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Short communication

Impurity profiling of ephedrines in methamphetamine by high-performance liquid chromatography

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Abstract

Separation of the enantiomers and diastereomers of ephedrines was investigated for impurity profiling of methamphetamine. We describe a method for the analysis of (1*S*,2*R*)-(+)-ephedrine, (1*R*,2*S*)-(−)-ephedrine, (1*S*,2*S*)-(+)-pseudoephedrine and racemic methylephedrine in bulk methamphetamine by HPLC using two different columns: a phenyl-β-cyclodextrin-type column and an ODS-type column. The analytes were detected by UV absorbance measurement at 210 nm. As little as 0.05% of each ephedrine in bulk methamphetamine could be determined. In the impurity profiling of methamphetamine, the identification of ephedrines may provide valuable information about the precursor. This method was confirmed to be sufficiently sensitive to identify trace amounts of (1*R*,2*S*)-(−)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine in bulk methamphetamine synthesized by the Emde method.

Keywords: Impurity profiling; Enantiomer separation; Ephedrines; Methamphetamine

1. Introduction

Drug characterization by impurity profiling is a very useful tool for monitoring the source and distribution of illicit drugs and precursors. For a long period, the methamphetamine seized in Japan was the (*S*)-(+)-form prepared from (1*R*,2*S*)-(−)-ephedrine by the Emde method. Recently, (*S*)-(+)-methamphetamine synthesized by the Nagai method has been appearing in Japan. Many methods have been reported for the isolation and identification of the characteristic impurities of the various synthetic pathways of methamphetamine [1]. It is useful when enforcing laws concerning the precursor chemicals of methamphetamine to have information on the precursors of methamphetamine produced illicitly from ephedrines. Separation of the diastereomers and enantiomers of ephedrines in bulk methamphetamine by GC or GC–MS is not easy without extraction and derivatization. Several HPLC methods have been reported for the determination of ephedrines in biological fluids and in pharmaceutical preparations [2,3]. However, they are not always simple and sufficiently efficient for profiling of the ephedrines present as impurities in methamphetamine. In 1999, we reported a method for the direct determination of methamphetamine enantiomers by HPLC using a phenyl-β-cyclodextrin (CD)-type column (Chiral

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Drug™) [4]. As a continuation of that work, the present paper describes a simple, rapid and selective HPLC method for the determination of (1*S*,2*R*)-(+)-ephedrine, (1*R*,2*S*)-(−)-ephedrine, (1*S*,2*S*)-(+)-pseudoephedrine, and racemic methylephedrine in bulk methamphetamine by HPLC using a phenyl-β-CD-type column and an ODS-type (C_{18}) column with ultraviolet absorption detection. Samples of methamphetamines seized in Japan and other countries were analyzed and the method was confirmed to be very useful.

2. Experimental

2.1. Materials

(1*S*,2*R*)-(+)-Ephedrine hydrochloride and (1*R*,2*S*)-(−)-ephedrine hydrochloride were purchased from Fuji Chemical (Takaoka, Japan). (1*S*,2*S*)-(+)-Pseudoephedrine hydrochloride, (*R*)-(−)-methamphetamine hydrochloride and (*S*)-(+)-methamphetamine hydrochloride were purchased from Dainippon Pharmaceutical (Osaka, Japan). Racemic methylephedrine hydrochloride was purchased from Sanko Pharmaceutical Industry (Tokyo, Japan). Water was purified with a Milli-Q system (Nihon Millipore, Tokyo, Japan). All other solvents were of HPLC grade.

2.2. Instrumentation

A Shiseido Nanospace liquid chromatograph equipped with a UV detector linked to a data system (S-MC, Shiseido, Tokyo, Japan) was used for data acquisition and storage. The eluent was monitored by measuring UV absorbance at 210 nm. The system consisted of two Inert pumps, a column oven, a H-P valve, an autosampler and a degassing unit. Chromatographic separation was achieved by the use of two different columns: a phenyl-β-CD-type column (Chiral Drug™, 150 mm×1.5 mm I.D., Shiseido) and an ODS-type column (CAPCELL PAK C_{18} UG 120 S5, 250 mm×1.5 mm I.D., Shiseido).

2.3. HPLC conditions

The mobile phase used for the phenyl-β-CD-type column was 20 mmol/L KH_2PO_4 (pH 4.6)–CH_3CN (4:1). The mobile phase used for the ODS-type column was 5 mmol/L SDS in 20 mmol/L KH_2PO_4–CH_3CN (65:35). The flow-rate for each column was maintained at 0.1 mL/min. Both separations were carried out at 20 °C.

