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Solid-State Acetylation of Codeine Phosphate by Aspirin

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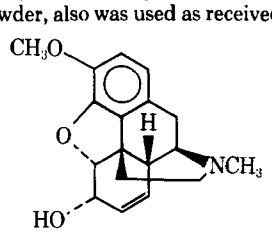
Abstract □ A nonsolvolytic (solid-state) acetylation of codeine phosphate in the presence of aspirin to yield acetylcodeine phosphate is reported. GLC assays for the simultaneous determination of aspirin and salicylic acid and codeine and acetylcodeine are described. The apparent heat of activation for codeine phosphate is estimated, and the possible reaction mechanisms are discussed.

Keyphrases □ Codeine phosphate—acetylation by aspirin, solid dosage forms, GLC analysis of aspirin and salicylic acid, and codeine and acetylcodeine, pharmacokinetics □ Aspirin—acetylation of codeine phosphate in solid dosage forms, GLC analysis of aspirin and salicylic acid, and codeine and acetylcodeine, pharmacokinetics □ Antitussive agents—codeine phosphate, acetylation by aspirin in solid dosage forms, pharmacokinetics □ Analgesics—aspirin, acetylation of codeine phosphate in solid dosage forms, pharmacokinetics

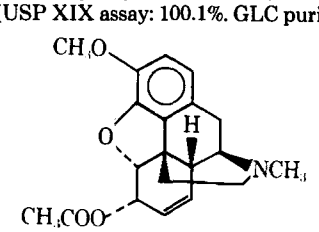
Solid-state acetylation of codeine (I) by aspirin to yield acetylcodeine (II) has been reported (1). Other workers investigated solid-state acetylation by aspirin on homatropine (2), acetaminophen (3), and phenylephrine hydrochloride (4). Capsule and tablet formulations containing aspirin and codeine phosphate have yielded detectable amounts of acetylcodeine on aging. GLC analyses of aspirin and salicylic acid have been reported (5–13). Various silylation and methylation reagents have been employed in aspirin and salicylic acid determinations in biological fluids and pharmaceutical solid dosage forms. Although the GLC analysis of codeine and related alkaloids has been reported (14–16), there has been no report concerning the simultaneous detection and quantitation of acetylcodeine by GLC in formulations containing aspirin and codeine. This study describes the kinetics and possible mechanisms of the nonsolvolytic reactions and quantitation by GLC.

EXPERIMENTAL

Materials—Aspirin USP, a crystalline powder, was used as received (USP XIX assay: aspirin, 100.2%; salicylic acid, <0.1%. GLC purity: aspirin, 99.90%; salicylic acid, 0.1%). Codeine phosphate USP, a crystalline powder, also was used as received (USP XIX assay: 100.1%. GLC purity: 100.0% with no detectable acetylcodeine). The two drugs were mixed (aspirin–codeine phosphate, 9:1 w/w) gently by hand in a glass mortar, transferred into a twin-shell dry blender, and mixed for 2 hr. The mixture was initially assayed by GLC with the following results: aspirin, 89.40%; codeine phosphate, 10.0%; and salicylic acid, 0.1%. The water content was 0.36%, as determined by the Karl Fischer titrimetric method.



I



II

Kinetic Studies—About 300 mg of the mixture was transferred into preweighed glass ampuls, and the ampuls were then weighed again. The ampuls were flame sealed and stored at 60, 70, 80, and 90° in constant-temperature water baths (±0.2°). Water baths were kept covered from light, and samples were periodically removed and assayed. Samples that were removed and not assayed the same day were stored at 5°. Because a eutectic forms after a period of time, the entire contents of the ampul were used for analysis to ensure no loss of material.

Acetylcodeine Synthesis—About 400–500 mg of codeine phosphate, accurately weighed, was transferred into a 50-ml screw-capped test tube. Two milliliters of acetic anhydride and 0.5 ml of pyridine were added. The test tube was tightly capped and placed in a water bath maintained at 80° for 2 hr. Then it was placed in an ice bath for 10 min, following which 2 ml of water was added. Cautiously, stronger ammonia water was added dropwise until the mixture was distinctly alkaline.

