Table V—Mean Urine pH at Steady State and Results of Statistical Analysis

Urine Collection Interval, hr	Capsules pH[a]	Capsules p^b	Reference Tablets pH[a]	Reference Tablets p^b
156–168	5.78 ± 0.36		5.84 ± 0.51	
168–174	6.08 ± 0.65	<0.01	6.23 ± 0.68	<0.01
174–180	6.20 ± 0.67	<0.01	6.20 ± 6.16	<0.05
168–180[c]	6.14 ± 0.62	<0.01	6.21 ± 0.55	<0.01

[a] Mean ± *SD*, $n = 24$; there was no statistically significant difference between two treatments. [b] Statistically significant difference from 156–168-hr urine sample pH. [c] Average of 168–174- and 174–180-hr pH values.

changes in urinary excretion of either drug. While the urinary excretion of unchanged chlorpheniramine is a small fraction of the administered dose (4), the urinary excretion of unchanged pseudoephedrine is the major fraction of the administered dose and can be a reliable indicator for bioequivalency tests.

The bioequivalency test for sustained-release dosage forms can be best made at steady state when the amount excreted in urine reflects the amount absorbed. Table II substantiates this premise since the 0–24-hr *AUC* does not accurately reflect the amount of chlorpheniramine absorbed. At steady state, the *AUC* for a single dosing interval was more than twice as large as that found during the 0–24-hr interval following a single dose of the capsule. The slow absorption associated with this sustained-action dosage form makes it difficult to evaluate such systems using a single-dose study design. When the ratio of parameters characterizing the bioavailability of two drugs is one, the dosage forms are considered to be bioequivalent. In this study, the average ratio (capsule to reference tablet) was 1.06. Thus, both the rate of drug absorption as given by the peak plasma concentration and time of peak (Table I) and the extent of absorption (Tables II and IV) showed virtually identical bioavailability for the sustained-action capsule and reference standard tablets.

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High-Performance Liquid Chromatographic Assay of Codeine in Acetaminophen with Codeine Dosage Forms

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Received March 4, 1980, from the *Pharmacy Research Department, McNeil Laboratories, Fort Washington, PA 19034.* Accepted for publication March 27, 1980.

Abstract □ An accurate, rapid, and specific high-performance liquid chromatographic (HPLC) assay was developed for codeine in acetaminophen with codeine combination products. The internal standard (chlorpheniramine maleate), codeine, acetaminophen, and several other test compounds or impurities were well separated. A complete analysis took <10 min. The relative standard deviations of the retention time, precision, and accuracy were 0.5, 0.4, and 0.5%, respectively. An excellent linear correlation was obtained between the HPLC and GLC methods.

Keyphrases □ Codeine—high-performance liquid chromatographic analysis of capsules, tablets, and elixirs with acetaminophen and codeine, comparison with GLC analysis □ Acetaminophen—high-performance liquid chromatographic analysis of codeine and acetaminophen in capsules, tablets, and elixirs, comparison with GLC analysis □ High-performance liquid chromatography—analysis, codeine and acetaminophen in capsules, tablets, and elixirs, comparison with GLC analysis

Various analytical methods (1–11) have been reported for codeine, a narcotic analgesic and antitussive drug. Sell and Rajzer (1) determined codeine in nonaqueous media using a differentiating potentiometric titration method. Mulé (2) reported UV, TLC, and GLC methods for the determination of narcotic analgesics in humans. GLC methods (3–5) also were used extensively to determine codeine in various media.

Steady progress in high-performance liquid chromatographic (HPLC) analyses of codeine has been reported (6–11). Following reports that the HPLC technique was useful for codeine analysis (6, 7, 11), reversed-phase and ion-pair HPLC techniques were developed (8, 9). Baker *et al.* (10) recently analyzed codeine using a reversed-phase HPLC system equipped with dual-wavelength UV detection. Gupta (12) reported the simultaneous separation of acetaminophen, aspirin, caffeine, codeine phosphate, phenacetin, and salicylamide using a reversed-phase chromatographic method.

