Table II—Recovery of Tiflamizole from Spiked Plasma

Tiflamizole, μg/mL	Recovery, %	Mean ± *SD*
0.1	90, 92, 89	90.3 ± 1.5
0.2	103, 97, 100	100.0 ± 3.0
0.5	97, 98, 99	98.0 ± 1.0
1.0	98, 100, 100	99.3 ± 1.2

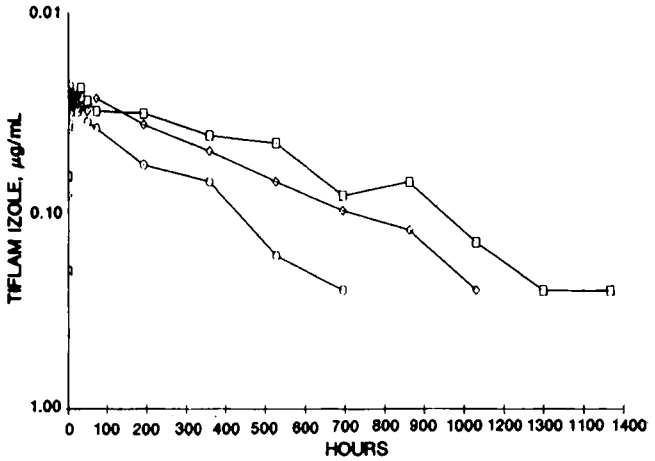

Figure 2—*Tiflamizole profiles in three healthy adult male subjects following a single oral 5-mg dose.*

overnight. Blood samples (10 mL) were withdrawn[11] prior to dosing and at specified times up to 57 d after dosing. The blood samples were centrifuged and the plasma was stored frozen in clean plastic tubes[10]. The elimination half-lives for these individuals were determined using linear regression analysis of the terminal plasma level–time data points.

[11] Heparinized vacutainers.

RESULTS AND DISCUSSION

Typical chromatograms of extracted control plasma and plasma spiked with tiflamizole are shown in Fig. 1. Tiflamizole/naphthalene peak area ratios were linear (from 0.1 to 1.0 μg/mL) and the correlation coefficients for the fit of experimental points were 0.99995. The intercepts were not significantly different from zero. There was no interference from constituents in control plasma or in the plasma from subjects or patients prior to administration of tiflamizole. Tiflamizole is stable in plasma stored at −20°C for at least 530 d. The results are shown in Table I.

Tiflamizole recoveries from spiked plasma (0.1–1.0 μg/mL) were 87.0–100% with *SD* values of 1.0–3.0% (Table II). Daily recoveries of 0.5 μg of tiflamizole spiked to 1 mL of control plasma were 99.7% ($n \simeq 131$) with a *SD* of 3.2%. Tiflamizole can be determined at levels as low as 0.01 μg/mL using 5 mL of plasma.

Figure 2 illustrates the plasma tiflamizole concentration profile in three healthy subjects given a single oral 5-mg dose. Peak concentrations of 0.36–0.61 μg/mL occurred between 4 and 12 h. The elimination half-lives were 9.9–18.0 d.

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Analysis of Tablets Containing Aspirin, Acetaminophen, and Ascorbic Acid by High-Performance Liquid Chromatography

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Received March 25, 1983, from the *Katholieke Universiteit Leuven, Laboratorium voor Farmaceutische Chemie, Instituut voor Farmaceutische Wetenschappen, B-3000 Leuven, Belgium.* Accepted for publication February 8, 1984.

Abstract □ The high-performance liquid chromatographic method described enables the quantitation of the components and the main impurities of tablets containing aspirin, acetaminophen, and ascorbic acid. A C_8 reverse-phase column was used; the mobile phase was methanol–0.2 M phosphate buffer (pH 3.5)–water (20:10:70). Results obtained for a brand of effervescent tablets, normally aged for 5 years and stressed at 37°C, 50°C, or in 79% relative humidity at room temperature, are reported. Salicylic acid was the main product of decomposition. Diacetyl-*p*-aminophenol was observed to be formed by transacetylation.