The test tube was replaced into the ice bath for ~15 min with occasional shaking to complete acetylcodeine precipitation. About 10 ml of chloroform was added to the test tube, and the mixture was shaken vigorously for 2 min. The upper aqueous layer was removed by vacuum, the chloroform was washed with 2 × 5-ml portions of water, and the water was removed by vacuum. About 500 mg of anhydrous sodium sulfate was added to the test tube, which was shaken to remove residual water.

The chloroform was decanted carefully through glass wool into a suitable evaporating dish. The test tube was rinsed with two additional 10-ml portions of chloroform and passed through the glass wool into the same dish. Then the chloroform was evaporated carefully to near dryness on a steam bath under a nitrogen stream. The residue was air dried at room temperature for 2 hr and then dried in a vacuum oven at 60° for 4 hr. The dry residue weight corresponded to a 96% yield of acetylcodeine.

Anal.—Calc. for $C_{20}H_{23}NO_4$: C, 70.40; H, 6.80; N, 4.10. Found: C, 70.42; H, 6.78; N, 4.02.

GLC Purity—The purity was 99.14% calculated by area percent.

TLC Purity—One spot was observed at R_f 0.67 when the sample was chromatographed on precoated silica gel G plates[1] in chloroform–methanol (10:1) and sprayed with Dragendorff's reagent.

NMR and IR—NMR and IR were used to confirm the identity of acetylcodeine.

High-Pressure Liquid Chromatography (HPLC)—Acetylcodeine phosphate and codeine phosphate were separated by isocratic reversed-phase HPLC using a literature method (17). The mobile phase was 0.1 *M* NaH_2PO_4 in 25% acetonitrile–water. The retention times for codeine phosphate and acetylcodeine phosphate were 6 and 16 min, respectively. Codeine was not detected in the synthesized acetylcodeine.

Isolation and Identification of Reaction Product—Acetylcodeine was characterized in the degraded samples of codeine phosphate and aspirin by fractionating the mixture using preparative TLC. The sepa-

[1] Analtech, Newark, Del.

0022-3549/79/1200-1494$01.00/0

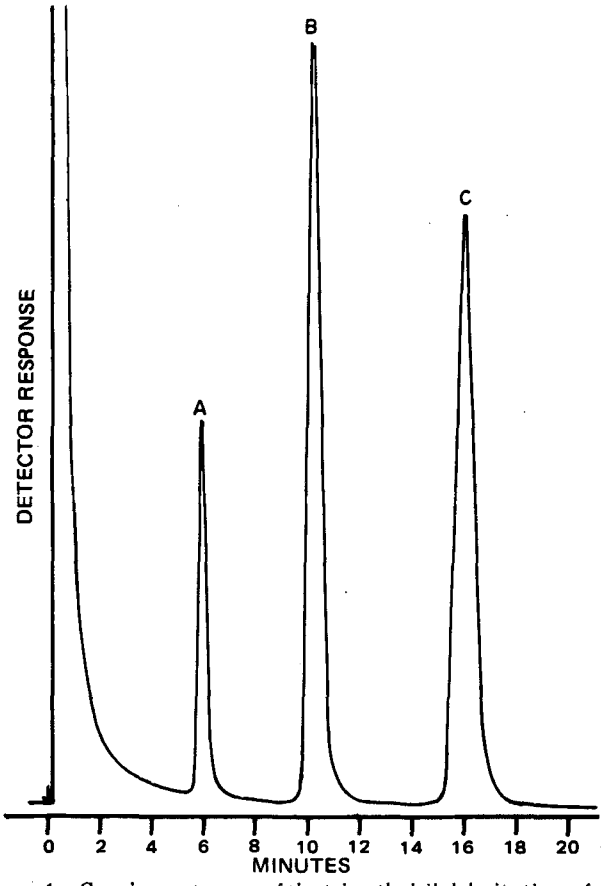


Figure 1—*Gas chromatogram of the trimethylsilyl derivatives of salicylic acid (A), aspirin (B), and the internal standard propylparaben (C).*

