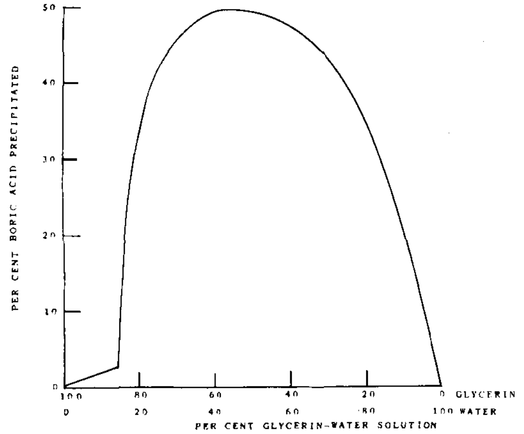

Fig. 5.—Precipitation of boric acid from glycerin-water solutions.

As expected, maximum precipitation of boric acid occurs about 45% water and 55% glycerin. About 15% water can be added without causing precipitation of boric acid. However, additional quantities of water will cause a large increase in the amount of precipitation. This observation would limit the use of boroglycerin glycerite when diluted with certain amounts of water.

SUMMARY AND CONCLUSIONS

1. A solubility study of the boric acid-water-glycerin system has been made at temperatures of 30, 40, 50, and 60°.
2. The degree of complex formation between boric acid and glycerin was found to increase with an increase in temperature.
3. Concentrations of glycerin from 0 to 40% had little effect, if any, upon the degree of complex formation as indicated by a solubility determination. This complex was found to increase as the concentration of glycerin was increased from 40 to 100%.
4. The heat of solution for each of the solvent systems was calculated through use of the van't Hoff relationship.
5. Maximum precipitation of boric acid from solutions of boric acid in glycerin was found to take place at a concentration of 45% water and 55% glycerin.

REFERENCES

(1) Krantz, J. C., Jr., Carr, C. J., and Beck, F. F., *J. Phys. Chem.*, **40**, 927(1936).

(2) Boeseken, J., *ibid.*, **41**, 1087(1937).

(3) Sciarra, J. J., Autian, J., and Foss, N. E., *J. Am. Pharm. Assoc., Pract. Pharm. Ed.*, **18**, 366(1957).

(4) Sciarra, J. J., Autian, J., and Foss, N. E., This Journal, **47**, 144(1958).

(5) Sciarra, J. J., and Elliott, D. B., *ibid.*, **49**, 115(1960).

(6) Daniels, F., and Alberty, R., "Physical Chemistry," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1961, pp. 64–69.

(7) Daniels, F., *et al.*, "Experimental Physical Chemistry," 5th ed., McGraw-Hill Book Co., Inc., 1956, pp. 113–114.

(8) "The National Formulary," 11th ed., J. B. Lippincott Co., Philadelphia, Pa., 1960, p. 56.

(9) Martin, E. W., and Cook, E. F., "Remington's Practice of Pharmacy," 12th ed., Mack Publishing Co., Easton, Pa., 1961, pp. 1124–1125.

(10) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 103.

Infrared Method for the Determination of Ethanol and Acetone in Thimerosal Tincture N.F.

By FREDERIC A. GRONAU, DONALD E. BROADLICK, and JAMES E. HAMILTON

The distillation method for determining ethanol in thimerosal tincture N.F. is time consuming and involves special handling to prevent interference of the acetone in the preparation. A shorter method is described based on the extraction of the ethanol into carbon tetrachloride and the measurement of the infrared absorption at 11.37 μ. The relative freedom from the interference by other alcohols and acetone assures greater specificity than the distillation method. The acetone present in tincture thimerosal N.F. can also be determined using the same extracted solution by reading the absorption of the carbonyl band at 5.86 μ.

The determination of ethanol in thimerosal tincture N.F. as described in the National Formulary (1) is that of Thorpe and Holmes (2). It has the disadvantage of being time consuming. It is also possible that it may not give a true estimate of the amount of ethanol in the preparation due to incomplete recovery of the ethanol in the distillate. The method formerly used in this laboratory was a modification of that of Hoff and Macoun (3) using paraformaldehyde and sodium hydroxide to form a nonvolatile reaction product with the acetone before distilla-

---

Received April 28, 1961, from the Analytical Department, Eli Lilly and Co., Indianapolis, Ind.
Accepted for publication June 23, 1961.
Presented to the Scientific Section, A.Ph.A., Chicago meeting, April 1961.

tion. The ethanol content is then determined by measuring the specific gravity of the distillate. In an attempt to overcome these disadvantages, an infrared spectrophotometric method has been developed. It has proved to be faster, more accurate, and is specific for ethanol.

