(299) A. B. Morrison and J. A. Campbell, *J. Nutr.*, **72,** 435 (1960).
(300) A. S. Schultz, R. F. Light, and C. N. Frey, *Proc. Soc. Exp. Biol. Med.*, **38,** 404 (1938).
(301) G. Levy and R. R. Hewitt, *Am. J. Clin. Nutr.*, **24,** 401 (1971).
(302) H. Linkswiler and M. S. Reynolds, *J. Nutr.*, **41,** 523 (1950).
(303) S. H. Rubin, J. M. Cooperman, M. E. Moore, and J. Scheiner, *ibid.*, **35,** 499 (1948).
(304) L. Drekter, J. Scheiner, E. DeRitter, and S. H. Rubin, *Proc. Soc. Exp. Biol. Med.*, **78,** 381 (1951).
(305) T. Tamura and E. L. R. Stokstad, *Br. J. Haematol.*, **25,** 513 (1973).
(306) C. C. Booth, I. Chanarin, B. B. Anderson, and D. L. Mollin, *ibid.*, **13,** 253 (1957).
(307) C. C. Booth and D. L. Mollin, *Lancet*, **1,** 13 (1959).
(308) P. R. Dallman and L. K. Diamond, *J. Pediatr.*, **57,** 689 (1960).
(309) J. A. Campbell and A. B. Morrison, *Am. J. Clin. Nutr.*, **12,** 162 (1963).
(310) C. L. Conley, J. R. Krevans, B. F. Chow, C. Barrows, and C. A. Lang, *J. Lab. Clin. Med.*, **38,** 84 (1951).
(311) J. F. Adams, D. J. Clow, S. K. Ross, K. Boddy, P. King, and M. A. Mahaffy, *Clin. Sci.*, **43,** 233 (1972).
(312) J. T. L. Nicholson and F. W. Chornock, *J. Clin. Invest.*, **21,** 505 (1942).
(313) W. Kübler and J. Gehler, *Int. Z. Vitaminforsch.*, **40,** 442 (1970).
(314) J. S. Stewart and C. C. Booth, *Clin. Sci.*, **27,** 15 (1964).
(315) M. Chieffi and J. E. Kirk, *J. Nutr.*, **59,** 273 (1956).
(316) A. E. Sobel and A. A. Rosenberg, *Am. J. Dis. Child.*, **84,** 609 (1952).
(317) L. J. Filer, Jr., S. W. Wright, M. P. Manning, and K. E. Mason, *Pediatrics*, **8,** 328 (1951).
(318) E. F. Week, F. J. Sevigne, and M. E. Ellis, *J. Nutr.*, **46,** 353 (1952).
(319) R. S. Overman, M. M. McNeely, N. E. Todd, and J. S. Wright, *Am. J. Clin. Nutr.*, **2,** 168 (1954).
(320) D. Melnick, M. Hochberg, and B. L. Oser, *J. Nutr.*, **30,** 67 (1945).
(321) B. L. Oser, D. Melnick, and M. Hochberg, *Ind. Eng. Chem. Anal. Ed.*, **17,** 405 (1945).
(322) E. H. Mawson and S. Y. Thompson, *Biochem. J.*, **43,** 2 (1948).
(323) O. Pelletier and J. A. Campbell, *Anal. Biochem.*, **3,** 60 (1962).
(324) H. R. Skeggs and L. D. Wright, *J. Biol. Chem.*, **156,** 21 (1944).
(325) W. N. Pearson, in "The Vitamins," vol. VII, P. György and W. N. Pearson, Eds., Academic Press, New York, N.Y., 1967, p. 191.
(326) J. C. Rabinowitz and E. E. Snell, *J. Biol. Chem.*, **169,** 131 (1947).
(327) S. H. Rubin, F. W. Jahns, and J. C. Bauernfeind, *Fruit Prod. J. Am. Food Manuf.*, **24,** 327 (1945).
(328) R. E. Johnson, L. A. Contreras, F. C. Consolazio, and P. F. Robinson, *Am. J. Physiol.*, **144,** 58 (1945).
(329) E. J. Middleton, J. Davies, and A. B. Morrison, *J. Pharm. Sci.*, **54,** 1 (1965).
(330) D. A. Libby, M. E. Schertel, and H. W. Loy, *J. Assoc. Off. Agr. Chem.*, **48,** 981 (1965).
(331) T. Ida, S. Takahashi, K. Noda, S. Kishi, S. Nakagami, and I. Utsumi, *J. Pharm. Sci.*, **52,** 472 (1963).

RESEARCH ARTICLES

Solid-State Stability of Aspirin in the Presence of Excipients: Kinetic Interpretation, Modeling, and Prediction

P. V. MROSO, A. LI WAN PO ˣ, and W. J. IRWIN

Received August 7, 1981, from the *Department of Pharmacy, University of Aston, Gosta Green, Birmingham B4 7ET England.* Accepted for publication December 14, 1981.

