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Gas Chromatographic Assay for Benzyl Alcohol and Phenylethyl Alcohol in Pharmaceutical Formulations

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Abstract □ A gas chromatographic method has been developed for the determination of benzyl alcohol and phenylethyl alcohol in pharmaceutical formulations. The method employs a column made of a silanized copolymer of ethylvinylbenzene–divinylbenzene and uses cyclohexanol as the internal standard. The method is applicable to various formulations which contain either benzyl alcohol or phenylethyl alcohol or the combination. Each analysis requires 10 min. This method showed a relative standard deviation of ±0.85% for benzyl alcohol and ±1.41% for phenylethyl alcohol.

Keyphrases □ Benzyl alcohol—analysis in dosage forms □ Phenylethyl alcohol—analysis in dosage forms □ Cyclohexanol—internal standard □ GLC—analysis

Pharmaceutical preparations frequently contain benzyl alcohol and/or phenylethyl alcohol as preservatives. Gas chromatographic methods for benzyl alcohol have been reported by Gallo and Chiesa (1), by Ragone and LaFata (2), and by Rhodes *et al.* (3), using columns other than a silanized copolymer of ethylvinylbenzene–divinylbenzene.[1] Burger (4) has reported the retention times of a large number of organic compounds on this copolymer; however, neither benzyl alcohol nor phenylethyl alcohol was included. This report describes a simple and rapid gas chromatographic method for the assay of benzyl alcohol and phenylethyl alcohol, singly or in combination, using a silanized copolymer of ethylvinyl–divinylbenzene column.

EXPERIMENTAL

Apparatus—A Micro-Tek MT 220 gas chromatograph equipped with a dual hydrogen-flame ionization detector was used for the experimental work. The 76.2-cm. (2.5-ft.) × 0.31-cm. (1/8-in.) o.d. stainless steel column was packed with a silanized copolymer of ethylvinylbenzene–divinylbenzene, 80–100 mesh. The column was operated at a temperature of 228° and the injection port was maintained at 275°. A Hamilton 10-μl. syringe with a 7.6-cm. (3-in.) needle was employed for injection of sample. The hydrogen gas flow was 48 ml./min., the air 1.2 cu. ft./hr., and the helium 120 ml./min.

Solutions and Reagents—A standard stock solution of benzyl alcohol and phenylethyl alcohol was prepared by weighing accurately 200 mg. of both benzyl alcohol and phenylethyl alcohol into a 200-ml. volumetric flask and diluting to volume with distilled

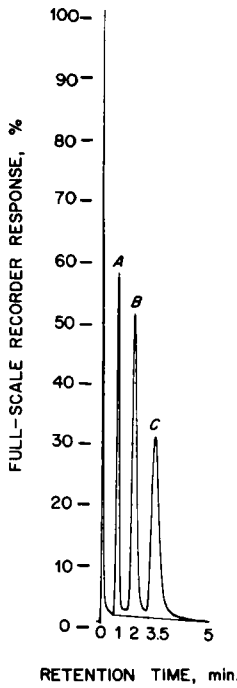

Figure 1—*Typical chromatogram of: A, cyclohexanol; B, benzyl alcohol; and C, phenylethyl alcohol.*

[1] Porapak Q. S., Waters Associates, Framingdam, Mass.

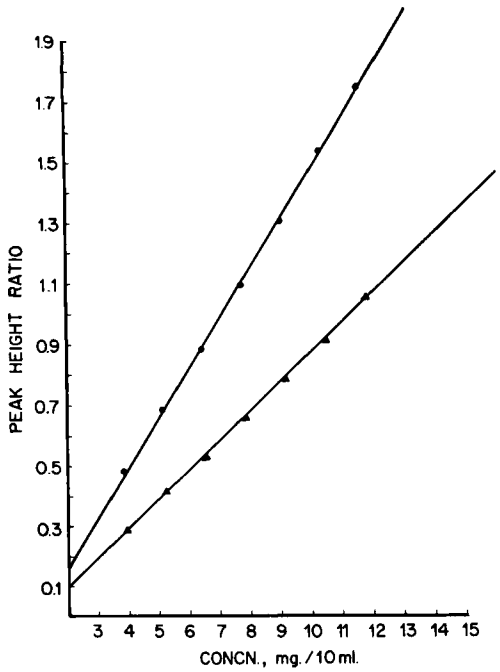

Figure 2—*Peak height ratios as a function of concentration. Key:* ●, *benzyl alcohol;*▲, *phenylethyl alcohol.*

water. Cyclohexanol was used as the internal standard and was prepared by diluting 0.5 ml. of cyclohexanol to 100 ml. with water.

