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Quantitation of Acetaminophen, Chlorpheniramine Maleate, Dextromethorphan Hydrobromide, and Phenylpropanolamine Hydrochloride in Combination Using High-Performance Liquid Chromatography

V. DAS GUPTA *x and ARUN R. HEBLE ‡

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Abstract □ A high-performance liquid chromatographic (HPLC) method has been developed for the quantitation of acetaminophen, chlorpheniramine maleate, dextromethorphan hydrobromide, and phenylpropanolamine hydrochloride in combination in pharmaceutical dosage forms using a single column and three different mobile phases. The method developed is sensitive for the content uniformity test for tablets. No preliminary extraction procedure is required for liquid preparation and a very simple extraction procedure is required for tablets. The method is accurate and precise with *RSD* (based on five injections) of 1.2, 2.4, 1.9, and 1.6% for acetaminophen, chlorpheniramine, dextromethorphan, and phenylpropanolamine, respectively.

Keyphrases □ Acetaminophen—HPLC, content uniformity □ Chlorpheniramine maleate—HPLC, content uniformity □ Dextromethorphan hydrobromide—HPLC, content uniformity □ Phenylpropanolamine hydrochloride—HPLC, content uniformity

One popular commercial product[1] contains an analgesic (acetaminophen), an antihistamine (chlorpheniramine maleate), an antitussive (dextromethorphan hydrobromide), and a decongestant (phenylpropanolamine hydrochloride). The product is extensively used for the relief of symptoms of coughs and colds. The dosage forms also contain excipients, some of which may interfere with the analysis of the active ingredients. The problem of analysis is further complicated by the presence of 325 mg of acetaminophen *versus* only 1 mg of chlorpheniramine maleate per tablet (or per 15 mL of the liquid). The quantities of dextromethorphan hydrobromide and phenylpropanolamine hydrochloride present are 10 and 12.5 mg per tablet (or 15 mL of the liquid), respectively. Acetaminophen has high absorbance in the useful UV range, but that of phenylpropanolamine hydrochloride is very poor. For example, at 256 nm (the wavelength of maximum absorption of phenylpropanolamine hydrochloride) a 1350-μg/mL aqueous solution of phenylpropanolamine hydrochloride has an absorption similar to a 20-μg/mL solution of acetaminophen. No single method is available to determine the active ingredients quantitatively in this combination.

High-performance liquid chromatographic (HPLC) methods for the quantitation of acetaminophen (1–4), chlorpheniramine maleate (5, 6), dextromethorphan hydrobromide (3, 7, 8), and phenylpropanolamine hydrochloride (6, 9–11) have been reported. None of the reported methods is applicable when ingredients are present in this combination.

This paper reports the quantitation of acetaminophen (I), chlorpheniramine maleate (II), dextromethorphan hydrobromide (III), and phenylpropanolamine hydrochloride (IV) in combination, using HPLC. The method requires three different mobile phases for complete analysis.

EXPERIMENTAL SECTION

Materials—All chemicals and reagents were USP, NF, or ACS quality and used without further purification. The sodium salt of 1-heptanesulfonic acid[2] was used as received.

A liquid chromatograph[3] attached to a multiple-wavelength detector[4] and a recorder[5] was used. The column[6] (30 cm × 4 mm i.d.) was purchased and

[1] Comtrex; Bristol-Myers Products, New York, N.Y.

[2] Eastman Kodak Co., Rochester, N.Y.

[3] Waters ALC202 equipped with a U6K Universal injector; Waters Associates, Milford, Mass.

[4] Spectroflow Monitor 770; Schoeffel Instruments, Ramsey, N.J.

[5] Omniscribe 5213-12; Houston Instruments, Austin, Tex.

[6] μ-Bondapak phenyl; Waters Associates, Milford, Mass.