Keyphrases □ Acetaminophen—HPLC with ascorbic acid and aspirin □ Aspirin—HPLC with acetaminophen and ascorbic acid □ Ascorbic acid—HPLC with acetaminophen and aspirin

During the last decade, phenacetin has been often replaced by acetaminophen in analgesic tablet formulations containing aspirin as the main component (1). Acetaminophen–aspirin mixtures have lower stability due to acetylation of the former by the latter, producing diacetyl-*p*-aminophenol (2, 3). This acetylation, however, was not evident in another study (4).

Tablets containing ascorbic acid were reported to be stable for over 5 years under normal storage conditions (5), but in combination with aspirin the eventual acetylation of ascorbic acid should be considered. Acetylation, in aqueous medium, of ascorbic acid by acetic anhydride has been described (6). Acetylation of other compounds present in tablet formulations,

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such as phenylephrine (7), codeine (8), or homatropine (9), has also been reported. Acetylation of proteins by aspirin was proposed as an explanation for the hypersensitivity to aspirin in humans (10).

This paper reports on the stability of an effervescent tablet from one manufacturer[1]. The tablets contain aspirin, acetaminophen, and ascorbic acid as the active components. High-performance liquid chromatography (HPLC) was chosen as the method for analysis. HPLC has been used previously for the analysis of multicomponent tablets containing aspirin and acetaminophen (11-17), but to our knowledge this is the first time that ascorbic acid was included in the analysis.

EXPERIMENTAL SECTION

Reagents and Chemicals—Some of the reference products were obtained through synthesis according to literature procedures: diacetyl-*p*-aminophenol, mp 151-154°C [lit. (2, 18) mp 152-156°C and 151-154°C]: *O*-acetyl-*p*-aminophenol, mp 79-81°C [lit. (19) mp 73-74°C and 75°C][2]. A mixture of 3-*O*-acetylascorbic acid and 2-*O*-acetylascorbic acid was obtained in solution[3] (6). Aspirin, salicylic acid, acetaminophen, and ascorbic acid were of Ph. Eur. quality. Sodium saccharin[4], *p*-hydroxybenzoic acid[4], and *p*-aminophenol[4] were of reagent quality. Formic acid[5], potassium hydrogen phosphate[5], and phosphoric acid[5] were of *pro analysi* quality. Reagent-grade methanol[6] was distilled in glass before use; water was distilled twice.

Apparatus and Operating Conditions—A high-pressure pump[7] was connected to a 10-μL loop injector[8], a column packed in-house with 10-μm C_8 reverse-phase material[9], a 254-nm fixed-wavelength detector[10], an integrator (used in the area mode)[11], and a recorder[12]. Some chromatograms were obtained with a variable-wavelength detector[13].

The mobile phase, CH_3OH-0.2 M phosphate buffer (pH 3.5)-water (20:10:70, v/v) was deaerated by sonication; the flow rate was 1 mL/min. The UV detector was set at 0.05 AUFS and the integrator at attenuation 4; the chart speed was 5 mm/min. The column was kept at room temperature (~20°C). The variable-wavelength detector was used at 280 nm.

Preparation of Sample Solutions—Two tablets (average mass, 3.45 g) were pulverized, and 1.000 g was weighed into a 50.0-mL volumetric flask. Formic acid (1.0 mL) and methanol (25 mL) were added, and the flask was mechanically shaken for 10 min. The mixture was brought to volume with methanol, 10 mL was clarified by centrifugation, and 5.0 mL of the supernatant was transferred into a 25.0-mL volumetric flask. Internal standard solution (5.0 mL) was added, and the solution was diluted to volume with water. The solution was analyzed within 1 h after preparation. A 0.0025% (w/v) solution of *p*-hydroxybenzoic acid in methanol-water (20:80) was used as the internal standard solution.