2.4. Methamphetamine sample

Three samples were taken from drugs seized by the Narcotics Control Department, Kanto-Shin'etu Bureau of Health and Welfare, and another three samples were obtained from UNDCP. Methamphetamine hydrochloride (10 mg) was dissolved in 1 mL of water and a 1 μL aliquot of the sample solution was injected into the HPLC instrument.

3. Results and discussion

3.1. HPLC

The structures of the compounds studied in this work are shown in Fig. 1. For the present purpose, we modified the method that we previously reported for the direct determination of methamphetamine enantiomers [4]. With the phenyl-β-CD-type column, ephedrines are eluted prior to methamphetamine enantiomers. We investigated the optimum ratio of acetonitrile in buffer solution to obtain a good separation of trace amounts of ephedrines in bulk methamphetamine. It was possible to separate the ephedrines without interference from the methamphetamine enantiomers in a 20 mmol/L phosphate buffer with 20% acetonitrile. The elution of the

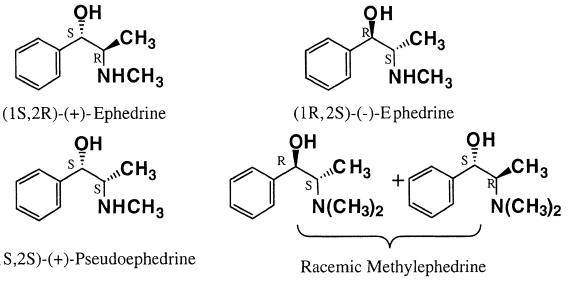

Fig. 1. Chemical structures of the ephedrines investigated in this study.

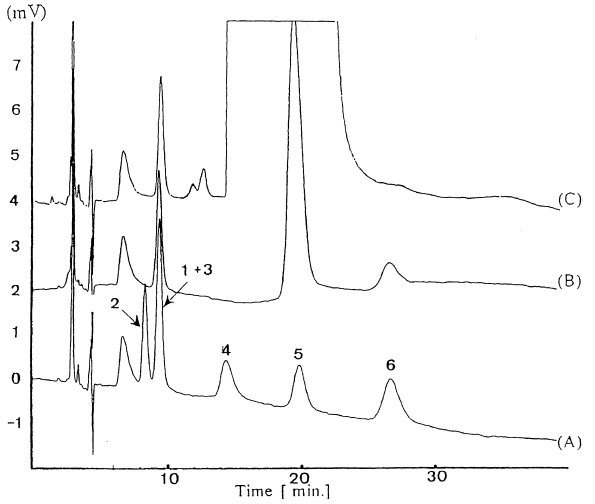

Fig. 2. Chromatograms obtained using the phenyl-β-CD-type column. (A) Mixture of standard substances. The peaks correspond to 1=(1*S*,2*S*)-(+)-pseudoephedrine, 2=(1*S*,2*R*)-(+)-ephedrine, 3=(1*R*,2*S*)-(−)-ephedrine, 4=racemic methylephedrine, 5=(*S*)-(+)-methamphetamine, and 6=(*R*)-(−)-methamphetamine. (B) Crystal of methamphetamine seized in September 2000 in Tokyo. (C) Crystal of methamphetamine purchased from Dainippon Pharmaceutical.

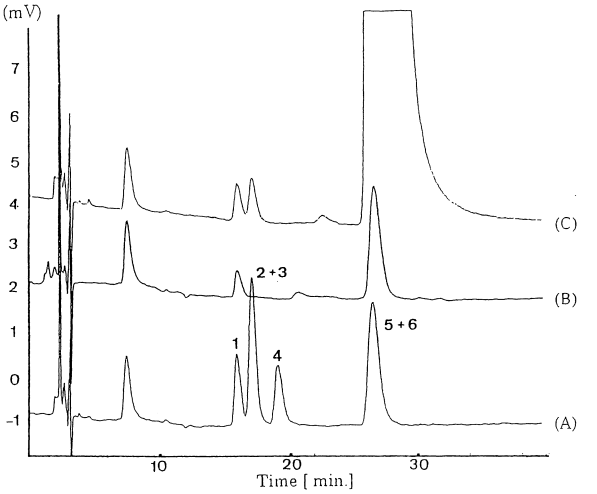

Fig. 3. Chromatograms obtained using the ODS-type (C_{18}) column. (A), (B) and (C): same as in Fig. 2.