The purpose of this study was to develop an HPLC method that could be used routinely to assay codeine in acetaminophen with codeine combination products. This method is fast, simple, specific, precise, and accurate.

EXPERIMENTAL

Reagents and Materials—The *n*-hexane used was distilled in glass. Ammonium hydroxide was ACS grade. Chloroform[1], methanol[1], and sodium hydroxide[1] were analytical reagent grade. The codeine phosphate,

[1] Mallinckrodt, St. Louis, MO 63147.

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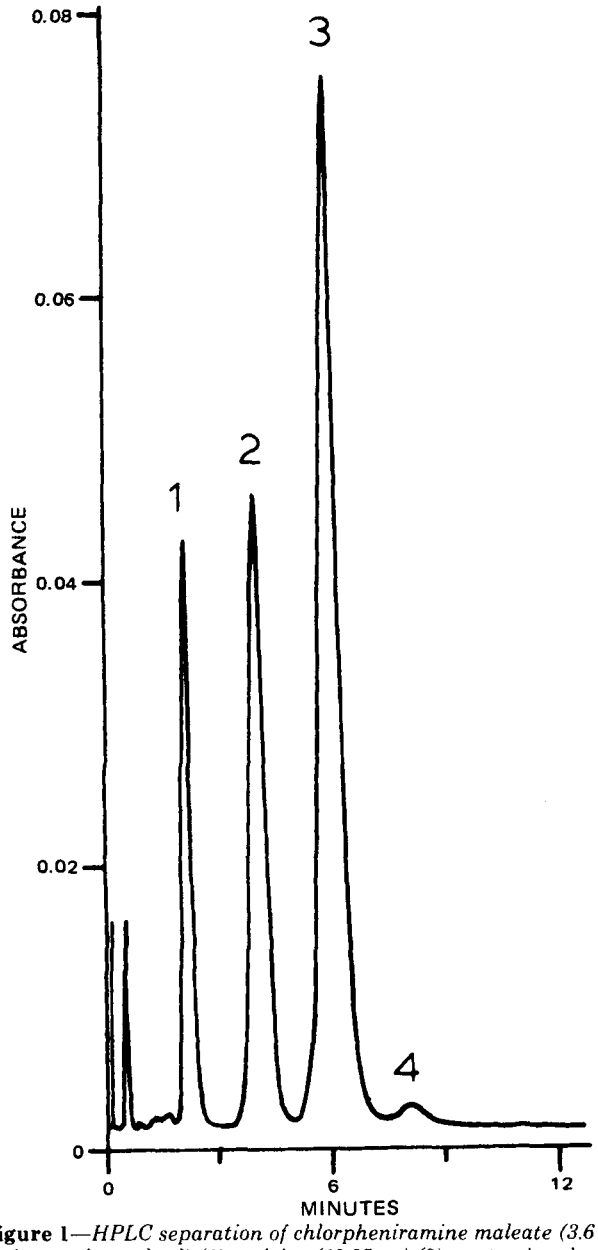

Figure 1—*HPLC separation of chlorpheniramine maleate (3.6 μg as an internal standard) (1), codeine (10.85 μg) (2), acetaminophen (unknown amount) (3), and an unknown compound (4) from an acetaminophen (325 mg) with codeine phosphate (30 mg) tablet sample.*

morphine sulfate, and chlorpheniramine maleate were USP reference standards. Atropine sulfate[2], apomorphine hydrochloride[3], nalorphine hydrochloride[3], naloxone hydrochloride[4], 4-aminophenol[5], acetaminophen[5], and acetaminophen with codeine products[5] were used as received.

Instrumentation—The high-performance liquid chromatograph[6] was equipped with a UV detector (254 nm), a 6000-psi pump, and a loop injector. The output of the UV detector was connected to a recorder and a minicomputer[7]. An automatic sampler[8] also was used.

Silica gel[9], 10 μm, was slurry packed, using a slightly modified packing procedure (13), into a 25-cm × 2.1-mm i.d. stainless steel column. The mobile phase was 23.2% methylene chloride, 4.4% methanol, 72.3% *n*-hexane, and 0.1% ammonium hydroxide. The column flow rate was set at 3.0 ml/min, and the UV detector was set at 0.10 aufs.