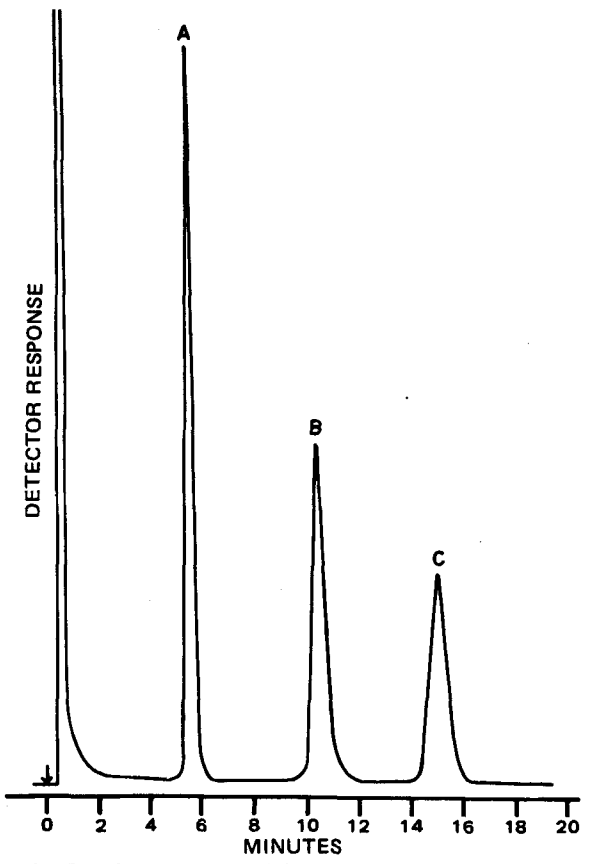


Figure 2—*Gas chromatogram of the internal standard methaqualone (A), codeine (B), and acetylcodeine (C).*

rated degradation spot was scraped from the plate and extracted with chloroform. The chloroform was evaporated to dryness, and the residue was subjected to a comparative IR analysis with synthesized acetylcodeine. The spectra were identical. This finding confirmed the presence of acetylcodeine in the degraded mixture of codeine phosphate and aspirin as reported previously (1).

Simultaneous GLC Analysis of Aspirin and Salicylic Acid—*Instrumentation*—A gas chromatograph[2] and an electronic integrator[3] equipped with a flame-ionization detector and a glass column [1.8 m (6 ft) × 2 mm i.d., packed with 3% phenyl methyl silicone[4] on 100–120-mesh silanized diatomaceous earth[5]] were used. The operating temperatures were: column, 120°; detector, 225°; and injection port, 225°. Nitrogen, with a flow rate of 35 ml/min, was the carrier gas. The injection volume was 2.0 μl.

Internal Standard Preparation—About 500 mg of propylparaben USP was diluted to 100 ml with chloroform and mixed.

Aspirin Standard Preparation—About 60–65 mg of aspirin USP reference standard, accurately weighed, was transferred into a 25-ml volumetric flask, diluted to volume with chloroform, and mixed. Once prepared, the aspirin standard was derivatized within 2 hr. The trimethylsilyl derivative was stable for 48 hr in an airtight container.

Salicylic Acid Standard Preparation—About 35 mg of salicylic acid USP reference standard, accurately weighed, was transferred into a 25-ml volumetric flask, diluted to volume with chloroform, and mixed.

Sample Preparation—The entire contents of the ampul were quantitatively transferred into a 100-ml volumetric flask, diluted to volume with chloroform, and mixed. Aged samples that were slightly turbid in chloroform were not filtered prior to derivatization. Sample preparations were derivatized within 2 hr.

Procedure—A 2.0-ml aliquot of the sample preparation was transferred into a suitable reaction vial. A 2.0-ml aliquot of the aspirin standard preparation and a 1.0-ml aliquot of the salicylic acid standard preparation were combined in a second reaction vial. A 1.0-ml aliquot of the internal standard preparation was transferred into each of the sample and standard vials. All vials were derivatized with 200 μl of *N,O*-bis(trimethylsilyl)acetamide[6].

The vials were capped and shaken for 1 min and then were allowed to stand at room temperature for at least 1 hr for complete derivatization. The peak area ratios of the trimethylsilyl derivatives were determined, and the percentages of aspirin and salicylic acid were calculated in the samples. The retention times for salicylic acid, aspirin, and the propylparaben trimethylsilyl derivatives were 6.0, 10.2, and 16 min, respectively (Fig. 1). At the end of each day's run, the column temperature was raised to 250° to elute codeine and acetylcodeine, which do not elute under the conditions for analysis of salicylic acid and aspirin.