Sample and Storage Conditions—The tablets were prepared to contain 300 mg of aspirin, 200 mg of acetaminophen, and 300 mg of ascorbic acid. Sodium hydrogen carbonate, tartaric acid, citric acid, sodium saccharin, lactose, starch, dimethyl polysiloxane, povidone, and citrus oil were the excipients. Eleven batches, naturally aged 4-61 months at the time of analysis, were available. All samples were kept in their original, unopened plastic tubes; the stoppers had a drying agent. Tubes from the most recent batch were stored for 12 weeks in stressed conditions, *i.e.*, at 37°C (closed tubes), at 50°C (closed tubes), and at room temperature (~20°C) with a relative humidity of 79% (closed and open tubes).

Chromatographic Analysis—Least-squares regression lines (y, peak area ratio; x, amount injected in μg) were obtained with suitably prepared standard solutions for ascorbic acid ($y = 2.235x + 0.0005$), acetaminophen ($y = 2.717x + 0.0153$), salicylic acid ($y = 0.1226x + 0.0012$ at 254 nm, $y = 0.3774x + 0.0001$ at 280 nm), aspirin ($y = 0.2022x + 0.0010$), and diacetyl-*p*-aminophenol ($y = 2.182x + 0.0031$). The coefficient of correlation was >0.999 in all cases. When immediate analysis was impossible, standard solutions were kept at 5°C. The reproducibility was checked by a quadruple extraction of the same powdered tablet mixture and a twofold injection of each resulting solution. The mean and *CV* values obtained for the eight experiments were: ascorbic acid (107.0%, 0.9); acetaminophen (99.8%, 1.0); salicylic acid, measured at 280 nm, (0.81%, 1.8); aspirin (98.9%, 0.6); diacetyl-*p*-aminophenol (0.14%, 3.8). The results are expressed as a percentage of the label claim, except for the impurities where the mass of substance found (*e.g.*, salicylic acid) is reported as a percentage of the label content of the corresponding component (*e.g.*, aspirin).

Four tablets were retained for analysis from each tube, *i.e.*, the pair closest to the orifice and that closest to the bottom. Both pairs were extracted and the solutions were analyzed twice. Significant differences between top and bottom tablets were never found; therefore, the mean of four results is reported.

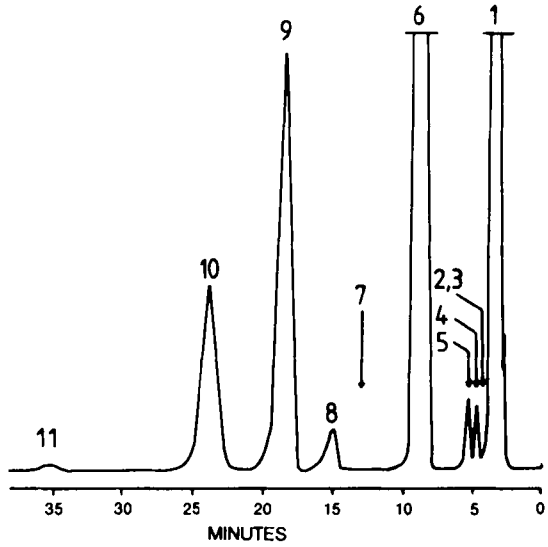

Figure 1—*Chromatogram of 45-month-old tablets; detection at 254 nm. Key: (1) ascorbic acid; (2) p-aminophenol; (3) 3-O-acetylascorbic acid; (4) 2-O-acetylascorbic acid; (5) sodium saccharin; (6) acetaminophen; (7) O-acetyl-p-aminophenol; (8) salicylic acid; (9) p-hydroxybenzoic acid (internal standard); (10) aspirin; (11) diacetyl-p-aminophenol.*

RESULTS AND DISCUSSION

A typical chromatogram, obtained for 45 month-old tablets, is shown in Fig. 1. The influence of the pH of the mobile phase on the separation of *p*-hydroxybenzoic acid, salicylic acid, and aspirin is shown in Fig. 2. A mobile phase containing methanol and a buffer (pH 3.4) was described recently for the analysis of bulk aspirin (20, 21). In all tablets examined, a small peak possibly corresponding to 2-*O*-acetylascorbic acid is present, but a peak cor-