Internal Standard Preparation—A 22.5-mg sample of chlorpheniramine maleate was weighed accurately into a 25-ml volumetric flask, chloroform was added, and the flask was shaken until the compound dissolved. The sample was taken to volume with chloroform (0.9 mg/ml).

Codeine Standard Preparation—A 60-mg sample of codeine phosphate (equivalent to 45.20 mg of codeine) was weighed accurately into a 120-ml screw-capped bottle. Exactly 50 ml of chloroform and 40 ml of 0.1 *N* NaOH were added to the sample. It was capped tightly and shaken on a mechanical shaker for 1 hr. After centrifugation, the aqueous layer was aspirated and discarded.

The chloroform layer was filtered through a small pledget of cotton into a clean 60-ml bottle. Fifteen milliliters of the standard solution was pipetted into a 25-ml volumetric flask, 5 ml of the internal standard solution was added, and the solution was diluted to volume with chloroform. Twenty microliters of this solution was injected into the high-performance liquid chromatograph. This volume deposited 3.6 μg of chlorpheniramine maleate and 10.85 μg of codeine on the column.

Sample Preparation—For tablets, 20 tablets were selected randomly, weighed, and triturated to a fine powder. An accurately weighed amount of powder equivalent to 30 mg of codeine phosphate (22.60 mg of codeine) was transferred to a 120-ml screw-capped bottle.

For capsules, 20 capsules were randomly selected and weighed. The average capsule fill was determined. The contents of the capsules were emptied and mixed. An accurately weighed amount of powder equivalent to 30 mg of codeine phosphate (22.60 mg of codeine) was transferred to a 120-ml screw-capped bottle.

For the elixirs, an amount equivalent to 30 mg of codeine phosphate (22.60 mg of codeine) was transferred accurately to a 120-ml screw-capped bottle.

Exactly 25 ml of chloroform and 20 ml of 0.1 *N* NaOH were added to the sample. The bottle was capped tightly, shaken on a mechanical shaker for 1 hr, and centrifuged. The aqueous layer was aspirated and discarded. The chloroform layer (0.904 mg/ml) was filtered through a small pledget of cotton into a clean 60-ml bottle. A 15-ml aliquot of the 0.904-mg/ml chloroform solution was transferred to a 25-ml volumetric flask containing exactly 5 ml of the internal standard solution. It then was diluted to volume with chloroform and shaken. A 20-μl aliquot of this solution was injected into the high-performance liquid chromatograph. Two injections were made for each solution.

Calibration Curve—The relative calibration curve of the internal standard to codeine was prepared as follows. A known concentration of the internal standard was prepared, and different amounts of codeine phosphate were weighed and dissolved with the internal standard solution. The solutions were injected into the high-performance liquid chromatograph, and peak area ratios of codeine to the internal standard *versus* weight ratios of codeine to the internal standard were plotted.

Calculation—The peak area ratio, R, was determined from:

$$R = \frac{\text{area of codeine peak}}{\text{area of internal standard peak}} \qquad \text{(Eq. 1)}$$

The concentration of codeine then was determined from:

$$\text{sample concentration} = \text{codeine standard concentration} \times \frac{R_{\text{sample}}}{R_{\text{standard}}} \qquad \text{(Eq. 2)}$$

The percent of codeine was determined from:

$$\%\ \text{label} = \frac{\text{sample concentration}}{\text{theoretical sample concentration}} \times 100 \qquad \text{(Eq. 3)}$$

Precision Study—Twenty tablets containing acetaminophen with codeine were weighed and triturated to a fine powder. From this powder, seven samples, each containing the equivalent of 30 mg of codeine phosphate (22.60 mg of codeine), were weighed and treated as already described. Duplicate injections were made for each sample.

Accuracy Study—Known weights of codeine phosphate USP and acetaminophen USP were added to four placebo tablets. Samples were prepared as described and then were injected into the high-performance liquid chromatograph.