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Table I—Chromatographic Conditions

Compound	Mobile Phase	Flow Rate, mL/min	Sensitivity	Wavelength, nm
Acetaminophen	1	1.5	0.04	256 (Fig. 1)
Phenylpropanolamine	2	2.5	0.02	256 (Fig. 1)
Chlorpheniramine and dextromethorphan	3	2.0	0.02	262 (Fig. 2)
Dextromethorphan[a]	4	2.0	0.02	279 (Fig. 3)
Chlorpheniramine and dextromethorphan[a]	4	2.3	0.02	262 (Fig. 4)

[a] It was necessary to develop another mobile phase due to interference from the excipients in liquid dosage form.

used as received. The four different mobile phases used were an aqueous buffer (pH ~ 7) containing 0.02 M ammonium acetate and 15% v/v of methanol (mobile phase 1); an aqueous buffer containing 0.02 M KH_2PO_4 with pH adjusted[7] to ~2.6 with an 85% aqueous solution of phosphoric acid (0.4 mL/L) (mobile phase 2); an aqueous buffer (pH ~ 3.3) containing 0.005 M sodium 1-heptanesulfonate, 1% v/v of glacial acetic acid, and 48% v/v of methanol (mobile phase 3); and an aqueous buffer (pH ~ 4.1) containing 1% v/v of ammonium formate buffer (3) and 40% v/v of methanol (mobile phase 4). The temperature was ambient and the chromatograph chart speed was 30.5 cm/h. Other chromatographic conditions are listed in Table I.

Preparation of Stock and Standard Solutions—The stock solution of acetaminophen (1.0 mg/mL) was prepared by dissolving 100 mg of acetaminophen in methanol to make 100 mL of the solution. A stock solution of chlorpheniramine maleate was prepared by dissolving 50 mg in water to make 100 mL. The standard solutions were prepared as follows: for acetaminophen, 2 mL of the stock solution was diluted to 100 mL with water; for phenylpropanolamine hydrochloride, 50 mg of the powder was dissolved in water to make 100 mL; for dextromethorphan hydrobromide, 40 mg of the powder was dissolved in water to make 200 mL; for a mixture of chlorpheniramine maleate and dextromethorphan hydrobromide, dextromethorphan hydrobromide powder (40 mg) was mixed with 8.0 mL of the stock solution of chlorpheniramine maleate and brought to 100 mL with water. Other solutions of different concentrations were prepared as needed.

Sample Preparation—*Commercial Liquid*—For the acetaminophen assay, a 2.3-mL quantity of the commercial liquid was diluted to 50 mL with water. A 2-mL quantity of this solution was mixed with 2 mL of methanol and diluted to 100 mL with water. For all others, 15 mL of the liquid was diluted to 25 mL with water. If dextromethorphan hydrobromide was to be assayed at 279 nm (Table I), then 7.5 mL of the liquid was diluted to 25 mL with water.

Tablets—Ten tablets were accurately weighed and ground to a fine powder. For the acetaminophen assay, enough powder to represent 50 mg of acetaminophen was mixed with ~40 mL of methanol. The mixture was stirred for 2–3 min, brought to volume (50 mL) with methanol, and filtered. The first 10 mL of the filtrate was rejected, and then a portion was collected and diluted (2 mL to 100 mL) with water. For all others, enough powder to represent two tablets was mixed with ~45 mL of water and stirred for 4–5 min. The mixture was brought to volume (50 mL) with water and filtered. The first 10 mL of the filtrate was rejected, and then a portion of the clear filtrate was collected for assay. If dextromethorphan was to be assayed at 279 nm, then powder representing one tablet was used. The rest of the procedure was as described.

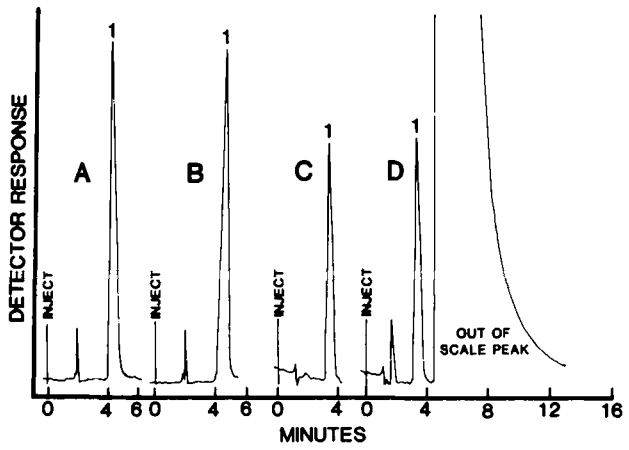

Figure 1—*Sample chromatograms. Key: (A) standard solution of acetaminophen (I); (B) tablet of I; (C) standard solution of phenylpropanolamine hydrochloride (IV); (D) tablet of IV. Peak 1 is the respective drug peak; the out of scale peak in chromatogram D is from acetaminophen.*

[7] Beckman Zeromatic SS-3 pH meter; Beckman Instruments, Fullerton, Calif.