Simultaneous GLC Analysis of Codeine Phosphate and Acetylcodeine Phosphate—*Instrumentation*—The instrumentation was the same as described earlier, except that a glass column [1.2 m (4 ft) × 4 mm i.d., packed with 3.8% methyl vinyl silicone gum rubber[7] on 80–100-mesh silanized diatomaceous earth[8]] was used. The operating temperatures were: column, 230°; detector, 250°; and injection port, 250°. Nitrogen, with a flow rate of 45 ml/min, was the carrier gas. The injection volume was 2.0 μl.

Internal Standard Preparation—About 80 mg of methaqualone NF was diluted to 100 ml with chloroform and mixed.

Codeine Phosphate Standard Preparation—About 30 mg of codeine phosphate, accurately weighed, was transferred into a 125-ml separator containing 30 ml of chloroform, 20 ml of water, and 2 ml of stronger ammonia solution. The separator was shaken for 1 min, and the lower chloroform layer containing the codeine base was transferred through glass wool into a 100-ml volumetric flask. The extraction was repeated with two additional 30-ml portions of chloroform, and the contents were diluted to volume and mixed.

[2] Hewlett-Packard 7620A.
[3] Hewlett-Packard 3370A.
[4] OV-17, Analabs, Northhaven, Conn.
[5] Gas Chrom Q, Applied Science Laboratories, State College, Pa.
[6] Pierce Chemical Co., Rockford, Ill.
[7] UC-W98, Analabs, Northhaven, Conn.
[8] Chromosorb W-H.P., Celite Division, Johns Manville.

Table I—Assay Data for Kinetic Mixtures[a]

Temperature	Hours	Codeine Phosphate, %	Codeine Phosphate[b] Degraded, %	Aspirin, %	Aspirin[c] Degraded, %
90°	504	<0.5	58.2	67.2	6.4
80°	747	<0.5	51.7	80.0	6.3
70°	842	<0.5	50.1	87.0	6.8
60°	4000	<0.5	50.5	82.5	6.9

[a] All percentages are expressed as a percent of the theoretical amount of aspirin and codeine phosphate in the initial mixture. [b] Percent codeine phosphate degraded to acetylcodeine phosphate. [c] Percent aspirin degraded to salicylic acid.

Acetylcodeine Standard Preparation—About 20 mg of acetylcodeine, accurately weighed, was transferred into a 100-ml volumetric flask, diluted to volume with chloroform, and mixed.

Sample Preparation—The contents of each ampul were quantitatively transferred into a 100-ml volumetric flask with chloroform, diluted to volume, and mixed.

Procedure—A 10.0-ml aliquot of the sample preparation was transferred into a 125-ml separator containing 20 ml of water and 2 ml of stronger ammonia solution. The separator was shaken for 1 min, and the lower chloroform layer was filtered through glass wool and collected in a beaker containing 3.0 ml of the internal standard preparation. The extraction was repeated with two additional 15-ml portions of chloroform.

The standard was prepared by transferring and combining 10.0-ml aliquots each of the codeine and acetylcodeine standard preparations into a beaker containing 3.0 ml of the internal standard preparation. Both the sample and standard beakers were placed on a steam bath, and the volume was reduced to 2–3 ml with a nitrogen stream. The peak area ratios were determined, and the percentages of codeine phosphate and acetylcodeine phosphate were calculated in the samples. The retention times for methaqualone, codeine, and acetylcodeine were 5.8, 10.4, and 15.0 min, respectively (Fig. 2).

RESULTS AND DISCUSSION

Linearity and Precision—The response linearity of the described GLC methods was suitable for the entire assay range. The precision, on multiple injections, was ±0.42% for the codeine–acetylcodeine procedure and ±0.50% for the aspirin–salicylic acid procedure.

Codeine Phosphate Disappearance—The evaluation of such a complex system did not lend itself to a detailed kinetic analysis. Table I shows the percentages of codeine phosphate degraded to acetylcodeine phosphate and of aspirin degraded to salicylic acid when the codeine phosphate remaining was <0.5% at various temperatures. From the kinetic plots shown in Figs. 3 and 4, the correlation coefficients at 60, 70, 80, and 90° were 0.998, 0.998, 0.998, and 0.998, respectively.