standard substances from the phenyl-β-CD-type column is shown in the lower chromatogram (A) of Fig. 2. However, (1*S*,2*S*)-(+)-pseudoephedrine and (1*R*,2*S*)-(−)-ephedrine were not separated on this column. Gurley et al. have reported the determination of ephedrine-type alkaloids by HPLC [5]. Separation of the diastereomers in bulk methamphetamine was carried out by a minor modification of their method with regard to column type, mobile phase composition, and column temperature. Elution of the standard substances from the ODS-type column is shown in the lower chromatogram (A) of Fig. 3. It is possible to monitor trace amounts of the ephedrines used for methamphetamine synthesis by using the phenyl-β-CD-type and ODS-type columns. Linearity was examined using standard aqueous solutions of (1*S*,2*R*)-(+)-ephedrine hydrochloride, (1*R*,2*S*)-(−)-ephedrine hydrochloride, and (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride at 5.0, 10.0, 20.0, 30.0 and 40.0 μg/mL. Good linearity of the method was confirmed over the concentration range 5–40 μg/mL ($R^2 = 0.999$ for each ephedrine). Precision was calculated as: RSD=standard deviation/mean·100, with samples of 5.0, 20.0 and 40.0 μg of (1*R*,2*S*)-(−)-ephedrine/HCl in 10 mg of methamphetamine/HCl. The values obtained were 1.9, 2.0 and 1.9%, respectively ($n=5$). Accuracy was calculated as: (measured value−actual value)/actual value·100, using the same samples as for the measurement of precision. The values obtained were 3.1, 4.4 and 3.6%, respectively ($n=5$). As little as 0.05% of each ephedrine in bulk methamphetamine could be determined.

3.2. Profiling of ephedrines as impurities in methamphetamine by HPLC

The phenyl-β-CD-type column and ODS-type column were applied to the profiling of ephedrines in seven samples. The results are presented in Table 1. Figs. 2 and 3 display representative chromatograms of samples 1 and 3 obtained using the phenyl-β-CD-type column and the ODS-type semi-microcolumn. As shown in the middle chromatogram (B) of Fig. 2, a trace amount of (*R*)-(−)-methamphetamine was detected in sample 3. It has been reported that Ephedra plants produce (1*R*,2*S*)-(−)-ephedrine, (1*S*,2*S*)-(+)-pseudoephedrine, (1*R*,2*S*)-(−)-norephedrine, (1*S*,2*S*)-(+)-norpseudoephedrine, (1*R*,2*S*)-(−)-*N*-methylephedrine and (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine, and a product is likely to be

Table 1
Results of profiling analysis

Sample No.	(1*S*,2*R*)-(+)-Ephedrine	(1*R*,2*S*)-(−)-Ephedrine	(1*S*,2*S*)-(+)-Pseudoephedrine	Methamphetamine enantiomer
1	−	+	+	(*S*)-(+)-
2	−	+	+	(*S*)-(+)-
3	−	−	+	(*S*)-(+)-
4	−	−	−	(*R*)-(−)-
5	−	−	−	Racemic
6	−	−	+	(*S*)-(+)-
7	−	−	+	(*S*)-(+)-

+, Detected; −, not detected. Samples: 1=(*S*)-(+)-methamphetamine hydrochloride from Dainippon Pharmaceutical, 2=(*S*)-(+)-methamphetamine hydrochloride seized in Japan in December 2000, 3=(*S*)-(+)-methamphetamine hydrochloride seized in Japan in September 2000, 4=(*R*)-(−)-methamphetamine hydrochloride seized in Japan in December 1999, 5=racemic methamphetamine seized in Sweden, 6=(*S*)-(+)-methamphetamine hydrochloride seized in the USA, 7=(*S*)-(+)-methamphetamine hydrochloride seized in Australia.

synthetic in origin if it contains a single ephedrine [6].

From the results of the profiling of ephedrines, we can presume that sample 1 was synthesized with ephedrine from an Ephedra plant as the starting material. We have information that this sample of (*S*)-(+)-methamphetamine hydrochloride from Dainippon Pharmaceutical was indeed synthesized via the Emde route with ephedrine from an Ephedra plant as the starting material. Therefore, the result is reasonable. The methamphetamine seized in Sweden (sample 5) seems to have been synthesized from 1-phenyl-2-propanone (P-2-P). It contains no ephedrine. Only (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride was detected in samples 6 and 7. It has been reported that illicit methamphetamine is synthesized with (1*S*,2*S*)-(+)-pseudoephedrine as the starting material in the USA and Australia [7,8].

4. Conclusion

In the impurity profiling of methamphetamine, the identification of ephedrines can provide valuable information about the precursor. Our HPLC method was confirmed to be sufficiently sensitive to identify trace amounts of (1*R*,2*S*)-(−)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine in illicit methamphetamine. It is of interest that ephedrines were not detected in the (*R*)-(−)-methamphetamine seized in Japan. The present method should be useful for monitoring new trends in synthetic methods and the precursors used for the illicit production of methamphetamines.

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