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Simultaneous GLC Analysis of Salicylamide, Phenylpropanolamine Hydrochloride, Caffeine, Chlorpheniramine Maleate, Phenylephrine Hydrochloride, and Pyrilamine Maleate in Capsule Preparations

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Abstract □ A GLC method is described for the quantitative determination of salicylamide, phenylpropanolamine hydrochloride, caffeine, chlorpheniramine maleate, phenylephrine hydrochloride, and pyrilamine maleate. The sample was dissolved in ethanol, and an aliquot of the solution was brought to dryness and treated with 0.1 ml of 4-(dimethylamino)pyridine in pyridine–acetic anhydride (1:1). The components were isolated and measured by applying 1 μl of the reaction mixture to a chromatograph equipped with a flame-ionization detector and fitted with 8% OV-101 glass columns. The accuracy was good. Dicyclohexylphthalate was used as the internal standard.

Keyphrases □ GLC, flame ionization—simultaneous analysis of salicylamide, phenylpropanolamine, caffeine, chlorpheniramine, phenylephrine, and pyrilamine, capsule preparations □ Salicylamide—GLC analysis, capsule preparations □ Phenylpropanolamine hydrochloride—GLC analysis, capsule preparations □ Caffeine—GLC analysis, capsule preparations □ Chlorpheniramine maleate—GLC analysis, capsule preparations □ Phenylephrine hydrochloride—GLC analysis, capsule preparations □ Pyrilamine maleate—GLC analysis, capsule preparations

GLC procedures have been used extensively for the determination of salicylamide (I), phenylpropanolamine hydrochloride (II), caffeine (III), chlorpheniramine maleate (IV), phenylephrine hydrochloride (V), and pyrilamine maleate (VI) as drug substances and in certain combinations, but no single method has been developed for their simultaneous quantitation. In the preparation used in this study, phenylephrine was the only active ingredient that had to be derivatized before GLC. The other components could have been chromatographed directly using a suitable liquid phase (1, 2).

The determination of phenylephrine as the trifluoroacetate derivative (3) was not applicable to this preparation. The narrow margin allowed for temperature and reaction time was not compatible with those components that gave derivatives with the same reagent. Hista and Laubach (4) showed that a combination of phenylephrine, phenyltoloxamine, chlorpheniramine, and phenylpropanolamine could be chromatographed as trimethylsilyl derivatives using bis(trimethylsilyl)acetamide. However, following the same procedure during a preliminary analysis, the chromatogram exhibited interfering additional peaks, which made the determination of some components difficult.

In this work, the problems encountered were resolved by preparing acetyl derivatives of I, II, and V and using a mixture of 4-(dimethylamino)pyridine, pyridine, and acetic anhydride as the acetylating reagent. Connors and Albert (5) reported that 4-(dimethylamino)pyridine is an excellent catalyst for the formation of acetyl derivatives. It promoted the acetylation of various hydroxyl groups under milder conditions when compared with pyridine alone (6).

EXPERIMENTAL

Apparatus—The gas chromatograph[1] was equipped with a flame-ionization detector and an electronic integrator. The glass-coil columns, 1.8 m × 2 mm, were packed with 8% OV-101 on 80–100-mesh Chromosorb W-HP.

Reagents[2]—4-(Dimethylamino)pyridine (1.2%) in pyridine was prepared weekly. Acetic anhydride also was used.

Solution Preparation—Standard solutions[3] were prepared by weighing accurately ~58, 38, 72, and 49 mg of II, IV, V, and VI, respec-

Table I—Response Factors of I–VI with Respect to the Internal Standard [a]

Compound	Response Factor	*RSD, %*
I	0.890	1.83
II	0.995	1.11
III	0.470	1.41
IV	0.677	1.28
V	0.624	1.64
VI	0.346	2.18

[a] Five solutions were prepared and 15 measurements were made for each compound.

[1] Hewlett-Packard model 5048-A.
[2] All reagents and the internal standard were from Merck, Schuchardt, West Germany.
[3] All standard solutions were prepared from BP raw materials standardized against USP and NF reference standards.

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Table II—Precision and Accuracy of the Standard Solution

Trial	Recovery, % I	II	III	IV	V	VI
1	98.3	99.7	101.0	98.1	98.6	100.3
2	99.5	99.9	101.2	97.3	99.4	98.7
3	98.9	99.7	98.7	98.5	97.2	102.4
4	98.7	99.3	99.9	101.9	101.5	97.9
5	101.9	102.6	98.3	100.0	97.6	99.2
6	102.0	97.6	98.7	97.5	99.2	97.1
7	100.3	99.6	98.7	97.3	101.7	102.0
8	99.7	98.5	99.1	98.5	97.9	97.7
Mean relative error, %	1.11	0.85	0.90	1.03	1.34	1.61
$\bar{X}$	99.9	99.6	99.5	98.6	99.1	99.4
SD	1.33	1.43	1.12	1.54	1.72	1.99
RSD	1.34	1.44	1.13	1.56	1.73	1.99

tively, separately into 25-ml volumetric flasks and dissolving the solid and diluting the solution to 25 ml with ethanol. The internal standard solution was prepared by dissolving ~80 mg of dicyclohexylphthalate in 50 ml of chloroform.

Chromatography—The oven was programmed at 9°/min from 170 to 270° after an initial 3 min; the injection port and detector temperatures were 250 and 290°, respectively. The nitrogen carrier flow rate was 15 ml/min. Hydrogen and air flow rates were adjusted to give maximum response. The attenuation of 13 was reduced to 9 after 10 min.