HPLC and GLC Comparison—The GLC method was similar to the methods described previously (2, 3). The gas–liquid chromatograph[10] was equipped with a flame-ionization detector and a 1.83-m × 2-mm i.d. coiled-glass column packed with 3% OV-17 on Chromosorb W HP (80–100

[2] Sigma Chemical Co., St. Louis, MO 63118.
[3] Merck Chemical Division, Rahway, N.J.
[4] Endo Laboratories, Garden City, N.Y.
[5] McNeil Laboratories, Fort Washington, PA 19034.
[6] Waters Associates, Milford, MA 01757.
[7] Model 3352B laboratory data system, Hewlett-Packard, Avondale, PA 19311.
[8] WISP 710, Waters Associates, Milford, MA 01757.
[9] LiChrosorb Si-60, EM Laboratories, Elmsford, NY 10523.
[10] Model 900, Perkin-Elmer, Norwalk, CT 06856.

Table I—Retention Times and Minimum Detection Limits of Codeine and Related Compounds on a Silica Gel Column

Compound	Retention Time, min	Detection Limit, μg
Naloxone hydrochloride	0.79	0.10
Apomorphine hydrochloride	1.10	0.10
Chlorpheniramine maleate	1.88	—
Nalorphine hydrochloride	3.17	0.10
4-Aminophenol	3.26	0.01
Codeine	3.82	—
Acetaminophen	6.00	—
Morphine sulfate	14.02	0.75

Table II—Reproducibility of Retention Times for Codeine, Chlorpheniramine Maleate, and Acetaminophen

Run	Retention Time, min		
	Codeine	Chlorpheniramine Maleate	Acetaminophen
1	3.79	1.89	5.96
2	3.80	1.87	5.99
3	3.83	1.88	6.03
4	3.83	1.88	6.02
5	3.84	1.88	6.01
Mean ($\bar{x}$)	3.82	1.88	6.00
SD (σ)	0.02	0.01	0.03
RSD[a], %	0.5	0.5	0.5

[a] *RSD* is the relative standard deviation and is derived from 100 ($\sigma/\bar{x}$).

Table III—Precision of HPLC Assay of Codeine in Acetaminophen with Codeine Products

Sample	Percent of Label Found
1	99.8
2	100.2
3	100.1
4	101.2
5	100.1
6	100.2
7	100.2
Mean ($\bar{x}$)	100.3
SD (σ)	0.4
RSD[a], %	0.4

[a] Relative standard deviation derived from 100 ($\sigma/\bar{x}$).

mesh). The column temperature was set at 205°, and the carrier gas was nitrogen. The initial standard was atropine and was prepared by accurately weighing 50 mg of atropine sulfate into a 120-ml screw-capped bottle. Fifty milliliters of chloroform and 25 ml of 0.1 *N* NaOH were added. The bottle then was shaken for 1 hr and centrifuged, and the aqueous layer was aspirated and discarded. The codeine standard and sample preparations were similar to those already described.

Samples of acetaminophen with codeine elixirs, tablets, and capsules were prepared as described. Before addition of the internal standard solution, the sample was split into two parts. One part was assayed by HPLC, and the other part was assayed by GLC.

RESULTS AND DISCUSSION

Figure 1 shows the excellent separation of codeine from acetaminophen and chlorpheniramine maleate in <10 min. This method also separates structurally related compounds from codeine such as naloxone hydrochloride, apomorphine hydrochloride, nalorphine hydrochloride, and morphine sulfate, as well as 4-aminophenol, the hydrolysis product of acetaminophen. The structurally related compounds were chosen to demonstrate the specificity of the method. Their respective retention times and detection limits are listed in Table I. The relative standard deviations of the retention times all were 0.5% (Table II).

Although both codeine and acetaminophen were well separated from each other, the simultaneous quantitation of a very large amount of acetaminophen and a small amount of codeine was chromatographically difficult. Acetaminophen had a much higher ϵ value than codeine at 254 nm. In addition, the simultaneous quantitative extractions of codeine and acetaminophen were unsuccessful. Either codeine or acetaminophen had to be extracted from the various dosage forms. It was decided to extract codeine quantitatively for HPLC analysis.

