Gas Chromatographic Determination of Glycerol Guaiacolate in Pharmaceutical Preparations

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Abstract □ A sensitive gas chromatographic method was developed for the assay of glycerol guaiacolate contained in various pharmaceutical preparations. The method, based upon the chromatography of the trimethylsilyl derivative, has good precision and the desired specificity. A choice of columns and operating conditions is given in order to facilitate assaying a variety of formulations.

Keyphrases □ Glycerol guaiacolate dosage forms—analysis □ Salicylate-glycerol guaiacolate dosage forms—analysis □ GLC—analysis

Glycerol guaiacolate, 3-(*o*-methoxyphenoxy)-1,2-propanediol, is used in various asthma, cough-preventive, and similar preparations as the expectorant-antitussive ingredient.

Its determination is difficult since it is usually found in formulations containing several ingredients and a satisfactory specific color reaction has not been reported. A separation of the compound from the other ingredients is generally required prior to assay. Among the assay methods reported in the literature are: a thin-layer method (1), a paper chromatographic method (2, 3), and a gas chromatographic (4) method *via* the acetate derivative, with all of the methods being time consuming even though they do have a measure of specificity. The gas chromatographic method requires a 90-min. esterification step in addition to extraction.

A simpler and more rapid method was needed in the author's laboratory for the assay of the compound in a variety of formulations, and it was found that the most suitable one was a gas chromatographic determination *via* the trimethylsilyl derivative. Using this approach, it was found that ingredients commonly found associated with glycerol guaiacolate such as ephedrine sulfate, theophylline, chlorpheniramine maleate, and phenobarbital did not interfere. Interference from salicylates is eliminated by extracting glycerol guaiacolate from an alkaline solution with chloroform prior to formation of the derivative.

For the chromatography of the trimethylsilyl derivative, either a 45.72-cm. (1.5-ft.) column packed with 5% SE-52 on diatomaceous earth[1] or a 152.4-cm. (5-ft.) column packed with 5% SE-30 on diatomaceous earth[1] is satisfactory for use with a flame ionization-equipped gas chromatograph. The trimethylsilyl derivative of *n*-butyl-*p*-hydroxybenzoate is used as an internal standard when assaying for glycerol guaiacolate. Typical chromatograms are shown in Figs. 1 and 2. The retention times for the glycerol guaiacolate trimethylsilyl derivative are 8.5 min. on the SE-30 column at 150° and 7.5 min. on the SE-52 column at 130°. The *n*-butyl-*p*-hydroxybenzoate derivative has a retention time of 5.5 min. on the SE-30 column at 150° and 5.5 min. on the SE-52 column at 130°.

[1] Gas Chrom Q, Applied Science Laboratories, Inc., State College, Pa.

EXPERIMENTAL

Instrumentation—For the chromatography of the derivative, a gas chromatograph equipped with flame ionization detectors (Aerograph 1520, Varian) and operated in the isothermal mode is suitable. Either a 152.71-cm. (5-ft.) long, 0.38-cm. (0.125-in.) internal diameter stainless steel column packed with 5% SE-30 on diatomaceous earth or a 46.03-cm. (1.5-ft.) long, 0.38-cm. (0.125-in.) internal diameter stainless steel column packed with 5% SE-52 on diatomaceous earth is used. The SE-30 column is used with an oven temperature of 150° and the SE-52 column is operated at 130°. In either case, the injector temperature is 225° and the detector temperature is 250° with helium as the carrier gas at a flow rate of about 50 ml./min. The detector response is recorded on a strip-chart recorder (Sargent S.R.) having a 1.0-mv. span and a chart speed of 0.2 in./min.

Reagents—Commercial catalyst reagent (Tri-Syl, Pierce Chemical Co., Rockford, Ill.), acetone, chloroform, saturated aqueous sodium chloride solution, sodium hydroxide, *n*-butyl-*p*-hydroxybenzoate (Eastman Kodak), and anhydrous sodium sulfate. All chemicals are reagent grade and the solvents are redistilled.