Standard Preparation—About 240 mg of I and 40 mg of III were weighed accurately into a 50-ml volumetric flask. Standard solutions of II (4 ml), IV (1 ml), V (2 ml), and VI (4 ml) and 5 ml of the internal standard solution were added. The solution was brought to volume with ethanol. A 0.5-ml aliquot was evaporated in a 1-ml glass vial[4] with a gentle nitrogen stream at room temperature.

The residue was allowed to react with 0.1 ml of a 1:1 (v/v) mixture of

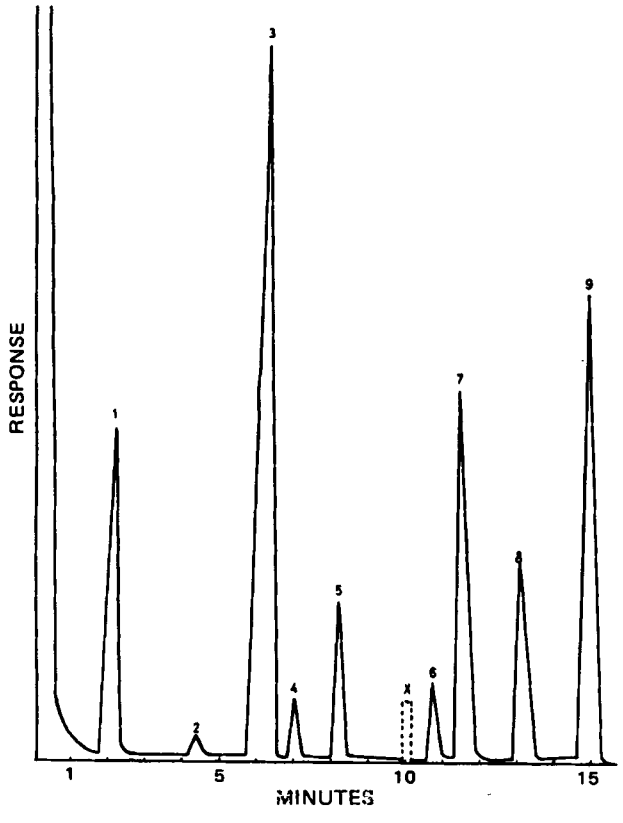

Figure 1—*Representative gas chromatogram. Key: 1 and 2, reagent peaks; 3, salicylamide; 4, phenylpropanolamine; 5, caffeine; 6, chlorpheniramine; 7, phenylephrine; 8, pyrilamine; and 9, internal standard.*

[4] Pierce Chemical Co., Rockford, Ill.

Table III—Precision Study of a Production Lot of Capsules

Parameter	Compound I	II	III	IV	V	VI
Theoretical content, mg/capsule	240	9.25	40	1.5	5.75	7.8
$\bar{X}^a$	241	9.30	40.6	1.56	5.82	7.91
RSD, %	1.41	1.50	1.12	1.34	1.88	1.83

[a] n = 10 determinations.

1.2% 4-(dimethylamino)pyridine solution and acetic anhydride (mixed just before use) for 18 ± 1 min at 40° in a screw-capped vial. One microliter of the reaction mixture was injected.

Sample Preparation—The contents of a representative number of capsules[5] were mixed, and an aliquot of powder corresponding to ~240 mg of I was weighed accurately into a 50-ml volumetric flask. About 30 ml of ethanol was added, and the flask was heated in a water bath at 80° for 15 min. The flask then was shaken mechanically until it was cool. Five milliliters of the internal standard solution was pipetted into the flask, and ethanol was added to the mark. An aliquot of the solution was centrifuged, and 0.5 ml of the clear supernate was treated as described for the standards.

RESULTS AND DISCUSSION

The performance of each component was evaluated by measurement of the response factor, the ratio of the peak area/weight of the substance to the peak area/weight of the internal standard (Table I). The results were obtained by preparing five solutions for each component having the same concentration range as in the commercial preparation. Each solution was analyzed five times.

When the concentration of each component was varied between 80 and 120% of the label claim, the response factor of salicylamide increased by ~3% with the same reproducibility. The pyrilamine maleate response factor decreased by ~5%, and the percent relative standard deviation of solutions of different concentrations was 3.48% compared to 2.18% for one concentration. The remaining components showed similar response factors and reproducibility as for solutions of one concentration.

The acetylation reaction was completed in 5 min for phenylephrine and phenylpropanolamine at room temperature, while salicylamide gave two peaks. Heating the reaction mixture at 40° for 18 min resulted in complete acetylation and a single peak for salicylamide (Fig. 1). The other components, III, IV, and VI, did not undergo nucleophilic catalysis since they did not have active hydrogen atoms. Preliminary injections of the reagent mixture alone after heating at 40° for 18 min showed two peaks at 1.67 and 4.65 min, which did not interfere. Prolonging the heating time beyond 30 min or maintaining the temperature at 90° for 5 min caused a third peak to appear at 13.96 min, which also did not interfere. The reaction mixture of all components was analyzed over a 3-hr period without a significant drifting of the response factor.

The accuracy and precision of the procedure were estimated by analyzing a standard solution containing all six active ingredients plus the internal standard. This solution was determined eight times (Table II). The precision study also was carried out by analyzing capsules of a production batch. The sample was injected 10 times (Table III). The data presented, including the reproducibility, accuracy, and response factor, establish the validity of the method. The procedure is relatively simple and rapid. The six active ingredients were chromatographed and determined in 17 min.

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[5] Each capsule contained I (240 mg), II (9.25 mg), III (40 mg), IV (1.5 mg), V (5.75 mg), and VI (7.8 mg).