mination are necessary for the complete separation of all the components used in the study. However, once an initial determination of the constituents present in the sample has been made, the column temperature may be increased to shorten the analysis time without affecting the precision and accuracy of the results.

Table II illustrates the results of the application of this procedure to the analysis of several commercial capsule and tablet preparations. The route of preparation of levodopa (synthetic or natural) may be determined by examining the related amino acids present. TLC (17) was used to identify the amino acid phenylalanine found in Tablet VI.

Since the procedure did not employ any cleanup or extraction procedures prior to analysis, diluents and binders used to formulate the dosage forms of levodopa could offer a potential source of interference. However, since there were no extraneous peaks observed in the chromatograms of any dosage form analyzed in this study, these materials apparently do not interfere with the assay procedure.

In conclusion, a GLC determination of levodopa has been developed and is proposed as an assay for the drug contained in both capsules and tablets. Related amino acids which were present as possible contaminants were also separated, identified, and quantified. In addition, these results indicate that analysis of α-methyldopa by the same or a closely related procedure may be feasible.

This procedure was applied to several commercial tablet and capsule preparations containing levodopa, with satisfactory results.

REFERENCES

(1) G. Coppi, A. Vidi, and G. Bonardi, *J. Pharm. Sci.*, **61**, 1460 (1972).

(2) N. Maggi and A. Cometti, *ibid.*, **61**, 927(1972).

(3) G. Curzon, B. D. Kantamamemi, and J. Trigwell, *Clin. Chim. Acta*, **37**, 335(1972).

(4) G. C. Cotzias, M. H. Van Woert, and L. M. Schiffer, *N. Engl. J. Med.*, **276**, 374(1967).

(5) C. J. Sih, P. Foss, J. Rosazza, and M. Lemberger, *J. Amer. Chem. Soc.*, **91**, 6204(1969).

(6) M. Damodaran and R. Ramasway, *Biochem. J.*, **31**, 2149 (1937).

(7) R. J. Baczuk, G. K. Landram, R. J. Dubois, and H. C. Dehm, *J. Chromatogr.*, **60**, 351(1971).

(8) L. P. O'Gorman, O. Borud, I. A. Khan, and L. R. Gjessing, *Clin. Chim. Acta*, **29**, 11(1970).

(9) J. I. Routh, R. E. Bannow, R. W. Fincham, and J. L. Stoll, *Clin. Chem.*, **17**, 867(1971).

(10) M. Nedergaard, *Pharm. Acta Helv.*, **45**, 373(1970).

(11) R. W. Zumwalt, K. Kuo, and C. W. Gehrke, *J. Chromatogr.*, **55**, 267(1971).

(12) K. L. Agarwal, R. A. W. Johnston, G. W. Kanner, and D. S. Millington, *Nature*, **219**, 498(1968).

(13) A. E. Pierce, "Silylation of Organic Compounds," Pierce Chemical Co., Rockford, Ill., 1968, p. 58.

(14) C. W. Gehrke, H. Nakamoto, and R. W. Zumwalt, *J. Chromatogr.*, **45**, 24(1969).

(15) K. M. Brobst and C. E. Lott, *Cereal Chem.*, **43**, 35(1966).

(16) B. J. Gadzinowicz, "Gas Chromatographic Analysis of Drugs and Pesticides," Dekker, New York, N. Y., 1967, p. 32.

(17) J. G. Heathcote, R. J. Washington, C. Haworth, and S. Bell, *J. Chromatogr.*, **51**, 267(1970).

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GLC Determination of Meclizine Hydrochloride in Tablet Formulations

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Abstract □ A method was developed for the quantitative determination of meclizine hydrochloride in tablet formulations by GLC after a suitable separation technique.

Keyphrases □ Meclizine hydrochloride tablets—GLC analysis after chloroform extraction □ GLC—analysis, meclizine hydrochloride tablets

Meclizine hydrochloride is an antihistamine which shows marked protective activity against nebulized histamine. It is indicated in the management of nausea, vomiting, and dizziness associated with motion sickness, and it has been found useful in the management of vertigo associated with diseases affecting the vestibular system. Various methods for the determination of meclizine hydrochloride have been reported, including TLC (1–4), polarography (5), NMR (6), fluorometry (7), nonaqueous titration (8), and UV spectroscopy (9–11). However, these methods do not have the rapidity, simplicity, and degree of sensitivity found in GLC methods.