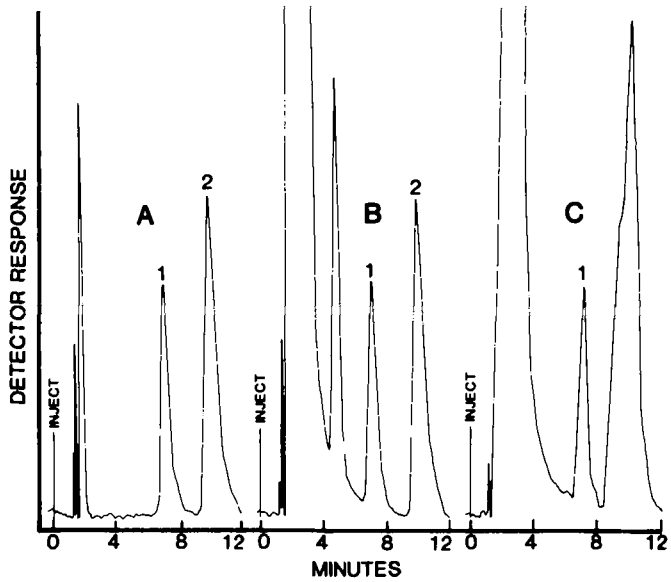

Figure 2—*Sample chromatograms from a standard solution (A), a tablet (B), and a liquid preparation (C) using mobile phase 3 at 262 nm. Key: (1) chlorpheniramine; (2) dextromethorphan. The out of scale peaks in chromatograms B and C are from acetaminophen. The other peak in chromatogram C is from the excipient and dextromethorphan (upper part).*

Content Uniformity of the Tablets (Except Acetaminophen)—A single tablet was ground to a fine powder, mixed with ~23 mL of water, and stirred for 4–5 min. The mixture was brought to volume (25.0 mL) with water and filtered. The first 7 mL of the filtrate was rejected, and then a portion of the clear filtrate was collected for assay. If dextromethorphan hydrobromide was to be assayed at 279 nm, the filtrate was diluted (1:1) with water. It was not considered necessary to determine the content uniformity of acetaminophen (325 mg/tablet) since it represented the bulk of the tablet.

Chromatographic Procedure—The assay sample (20.0 μL) was injected into the chromatograph under the described conditions. For comparison, an identical volume of the standard solution was injected after the assay sample eluted.

Since preliminary investigations indicated that peak heights were directly related to the concentrations (range tested ±50% of the standard solutions), the results were calculated by:

$$\frac{Ph_a}{Ph_s} \times 100 = \text{Percent of the label claim}$$

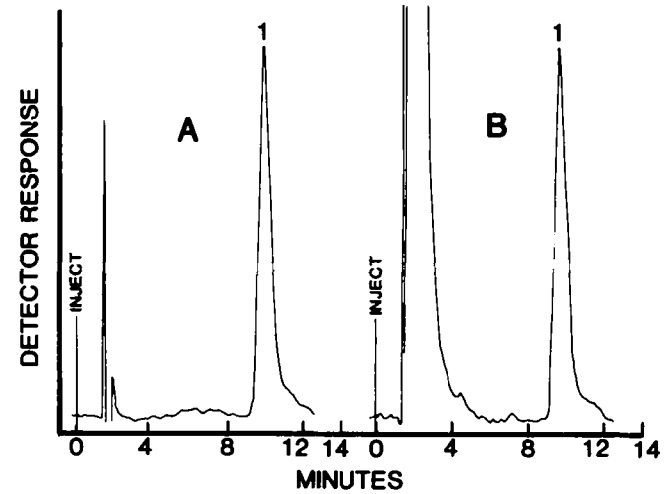

Figure 3—*Sample chromatograms from a standard solution and a liquid dosage form using mobile phase 4 at 279 nm. Key: (1) dextromethorphan. At this wavelength, the peak from chlorpheniramine was very small (peak before peak 1).*