The kinetics of codeine phosphate disappearance were pseudo-first order after an initial lag time. The lag time was attributed to a delay in aspirin hydrolysis to salicylic acid. This delay was more evident at 60 than at 90°. The reaction rate constants and half-lives for codeine phosphate disappearance are given in Table II. An Arrhenius plot (Fig. 5) yielded an activation energy of 35.8 kcal/mole. A composite representation of codeine phosphate degradation to acetylcodeine phosphate at various temperatures is given in Fig. 6. Since ~50–58% of the original codeine phosphate degraded to acetylcodeine phosphate, other degradation pathways were apparent.

TLC examination of the degraded samples, after spraying with Dragendorff's reagent, showed two or three other distinct spots of nitrogen-containing compounds. This finding indicated possible thermal decomposition of the codeine phosphate, Hoffman degradation, or acid-catalyzed rearrangements of the side chain and cleavage of the oxide bridge. The complex chemistry and mechanisms of these reactions were discussed by Manske and Holmes (18).

Acetylcodeine Appearance—Since acetic acid is necessary for acetylcodeine formation, aspirin hydrolysis must occur before any

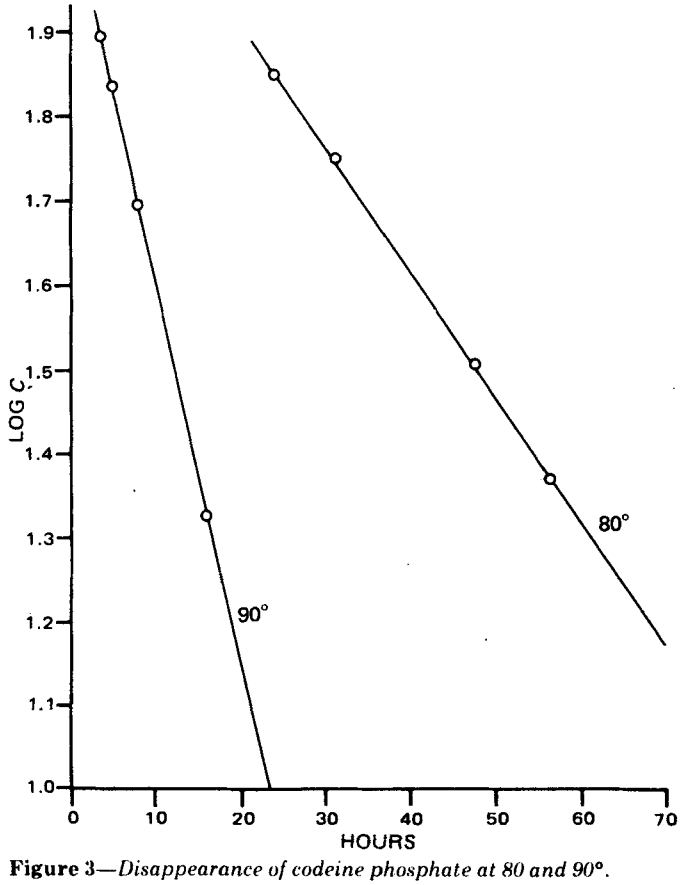


Figure 3—*Disappearance of codeine phosphate at 80 and 90°.*

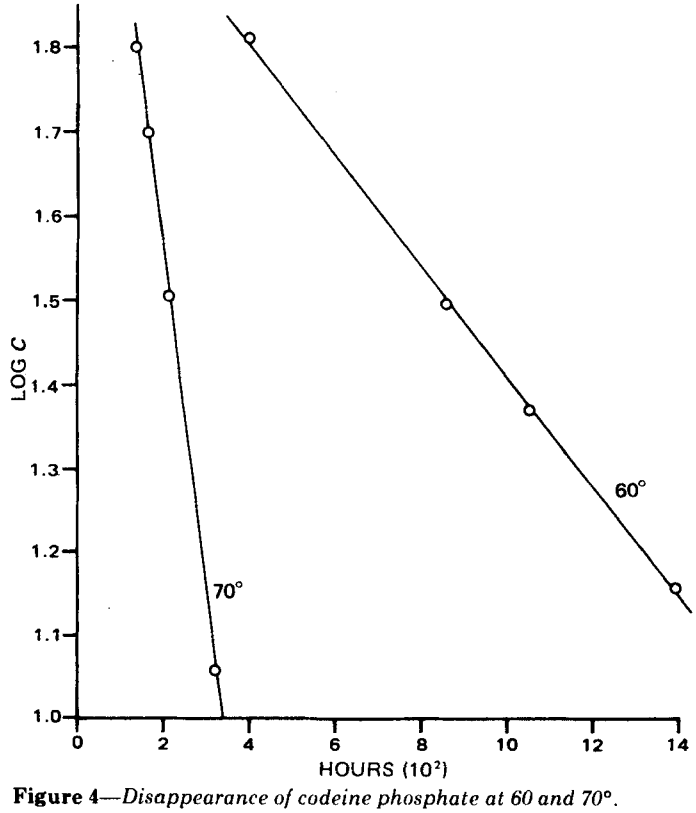


Figure 4—*Disappearance of codeine phosphate at 60 and 70°.*

Table II—Reaction Rate Constants and Half-Lives for Codeine Phosphate Disappearance

Temperature	Reaction Rate Constant, hr^{-1}	Half-Life, hr
90°	0.090040	7.7
80°	0.019810	35
70°	0.003962	175
60°	0.001020	680

