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GAS CHROMATOGRAPHIC ANALYSIS OF CHLORAL HYDRATE IN SOFT GELATIN CAPSULES

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ABSTRACT

A simple, rapid and sensitive GC method for the analysis of chloral hydrate in soft elastic gelatin capsules was developed using n-amyl alcohol as the internal standard. The samples were chromatographed using a glass column packed with chromosorb 102 and flame ionization detection. The operating temperatures were 175°, 190°, and 200°C for the column, detector, and injector, respectively. This method was shown to isolate chloral hydrate from its major degradation product chloroform. The method was also compared with compendial and colorimetric procedures. The accuracy, precision, linearity, and applicability to soft elastic gelatin capsules are also presented.

INTRODUCTION

Chloral hydrate (2,2,2 - trichloro-1,1-ethanediol) is a commonly used sedative, hypnotic agent available in solution, syrup, and soft elastic gelatin capsules. The United States Pharmacopeia (1) analytical method for chloral hydrate involves its reaction with excess sodium hydroxide to form chloroform and sodium formate, followed by the determination of the alkali consumed.

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Unfortunately, this method is not suitable for stability studies because it is nonspecific and is not stability indicating.

Published colorimetric procedures for the analysis of chloral hydrate are numerous (2). The one developed by Archer and Huagas (3) is based upon the reaction of chloral hydrate with quinaldine ethyl iodide to produce a stable, blue cyanine dye and shows no interference from polyhalogenated compounds. However, this method is tedious and time consuming.

Various gas chromatographic methods have appeared in the literature (4-10) for the determination of chloral hydrate in biological fluids. The majority of these procedures used electron capture detection.

The purpose of this investigation was to develop a rapid and simple procedure for the determination of chloral hydrate by a gas-liquid chromatograph equipped with a flame ionization detector.

EXPERIMENTAL

Materials - Chloral hydrate[1] was used as received. n-amyl alcohol[2] and water[2] were HPLC quality.

Apparatus - GLC analysis was performed with a gas chromatograph[3] equipped with a flame ionization detector and a 122-cm x 2 mm glass column packed with chromosorb 102[4]. The instrument was operated isothermally with column oven, detector, and injection port temperatures at 175°, 190°, and 200°C, respectively. The carrier gas (helium), hydrogen, and air flow rates were 40, 40, and 250 ml/min., respectively.

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[1] Mallinckrodtt Inc., St. Louis, Missouri

[2] Fisher Scientific Co., Fair Lawn, New Jersey

[3] Model 5791-A Hewlett-Packard, Orlando, Florida

[4] Johns-Manville, Denver, Colorado

Preparation of Internal Standard - Approximately 100 mg of n-amyl alcohol was accurately weighed into a 100 ml volumetric flask and diluted to volume with water to provide a concentration of about 1 mg/ml.

Preparation of Chloral Hydrate Standard Solution - Approximately 250 mg of chloral hydrate was accurately weighed in a 50 ml volumetric flask and diluted to volume with water for a concentration of about 5 mg/ml.

Preparation of Working Standard Solution - Ten ml of standard solution and five ml of internal standard were transferred to a 100 ml volumetric flask and were diluted to volume with water to provide a chloral hydrate concentration of about 0.5 mg/ml.

Sample Preparation - Two capsules each containing 500 mg of chloral hydrate were cut. The fill material was squeezed into a 100 ml volumetric flask and the volume was adjusted with water. The solution was allowed to stand for 24 hours. Five ml of this solution and five ml of internal standard were transferred to a 100 ml volumetric flask and was diluted to volume with water.

Calculations - The ratio of peak area of chloral hydrate to internal standard for each injection was determined. The amount of chloral hydrate was calculated as follows:

$$\text{mg/sample} = \frac{RsA}{RsT} \times \begin{matrix}\text{standard (mg/ml)}\\ \text{concentration}\end{matrix} \times \begin{matrix}\text{dilution}\\ \text{factor}\end{matrix} \quad \text{(Eq.1)}$$

Where Rs A is the ratio of the chloral hydrate peak area to the internal standard peak area for the sample solution, and RsT is the ratio of the chloral hydrate peak area to the internal standard peak area for the known standard solution.

RESULTS AND DISCUSSION

Figure 1 shows a typical gas chromatogram obtained for a chloral hydrate standard solution and soft elastic gelatin capsule formulation. When injected into the