Relative Responses of the Trimethylsilyl Derivatives of Glycerol Guaiacolate and *n*-Butyl-*p*-hydroxybenzoate—From a chloroform solution of glycerol guaiacolate (concentration of 10 mg./ml.), transfer aliquots representing 30, 40, and 50 mg. of glycerol guaiacolate to separate 15-ml. centrifuge tubes. To each add 40 mg. of *n*-butyl-*p*-hydroxybenzoate (from a chloroform solution) and evaporate to dryness on a steam bath under a gentle current of air. Add to each tube 0.5 ml. of Tri-Syl reagent, stopper, mix thoroughly, and allow to stand for about 2–3 min. Dilute each to 10 ml. with acetone and mix thoroughly.

Inject a 2.0-μl. aliquot of each solution into the chromatograph, using either the SE-30 or SE-52 column under the conditions previously described. Record the detector response using a chart speed

Table I—Recovery of Glycerol Guaiacolate from Prepared Mixtures

Batch No.	Glycerol Guaiacolate Added, mg.	Recovery, %
1	100	98.5
1	100	100.0
2	100	98.1
2	100	101.0
3	100	98.0
3	100	99.0

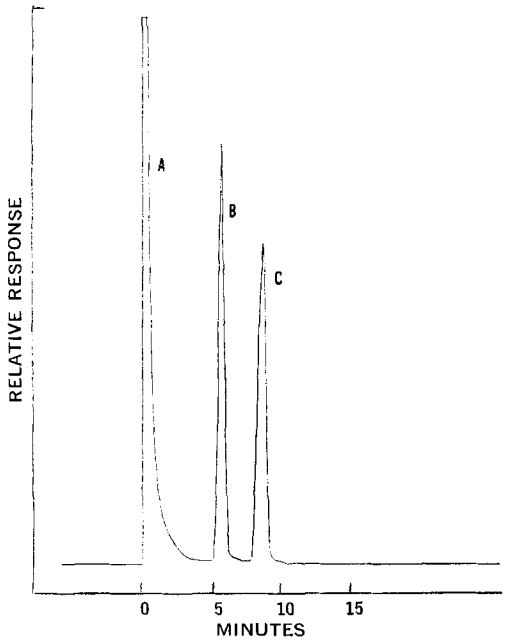

Figure 1—*Gas chromatogram of TMS derivatives of glycerol guaiacolate* (C) *and* n-*butyl*-p-*hydroxybenzoate* (B) *on 5% SE-30 at 150°. Peak* A *is the solvent.*

of 0.2 in./min. and a span voltage of 1.0 mv. Attenuation is about 32×. Calculate the relative response factor F using the equation:

$$F = (P_g/P_i) \times (W_i/W_g)$$

where P_i is the peak height of the *n*-butyl-*p*-hydroxybenzoate derivative, P_g is the peak height of the glycerol guaiacolate derivative, W_i is the weight of the *n*-butyl-*p*-hydroxybenzoate injected, and W_g is the weight of the glycerol guaiacolate injected.

The F factor used in subsequent analytical calculations is the average of the F's found.

Determination in Tablets Not Containing Salicylates—Thoroughly grind the tablets to a fine powder, weigh accurately a portion equivalent to about 100 mg. of glycerol guaiacolate, and transfer to a glass-stoppered conical flask containing 100 ml. of chloroform. Shake thoroughly for about 30 min. and then filter or centrifuge to obtain a clear solution. Transfer an aliquot containing the equivalent of about 40 mg. of glycerol guaiacolate to a glass-stoppered conical flask, add 40 mg. of the internal standard, and evaporate to dryness. Then add 0.5 ml. of Tri-Syl, stopper, and allow to stand for 2–3 min. Dilute the mixture to 10 ml. with acetone and mix thoroughly. Inject a 2.0-μl. aliquot into the chromatograph and record the response as previously described. Calculate the amount of glycerol guaiacolate per tablet as follows: glycerol guaiacolate mg./tablet $= (P_g/P_i) \times (W_b/F) \times (D/S)$, where P_g is the peak height of the glycerol guaiacolate, P_i is the peak height of the internal standard, W_b is the weight of the internal standard, D is the dilution factor, S is the sample weight, and F is the average response factor.