Table IV—Accuracy of HPLC Assay of Codeine in Acetaminophen with Codeine Products

Sample	Percent of Label	
	Theoretical	Found
1	100.00	101.2
2	100.00	100.0
3	100.00	100.7
4	100.00	100.7
Mean ($\bar{x}$)	100.00	100.7
SD (σ)	—	0.5
RSD[a], %		0.5
95% Confidence limit, %		0.8

[a] Relative standard deviation derived from 100 ($\sigma/\bar{x}$).

Table V—HPLC and GLC Assay Results of Codeine in Acetaminophen with Codeine Products

Sample	Percent of Label Claim		Variation[a]
	HPLC	GLC	
Elixir			
1	98.3	99.1	0.8
2	97.3	98.8	1.5
3	98.6	98.6	0.0
4	87.6	88.7	1.1
5	99.4	97.2	2.2
6	99.4	99.5	0.1
7	97.7	97.6	0.1
Tablet			
1	93.8	95.4	1.6
2	92.7	93.2	0.5
3	89.5	89.5	0.0
4	101.9	105.1	3.2
5	101.6	101.9	0.3
6	102.4	102.6	0.2
7	100.3	103.5	3.2
Capsule			
1	95.7	96.3	0.6
2	93.4	96.9	3.5
3	90.7	94.5	3.8
4	93.7	95.6	1.9
5	94.2	96.9	2.7
6	93.8	96.7	2.9
7	95.4	98.6	3.2
8	92.3	95.2	2.9

[a] The linear correlation coefficient was 0.9999, and the average variation was 1.7%.

The amount of ammonium hydroxide in the mobile phase was critical to the separation. Ammonia was lost slowly from the mobile phase. To keep the retention times constant and to maintain effective separation, fresh solvent should be used daily. Sometimes, it was necessary to adjust slightly the amount of ammonium hydroxide (between 0.1 and 0.2%) to obtain effective separation when a new column was used.

Chlorpheniramine maleate was chosen as the internal standard because its peak was sharp and symmetrical and it was well separated from codeine. Furthermore, chlorpheniramine maleate was stable and did not react with the mobile phase, other sample components, and the column packing. In addition, it is available commercially in high purity. The peak heights of chlorpheniramine maleate and codeine decrease slightly with time due to changing column conditions in the presence of ammonium hydroxide. However, the peak areas and their ratio remain unchanged, which is critical to an accurate assay. The precision of the method showed a relative standard deviation of 0.4% (n = 7) (Table III).

The accuracy of the assay is shown in Table IV. A relative standard deviation of 0.5% (n = 4) was obtained. When the internal standard method was not used, the relative standard deviations of precision and accuracy were >1.0%. For a routine assay with the automatic sampler, the standard codeine with the internal standard was injected as every third sample to ensure reliable results. In addition, the calibration curve obtained for the internal standard to codeine was linear.

The results of the comparison of the HPLC and GLC methods are shown in Table V. Three dosage forms with different amounts of acetaminophen with codeine were used. For 22 samples, the GLC assay results varied on an average of 1.7% from those of the HPLC assay. A linear correlation coefficient of 0.9999 was obtained. The precision of the GLC

assay was ~2%. Besides assaying for composite granulations, the HPLC assay also is applicable to content uniformity analysis.

In conclusion, the HPLC method is simple, precise, fast, specific, and accurate. A complete analysis takes ~10 min. All test compounds and known impurities can be detected. Since the analysis is conducted at ambient temperature, no thermal degradation of codeine is expected.

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High-Performance Liquid Chromatographic Analysis of Nitroglycerin Ointment

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Received August 24, 1979, from the *Winchester Engineering and Analytical Center, Food and Drug Administration, Winchester, MA 01890.* Accepted for publication March 22, 1980.

