GLC Determination of Methamphetamine Hydrochloride in Methyl Acrylate–Methyl Methacrylate Sustained-Release Tablets

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Abstract □ A rapid and precise GLC method was developed for the detection and determination of methamphetamine hydrochloride in methyl acrylate–methyl methacrylate copolymer sustained-release tablets. After dissolution of whole tablets in chloroform, *in situ* conversion of the methamphetamine hydrochloride to its free base with potassium hydroxide, and addition of *n*-tridecane internal standard, an aliquot of the resulting solution can be injected into a gas chromatograph for analysis. An OV-101 chromatographic column was used.

Keyphrases □ Methamphetamine HCl sustained-release dosage form—analysis □ Methyl acrylate–methyl methacrylate matrix—methamphetamine HCl dosage form □ GLC—analysis □ *n*-Tridecane—GLC analysis standard

A large number of pharmaceutical preparations has become available in recent years in the form of sustained-release tablets and capsules. Such products have the obvious advantage of maintaining drug blood concentrations at desired levels for prolonged periods. One method of preparing sustained-release tablets entails the use of a methyl acrylate–methyl methacrylate copolymer matrix (1, 2). In this system, the drug is intimately mixed with the plastic, compressed to a tablet, and treated to give the desired prolonged drug-release rate (3, 4). The resulting tablets are extremely hard and insoluble in most solvents.

In the development of assay procedures for the active components of such tablets, the extreme hardness frequently precludes manual grinding. Early experiments in this laboratory included attempts to leach the active components from tablets with water. The prolonged leaching times required for the tablet make it time consuming for recovery of drug for total assay. Maximum leaching efficiencies are about 98%.

Methods have been reported for the GLC resolution of amphetamine and methamphetamine after conversion of the former to 1-benzylethylisothiocyanate (5), for determination of methamphetamine in blood and/or urine (6–9), and for determination of that same drug in pharmaceutical preparations after extraction of the amine base into diethyl ether (10, 11).

A very convenient procedure was developed in the author's laboratory for the GLC determination of methamphetamine hydrochloride in methyl acrylate–methyl methacrylate tablets. The proposed method does not require extraction of the drug, but it involves dissolving entire tablets in chloroform, *in situ* conversion of the drug to its free base with methanolic potassium hydroxide, and injection of an aliquot of the reaction mixture into a gas chromatograph.

EXPERIMENTAL

Operational Parameters—The instrument used for this work was a Varian Aerograph model 1800, equipped with hydrogen-flame detectors. The column was a stainless steel coil, 1.52 m. (5 ft.) long and 0.15 cm. (0.062 in.) i.d., packed with 5% OV-101 on 80/100-mesh Gas Chrom Q. The temperatures were: column, 100°; injection port, 150° with a Pyrex insert; and detector, 150°. The flow rates were: carrier gas, nitrogen, 12–15 ml./min.; detector gas, hydrogen, 30 ml./min.; and air, 300 ml./min. All injections were made with a microsyringe, using an injection volume of approximately 1.5 μl. The instrument was operated at a range of 10^{-11} amp./mv. and 64× attenuation. The recorder used was a 0–1-mv. Varian Aerograph model 20. Peak areas were measured with a Varian Aerograph model 471 digital integrator. A sample chromatogram is shown in Fig. 1.

Standard Preparation—Accurately weigh about 70 mg. of *n*-tridecane[1] and 60 mg. of methamphetamine hydrochloride into a 50-ml. volumetric flask. Add about 20 ml. of chloroform, and swirl to dissolve. Add 5 ml. of 0.1 *N* methanolic potassium hydroxide, dilute to volume with chloroform, and mix.

Sample Preparation—Accurately weigh about 70 mg. of *n*-tridecane into a 50-ml. volumetric flask. Add whole methamphetamine hydrochloride tablets equivalent to about 60 mg. of drug. Add about 20 ml. of chloroform, and agitate on a wrist-action shaker until all the tablets are dissolved. Add 5 ml. of 0.1 *N* methanolic potassium hydroxide, dilute to volume with chloroform, and mix.

Sample Analysis—Aliquots of standard and sample (1.5 μl.) are alternately injected into the instrument under the aforementioned conditions. After elution of the *n*-tridecane peak, the instrument is ready for another injection. A total elution time of about 9–10 min. can be expected.