Determination in Tablets and Fluids Containing Salicylates—Transfer an accurately measured sample equivalent to about 200 mg. of glycerol guaiacolate to a separator, dilute to about 25 ml. with water, add 25 ml. of saturated sodium chloride, and make alkaline with sodium hydroxide. Extract with five 45-ml. portions of chloroform, filter through anhydrous sodium sulfate, and combine the chloroform extracts in a 250-ml. volumetric flask. Dilute to volume with chloroform. Withdraw an aliquot containing about 40 mg. of glycerol guaiacolate, add 40 mg. of internal standard, and proceed as previously described.

Recovery of Glycerol Guaiacolate from Mixtures—In order to test the recovery of glycerol guaiacolate when compounded into various mixtures, three batches of tablets were made containing the following ingredients: Batch 1, glycerol guaiacolate 100 mg., phenobarbital 16.25 mg. (0.25 grain), theophylline 162.5 mg. (2.5 grains), ephedrine sulfate 25 mg., and excipient. Batch 2, glycerol guaiacolate 100 mg., theophylline 162.5 mg. (2.5 grains), ephedrine sulfate 25 mg., chlorpheniramine maleate 2.0 mg., and excipient. Batch 3, glycerol guaiacolate 100 mg., sodium salicylate 130 mg. (2.0 grains), ephedrine sulfate 25 mg., theophylline 130 mg. (2.0 grains), and excipient.

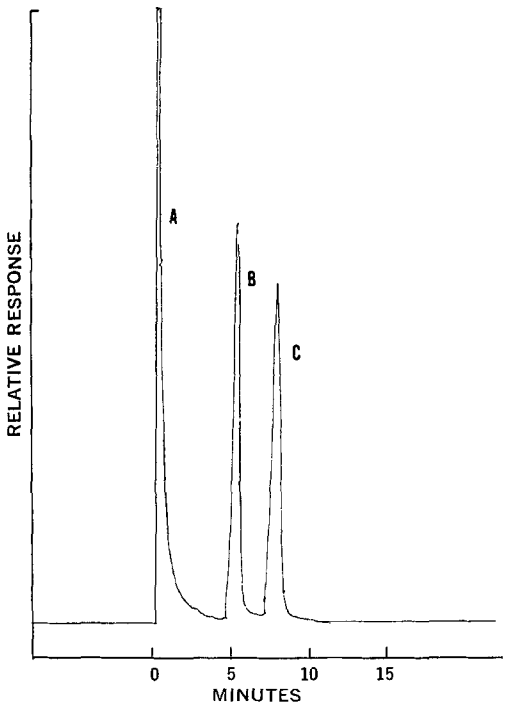

Figure 2—*Gas chromatogram of TMS derivatives of glycerol guaiacolate* (C) *and* n-*butyl*-p-*hydroxybenzoate* (B) *on 5% SE-52 at 130°. Peak* A *is the solvent.*

The results of the assays are shown in Table I.

CONCLUSIONS

An average recovery of 99.1% (SD = 1.1) may be achieved by the gas chromatographic method of assay of fluids and tablets. The method is straightforward, rapid, and has the desired specificity. A choice of columns and operating conditions is given for assaying various formulations. The amount of glycerol guaiacolate that can be estimated may be quite small by using the gas chromatograph to the limit of its sensitivity and by manipulation of the sample size.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 11, 1969, from the *Rexall Drug Co., The St. Louis Laboratories, St. Louis, Mo.*
Accepted for publication September 3, 1969.