Table II—Assay Results

Dosage Forms	Acetaminophen	Chlorpheniramine	Dextromethorphan	Phenylpropanolamine
		Assay Results, % of the Label Claim[a]		
Commercial Formulations				
Tablet[b]	98.7	99.5[c]	97.1[c]	96.2
Tablet[d]	99.2	99.0[c]	100.2[c]	98.7
Tablets[d] (Different lot)	100.8	99.0[c]	99.4[c]	100.0
Elixir[d]	101.4	99.4[e]	100.5[e]	100.2
Elixir[d] (Different lot)	100.8	99.9[c]	100.5[f]	101.1
Synthetic Mixture[g]	100.8	99.5	100.0	99.2
		Content Uniformity Results		
Tablet 1[b]	—[h]	97.2	99.4	98.1
Tablet 2[b]	—	93.1	100.2	99.7
Tablet 3[b]	—	94.2	97.4	94.4
Tablet 4[b]	—	105.4	103.4	102.5
Tablet 5[b]	—	103.2	101.7	102.1
Tablet 6[d]	—	97.4	96.8	98.5
Tablet 7[d]	—	96.8	97.9	99.1
Tablet 8[d]	—	102.7	102.1	101.8
Tablet 9[d]	—	99.6	99.1	100.0
Tablet 10[d]	—	103.0	102.3	103.1

[a] The label claim per tablet or per 15 mL of the liquid was: acetaminophen, 325 mg; chlorpheniramine maleate, 1 mg; dextromethorphan hydrobromide, 10 mg; phenylpropanolamine hydrochloride, 12.5 mg. [b] Ohm Laboratories; N. Brunswick, N.J. [c] Using mobile phase 3. In tablets of one manufacturer, the excipients interfered with dextromethorphan assay when mobile phase 4 was used. [d] Bristol-Myers; New York, N.Y. [e] Using mobile phase 4 at 262 nm. There was interference with dextromethorphan assay from the excipients when mobile phase 3 was used. [f] Using mobile phase 4 at 279 nm. [g] Contained the same active ingredients as stated under footnote *a* per 500 mg of powder plus 31.5 mg of corn starch and 120 mg of lactose. [h] Not determined.

where Ph_a is the peak height of the assay sample and Ph_s is that of the standard solution, which contained identical concentrations of drugs based on the label claim.

RESULTS AND DISCUSSION

Acetaminophen Assay—The results (Table II) indicate that the developed method can be adopted for the quantitation of acetaminophen in tablets and liquids without any interference from other active ingredients and excipients (Fig. 1A and B). This was expected since the bulk of the tablet was acetaminophen and the liquid contained 325 mg/15 mL. The peak heights were related to the concentrations (range tested, 0.2–0.6 μg) with an *RSD* of 1.2% based on five injections.

Phenylpropanolamine Hydrochloride (IV)—The results (Table II) indicate that the developed method can be used to quantify IV in tablets and liquids. It was tedious to separate phenylpropanolamine from other ingredients, especially from the out of scale peak (Fig. 1D) of acetaminophen. Many different mobile phases were tried, including an aqueous solution buffered with either 0.02 M ammonium acetate or 0.02 M KH_2PO_4, with the pH adjusted to ≥3.2 with acetic acid. In each case, I did not separate from IV, *i.e.*, acetaminophen started eluting before all of the phenylpropanolamine had eluted. It was necessary to decrease the retention time of IV and increase that of I. Initially, the mobile phases had methanol (≤15%) and the pH was >3. Subsequently, only water was used in the mobile phase (to increase the retention time of I), and the pH was adjusted to 2.6 (to decrease the retention time of IV) with phosphoric acid. This mobile phase (Table I), which gave excellent separation (Fig. 1C and D), could be used to analyze IV in tablets and liquids (Table II) and for content uniformity tests. The peak heights were related to the concentrations (range tested, 5–15 μg) with an *RSD* of 1.6% based on five injections.

Chlorpheniramine Maleate (II) and Dextromethorphen Hydrobromide (III)—The assay method can be adapted for the quantitation of chlorpheniramine and dextromethorphan (Table II) in tablets and liquids using mobile phase 3 or 4. Initially, mobile phase 3, similar to one reported in the literature (6), was developed. This mobile phase separated both chlorpheniramine (II) and dextromethorphan (III) from the other tablet ingredients (Fig. 2A and B). In the liquid dosage form, the excipients (probably a preservative not disclosed on the label) interfered (Fig. 2C) with the dextromethorphan assay peak. Therefore, it was necessary to develop another mobile phase for dextromethorphan in the liquid dosage form. Mobile phase 4, similar to that reported previously (3), was used (Fig. 3) to successfully quantify dextromethorphan in the liquid dosage form at 279 nm (wavelength of maximum absorption). By selecting this wavelength, it was possible to increase the sensitivity of the method twofold for the analysis of dextromethorphan. However, mobile phase 4 at 262 nm could also be used to analyze both chlorpheniramine and dextromethorphan (Fig. 4) in the liquid dosage and tablet forms from one manufacturer. In tablets from a different manufacturer, there was interference with the dextromethorphan peak from the excipients (probably the yellow color) not disclosed on the label (Fig. 4C) when mobile phase 4 was used. Although either mobile phase 3 or 4 could be used to analyze II and III for one manufacturer's tablets, only mobile phase 3 could be used to assay the same ingredients in the second manufacturer's tablets. In the liquid dosage form from the second manufacturer, only mobile phase 4 could be used to analyze II and III.