Papers (12–15) published on the GLC determination of meclizine hydrochloride lack quantitative data or include chromatograms showing serious peak tailing. This paper describes a simple and direct GLC procedure for the quantitative determination of meclizine hydrochloride after extraction from a tablet formulation with chloroform.

EXPERIMENTAL

Equipment—A gas chromatograph[1], equipped with a dual flame detector and an electronic integrator[2], was used throughout this study. The column was 1.82-m. × 4-mm. (6-ft. × 0.25-in.) stainless steel tubing packed with diatomaceous earth[3], 80–100 mesh, coated with 3% OV-17. The operating temperatures were: column, 290°; de-

[1] Hewlett-Packard 5750.
[2] Hewlett-Packard 3370A.
[3] Chromosorb W, AW-DMCS, Supelco Inc., Bellefonte, Pa.

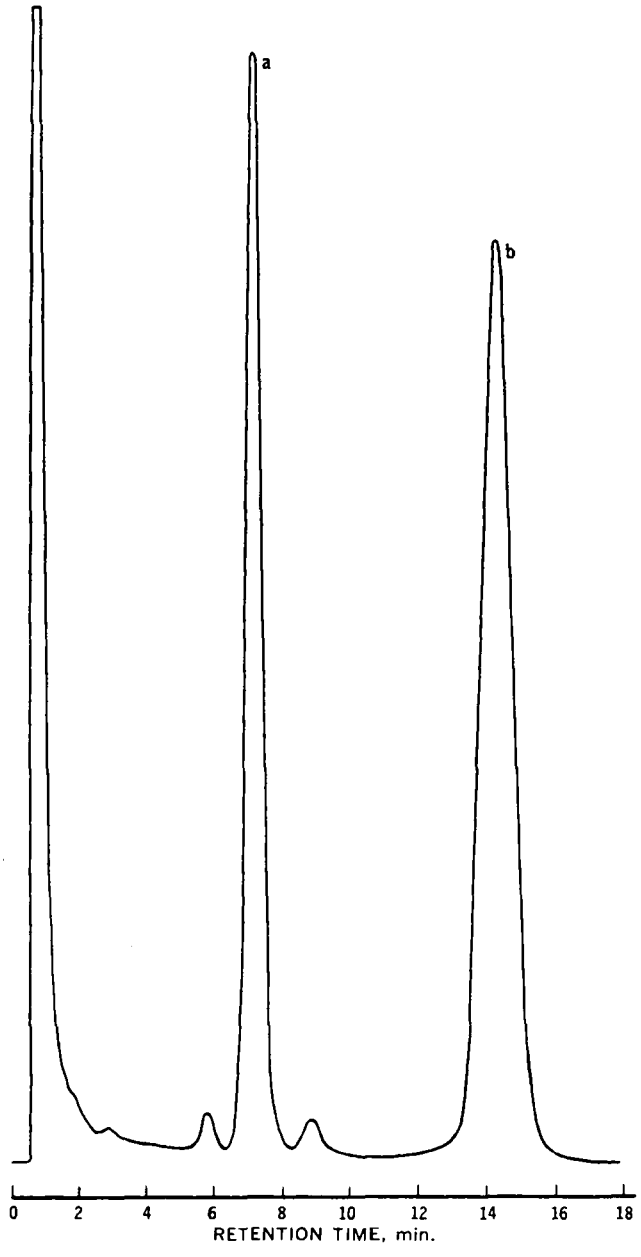

Figure 1—*Representative chromatograms. Key: a, dinonyl phthalate; and b, meclizine.*

tector, 330°; and injection port, 320°. Helium, with a flow rate of 75 ml./min., was the carrier gas. The hydrogen flow rate was adjusted to optimum sensitivity without causing high noise background in the electronic integrator. Oxygen was maintained at 30 psig. head pressure.

Reagents—Meclizine hydrochloride USP XVIII reference standard was dried at 100° for 2 hr. before use. Dinonyl phthalate[4], practical grade, was the internal standard. Chloroform[5] was GC spectrophotometric quality.

Preparation of Standard Solution—Dissolve approximately 500 mg. of dinonyl phthalate in 500 ml. chloroform. Accurately weigh approximately 100 mg. of meclizine hydrochloride standard and transfer to a 125-ml. conical flask. Pipet 50 ml. of the dinonyl phthalate solution into the conical flask containing the meclizine hydrochloride and swirl to make a uniform solution.

