that affect the pH of the suspension initially, thus causing a slight increase in the amount of salicylic acid formed. However, this does not influence the over-all reaction rate (Table I). Talc can be used with mixtures of stearic acid and hydrogenated vegetable oil, but is not usually employed solely as a tablet lubricant due to its low ratio of efficiency.

Stearic acid appears to be suitable from the suspension studies. However, it has been noted that stearic acid may function as a medium for aspirin degradation at temperatures slightly above room temperature.

REFERENCES

(1) Edwards, L. J., *Trans. Faraday Soc.*, **46**, 723(1950).
(2) Leeson, L. J., and Mattocks, A. M., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 329(1958).
(3) Kubo, F., Imaoka, K., and Kaneko, A., *Kyoritsu Yakka Daragaku Nempo*, **617**, 1(1961–1962).
(4) Lippman, I., and Mattocks, A. M., Reprint of Symposium Papers, APHA, Las Vegas meeting, 1962.
(5) Nazareth, M., and Huyck, C., *J. Pharm. Sci.*, **50**, 608(1961).
(6) Kral, J., Breleszova, H., and Drozkova, Z., *Farm. Obzor.*, **29**, 298(1960).