The peak heights were related to concentrations (range tested, 0.4–1.2 μg for II and 4–12 μg for III at 262 nm or 2–6 μg at 279 nm) and the *RSD* values, based on five injections, were 2.4 and 1.9% for II and III, respectively.

The developed method can be adapted for the quantitation of I–IV in pharmaceutical dosage forms using a single column and three different mobile phases. The method can also be used for the determination of the content uniformity of the tablets (Table II). This is important since the quantity of chlorpheniramine maleate was only 1 mg in a >500-mg tablet.

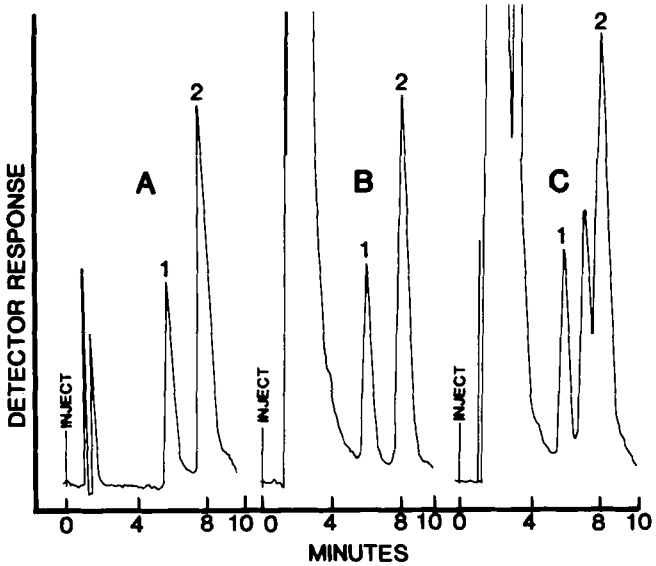

Figure 4—*Sample chromatograms from a standard solution, a liquid dosage form, and a tablet using mobile phase 4 at 262 nm. Key: (1) chlorpheniramine; (2) dextromethorphan. At this wavelength, chlorpheniramine could also be assayed. In chromatogram C, the excipients from the tablet interfered with the peak of dextromethorphan.*

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Determination of Codeine in Human Plasma by Reverse-Phase High-Performance Liquid Chromatography

V. NITSCHE *x and H. MASCHER

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Abstract □ A high-performance liquid chromatographic (HPLC) method for the determination of codeine in human plasma is described. The specific, precise, and sensitive method can be used to determine plasma codeine levels after administration of therapeutic doses of codeine. After purification on a C_{18} extraction column, codeine in the form of hydrochloride is eluted. After addition of the internal standard, the codeine is separated on a reverse-phase C_{18} column using a slightly alkaline mobile phase and is then determined by UV detection. The analysis takes 3.5 min per run; the limit of detection is ~3 μg/L for a 50-μL loop and 800 μL of plasma. The absolute recovery is 98.4 ± 6.7% (n = 14) in the 10-300-μg/L range. Within the range, the calibration curve is linear.

Keyphrases □ Bioavailability—codeine, human plasma, HPLC □ Codeine—bioavailability, HPLC □ HPLC—bioavailability of codeine

Numerous methods for the detection of codeine are reported in the literature, including GC (1-5), GC-MS (6-9), TLC (10-12), RIA (3, 13-15), radioactive labeling (16, 17), and several high-performance liquid chromatographic (HPLC) methods. However, with one exception (18), these have not been used to detect codeine in plasma (19-21).

Some of the detection methods are not sufficiently sensitive or selective and others require sophisticated equipment (GC-MS) or specialized techniques (RIA). Our objective was to develop an HPLC method which is well suited for routine determination of codeine in plasma.