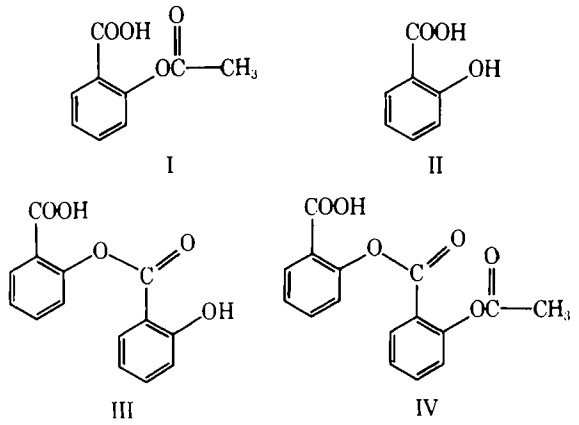
Abstract □ Salicylsalicylic acid and acetylsalicylsalicylic acid were identified as decomposition products of aspirin when mixtures of the drug, with magnesium stearate, were stored in the solid state at 60° and 75% relative humidity. The effect of increasing the concentration of magnesium stearate and the addition of other alkali stearates on the rate of decomposition of aspirin were studied. The validity of the theory that pH changes induced by the alkali stearates account for the catalytic effect of the lubricants on the decomposition was tested. The changes observed were modeled and the mechanism involved elucidated. The potential use of the melting points of aspirin mixtures in predicting the stability of the drug in such drug–excipient mixtures is demonstrated.

Keyphrases □ Aspirin—solid-state stability in presence of excipients, kinetic interpretation, modeling and prediction, decomposition □ Decomposition—solid-state stability, aspirin, excipients, kinetic interpretation, modeling and prediction □ Stability—solid state, aspirin, in presence of excipients, kinetic interpretation, modeling and prediction

The mechanisms of decomposition of drugs in the solid state are complex and difficult to unravel (1–3). The problems are compounded by the fact that most drugs are formulated with excipients, and decomposition in such systems is even more complicated. This, together with the usually slow rates of decomposition in the solid state relative to solutions, may explain the comparatively small number of reports on the quantitation of decomposition of drugs in formulated solid-dosage forms. Many of the reports that have appeared have tended to be semiquantitative, although a few detailed studies have been reported (4–9). To overcome the time constraints, some workers have resorted to the prediction of the solid-state stability of hydrolabile drugs by studying their decomposition in suspension systems. Kornblum and Zoglio (10) for example attempted to predict the stability of aspirin in the presence of tablet lubricants in the solid state by this approach. Although the method described is attractive, the mechanisms of decomposition in solid dosage systems may be different from those observed in systems containing a higher proportion of water.

More recent studies have shown that in addition to

0022-3549/82/01000-1096$01.00/0



salicylic acid (II), salicylsalicylic acid (III) and acetylsalicylsalicylic acid (IV) could be detected in aspirin tablets (11–13). Since these compounds (III and IV) have been shown (14, 15) to be potentially immunogenic, limiting their presence in formulated products is important. It has been previously reported that although III was detected in aspirin tablets, it was not detected in various aspirin samples, thus suggesting that its formation could be excipient-induced (12).

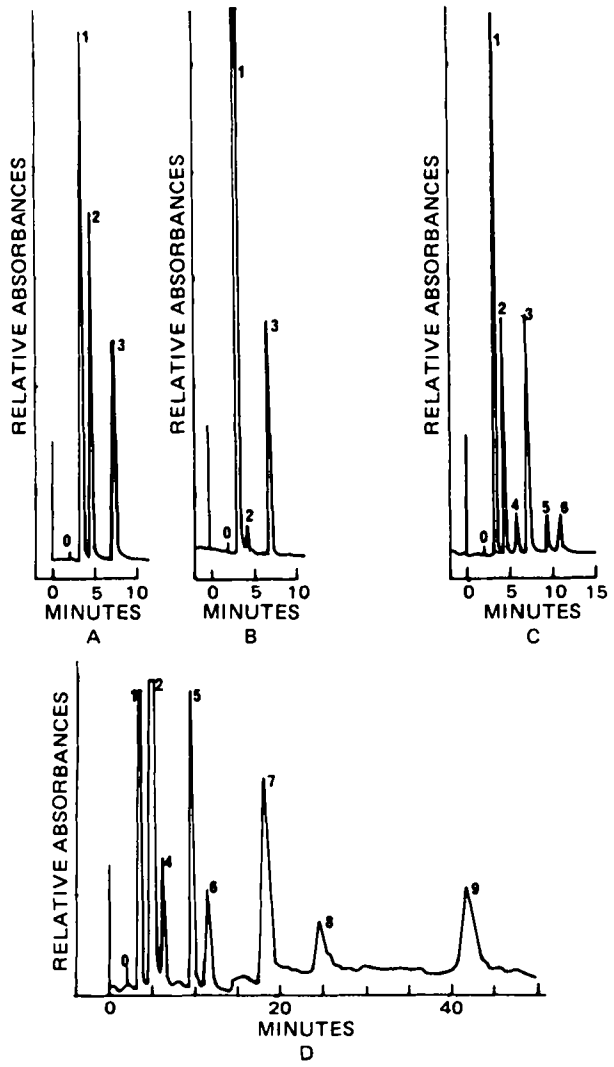


Figure 1—*High-performance liquid chromatograms of aspirin and its decomposition products: (A) aspirin in the presence of salicylic acid and propyl paraben (n-propyl-p-hydroxybenzoate); (B) aspirin–1% magnesium stearate mixture at time 0; (C) mixture after storage for 18 days at 60° and 75% humidity; (D) mixture after 21 days without internal standard. Key: (0) solvent front; (1) aspirin; (2) salicylic acid; (3) internal standard; (4) acetylsalicylsalicylic acid; (5) salicylsalicylic acid; (6–9) unidentified products.*