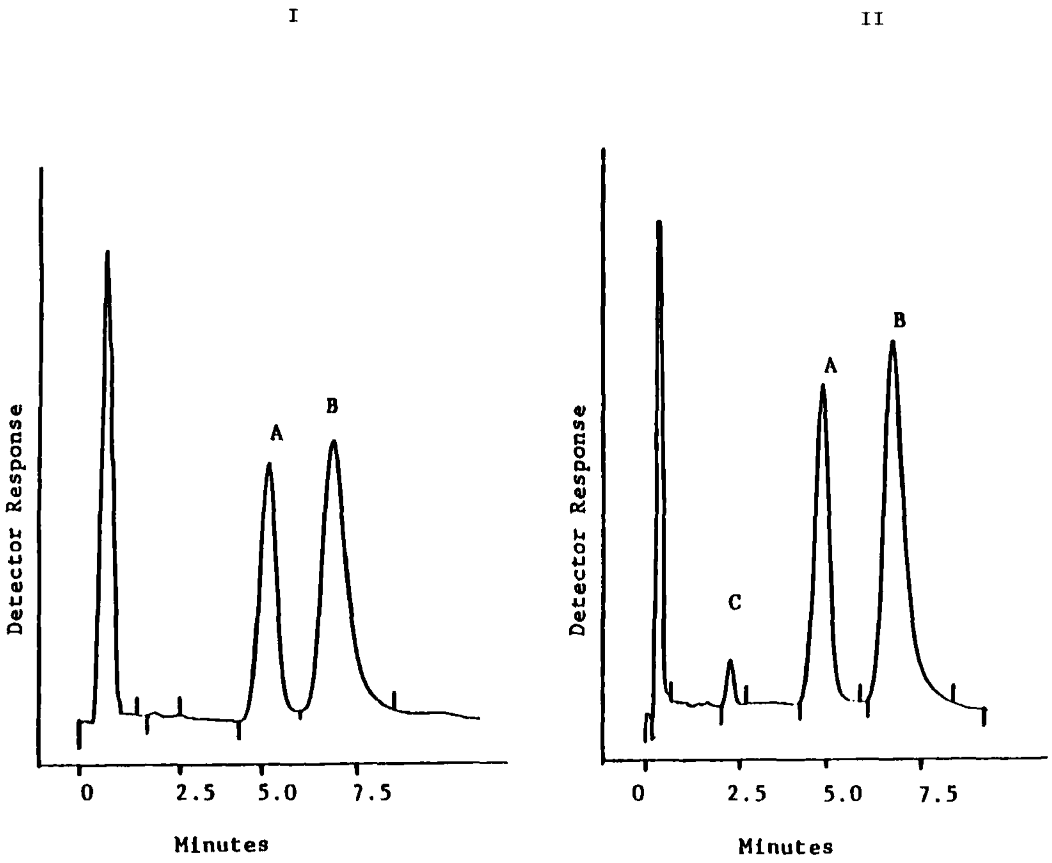

FIGURE 1
Representative chromatograms obtained for a (I) standard solution of chloral hydrate and (II) soft elastic gelatin capsule formulation. Key: Peak A, chloral hydrate; Peak B, n-amyl alcohol; Peak C, chloroform.

chromatograph, chloroform was eluted first, followed by chloral hydrate and internal standard at retention times of 2.4, 5.0, and 7.0 minutes respectively.

The calibration curve for chloral hydrate was linear ($r^2 = 0.99$) over the concentration range of 0.3-0.7 mg/ml. The precision of this method was determined using ten one µl injections of a standard solution containing 0.5 mg/ml The coefficient of variation was 1.68%.

TABLE I - RESULTS OF ANALYSIS OF CHLORAL HYDRATE USING GAS CHROMATOGRAPHIC, COLORIMETRIC AND USP METHODS.

LOT NUMBER	GC METHOD		COLORIMETRIC METHOD		USP METHOD	
	mg/cap	Percent of Claim[a]	mg/cap	Percent of Claim[a]	mg/cap	Percent of Claim[a]
1	508.20	101.64	503.50	100.70	511.60	102.32
2	505.50	101.10	496.50	99.30	509.70	101.94
3	485.00	97.00	480.90	96.18	500.80	100.16
4	499.80	99.96	492.80	98.56	513.60	102.72
5	506.30	101.26	500.60	100.12	512.40	102.48
MEAN	500.96	100.19	494.86	98.97	509.62	101.92
S.D.	9.46	1.89	8.80	1.76	5.13	1.03

a = Theoretical Label Claim, 500 mg.

S.D. = Standard Deviation

The recovery data for chloral hydrate were determined by adding different amounts of reference standard to a known amount of chloral hydrate solution. The analysis of four such samples resulted in recovery values of 98.2, 98.5, 100.7, and 101.7% of the total quantity expected. The mean and relative standard deviation was found to be 99.8% and ± 1.7 respectively. Therefore, it was determined from the above data that the assay provides satisfactory accuracy and precision.

Five different lots of soft elastic gelatin capsules each containing 500 mg of chloral hydrate, were assayed using the proposed GLC method, USP method (1), and colorimetric procedure (3). The data are summarized in Table I. The USP method produced slightly higher percentages of chloral hydrate since it does not differentiate between chloral hydrate and chloroform (2). This nonspecific method, while adequate for the assay of chloral hydrate crystals, is unsuitable for monitoring the stability of chloral hydrate formulations.

In summary, the GLC determination of chloral hydrate in soft elastic gelatin capsules offers a simpler and faster method than the USP and colorimetric methods. It is accurate, precise, and stability indicating which is advantageous for the monitoring of pharmaceutical formulations.

REFERENCES

1) "The United States Pharmacopeia XX", U.S. Pharmacopeial Convention, Rockville, MD, 1980.
2) A. W. Davidson, JAOAC, 51, 626 (1968).
3) A. W. Archer and E. A. Huagas, J. Pharm. Pharmacol., 12, 754 (1960).
4) E. R. Garrett and H. J. Lambert, J. Pharm. Sci., 55, 812 (1966).

5) N. C. Jain, H. L. Kaplan, R. B. Forney and F. W. Hughes, J. Forensic Sci., 12, 497 (1967).

6) D. D. Breimer, H. C. J. Ketelaars and J. M. Van Rossum, J. Chromatogr., 88, 55 (1974).

7) M. Ogata and T. Saeki, Int. Arch. Arbeitsmed., 33, 49 (1974).

8) W. J. Cole, R. G. Mitchell and R. F. Salamonsen, J. Pharm. Pharmae., 27, 167 (1975).

9) J. Berry, J. Chromatogr., 107 (1975).

10) B. Rollmann, M. Mercier, J. Rondelet and M. Roberfroid, Chromatogr. Symp. Ser. 1, 115 (1979).