Preparation of Sample Solution—Determine the average tablet weight of 20 tablets. Pulverize the tablets, weigh an amount equivalent to 100 mg. of meclizine hydrochloride, and transfer the powder to a 125-ml. conical flask. Pipet 50 ml. of the dinonyl phthalate solution into the conical flask and shake for 30 min. Centrifuge the solution and use the supernate for the GLC determination.

[4] Eastman Kodak.
[5] J. T. Baker Chemical Co.

Table I—Percent Recovery of Meclizine Hydrochloride

Day	Weight Number	Injection 1	Injection 2	Injection 3
1	1	100.9	102.8	102.9
	2	99.5	100.2	100.1
2	3	99.0	100.8	101.1
	4	100.9	101.6	101.7
3	5	99.4	98.4	99.2
	6	99.0	99.0	100.7
		Overall average	100.4%	

Table II—Estimates of Precision for Determination of Meclizine Hydrochloride in a Pharmaceutical Formulation

Number of Days	Number of Weights per Day	Number of Injections per Weight	Estimates of Precision[a], %
1	1	1	±2.8
1	1	3	±2.4
1	2	3	±1.9
2	1	3	±1.7
Injection to injection within a weight on a day			±1.7

[a] Ninety-five percent of individual results or average of three or six results will not vary from each other by more than the percentages quoted. These estimates include variability due to days, weights, aliquots, and injections.

Chromatography—After conditioning the column with four injections of the sample solution, approximately 5 μl. each, inject 5 μl. of the standard solution followed by three 5-μl. injections of the sample solution and one 5-μl. injection of the standard solution. The peak areas obtained from the electronic integrator are used for the calculation.

Calculations—Calculate the potency of meclizine hydrochloride in milligrams per tablet according to the following formula:

$$\text{milligrams per tablet} = \frac{R_{spl} \times \text{standard weight (mg.)} \times \text{average tablet weight (mg.)}}{R_{std} \times \text{sample weight (mg.)}} \quad \text{(Eq. 1)}$$

where R_{spl} is the ratio of meclizine peak area to dinonyl phthalate peak area in the sample solution, and R_{std} is the average ratio of

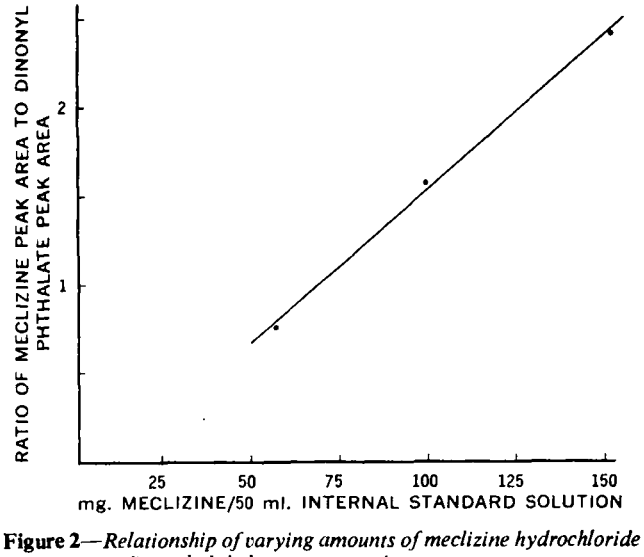

Figure 2—*Relationship of varying amounts of meclizine hydrochloride to a constant dinonyl phthalate concentration.*

the meclizine peak area to the dinonyl phthalate peak area in the standard solution before and after sample injections.

RESULTS AND DISCUSSION

A typical chromatogram of meclizine and dinonyl phthalate is shown in Fig. 1. Figure 2 shows the linear relationship of various amounts of meclizine to a constant amount of dinonyl phthalate.

The accuracy and precision of the method were tested by the following experiment. Two weights of a placebo blend in which known quantities of meclizine hydrochloride had been added were assayed per day for 3 consecutive days. The average recovery (Table I) was 100.4%. The estimate of precision (Table II) for injection to injection within a weight on a day, excluding variability due to days and weights, was ±1.7%. The standard error for the average of three injections is ±2.4%.