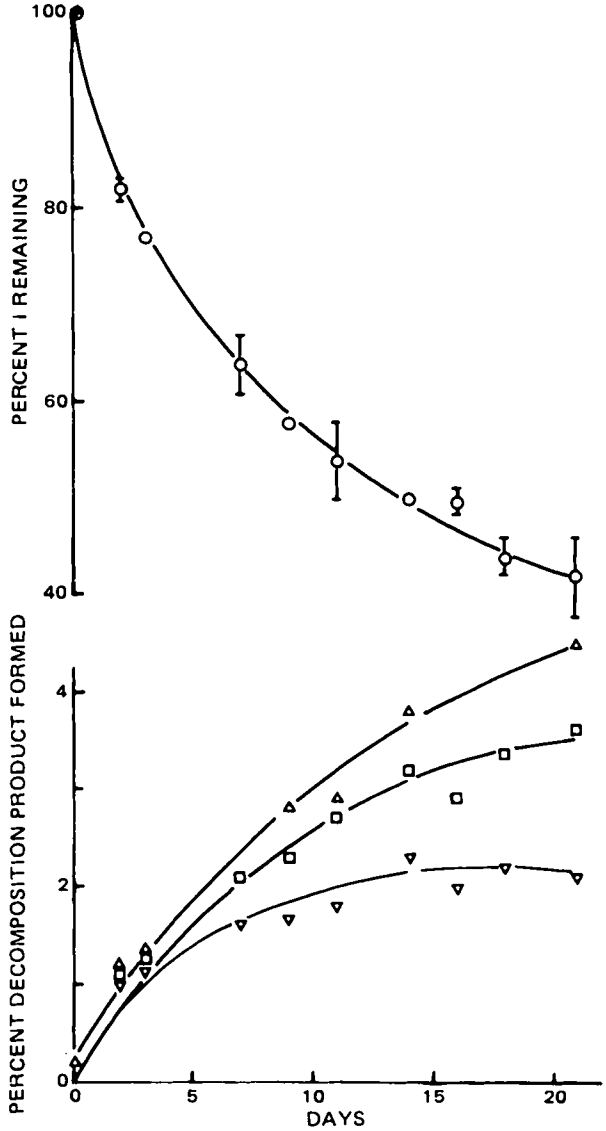


Figure 2—*Kinetics of decomposition of aspirin (I) in the presence of 1% magnesium stearate (60° and 75% relative humidity) and amounts of II, III, and IV. Key: (○) aspirin remaining; (△) II detected, (□) III; (▽) IV.*

The present study was initiated to determine whether III and IV were formed during the decomposition of aspirin in the presence of excipients in the solid state, to quantify the kinetics of decomposition of aspirin in the presence of excipients, and to elucidate the mechanisms of interaction of aspirin with tablet lubricants and in particular with magnesium stearate.

EXPERIMENTAL

Materials—Salicylic acid[1], phosphoric acid[1], *n*-propyl-*p*-hydroxy benzoate[2], and calcium, aluminum, sodium, and zinc stearates[3] were obtained from a single manufacturer[4]. Magnesium stearate samples were

[1] Analar grade.
[2] Laboratory grade.
[3] Technical grade.
[4] British Drug Houses, Poole, England, UK.

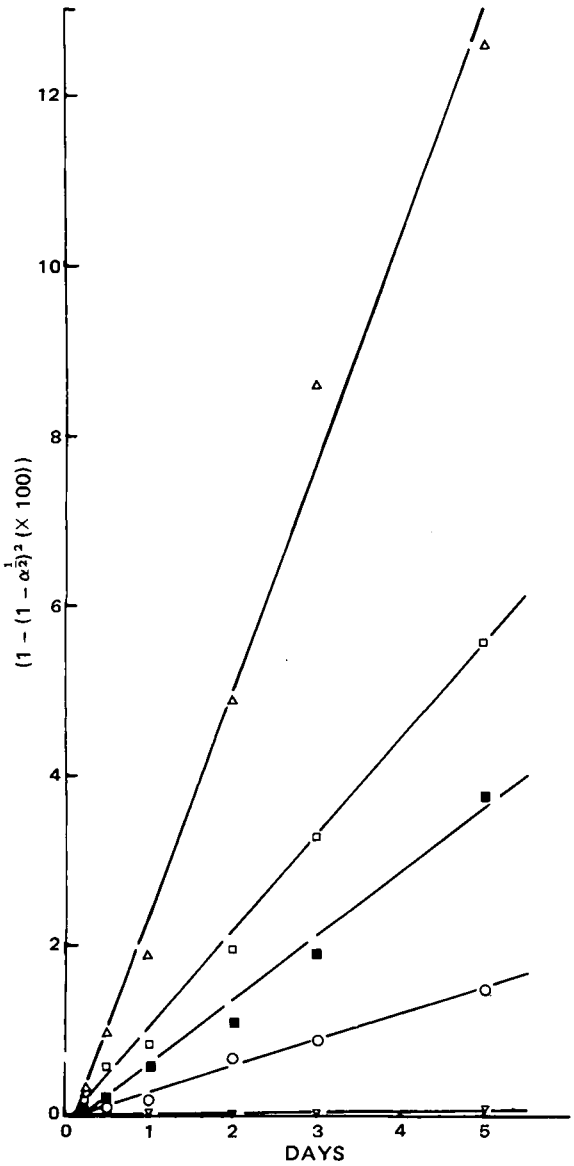


Figure 3—*Effect of magnesium stearate concentration on the rate of decomposition of aspirin plot according to Eq. 6. Key: (▽) aspirin without additive; (○) 1%; (■) 2%; (□) 3%; (△) 5% magnesium stearate.*

obtained from two different sources[4,5]. Sodium chloride (BP)[6], methanol[7], and salicylsalicylic acid[8] were used as obtained. Acetylsalicylsalicylic acid was synthesized as described (16) and tested for chromatographic purity by high-performance liquid chromatography (HPLC).