acetylcodeine is detected. The rate of acetylcodeine phosphate formation followed no specific order, and the kinetics were of some complex order not directly related to codeine phosphate disappearance.

Salicylic Acid Appearance—Aspirin degradation to salicylic acid levels off to 6–7% at all temperatures. However, the theoretical amount of salicylic acid formation should be 4.0%, calculated from the 0.36% water content in the mixture. Additional water is generated from the following reactions:

1. One molecule of water is generated from each molecule of codeine phosphate acetylated by aspirin.
2. Acid-catalyzed rearrangement of the side chain of the codeine phosphate produces one molecule of water for each molecule of codeine phosphate undergoing decomposition.
3. Cleavage of the oxide bridge in the codeine phosphate degradation produces additional water.
4. One molecule of water is generated in the reaction of two molecules of aspirin to form acetylsalicylic acid anhydride.
5. Acetic anhydride may be generated from acetic acid, resulting in one molecule of water for each molecule of acetic anhydride formed.

The calculated amount of additional water required to produce the 6–7% level of salicylic acid formation is 0.81 mg/300 mg of mixture. From the acetylation reaction, 0.66 mg of water was generated at all temperatures based on the average of 50% degradation of codeine phosphate to acetylcodeine phosphate. This amount accounts for ~80% of the additional water required. The other reactions listed, occurring concomitantly, would easily account for the additional water required to justify the 6–7% salicylic acid formation. The rate of salicylic acid formation in this study did not follow any specific kinetic order because of the complex reactions involved.

