Determination of Camphor and Menthol in Pharmaceutical Products by Gas Chromatography

By KHALID S. BAHJAT†

A simple, reliable method for the quantitative determination of camphor and menthol in pharmaceutical preparations has not been available until now. A practical gas chromatography method has been developed for the simultaneous quantitative determination of camphor and menthol in pharmaceutical preparations, using a flame ionization detector, Apiezon L column, and an internal standard. The method was successfully applied to both cream and liquid preparations. It is a simple, rapid, and reliable method with an accuracy of ±5 per cent.

SINCE many pharmaceutical preparations contain camphor and menthol, it is desirable to use a method which is both fast and accurate for the simultaneous determination of camphor and menthol. The presently used methods, described in the "Official Methods of Analysis of the Association of Official Agricultural Chemists" (1) are time consuming, requiring at least 4.5 hours for camphor and 2 hours for menthol.

The successful separation of menthol-menthone stereoisomers (2–5) and camphor (6) by gas chromatography suggests that it might be used for the simultaneous determination of camphor and menthol in pharmaceutical preparations. Preliminary work showed that the method is simple and rapid. Also it is possible to determine camphor and menthol at concentrations as little as 0.1%.

EXPERIMENTAL

Apparatus.—F and M model 609 flame ionization gas chromatograph[1] equipped with Disc chart integrator.[2] Nitrogen was the carrier gas. Flow rates were measured by the instrument flow meters. The carrier gas pressure was regulated to approximately 30 psig to maintain a flow rate of about 50 ml. per minute. The air flow rate was 365 ml. per minute, while the hydrogen flow rate was 47 ml. per minute. The column was stainless steel, 8 ft. long, with 0.25 in. O.D. The Hamilton 10-μl. syringe,[3] with Chaney adaptor, was used for sample injection.

Column Packing.—In the search for a suitable liquid phase, Apiezon L, silicone gum rubber, silicone oil 200, Quadrol-Saib, and Carbowax 20M were examined. Finally, 20% Apiezon L on Chromosorb W was selected, since it resolves camphor and menthol completely and the retention times are short—an important factor when many samples are to be assayed.

Chromatography.—The column was conditioned at 250° for 24 hours with a nitrogen flow rate of 50 ml. per minute. The column was not connected to the detector during this period. When running analyses, the column was maintained at 160°, detector block at 240°, and injection port at 274°. Sample size range was from 2.0 to 6.0 μl.

Calibration.—The internal standard technique introduced by Ray (7) was used since it was found to be the most accurate, ±1% being easily achieved. Calibration curves were obtained by measuring the ratio of the peak areas of camphor to internal stand-

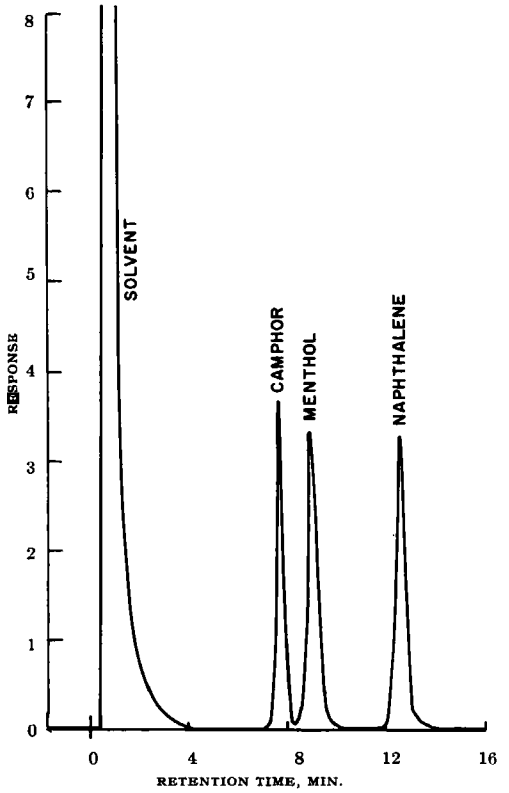

Fig. 1.—Gas chromatogram of an alcoholic solution of camphor, menthol, and naphthalene.

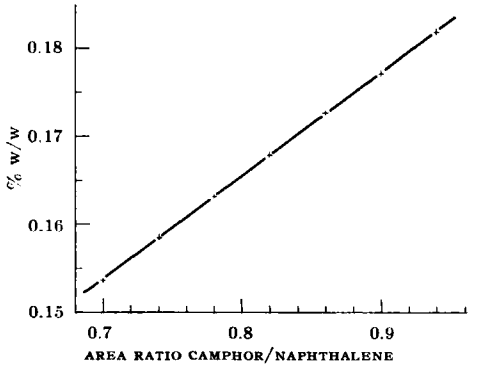

Fig. 2.—Calibration curve for camphor determination.

Received February 21, 1963, from Quality Control Laboratories, Miles Laboratories, Inc., Elkhart, Ind.
Accepted for publication March 29, 1963.
† Present address: Xerox Corp., Webster, N.Y.
[1] F and M Scientific Corp., Avondale, Pa.
[2] Disc Instruments, Inc., Santa Ana, Calif.
[3] Hamilton Co., Inc., Whittier, Calif.