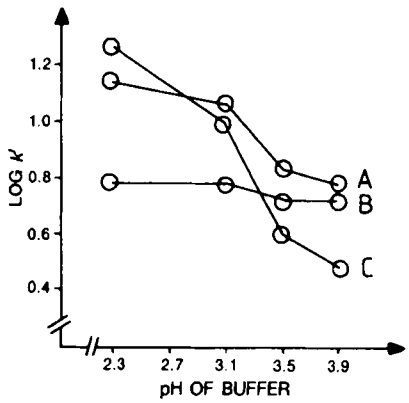

Figure 2—*Influence of the mobile phase buffer pH on the capacity factor (k') of aspirin (A), p-hydroxybenzoic acid (B), and salicylic acid (C).*

[1] S.M.B., Belgium.
[2] This product was purified by column chromatography [silica gel, dichloromethane-acetone (95:5)].
[3] The Paulssen experiment with acetic anhydride in water-dioxane was repeated and followed by HPLC for 1 h. Two secondary peaks were observed. In analogy with the published results, the 3-*O*-acetyl structure was assigned to the first (decreasing) peak (k', 0.5) and the 2-*O*-acetyl structure to the second (increasing) peak (k', 0.6).
[4] Fluka AG, Buchs, Switzerland.
[5] E. Merck, Darmstadt, F.R.G.
[6] Aldrich Europe, Beerse, Belgium.
[7] Model M 6000 A; Waters Associates, Milford, Mass.
[8] Model CV-6-UHPa-N60; Valco, Houston, Tex.
[9] LiChrosorb RP8, (25 cm × 4.6 mm i.d.); E. Merck, Darmstadt, F.R.G.
[10] Model 440; Waters Associates.
[11] Model DP88; Pye Unicam, Cambridge, England.
[12] Model BD40; Kipp & Zonen, Delft, The Netherlands.
[13] Model LC3UV; Pye Unicam.

Table I—Results of the Analysis for Different Batches of Tablets [a]

Batch Age, months	Ascorbic Acid, %	Acetaminophen, %	Diacetyl-*p*-aminophenol, %	Aspirin, %	Salicylic Acid, %[b]
4	106	99.2	0.2	98.5	0.8
9	106	99.2	0.2	99.2	1.2
13	106	100.4	0.3	97.5	1.5
20	105	100.1	0.3	97.0	2.6
24	106	99.9	0.4	95.1	3.6
34	106	98.4	0.4	93.3	4.9
37	105	99.9	0.5	92.0	6.2
45	107	99.0	0.9	76.3	18.1
49	105	99.5	0.6	87.0	9.8
55	106	98.9	0.8	80.9	14.3
61	105	99.3	0.6	88.4	9.4

[a] Percentage of label claim, except as noted in the text. [b] Measured at 280 nm.

recoveries, and since all lots were kept in the same conditions, this must be due to striking differences in the manufacturing quality.

The results obtained in stressed conditions are given in Table II. At 37°C, the USP 3% limit for salicylic acid is reached after ~1 month; at 50°C, the limit is reached after 2 weeks. In open tubes, kept at room temperature and in humid conditions such as frequently occurs in bathrooms, this limit can be reached in ~1 d. Results for the experiment with closed tubes at room temperature and in 79% relative humidity are not reported in detail since the stability was not affected, thus proving the quality of the container.

Although ascorbic acid seems to withstand moderate heating quite well, the effect of high humidity is disastrous. It should, however, be kept in mind that the stability is influenced not only by the conditions of conservation, but also by the presence of other tablet components. The hydrolysis of aspirin involves formation of acetic acid, which lowers the pH and acts as a solvent, thus facilitating reaction. The eventual influence of acetic acid formation is supported by the fact that in the 50°C experiment, ascorbic acid starts to decompose only after 4 weeks, when appreciable amounts of acetic acid have already been formed. A similar effect is observed for diacetyl-*p*-aminophenol

Table II—Results of the Analysis of Stressed Tablets [a]