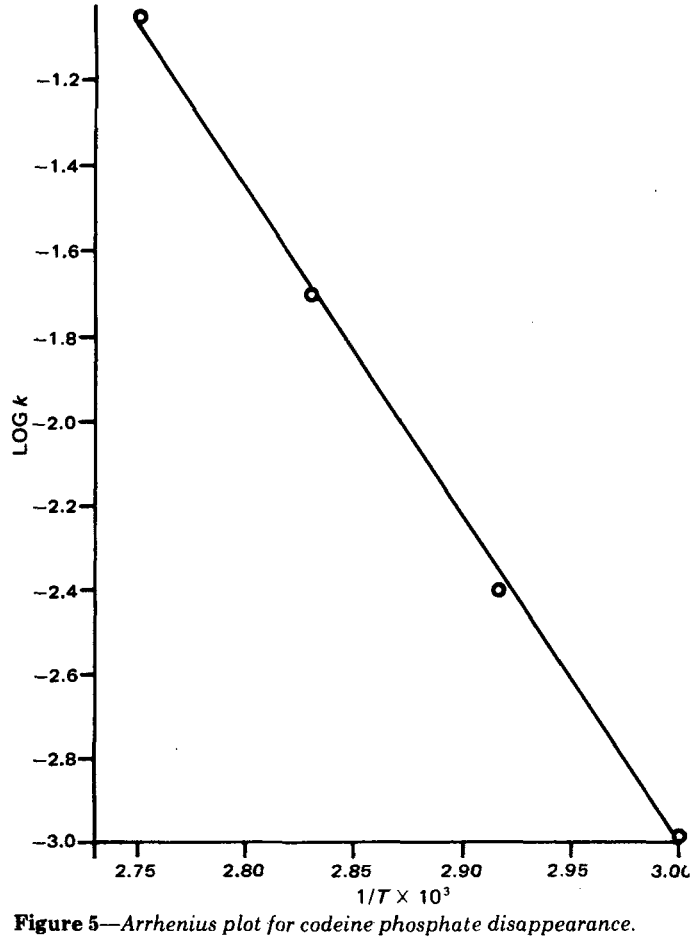


Figure 5—*Arrhenius plot for codeine phosphate disappearance.*

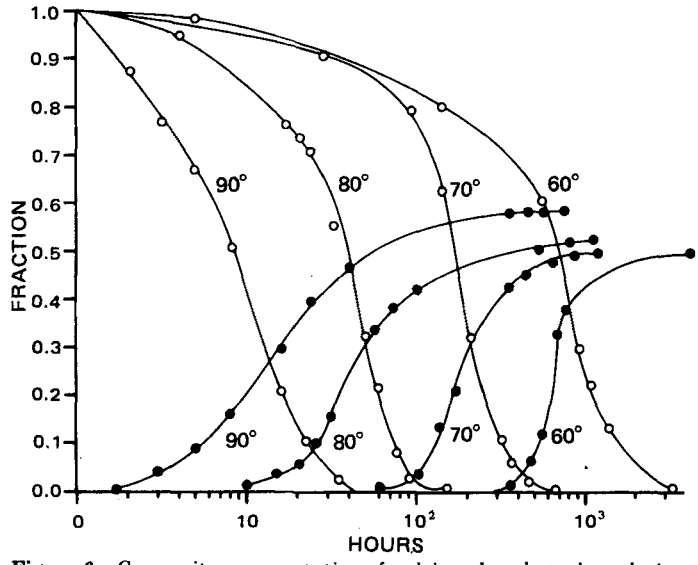


Figure 6—*Composite representation of codeine phosphate degradation to acetylcodeine phosphate under varying temperature conditions. Key:* ○, *codeine phosphate remaining; and* ●, *codeine phosphate degraded to acetylcodeine phosphate.*

Aspirin Disappearance—Aspirin continued to degrade slowly even after salicylic acid formation leveled off. Aspirin degradation may also include the formation of acetylsalicylsalicylic acid and acetylsalicylic anhydride (19, 20). Positive identification of these species was not made, but their formation cannot be excluded since the limited amount of water in the mixture prevents total hydrolysis of aspirin to salicylic acid.

SUMMARY

Pharmaceutical solid dosage forms containing aspirin in combination with codeine phosphate and other drug species are subject to nonsolvolytic acetylation by aspirin even at a low moisture level. Acid–base titrimetric methods for the analysis of codeine in combination with aspirin in pharmaceutical dosage forms cannot detect acetylcodeine formation. This study demonstrates the reactivity of aspirin; the drug acetylated 50–58% of the codeine phosphate in the experimental mixture.

Acetylation of a drug substance by aspirin may alter a drug's physiological activity or toxicity. However, for acetylcodeine, the physiological activity is reported to be about the same as codeine (21). The extensive use of aspirin in pharmaceutical solid dosage forms in combination with alkaloids, antihistamines, and other analgesics requires stability-specific methods of analysis to ascertain the molecular transformations of nonsolvolytic reactions.

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Effect of Interaction of Aluminum Hydroxycarbonate Gel and Magnesium Hydroxide Gel on Acid Neutralization

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Received March 19, 1979, from the **Industrial and Physical Pharmacy Department and the* ‡*Department of Agronomy, Purdue University, West Lafayette, IN 47907.* Accepted for publication June 7, 1979.

Abstract □ Acid neutralization by mixtures of aluminum hydroxycarbonate gel and magnesium hydroxide gel differs from the sum of the acid neutralization of each gel. Acid neutralization by magnesium hydroxide gel in the mixture is not observed until after a substantial portion of the aluminum hydroxycarbonate gel has reacted with acid, even though magnesium hydroxide gel is the faster reacting of the two gels. It is hypothesized that amorphous aluminum hydroxycarbonate forms a coating on the crystalline magnesium hydroxide particles due to electrostatic attraction. This coating prevents protons from reaching the highly reactive magnesium hydroxide until the coating is dissolved by the acid neutralization of aluminum hydroxycarbonate.