Methods—*Analysis of the Metal Stearates*—For the assay of free fatty acid 100 mg of each metal stearate was weighed out and extracted with 5 ml of chloroform. The chloroformic extract was filtered through a glass fiber filter paper and 1 ml of the filtrate was analyzed by GLC. For the assay of total fatty acid 60 mg of each stearate was weighed into a separating funnel and 30 ml of concentrated hydrochloric acid was added. The free acids liberated were extracted with 50 ml of chloroform and 1 ml of the extract assayed by GLC. Preliminary studies showed that concentrated acid was necessary to obtain clear chloroformic extracts.

GLC Analysis for Stearic, Palmitic and Myristic Acids—The GC system used for assaying the free and the total fatty acids in the alkali stearates consisted of a gas chromatograph[9] fitted with a silicone[10] coated open tubular glass capillary column (10 m × 0.8-mm o.d.) and an all-glass solids injector. Temperature settings were at 200° for the column and 250° for the detector and injector. Nitrogen, hydrogen, and air pressures were 0.9, 1.0, and 0.75 kg/cm^2, respectively. The nitrogen flow rate was 1 ml/min. Peak areas were obtained by integration.

One milliliter of extract was mixed with 0.8 ml of a chloroformic linoleic acid (1 mg/ml) solution and evaporated to dryness at 60° under nitrogen. The residues were methylated using a boron trifluoride–methanol mixture[11] maintained at 60° for 15 min. The product was extracted with 1 ml of *n*-hexane and 1 μl was injected into the chromatograph. Standard solutions prepared from the pure free acids[12] were derivatized and assayed simultaneously.

Analysis of the Salicylates—Analyses were performed using an HPLC constructed from a constant-flow solvent-metering pump[13], a valve[14] fitted with a 20-μl loop, and a variable wavelength monitor[15] equipped with an 8-μl flow cell and operated at 285 nm with a sensitivity of 0.32 aufs. Reversed-phase chromatography was performed using a 5-μm ODS (25-cm × 4.6-mm i.d.) column[16] and a mobile phase consisting of 0.02% phosphoric acid in 60% methanol in water and delivered at 1.4 ml/min.

Sample Preparation and Storage—Aspirin crystals were mixed with fixed proportions of magnesium, zinc, aluminum, sodium, or calcium stearate, and 100-mg quantities of each of the mixtures or of pure aspirin were weighed into individual glass vials[17] and loosely covered with cotton wool to prevent entry of condensed water droplets. The samples were then stored in a humidity cabinet[18] maintained at 60°. A 75% relative humidity environment was maintained at this temperature using a saturated sodium chloride solution. Samples were taken at predetermined intervals and assayed for aspirin and its decomposition products by the HPLC method.

Sample Preparation for HPLC—The contents of the vial sampled were dissolved in methanol, quantitatively transferred to a 25-ml volumetric flask, and brought up to volume with methanol. The resultant solution was analyzed by HPLC.

Particle-Size Analysis—The aspirin crystals were sized by sieve analysis (17) and a geometric mean of 280 ± 1.85 μm was obtained.

Washed Magnesium Stearate—Samples of magnesium stearate were washed by adding 5 g to 200 ml of 0.1 *M* HCl to remove any alkaline impurities and filtering the residues through a No. 3 sintered glass filter. The stearate was then washed by shaking with 50 ml of alcohol to remove stearic acid precipitated out during the acid wash. The powder was rinsed with several changes of double-distilled water until the resultant pH was in the 6.9–7.0 range. After a second filtration, the residues were dried overnight on filter paper at room temperature and finally at 50° for one-half hour before storage in tightly closed glass containers.

Melting-Point Determinations—The melting points of aspirin and its mixtures were determined by the standard capillary-tube method using an electrothermal melting point apparatus[19]. A second set of melting points were also obtained using a differential scanning calorimeter[20] operated at a heating rate of 8°/min and a nitrogen atmosphere of 2 bar. Samples (20–30 mg) were used with aluminum as the reference material.

Mathematical Model—The model used for explaining the results obtained in this study is based on liquid reaction-product layer formation during the decomposition of the aspirin. Jander (18) first showed that if one considers the formation of a liquid reaction-product layer, during the decomposition of spherical particles and if the reaction is diffusion limited, then it is possible to derive an expression relating the fraction decomposed with time. Such a model has been used previously (19).

Microscopic examination of the particles shows that the shape of the aspirin crystals used in this study were better approximated by cylinders than by spheres. Using Jander's assumptions of a diffusion-limited reaction and of a rate of thickening of the liquid layer dy/dt being inversely proportional to its thickness, y, Eq. 1 is obtained:

$$dy/dt = k/y \qquad \text{(Eq. 1)}$$

On integration:

$$y^2 = 2kt \qquad \text{(Eq. 2)}$$

[5] Griffin and George Ltd.
[6] McCarthys, UK.
[7] Analar Grade, Fisons, UK.
[8] Riker 3M, UK.
[9] Model Pye GC-V.
[10] CP-Sil 5.
[11] Pierce Chemical Co.
[12] Stearic and palmitic acids, specially pure grade, British Drug Houses myristic acid; Sigma Grade, Sigma Chemical Co., UK.
[13] Altex 100A.
[14] Rheodyne 7120.
[15] Pye LC3.
[16] Spherisorb.
[17] Fisons Ltd., Loughborough, UK.
[18] Townson and Mercer Ltd., Croydon, UK.
[19] Electrothermal Ltd., London, UK.
[20] Perkin-Elmer model DSC-1B.