Conservation Conditions	Conservation Time, weeks	Ascorbic Acid, %	Acetaminophen, %	Diacetyl-*p*-aminophenol, %	Aspirin, %	Salicylic Acid, %
Closed tube						
37°C	0	106	99.2	0.2	98.5	0.8[b]
	2	105	99.7	0.4	97.3	1.9
	4	104	99.0	0.8	96.5	2.7
	8	106	99.0	0.9	94.8	4.1
	12	105	99.2	1.1	93.0	5.4
50°C	0	106	99.2	0.2	98.5	0.8[b]
	2	107	98.9	0.8	96.0	3.0
	4	107	97.6	1.5	89.2	8.2
	8	102	98.7	1.1	59.5	30.0
	12	92	100.7	0.2	29.7	52.1
Open tube[c]	0	106	99.2	0.2	98.5	0.8[b]
	2	90	100.1	0.3	47.7	39.8
	4	33	99.3	0.2	11.4	68.4
	8	8	100.1	0.1	5.6	72.1
	12	4	100.3	0.1	0	75.9

[a] Percentage of label claim, except as noted in text. [b] Measured at 280 nm. [c] At ~20°C and 79% relative humidity.

responding to the assumed 3-*O*-acetylascorbic acid has never been detected. This substance was observed to be very unstable in solution, which confirms an earlier report (6). Quantitative determination of the ascorbic acid derivatives was not attempted since the only reference available was a solution containing a mixture of these impurities. *p*-Aminophenol, which has the same retention time as 3-*O*-acetylascorbic acid, was never detected during our experiments. Due to the rather poor separation in this area of the chromatogram, the detection limit for *p*-aminophenol was not better than 2%. *p*-Aminophenol has been reported as an impurity present in tablets containing acetaminophen, but only when codeine phosphate or magnesium stearate were also present (3); these products were not present in the tablets examined. *O*-Acetyl-*p*-aminophenol was never detected in significant amounts. Diacetyl-*p*-aminophenol was not detected at 280 nm (a more appropriate wavelength for the detection of salicylic acid, present in all the samples as the predominant impurity). Detection at ~300 nm (close to the absorption maximum for salicylic acid) was not applied due to the low absorbance of *p*-hydroxybenzoic acid, used as the internal standard. Samples were extracted with a mixture of formic acid and methanol. The presence of formic acid favors the drug release from the excipients (22). The stability at ~5°C of a solution to be analyzed was followed by HPLC, and the decrease of the content was noted: ascorbic acid, 0.003%/h; acetaminophen, 0.001%/h; aspirin, 0.02%/h; diacetyl-*p*-aminophenol, 0.001%/h. The value for aspirin corresponds well with a value reported for a chloroform–formic acid extract (22).

Table I lists the results for the naturally aged samples. No significant decrease in ascorbic acid or acetaminophen content was observed, and diacetyl-*p*-aminophenol was not formed in appreciable amounts although a small increase was observed. A linear correlation ($r = 0.983$) exists between diacetyl-*p*-aminophenol and salicylic acid formation. The formation of diacetyl-*p*-aminophenol from acetaminophen by transacetylation with aspirin has been discussed previously (3). The formation of salicylic acid is rapid. The 3.0% limit for buffered tablets of the USP XX (23) is exceeded in <2 years, and the BP 80 (24) 1.0% limit for dispersible tablets is exceeded after ~0.5 year. The decrease of aspirin is completely explained by the increase of salicylic acid. Some lots (45 and 55 months) show exceptionally high salicylic acid which, in the 50°C experiment, reaches a maximum after 4 weeks, corresponding to a minimum for acetaminophen. This maximum is followed by a rapid decrease, paralleled by an increase of acetic acid (or salicylic acid) and acetaminophen, which suggests formation of the latter through hydrolysis of diacetyl-*p*-aminophenol.

In all the stressed experiments, the loss of aspirin is completely explained by the formation of salicylic acid. This agrees with recently published results for aspirin tablets, stressed at 50°C and at 80°C, where appreciable amounts of non-salicylic-acid salicylates were only observed at the higher temperature (17).

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Effects of Benztropine Mesylate on Haloperidol-Induced Prolactin Secretion and Serum Haloperidol Levels in Rats

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Received November 7, 1983, from the **Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, NY 11201*, the ‡*Department of Pathology, The Valley Hospital, Ridgewood, NJ 07451*, §*Long Island University, Brooklyn, NY 11201*, and ¶*Kean College of New Jersey, Union, NJ 07087*. Accepted for publication February 22, 1984.