Calculations—*Relative Response Factor for Methamphetamine Hydrochloride*—

$$K = \frac{(\text{mg. of } n\text{-tridecane in standard})(\text{area of methamphetamine peak for standard})}{(\text{mg. of methamphetamine·HCl in standard})(\text{area of } n\text{-tridecane peak for standard})} \quad \text{(Eq. 1)}$$

$$\text{mg. methamphetamine hydrochloride per tablet} = \frac{(\text{mg. of } n\text{-tridecane in sample})(\text{area of methamphetamine peak for sample})}{(K)(\text{area of } n\text{-tridecane peak for sample})(\text{number of tablets used for sample})} \quad \text{(Eq. 2)}$$

RESULTS AND DISCUSSION

Chloroform was the only solvent tried in which the methyl acrylate–methyl methacrylate copolymer was sufficiently soluble to permit dissolution of the tablets. The appreciable solubility of both methamphetamine and methamphetamine hydrochloride in chloroform, combined with the relatively low response it induces in a hydrogen-flame detector, made this the solvent of choice.

In the author's laboratory, it was found that a complete analysis could be completed within about 1 hr. of receipt of a sample. This combination of speed and simplicity makes the method most attractive.

Although a small amount of the dissolved plastic matrix was injected into the chromatograph with the sample, no interference was noted in any of the chromatograms due to pyrolysis of the polymer. The simple composition of this type of tablet greatly

[1] K & K Laboratories, Inc., Plainview, N. Y.

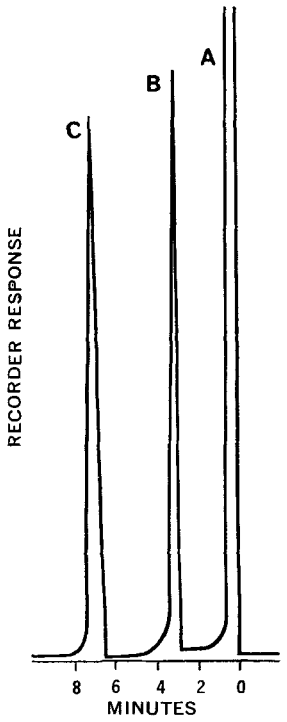

Figure 1—*Gas chromatogram showing relative retention times of methamphetamine and* n-*tridecane. Key: A, solvent; B, methamphetamine; and C,* n-*tridecane.*

simplifies analysis. It was found that unless the methamphetamine hydrochloride is converted to its free base, chromatographic results are spurious and unpredictable.

Both recovery of a known amount of methamphetamine hydrochloride and precision were excellent. Addition of measured amounts of drug to a placebo, with subsequent analysis, yielded 100.3% recovery. Relative standard deviations of numerous analyses were about ±1%.

Investigations are being conducted on the application of this approach to the analysis of other drugs in similar matrixes.

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Determination of Lactate in Parenterals Containing Reducing Sugars

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Abstract □ Reducing sugars in parenterals containing sodium lactate interfere with the determination of the lactate. An acid–diatomaceous earth column separation of sodium lactate (as lactic acid) is proposed which uses ether as the eluting solvent. After esterification, the lactate is converted to a hydroxamic acid which reacts with iron(III) to form a reddish-purple complex which absorbs at 515 nm. The standard deviation of the method is 1.07% of the average amount declared as being present. The method is rapid and can be used for parenterals containing 20% or less of reducing sugar. Parenterals containing partially hydrolyzed protein give high results.

Keyphrases □ Lactate determination—parenterals containing reducing sugars □ Hydroxamic acid formation—lactate analysis □ Column chromatography—separation □ Colorimetric analysis—spectrophotometer

The charring and titration method for the determination of sodium lactate given in the USP (1) is satisfactory for preparations listed in that compendium. The official method, however, does not work satisfactorily for the analysis of sodium lactate in parenterals and other nonofficial products that contain reducing sugars, phosphates, stabilizers, and other substances which produce titratable bases or color interferences when charred.

Hillig (2) suggested a continuous ether extraction of lactic acid from an acidified dairy product sample followed by a colorimetric assay. Boisson (3) used a similar extraction procedure for the removal of lactic acid from solutions that also contain dextrose, except the sample solution was saturated with ammonium sulfate prior to extraction. Dalrymple (4) analyzed nonofficial parenterals for sodium lactate by using the Hillig extraction procedure followed by titration of the extracted lactic acid with sodium hydroxide solution. Staruszkiewicz (5) proposed a GLC method for lactic and succinic acids in eggs, in which the acids were extracted into ether by a continuous extraction procedure, esterified, and extracted into chloroform before injection. These methods are time consuming and