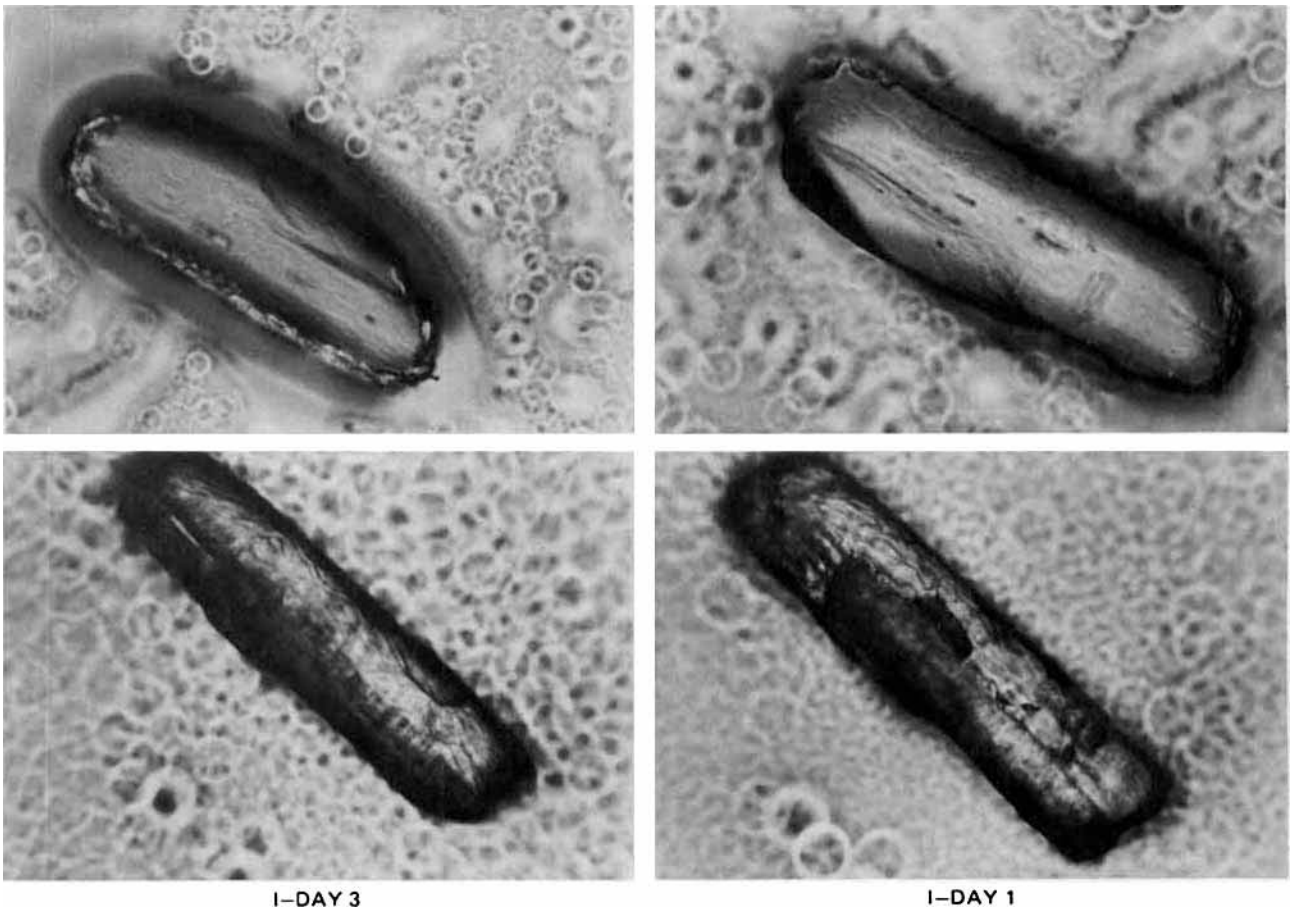


Figure 4—*Photomicrographs of decomposing aspirin (I) crystals with and without magnesium stearate at 50° and 75% relative humidity.*

The fraction decomposed (x) after time (t) can be expressed in terms of the total weight of the cylindrical particles studied:

$$\frac{\eta\rho\pi r_0^2 h - \eta\rho\pi(r_0 - y)^2}{\eta\rho\pi r_0^2 h} h = x \qquad \text{(Eq. 3)}$$

where r_0 = initial radius, h = height of cylinder, η = number of cylinders, ρ = density.

$$r_0^2 - (r_0 - y)^2 = x r_0^2 \qquad \text{(Eq. 4)}$$

Rearranging Eq. 4:

$$r_0[1 - (1 - x)^{1/2}] = y \qquad \text{(Eq. 5)}$$

Substituting for y in Eq. 5 from Eq. 2 and squaring:

$$[1 - (1 - x)^{1/2}]^2 = \frac{2k}{r_0^2} t \qquad \text{(Eq. 6)}$$

A plot of $[(1 - (1 - x)^{1/2}]^2$ against t should therefore give a straight line with zero intercept if the liquid-layer diffusion-controlled model describes the system studied. The model assumes that the length–diameter ratio of the aspirin crystals is such that end effects are negligible.