Procedure—Exactly 4, 5, 6, 7, 8, and 9 ml. of the standard stock solution were transferred to separate 10-ml. volumetric flasks, and exactly 1.0 ml. of the cyclohexanol internal standard was added and the solutions diluted to volume with water.

The sample was diluted so that it contained about 7 mg. of either benzyl alcohol and/or phenylethyl alcohol and exactly 1.0 ml. of the cyclohexanol internal standard/10 ml. of aqueous solution. One microliter of the standard and sample solutions was injected using the operating conditions already described. The order of elution is cyclohexanol, benzyl alcohol, and phenylethyl alcohol and a sample chromatogram is seen in Fig. 1. The peak height ratios of benzyl alcohol to cyclohexanol and phenylethyl alcohol to cyclohexanol were calculated and plotted *versus* the concentrations of the standard solutions, and a typical plot is illustrated in Fig. 2. The peak height ratios of the sample solutions were obtained and

Table I—Benzyl Alcohol Recoveries

Sample	Initial Assay, mg.	+ Standard Added, mg.	Theoretical	Found	% of Theoretical
1	7.58	1.29	8.87	8.85	99.8
2	7.52	1.29	8.81	8.98	101.9
3	5.54	1.29	6.83	6.98	102.2
4	5.66	1.29	6.95	7.05	101.4
5	5.70	1.29	6.99	7.05	100.8
6	7.20	1.29	8.49	8.54	100.6
7	7.64	1.29	8.93	9.04	101.2
8	7.52	1.29	8.81	8.79	99.8
9	5.74	1.15	6.89	6.88	99.9
10	5.82	1.15	6.97	7.03	100.9
Relative *SD* ±0.85%					

Table II—Phenylethyl Alcohol Recoveries

Sample	Initial Assay, mg.	+ Standard Added, mg.	Theoretical	Found	% of Theoretical
1	7.39	1.31	8.70	8.70	100.0
2	7.32	1.31	8.63	8.86	102.7
3	4.90	1.31	6.21	6.26	100.8
4	4.92	1.31	6.23	6.32	101.4
5	4.85	1.31	6.16	6.29	102.1
6	6.85	1.31	8.16	8.28	101.5
7	7.30	1.31	8.61	8.68	100.8
8	7.22	1.31	8.53	8.45	99.1
9	4.80	1.18	5.98	5.88	98.3
10	4.93	1.18	6.11	6.07	99.3
Relative *SD* ±1.41%					

the concentrations of the benzyl alcohol and phenylethyl alcohol were determined from the graphs.

RESULTS AND DISCUSSION

Tables I and II show results of 10 solutions of formulations which contained both benzyl alcohol and phenylethyl alcohol. These samples were assayed, then a known concentration of standard was added to each and the samples reassayed. The relative standard deviation was ±0.85% for benzyl alcohol and ±1.41% for phenylethyl alcohol.

It was found that this packing does not require lengthy conditioning periods, retention times remain constant from column to column, and the calibration curves obtained on different days are practically superimposable.

The experience has been that with the concentration of internal standard indicated, the calibration curve is linear from 3 to 15 mg. of benzyl alcohol and/or phenylethyl alcohol/10 ml. of final solution. Most of the samples fell within this concentration range; however, by changing the concentration of the internal standard, either much lower or higher concentrations of benzyl alcohol and phenylethyl alcohol may be determined.

SUMMARY

A gas chromatographic method for the determination of benzyl alcohol and/or phenylethyl alcohol in various pharmaceutical preparations has been developed. The procedure involves dilution with water, addition of cyclohexanol as the internal standard, and chromatography using a 76.2-cm. (2.5-ft.) × 0.31-cm. (1/8-in.) silanized copolymer of ethylvinylbenzene–divinylbenzene column. The relative standard deviation was ±0.85% for benzyl alcohol and ±1.41% for phenylethyl alcohol. After the calibration curve is obtained, each analysis requires about 10 min.

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