TABLE I.—TYPICAL RECOVERY OF CAMPHOR AND MENTHOL

Menthol			Camphor		
Taken, %	Found, %	Recovered, %	Taken, %	Found, %	Recovered, %
0.150[a]	0.150	100.0	0.173	0.176	101.6
0.175[a]	0.160	96.5	0.500	0.480	96.0
0.200[a]	0.192	96.0	0.200	0.199	99.5
0.300[a]	0.303	101.0	0.300	0.303	101.0
0.400[a]	0.400	100.0	0.225	0.230	102.0
0.100	0.101	101.0	0.100	0.097	97.0
0.150	0.143	95.3	0.250	0.247	98.8
0.250	0.242	97.0	0.150	0.152	101.2
0.350	0.357	102.0	0.400	0.392	98.0
0.500	0.485	97.0	0.350	0.364	104.0
		Av. 98.53%			Av. 99.93%
		Range 95.3 to 102.0%			Range 96.0–104.0%

[a] Cream samples (others are liquid samples).

ard, or menthol to internal standard and plotting the ratio against the percentage of camphor or menthol. This provided a straight line plot.

Naphthalene was selected as an internal standard after examining cetyl alcohol, ethylbenzene, naphthylamine, decyl alcohol, dodecyl alcohol, and eicosyl alcohol. Naphthalene was purified by sublimation before it was used in the experiment. Alcohol solutions having known amounts of camphor, menthol, and naphthalene were used to construct the calibration curves.

Sample Preparation.—(*a*) The liquid sample was injected directly into the gas chromatograph after the addition of the internal standard. (*b*) For the cream sample, a known weight of the sample was extracted with a known volume of 3A ethanol which contained a known amount of the internal standard. Then the alcoholic solution was injected in the gas chromatograph.

The amount of naphthalene, added to both the liquid sample and the alcoholic sample, should be the same as the amount added to the synthetic samples used in construction of the calibration curves.

RESULTS AND DISCUSSION

Under the conditions chosen, retention times for camphor, menthol, and naphthalene were 7.6, 8.8, and 12.4 minutes, respectively (Fig. 1).

Standard solutions, containing known concentrations of the component (camphor and menthol) being determined, were prepared; the ratios of the peak area of this material to the internal standard were measured. Calibration curves were then obtained (Figs. 2 and 3).

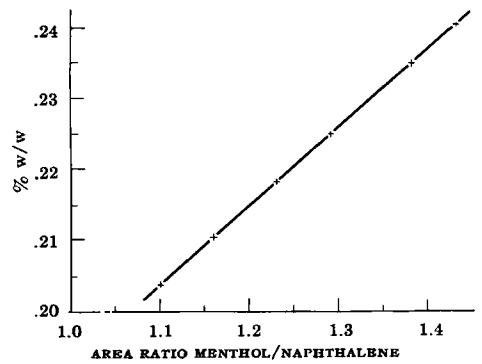

Fig. 3.—Calibration curve for menthol determination.

TABLE II.—PRECISION OF THE METHOD

Menthol		Camphor	
Found, % w/w	Dev. from Mean	Found, % w/w	Dev. from Mean
0.150	+0.003	0.203	+0.003
0.151	+0.004	0.194	−0.006
0.144	−0.003	0.199	−0.001
0.143	−0.004	0.198	−0.002
0.146	−0.001	0.202	+0.002
0.151	+0.004	0.202	+0.002
Av. 0.147		Av. 0.200	

Accuracy.—Samples of cream and liquid preparations were prepared accurately, each with known amounts of camphor and menthol, and were examined under the same conditions as those for camphor and menthol. The results are shown in Table I and are the average of duplicate determinations. The recovery for menthol was 98.53% and for camphor was 99.93%.

Precision.—The precision obtainable with the method applied to duplicate determinations of a synthetic liquid sample is illustrated in Table II. With the camphor, a standard deviation of 1.65% with 95% confidence intervals, ±3.24%, was obtained on six replicate runs, while the menthol results had a standard deviation of 2.45% and 95% confidence intervals, ±4.80%.

SUMMARY

It has been shown that gas chromatography offers a reliable and rapid method for the determination of camphor and menthol simultaneously in cream and liquid pharmaceutical preparations. This assay requires about 30 minutes, and the method is applicable to materials containing concentrations as low as 0.1% (w/w).

REFERENCES

(1) "Official Methods of Analysis of the Association of Official Agricultural Chemists," 9th ed., Association of Official Chemists, Washington, D. C., 1960, pp. 539, 543.
(2) Tagaki, W., and Mitsui, T., *Bull. Agr. Chem. Soc. Japan*, 24, 217(1960).
(3) Moor, D. R., and Kossosy, A. D., *Anal. Chem.*, 33, 1437(1961).
(4) Poicars, P. J., and Johnston, V. D., *ibid.*, 33, 1748 (1961).
(5) Houlihan, W. J., *ibid.*, 34, 1886(1962).
(6) Hanada, Y., and Kitajima, M., *J. Chem. Soc. Japan*, 80, 1272(1959).
(7) Ray, N. H., *J. Appl. Chem.*, 4, 21(1954).