RESULTS AND DISCUSSION

Analysis of the stored samples by HPLC showed that II, III, and IV (Fig. 1) were formed during storage of aspirin at 60° and 75% relative humidity in the presence of magnesium stearate. Samples of aspirin on its own stored under identical conditions did not lead to the formation of III and IV when followed over the same time period. Figure 1 shows chromatograms of nonstored (Fig. 1B) as well as of stored samples (Fig. 1C) of aspirin.

Peak identification was achieved by comparison of retention times with authentic specimens as well as the ratio of the wavelength (20). HPLC of samples stored for longer periods of time showed that the decomposition is even more complex and several products which have not yet been identified were observed (Fig. 1D). These results are in agreement with those reported by Taguchi *et al.* (21) who showed that storage of aspirin tablets at 50° led to the formation of II, III, and IV, and that when further stressed at 95°, additional components could be detected in significant amounts. HPLC analysis of an aspirin sample stored for 4 weeks at 60° and 75% relative humidity showed traces of all the decomposition products detected in the presence of magnesium stearate. This shows that the stearates accelerate rather than induce their formation.

The decomposition of aspirin in the presence of 1% magnesium stearate is shown in Fig. 2 together with the amounts of II, III, and IV detected in the samples. It is important to note that these amounts of decomposition products can only be used as guide values since an open system was used. This particularly applies to salicylic acid which has been shown to sublime readily (22). Studies in which aspirin decomposition has been followed in the solid state, by following the kinetics of formation of salicylic acid, will therefore lead to erroneous results unless closed systems are used. In the present study an open system that allowed exposure of the samples to a constant relative humidity was preferred. Aspirin was assayed in addition to salicylic acid.

To investigate whether the concentration of lubricant present affected the rate of decomposition of aspirin, the degradation was followed in the presence of a series of concentrations of magnesium stearate. The results of these studies are shown in Fig. 3. An increase in magnesium stearate concentration quite clearly accelerated the decomposition of aspirin.

Various authors have reported on the catalytic effect of excipients on aspirin decomposition (23–25). The explanation put forward for explaining the effect of magnesium stearate has generally been based on hydrolysis taking place in an adsorbed moisture layer and on an alteration in the pH of this layer by the added excipient (26). It is known that the magnesium stearate used for tablet lubrication contains a significant amount of magnesium oxide. The USP and the BP specifications for magnesium stearate allow for up to 8.5% of magnesium oxide (27, 28). The 1980 BP however now defines the pH range of a 5% suspension and states that it should be between 6.2 and 7.4 (29).

A relationship between the observed zero rate constant of salicylic acid formation and the pH of the suspension after addition of the lubricants has been shown previously (10) in aspirin–tablet lubricant suspension

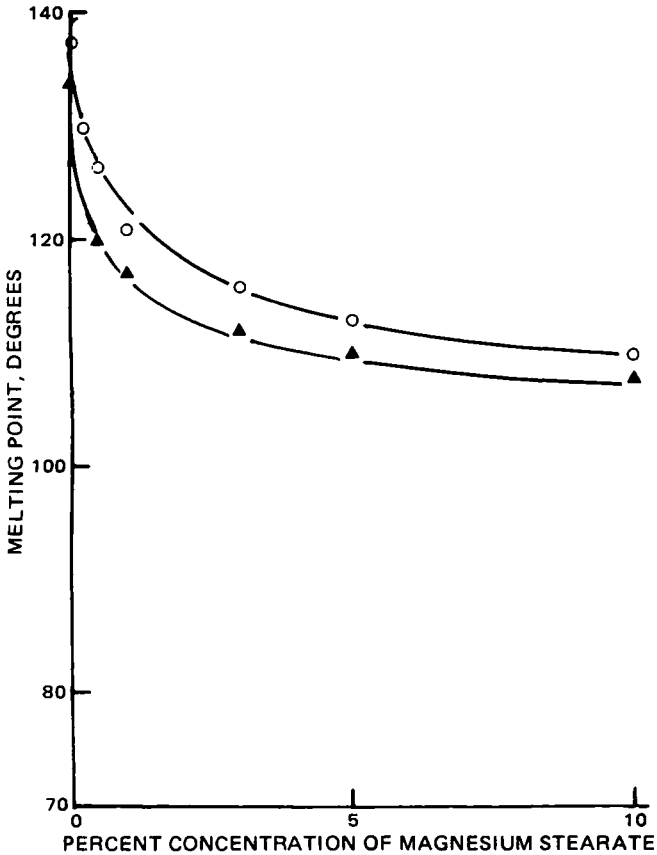


Figure 5—*Effect of addition of different concentrations of magnesium stearate on the melting point of aspirin; (○) using traditional melting point apparatus and (▲) using differential scanning calorimetry.*

systems. Magnesium stearate produced the largest pH shift and the highest rate constant. It has not been conclusively shown, however, that the pH change plays a significant part in the decomposition of aspirin in the solid state. To test this, the rate of decomposition of aspirin was measured in the presence of washed and unwashed magnesium stearate. The washed sample gave a suspension (1%) with a pH near neutrality (6.9), whereas an unwashed sample prepared similarly gave a pH of 9.9. The observed rate constants as mirrored by the slope of Eq. 6 were almost identical; the slopes were 0.0033 and 0.0030/day, respectively. Clearly the results do not exclude pH-induced changes in the rates of decomposition. The results indicate that any such change was too small to be detected during the study and was swamped by other effects when the stability of pure aspirin is compared with aspirin in the presence of magnesium stearate. GLC analysis of the magnesium stearate used both before and after washing showed that the total acids recovered (89.5 and 88.3%) were not significantly different. The amount of free acid recovered increased from 0.6 to 5.8% upon washing. It has been suggested (30) that because sublimation of II is observed on the surface of aspirin under stress conditions (22), factors other than those involved in solutions must be operable. However, sublimation out of a solution is also conceivable. Once the moisture microfilm is saturated with II, additional formation will lead to precipitation, decomposition onto adjacent surfaces, and eventually sublimation.