Souder and Deluca (4) reported the determination of chloroform in pharmaceuticals by infrared absorption measurement. This procedure has been adapted to the determination of ethanol in tincture thimerosal. The method involves extraction of the ethanol from the sample into carbon tetrachloride. The carbon tetrachloride is dried and the absorption measured at an ethanol band at 11.37 μ. Although not of primary concern, the acetone content of the sample can be determined on the same extracted solution by measuring the absorption of the carbonyl band at 5.86 μ.

EXPERIMENTAL

Band Selection.—The infrared spectra of the common pharmaceutical solvents used in external preparations—ethanol, acetone, methanol, and isopropanol—were obtained on a Beckman IR-5 recording spectrophotometer. The ethanol band at 11.37 μ was chosen for quantitative estimation for several reasons. This unique band does not seem to be associated with the hydroxyl portion of the molecule (5) which eliminates the interference of many compounds such as other alcohols. The band appears in a generally nonabsorptive region of the spectrum where the common solvents listed show little absorption (Fig. 1). The band also follows Beer's law in the concentration range expected to be found in the tincture thimerosal N.F., that is, ±10% of the theoretical amount. In this region of the spectrum, carbon tetrachloride shows very little absorption.

General Technique.—To a suitable glass-stoppered flask containing exactly 50 ml. of carbon tetrachloride, 1 ml. of the tincture is added. About 30 Gm. of anhydrous sodium sulfate is added to form a hydrate with the water in the sample, allowing more of the ethanol to be dissolved in the carbon tetrachloride. The mixture is shaken for 1 minute. Several anhydrous salts capable of binding the water were tried and sodium sulfate was found to be the most suitable. By removing water in this manner one may transfer 98%+ of the ethanol into the carbon tetrachloride. About 5 ml. of the extracted solution is removed and dried in a suitable flask with about 2 Gm. of anhydrous sodium sulfate. This is a precautionary measure to protect the sodium chloride cells. The absorption of this solution is then determined at 11.37 μ in 1.0-mm. sodium chloride cells against a blank of carbon tetrachloride. After correcting for any cell blank, the absorption is compared to that of a standard run in the same manner. A Beckman model IR-2 spectrophotometer with sodium chloride optics was used for all quantitative results reported here.

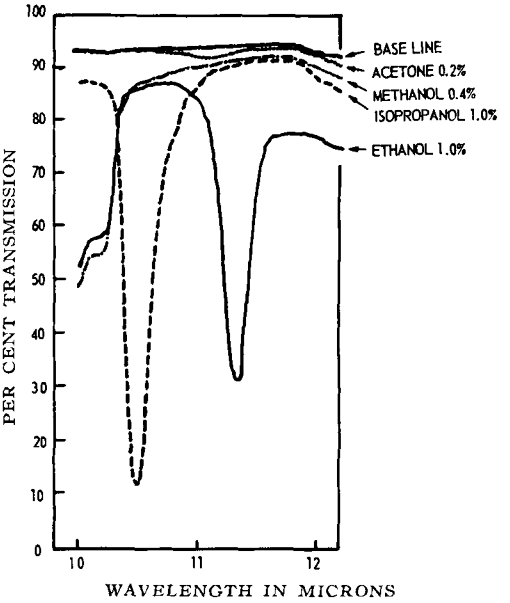

Fig. 1.—Infrared spectra of ethanol, methanol, acetone, and isopropanol in carbon tetrachloride.

Standard Preparation.—Standards were prepared in two ways. The alcohol and acetone were removed from a sample of tincture thimerosal by evaporating under vacuum until the absorption maximum of ethanol at 11.37 μ and of acetone at 5.86 μ disappeared. This blank material was then reconstituted by adding it to exactly 50 ml. of absolute ethanol and 10 ml. of acetone in sufficient volume to make 100 ml. A mixture of water, ethanol, and acetone was prepared by diluting 50 ml. of absolute ethanol and 10 ml. of acetone to 100 ml. with water. The absorption of carbon tetrachloride extracts of these solutions was determined at both the ethanol band at 11.37 μ and at the acetone band at 5.86 μ and found to be identical. All results reported in this work are determined against the water-ethanol-acetone standard. It became apparent from the work done on the standards that acetone could be determined on the same solution by reading the carbonyl band at 5.86 μ. Although the tincture contains only one-fifth as much acetone as ethanol, the unusually strong absorption of the carbonyl band resulted in an absorption almost as great as that of ethanol.