EXPERIMENTAL SECTION

Material and Methods—A liquid chromatograph[1] equipped with a UV detector[2] was used. The loop volume was 50 μL, but could be increased to 150 μL without affecting separation performance. Membrane filters[3] (pore size, 0.45 μm) and a 10-μL syringe[4] were also used.

Codeine hydrochloride[5] and diazepam[5] (internal standard) were used as supplied. Methanol[6] and ammonium carbonate[7] were AR grade. The C_{18} extraction columns[6] had a volume of 1 mL. Solutions of 0.1 M HCl, 1 M ammonium hydroxide, methanol-0.1 M ammonium hydroxide (20:80; mixture A), and methanol-0.1 M HCl (50:50; mixture B) were prepared. The internal standard solution was ~200 μg of diazepam/20 mL of methanol.

The buffer (pH 8.9) was made with 80.5 mL of 0.1 M borate solution (1.237 g of boric acid in 10 mL of 0.1 M NaOH) and 19.5 mL of 0.1 M HCl. Distilled water was used throughout.

The mobile phase was methanol-0.1 M ammonium carbonate (70:30). The mixture was used within 2-3 d, because tailing at the codeine peak was sometimes observed with older mixtures.

The chromatographic conditions included a 250 × 4-mm column[8], filled in-house[9] with Polygosil C 18, 7.5 μm; the flow rate was 2.0 mL/min; the column oven temperature was 45°C; the detector wavelength was 220 nm, 0.01 AUFS, time constant 1 min; the injection volume was 50-150 μL by loop; and the recorder advance was 10 mm/min.

Sample Preparation—Plasma (citrate anticoagulant) was filtered through a 0.45-μm membrane filter and 0.8 mL was mixed with 0.3 mL of buffer (pH 8.9). The mixture was quantitatively transferred into a C_{18} extraction column[6] and centrifuged at 500×g for 1-2 min; the plasma passed completely through the tube. To eliminate interfering substances, the extraction column was washed with 1 mL of 0.1 M HCl, 1 mL of mixture A, and 0.3 mL of 0.1 M HCl (each wash was followed by a 1-min centrifugation at 500×g). The eluates were discarded. Codeine was then eluted with 300 μL of mixture B. With commonly used centrifuges, 10-40 extraction columns can be eluted at the same time, which shortens the analysis time. The ammonium hydroxide solution (~30 μL, pH >8) and 5 μL of the internal standard solution were added to the eluate. After thorough mixing, the loop was rinsed and filled with ~100 μL (~180 μL if a 150-μL loop was used) of this solution.

Standard Preparation—Samples (2, 8, 20 and 40 μL) of a solution containing 4 ng of codeine base/μL (weighed as codeine hydrochloride, dissolved in water and diluted accordingly) were added to 0.8-mL plasma blanks. The remainder of the procedure is as described in *Sample Preparation*.

The quotients of the peak areas (codeine-internal standard) of the samples were compared with a calibration curve.

Bioavailability Study—In a randomized crossover study, bioavailability was determined with six healthy male volunteers (mean age, 46.8 ± 15.2; mean weight, 74.1 ± 9.7 kg; and mean height 178.3 ± 6.25 cm). The subjects underwent medical examinations and laboratory tests which showed them to be in good health. All subjects had been informed of the investigation procedures and had expressed their agreement in writing.

The subjects received two different oral codeine-doxycycline preparations on different days. The test preparations were 100 mg of doxycycline with 30 mg of codeine base as the phosphate in diffusion pellets (preparation 1)[10] and 100 mg of doxycycline with 30 mg of codeine base as resinate (preparation 2)[11]; both were sustained-release preparations. The dose was two capsules per

[1] Model 8000; Spectra Physics, Santa Clara, Calif.
[2] Spectromonitor III; Laboratory Data Control, Riviera Beach, Fla.
[3] Sartorius; Göttingen, F.R.G.
[4] Hamilton, Bonaduz, Switzerland.
[5] Gerot Pharmazeutika, Vienna, Austria.
[6] Baker, Deventer, The Netherlands.
[7] Merck.
[8] Hibar RT; Merck.
[9] Machery/Nagel, Düren, F.R.G.
[10] Batch 4PA-222, Doxitussin; Gerot Pharmazeutika.
[11] Batch 810238, Vibratussal; Pfizer, Karlsruhe, F.R.G.

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