Microscopic (Fig. 4) and visual examination of the stored samples showed the presence of liquid films around the decomposing particles. Any theory put forward for explaining the observed increase in decomposition of aspirin in the presence of magnesium stearate must therefore take this into account.

A linear relationship between the logarithm of the observed rate constant of decomposition, and the reciprocal of the melting temperature (°K), has been found in a previous study on the solid-state stability of Vitamin A compounds (5). This was derived from the relationship between the fraction of material in the liquid state (x_1) and the melting point of the pure crystalline solid (T_m):

$$\ln x_1 = \frac{-L_f}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right) \qquad \text{(Eq. 7)}$$

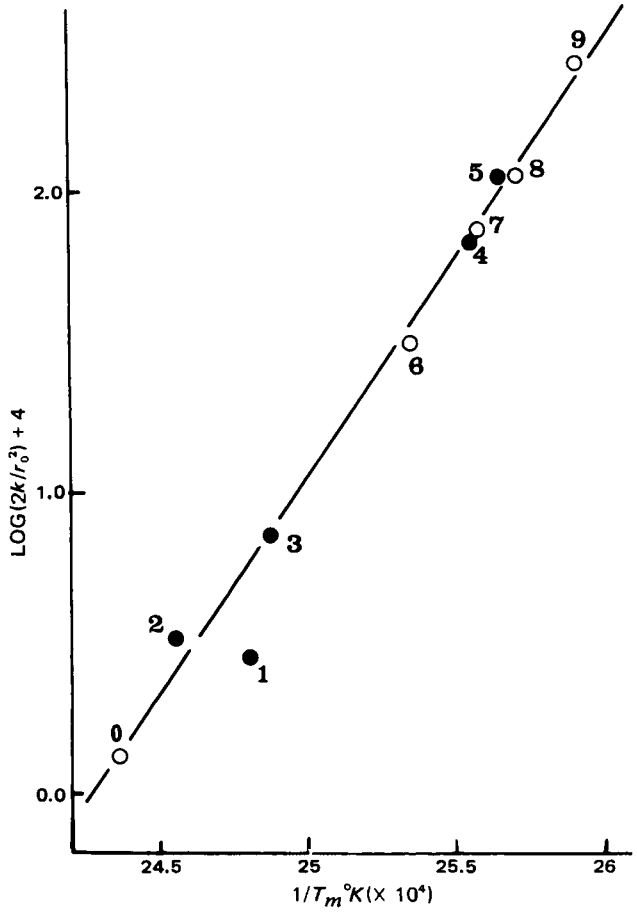


Figure 6—*Relationship between the rate constant of decomposition of aspirin in the presence of alkali stearates as mirrored by the slopes of Eq. 6 and the reciprocal of the melting points of the mixtures. Key: (0) aspirin on its own; (●) with 3% Zn (1), Al (2), Na (3), Ca (4), and Mg (5) stearates; (○) aspirin with 1% (6), 2% (7), 3% (8) and, 5% (9) magnesium stearates.*

where L_f is the molar heat of fusion and represents the difference in internal energy between the two states, the liquid being much more reactive than the solid; T is the temperature of storage; and R is the gas constant.

To test whether this relationship might explain the effect of magnesium stearate on the decomposition of aspirin the melting points of the mixtures were determined. Figure 5 shows the relationship between the melting point observed and the magnesium stearate content. The same trend was observed using both the traditional capillary tube melting point determinations and differential scanning calorimetry although differences in the absolute values were observed.

The slopes of Eq. 6 for the reactions shown in Fig. 4 were then plotted against the reciprocal of the corresponding melting points. Figure 6 shows that this relationship holds for the systems studied. One would also expect that other stearates would also alter the decomposition rates of aspirin, the magnitude of the change being determined by the size of the depression in melting point. Experiments were carried out to test this and the results are superimposed on the magnesium stearate results (Fig. 6). It is evident that the general relation holds here too.

Analysis of the stearates used in this study showed that the acid composition of the samples was significantly different (Table I). In addition to the samples used in the stability studies, other batches of magnesium and sodium stearates were also assayed for the three acids. As can be seen, interbatch and intermanufacturer variability in relative compositions were obvious. These can, in turn, be expected to produce different effects on aspirin decomposition and should be screened for during formulation studies.

CONCLUSIONS

The present study shows that III and IV are decomposition products of aspirin when the latter is stored in the solid state in the presence of alkaline lubricants such as magnesium stearate. Compounds III and IV

Table I—GLC Analysis of Alkali Stearates Used in the Stability Study

Metal Stearate	Relative Composition, % Myristate	Palmitate	Stearate	Recovery, %[a]	Free Acid, %[a]
Zinc stearate	1.9	39.2	58.9	90.5	0.3
Calcium stearate	3.7	33.4	62.9	97.1	2.8
Aluminum stearate	2.8	33.9	63.3	85.7	3.5
Sodium stearate (Manufacturer A, Batch 1)	2.4	53.0	44.6	89.1	2.8
Sodium stearate[b] (Manufacturer A, Batch 2)	4.0	40.6	55.4	95.5	1.8
Magnesium stearate (Manufacturer A, Batch 1)	5.7	37.2	57.1	87.1	0.6
Magnesium stearate (Manufacturer A, Batch 2)[b]	5.2	38.5	56.3	83.7	0.6
Magnesium stearate (Manufacturer B, Batch 1)[b]	3.2	54.0	42.8	76.7	1.2