Meclizine hydrochloride yields a symmetrical peak, identical with meclizine base. A possible explanation for this phenomenon is that two HCl molecules are thermally removed from the meclizine molecule inside the injection port (16). By taking advantage of this effect, sample preparation is simplified since a two-phase liquid extraction step is eliminated.

REFERENCES

(1) I. Sunshine, W. W. Fike, and H. Landesman, *J. Forensic Sci.*, **11**, 428(1966).

(2) W. W. Fike, *Anal. Chem.*, **38**, 1697(1966).

(3) W. Awe and W. Schulze, *Pharm. Ztg.*, **107**, 1333(1962).

(4) T. Fuwa, T. Kido, and H. Tanaka, *Yakizaigaku*, **25**, 138 (1965).

(5) Abdel-Wahab, F. Mohamed, and H. F. Mostafa, *Isotopenpraxis*, **4**, 69(1968).

(6) G. Ruecker and P. N. Natarajau, *Arch. Pharm.*, **300**, 276 (1967).

(7) R. E. Jensen and R. T. Pflaum, *J. Pharm. Sci.*, **53**, 835 (1964).

(8) M. Rink and M. Riemhofer, *Mitt. Deut. Pharm. Ges.*, **31**, 197(1961).

(9) P. Rajeswaran and P. L. Kirk, *Bull. Narcotics*, **13**, 21(1961).

(10) M. Bramdstaetter-Kuhnert, R. Hoffman, and M. Stenn, *Microchem. J.*, **7**, 357(1963).

(11) F. M. Ispana Sanchez, *Rev. Fac. Farm. Univ. Cent. Venez.*, **5**, 69(1964).

(12) L. Kazyak and E. C. Knoblock, *Anal. Chem.*, **35**, 1448 (1963).

(13) N. C. Jain and P. L. Kirk, *Microchem. J.*, **12**, 242(1967).

(14) A. McDonald and R. T. Pflaum, *J. Pharm. Sci.*, **52**, 816 (1963).

(15) *Ibid.*, **53**, 887(1964).

(16) H. M. Fales and J. J. Pisano, in "Biomedical Application of Gas Chromatography," Herman A. Szymanski, Ed., Plenum, New York, N. Y., 1964, p. 33.

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Spectrophotometric Determination of Thyroxine Iodine in Thyroid Preparations

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Abstract □ An improved quantitative determination of thyroxine iodine in USP thyroid preparations is described. The iodine-containing proteins are dissolved in 8 *M* urea and separated from cell debris and excipient materials by centrifugation and filtration. One aliquot of the clear yellow filtrate is adjusted to pH 9.0, and a second aliquot is adjusted to pH 5.0. The difference in absorbance between the two is observed at 325, 350, and 360 nm. These values are inserted into an equation utilizing the appropriate absorptivities of the iodoamino acids and dilution factors, and the amount of thyroxine iodine is calculated. The relative standard deviation of the method is ±6.0%. Data are presented to demonstrate the application of this method to several thyroid formulations, thyroid powder USP, tablets, and enteric-coated tablets. Correlation with biological data is shown.

Keyphrases □ Thyroxine iodine—UV titrimetric analysis in thyroid preparations □ Thyroid preparations—UV titrimetric analysis of thyroxine iodine □ UV spectrophotometric titration—analysis, thyroxine iodine in thyroid preparations

Thyroxine contained in pure proteins can be determined by spectrophotometric titration, taking advantage of the unique ionization and absorption properties of the iodoamino acids (1, 2). Various other methods to measure chemically both thyroxine and triiodothyronine (liothyronine) in pharmaceutical thyroid preparations have been described (3–13). These methods involve: chemical or enzymic hydrolysis of the thyroproteins; extraction of the released iodoamino acids; separation of these acids by paper chromatography, TLC, or gel permeation chromatography; and quantitation by iodometry. The methods are time consuming and the stability of the iodoamino acids in solution also has been a problem (14–16). The USP

Table I—Precision of Measurement of Thyroxine in Thyroid Preparations

Preparation	Average Value	Range	*RSD*, %
Powder USP, mcg./g.	207.0	191.0–222.0	±6
120-mg. tablets USP, mcg./tablet	24.2	22.7–25.3	±5
200-mg. enteric-coated tablets USP, mcg./tablet	32.8	30.2–33.9	±6