Abstract □ The assay of ointments containing nitroglycerin is described. Sample preparation by direct dissolution in warm dimethyl sulfoxide appeared to be more accurate than extraction. Anisole was used as an internal standard. Chromatographic conditions included a C_{18} microporous silica column and a methanol–water mobile phase (40:60). Detection at 215 nm was superior to detection at 254 nm.

Keyphrases □ Nitroglycerin—ointment, reversed-phase high-performance liquid chromatographic analysis □ Ointments—nitroglycerin, reversed-phase high-performance liquid chromatographic analysis □ High-performance liquid chromatography—analysis, nitroglycerin ointment

The use of topical nitroglycerin for patients with congestive heart failure was reported recently (1). Existing methods for the analysis of nitroglycerin (2–9) lack specificity (7), are too time consuming for convenient uniformity determinations, or require prolonged heating that could lead to decomposition of nitroglycerin, which occurs at 50–60° (10).

Several high-performance liquid chromatographic (HPLC) assays for nitroglycerin dosage forms were reported recently (11, 12). These methods can separate nitroglycerin from its mono- and dinitrate degradation products. Since HPLC has none of the disadvantages of the other methods, its applicability to the analysis of nitroglycerin ointment was studied. A sample preparation method was developed so that the method of Crouthamel and Dorsch (11) could be applied to ointment samples. It was chosen for initial investigation because it uses an octadecylsilane column, which is widely available in HPLC laboratories, and a simple, less expensive, water–methanol mobile phase. The method of Baske *et al.* (12) uses a less retentive phenyl column and a more expensive and complex water–acetonitrile–tetrahydrofuran mobile phase. Contrary to a previous observation (12), no problems of clogging of inlet filters were encountered.

EXPERIMENTAL

Materials—The water used was HPLC grade[1]. The methanol was distilled in glass[2]. Dimethyl sulfoxide (I), butylated hydroxyanisole[3], isooctane, sodium acetate, acetic acid, potassium nitrate, ammonium hydroxide, lanolin, and petrolatum[4] were ACS reagent grade.

A 10% nitroglycerin on lactose triturate[5] was used as a standard and was calibrated by the USP phenoldisulfonic acid method for the assay of nitroglycerin (2). It assayed at 9.62%. The standard solutions were 1 mg/ml in methanol for Method 1, 2 mg/ml in I for Method 2, and 2 mg/ml in the internal standard solution for Method 2a.

Instrumentation—Two liquid chromatographic systems were used. The first system consisted of a dual-head reciprocating piston positive-displacement pump[6], a septumless syringe-loaded loop injector with a 10-μl loop[7], a variable-wavelength detector operated at 254 or 216 nm[8], a 10-mv recorder[9], and a 15-cm × 4-mm column of a slurry of chemically bonded octadecyl reversed-phase material[10] packed in aqueous sodium acetate and methanol according to the manufacturer's directions. The second system contained a dual-head reciprocating piston pump[11], an automatic injector[12], a variable-wavelength detector operated at 215 nm[13], a flat-bed recorder[14], and a 15-cm × 4.6-mm column of chemically

[1] J. T. Baker Chemical Co., Phillipsburg, N.J.
[2] Burdick & Jackson Laboratories, Muskegon, Mich.
[3] Sigma Chemical Co., St. Louis, Mo.
[4] Fisher Scientific Co., Fair Lawn, N.J.
[5] Marion Laboratories, Kansas City, Mo.
[6] Model 100A with preparative scale head, Altex Scientific Inc., Berkeley, Calif.
[7] Model 70-10 with model 70-11 loop filler port, Rheodyne Inc., Berkeley, Calif.
[8] Model 837 spectrophotometer, DuPont Instruments, Wilmington, Del.
[9] Servariter II, Texas Instruments, Houston, Tex.
[10] ODS-Hypersil, Hyperspheres (5 μm), Shandon Southern Products Ltd., Cheshire, England.
[11] Model 6000A, Waters Associates, Milford, Mass.
[12] WI-SP, Waters Associates.
[13] Model LC-75, Perkin-Elmer, Norwalk, Conn.
[14] Model 595, Linear Instruments Corp., Irvine, Calif.

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