[a] Refers to percent of initial weight accounted for by the three stearates. [b] These batches were not used in the stability studies.

were not detected in samples of aspirin stored under identical conditions for the same length of time. More prolonged storage, however, led to the formation of traces of the products. These data would suggest that the stearates accelerate the formation of these products and provide an explanation for the earlier report showing that III was detected in most of the commercial aspirin tablets analyzed but not in bulk aspirin samples. A direct relationship was shown between the rate constant of decomposition, as expressed by the slopes of plots of Eq. 6, and the concentration of magnesium stearate present. It has further been demonstrated that there was a linear relationship between the logarithm of slopes of Eq. 6 and the reciprocal of the melting points of the aspirin–stearate mixtures. Using a series of stearates it was shown that the relationship is of wide applicability. Changes in melting point rather than shifts in pH of the moisture microfilms surrounding the particles would appear to be the more plausible explanation for the observed effects of magnesium and other alkali stearates on aspirin stability. Melting point determinations would appear to provide a rapid method for predicting the stability of aspirin in aspirin–lubricant mixtures. The inverse relationship between aspirin decomposition in aspirin–lubricant mixtures and the reciprocal of the melting point (31) is quantitatively confirmed. Alkali stearates show batch-to-batch and intermanufacturer variability in acid composition and should be screened for during formulation studies.

REFERENCES

(1) J. T. Carstensen, *J. Pharm. Sci.*, **63,** 1 (1974).

(2) S. R. Byrn, *ibid.*, **65,** 1 (1976).

(3) E. R. Garrett, *Adv. Pharm. Sci.*, **2,** 1 (1967).

(4) E. R. Garrett, *J. Am. Pharm. Assoc., Sci. Ed.*, **43,** 539 (1954).

(5) J. K. Guillory and T. Higuchi, *J. Pharm. Sci.*, **51,** 100 (1962).

(6) L. J. Leeson and A. M. Mattocks, *J. Am. Pharm. Assoc., Sci. Ed.*, **47,** 329 (1958).

(7) J. T. Carstensen and M. N. Musa, *J. Pharm. Sci.*, **61,** 1112 (1972).

(8) J. T. Carstensen and P. Pothisiri, *ibid.*, **64,** 37 (1975).

(9) J. T. Cartensen and R. Kothari, *ibid.*, **69,** 123 (1980).

(10) S. S. Kornblum and M. A. Zoglio, *ibid.*, **56,** 1569 (1967).

(11) S. Patel, J. H. Perrin, and J. J. Windheuser, *ibid.*, **61,** 1794 (1972).

(12) H. Bundgaard and A. L. DeWeck, *Int. Arch. Allergy Appl. Immunol.*, **49,** 119 (1975).

(13) J. C. Reepmeyer and R. D. Kirchhoefer, *J. Pharm. Sci.*, **68,** 1167 (1979).

(14) H. Bundgaard, *J. Pharm. Pharmacol.*, **26,** 18 (1974).

(15) A. L. DeWeck, *Int. Arch. Allergy Appl. Immunol.*, **41,** 393 (1971).

(16) F. D. Chattaway, *J. Chem. Soc.*, **1931** 2495.

(17) I. C. Edmundson, in "Advances in Pharmaceutical Sciences," vol. 2. H. B. Bean, A. H. Beckett, and J. E. Carless, Eds., Academic, London, 1967, p. 95.

(18) W. Jander, *Z. Anorg. Allg. Chem.*, **163,** 1 (1927).

(19) E. Nelson, D. Eppich, and J. T. Carstensen, *J. Pharm. Sci.*, **63,** 755 (1974).

(20) A. Li Wan Po and W. J. Irwin, *J. Clin. Hosp. Pharm.*, **5,** 107 (1980).

(21) V. Y. Taguchi, M. L. Cotton, C. H. Yates, and J. F. Miller, *J. Pharm. Sci.*, **70,** 64 (1981).

(22) A. Y. Gore, K. B. Naik, D. O. Kildsig, G. E. Peck, V. F. Smolen, and G. S. Banker, *ibid.*, **57,** 1850 (1968).

(23) M. R. Nazareth and C. Lee Huyck, *ibid.*, **50,** 620 (1961).

(24) *Ibid.*, **50,** 608 (1961).

(25) H. Delonca, A. Puech, G. Seguva, and Y. Youakim, *J. Pharm. Belg.*, **24,** 5 (1969).

(26) Fr. Jaminet and G. Louis, *Pharm. Acta Helv.*, **43,** 153 (1968).

(27) "United States Pharmacopeia," 20th ed. United States Pharmacopoeial Convention, Rockville, Md., 1980.

(28) "British Pharmacopeia," Pharmaceutical Press (London) 1973.

(29) *Ibid.*, 1980.

(30) A. Y. Gore and G. S. Banker, *J. Pharm. Sci.*, **68,** 197 (1979).

(31) H. V. Maulding, M. A. Zoglio, and E. J. Johnston, *ibid.*, **57,** 1873 (1968).

ACKNOWLEDGMENTS

The authors thank the World Health Organization for the fellowship awarded to P. V. Mroso, and the West Midlands Regional Health Authority for the HPLC equipment used in this study.