Keyphrases □ Aluminum hydroxycarbonate gel—acid neutralization, effect of interaction with magnesium hydroxide gel □ Magnesium hydroxide gel—acid neutralization, effect of interaction with aluminum hydroxycarbonate gel □ Antacids—aluminum hydroxycarbonate, magnesium hydroxide, effect of interaction on acid neutralization

Aluminum hydroxycarbonate gel (1) and magnesium hydroxide gel are formulated in combination in many antacid products. Aluminum hydroxycarbonate gel exhibits antacid activity only when amorphous. With aging, order develops in the amorphous structure, which reduces the acid reactivity and ultimately leads to the formation of an inactive crystalline state (2, 3).

A chemical property of aluminum hydroxycarbonate gel that makes it useful as an antacid is its ability to maintain pH 3.5–4.0 while reacting with acid (4). Aluminum hydroxycarbonate is not systemically absorbed and, aside from causing constipation, is free of side effects (5).

BACKGROUND

The solid phase of magnesium hydroxide gel has a crystalline structure known mineralogically as brucite. However, in contrast to the behavior of crystalline aluminum hydroxide, the crystalline magnesium hydroxide gel rapidly reacts with acid (6). Due to its well-ordered crystal structure, it exhibits excellent stability.

Magnesium hydroxide gel reacts with acid at a constant pH of 8.0–8.5. This pH is not as desirable as the one maintained during acid neutralization by aluminum hydroxycarbonate gel and, therefore, magnesium hydroxide gel is not frequently used as an antacid. In addition, magnesium ion produced during acid neutralization may be systemically absorbed, so a warning to patients with kidney disease is required (5). Magnesium ion also causes a cathartic effect, which balances the action of aluminum hydroxide gel on the intestine and provides the rationale for combining aluminum hydroxycarbonate gel and magnesium hydroxide gel in antacid products.

The addition of less than stoichiometric amounts of acid does not lower the pH of magnesium hydroxide gel below 8. However, a mixture of aluminum hydroxycarbonate gel–magnesium hydroxide gel drops to ~pH 4 after the addition of a relatively small amount of acid. Furthermore, it remains at ~pH 4 even when more acid is added (7). This behavior suggests an interaction between the amorphous aluminum hydroxycarbonate and the crystalline magnesium hydroxide gels. The investigation was undertaken to study this interaction, with emphasis on its effect on acid neutralization.

EXPERIMENTAL

Materials—Aluminum hydroxycarbonate gel containing the equivalent of 4% Al_2O_3 was prepared by the reaction of aluminum chloride, sodium bicarbonate, and sodium carbonate to a final pH of 6.5 (8).

Magnesium hydroxide gel[1] was obtained commercially, and a gel containing the equivalent of 7% MgO was prepared by dilution.

All chemicals were either official or reagent grade.

Preparation of Gel Mixtures—Mixtures of aluminum hydroxycarbonate gel and magnesium hydroxide gel containing 0.6 mmole of metal ion/g were prepared on a weight basis. For example, a 200-g mixture with a 5:1 molar ratio of magnesium to aluminum was prepared by weighing magnesium hydroxide gel and aluminum hydroxycarbonate gel containing 100 mmoles of magnesium and 20 mmoles of aluminum, respectively. The final weight of the mixture was adjusted to 200 g with double-distilled water, and the mixture was stirred mechanically until uniform.

Analytical Procedures—The aluminum and magnesium contents of the mixtures were determined by chelatometric titration (9).

The acid-neutralization reaction was monitored by an automated[2] pH-stat titration (10). For a typical pH-stat titration, 20 ml of double-distilled water was added to the reaction flask and brought to pH 3.0. An accurately weighed gel mixture sample, which would theoretically neutralize 2.25 meq of acid, was added; the recorder was started simultaneously. The cumulative amount of acid needed to maintain pH 3.0 was recorded as a function of time.

Atomic absorption spectrophotometry was employed to determine the concentrations of aluminum and magnesium ions in solution during acid neutralization. The pH-stat titration was halted at various times, the reaction medium was filtered quickly through a 0.22-μm filter, and the filtrate was analyzed for aluminum and magnesium.

RESULTS

Characteristic pH-stat titrigrams of aluminum hydroxycarbonate gel and magnesium hydroxide gel are shown in Fig. 1.

Kerkhof *et al.* (10) characterized the pH-stat titrigram of an aluminum

[1] HydroMagma, Merck & Co., Rahway, N.J.
[2] PHM 26, TTT II, ABU 12 (2.5 ml), TTA 3, SBR 2, Radiometer, Copenhagen, Denmark.

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