Comparison of Methods.—Ten different production lots of the tincture were assayed using the general technique. These results are compared to those obtained by distillation (Table I). In the distillation procedure, 50 ml. of the tincture is diluted with 20 ml. of saturated sodium chloride solution in a liter boiling flask. A 7-Gm. quantity of paraformaldehyde and 5 ml. of a 50% solution of sodium hydroxide are added. This mixture is then distilled in a compact distilling apparatus using Friedichs condensers. About 50 ml. of distillate is collected and diluted to 100 ml. The specific gravity is measured on a Westphal balance and the per cent ethanol obtained from Standard Alcoholimetric Tables found in the U.S.P.

The per cent acetone found in the samples is included in Table I but the comparison to other methods is not made. It is noted that the infrared

TABLE I.—COMPARISON OF ETHANOL DETERMINATION BY INFRARED AND DISTILLATION

Sample	Distillation Ethanol, %	Infrared	
		Ethanol, %	Acetone, %
1	48.30	49.17	9.31
2	47.16	49.69	9.50
3	47.50	50.22	9.60
4	47.66	50.22	9.75
5	48.92	49.28	9.73
6	48.30	49.48	9.55
7	48.62	50.43	9.58
8	48.46	49.48	9.63
9	48.30	50.63	9.70
10	48.62	49.70	9.47
Average	48.18	49.83	9.58
Theoretical	50.00	50.00	10.00

TABLE II.—REPRODUCIBILITY OF INFRARED ASSAY

	Ethanol, %	Acetone, %
Run 1		
	50.32	9.87
	50.22	10.13
	50.32	10.00
	50.53	10.08
Run 2		
	50.85	9.98
	50.22	9.98
	50.53	9.87
	50.53	9.98
Average	50.44	9.99
Standard deviation (S.D.)	0.208	0.090
3 × S.D., %	1.25	2.70

method gives results which are closer to the theoretical amounts of ethanol in the product. An attempt was made to explain the higher results found by the infrared method. It had been felt that the distillation apparatus in use did not give complete recovery of the ethanol in the product. Using a system of added internal standard, the recovery efficiency of the distillation method for ethanol and the efficiency of the infrared method for both ethanol and acetone were measured. Absolute ethanol was added to a previously assayed sample and the ethanol content was redetermined. By subtracting the original ethanol result from the total and comparing this figure to the amount of ethanol added, the efficiency of recovery was found. This study shows the distillation procedure used recovers only 96.7% of the ethanol while the infrared technique recovers 99.8%. This difference of 3.1% is consistent with that of 3.29% experienced in assaying the 10 samples by each method. The same technique was applied to the acetone which also shows a 99.8% efficiency.

Reproducibility of Method.—One sample was assayed in two groups of four aliquots each. These results are shown in Table II. The estimated standard deviation on these data was found to be 0.208 or about 0.4%. The reproducibility for these eight samples (3 × S.D.) was ±1.25%. The acetone standard deviation is 0.09 or about 0.9%. The reproducibility is ±2.7%.

SUMMARY

An infrared method is presented for the determination of ethanol in thimerosal tincture N.F. The method is less time consuming than distillation procedures and gives results which are closer to the theoretical amounts of ethanol in the product. The acetone in the product may also be determined in the same sample. Additional data are being collected on other hydroalcohol preparations and will be included in subsequent manuscripts.

REFERENCES

(1) "The National Formulary," 11th ed., J. B. Lippincott Co., Philadelphia, Pa., 1960, p. 404.
(2) Thorpe, T. E., and Holmes, J., *J. Chem. Soc.*, **83**, 314(1903).
(3) Hoff, R. W., and Macoun, J. M., *Analyst*, **58**, 749(1933).
(4) Souder, J. C., and Deluca, P., THIS JOURNAL, **49**, 255(1960).
(5) Stuart, A. V., and Sutherland, G. B. B. M., *J. Chem. Phys.*, **24**, 559(1956).