Abstract □ The effects of benztropine mesylate on haloperidol-induced prolactin secretion and serum haloperidol levels were investigated in 240 rats. Animals were pretreated with benztropine mesylate or saline 20 min prior to receiving haloperidol or saline. Serum prolactin and haloperidol levels were analyzed at six time periods over 150 min. There was no significant difference in prolactin levels of control animals, *i.e.*, saline pretreated/saline treated rats compared to benztropine mesylate pretreated/saline treated rats. Haloperidol caused a significant rise ($p < 0.0001$) in serum prolactin compared with controls. The prolactin concentration for the 30–150-min sampling period was significantly higher when the rats received benztropine mesylate prior to haloperidol ($p < 0.05$). There was a significant correlation ($r = 0.57, p < 0.001$) between serum haloperidol levels and serum prolactin levels in haloperidol-treated animals pretreated with either saline or benztropine mesylate. Additionally, serum haloperidol levels were not significantly different in animals pretreated with benztropine mesylate compared with those pretreated with saline. Thus, the enhancement of prolactin levels by benztropine mesylate was independent of any effect of haloperidol metabolism. This study appears to indicate that in the rat, cholinergic mechanisms exert a weak inhibitory effect on prolactin secretion under conditions of dopamine blockade.

Keyphrases □ Benztropine mesylate—prolactin secretion, serum haloperidol levels, rats □ Haloperidol—prolactin secretion, benztropine mesylate, serum levels, rats

The secretion of the anterior pituitary hormone, prolactin, appears to be dominantly regulated by a prolactin-inhibitory factor liberated by the hypothalamus as a result of afferent dopaminergic impulses (1–3). Dopamine is believed to be the major prolactin-inhibitory factor (4). In addition, prolactin release appears to be mediated to some extent by prolactin-releasing factors (5). Evidence also exists in animals that cholinergic and serotonergic mechanisms modulate the secretion of prolactin at the level of the pituitary (6–9). Although pilocarpine and physostigmine inhibited prolactin secretion in rats (8, 10, 11), no effect was observed on neuroleptic-induced prolactin secretion in this species (11). There are complex and conflicting reports concerning the effects of cholinergic blocking drugs on serum prolactin levels in humans and animals (6, 11, 12).

A fairly good correlation between the antipsychotic potency of various neuroleptics and their prolactin-stimulating effects has been demonstrated both in humans and rats (9, 13–15). Neuroleptics differ considerably in their intrinsic central anticholinergic properties (16). According to Lal *et al.* (17) such differences may account, at least in part, for variations in serum prolactin-stimulating properties found among antipsychotic agents. This suggestion was based on their demonstration in humans that intramuscularly administered benztropine mesylate, a muscarinic receptor-blocking agent, significantly enhanced the elevated prolactin levels induced by intramuscularly administered haloperidol (17). However, no attempt was made to determine if benztropine mesylate influenced prolactin secretion by altering haloperidol metabolism (17).

In this laboratory, comparison of the rank-order of reported central anticholinergic activity of nine antipsychotic drugs belonging to five chemical classes of neuroleptics appeared not to have significant effect upon either the magnitude or duration of prolactin stimulation in rats (18). However, there are no assurances that central anticholinergic threshold levels had been reached with the doses of drugs utilized.

In light of the above, it appeared desirable to further investigate the possible role of anticholinergic activity in enhancing neuroleptic-induced prolactin secretion in rats, to help clarify if a species difference exists between humans and rats in regard to this effect, and to determine if benztropine mesylate influences haloperidol plasma levels. The present investigation examined the effects of benztropine mesylate on haloperidol-induced prolactin secretion and serum haloperidol levels in rats.

EXPERIMENTAL SECTION

Two hundred and forty male Sprague–Dawley adult rats[1] (225–300 g) were divided into 24 equal groups. The rats were housed for 14 d prior to the study

[1] Taconic Farms, Germantown, N.Y.

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