

THE ENANTIOMERIC STUDY OF METHAMPHETAMINE TABLETS IN THAILAND

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Abstract

Capillary electrophoresis using β -cyclodextrin and dimethyl- β -cyclodextrin as chiral selectors was performed in parallel to gas chromatography-mass spectrometry, in an effort to characterize the enantiomeric substances in 557 illicit methamphetamine tablets in Thailand collected during 1983-2000. The study revealed the stimulants in these tablets, namely ephedrine, methamphetamine and caffeine, appearing as single substances or in combination. Ephedrine was found in only the form of 1*R*,2*S*-ephedrine. Pseudoephedrine was not detected. At present, *S*-methamphetamine occupied 100% among methamphetamine epidemic in Thailand whilst *R*-methamphetamine was detected in the initial stage.

Keywords: amphetamine type stimulant, methamphetamine, illicit drug, enantiomer, capillary electrophoresis, chiral selector

Introduction

The amphetamine type stimulants (ATS) in Thailand have increased the abuse population in number and complexity. Illicit stimulant tablet containing amphetamine sulfate have been confiscated by law enforcement since 1959¹. In late 1970s, methamphetamine was found in the ATS tablet instead. Since then, other stimulant substances, namely ephedrine and caffeine, have appeared as single substance or in combination in look-alike ATS tablets. The recipe of combined ATS became common until present¹⁻³. The most common method of methamphetamine synthesis is *via* ephedrine or pseudoephedrine⁴⁻⁸. Other precursors can also be used, for instance, norephedrine, phenylacetic acid, phenylacetone, and phenylalanine^{4,5}. Racemic *S*-methamphetamine and *R*-methamphetamine can be synthesized *via* these latter precursors, whilst 1*R*,2*S*-ephedrine or 1*S*,2*S*-pseudoephedrine produce only *S*-

enantiomer of methamphetamine which is more potent stimulant and more addictive^{5,7,9-11}. Capillary electrophoresis (CE) becomes the method of choice for enantiomeric separation by using the appropriate chiral selectors¹¹⁻¹⁵. This paper describes the identification of enantiomeric forms of amphetamine type substances by CE in addition to gas chromatographic/ mass spectrometric (GC/MS) analysis of the illicit ATS tablets epidemic in Thailand during 1983-2000.

Materials and Methods

The enantiomers of amphetamine sulfate (AP), methamphetamine hydrochloride (MA), ephedrine hydrochloride (EP), pseudoephedrine hydrochloride (PE) and norephedrine hydrochloride (NE) were obtained from Alltech. Caffeine, phenethylamine and β -cyclodextrin (β -CD) and dimethyl- β -cyclodextrin (DM- β -CD) were from Sigma. Triethanolamine was supplied by Unilab. Phosphoric acid was from Carlo Erba.

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Sodium hydroxide and ethyl acetate were from J.T. Baker. Double deionized water was used for preparation of all solutions.

A triethanolammonium-phosphate buffer at pH 3.0 was prepared by titration 100 mM H_3PO_4 with triethanolamine. The appropriate amounts of β -CD and DM- β -CD were added to the triethanol ammonium-phosphate buffer to make the background electrolyte (BGE). The mixture of AP, MA, PE, EP at 0.15 mM for each isomer was dissolved in double deionized water.

Sample preparation procedure

Illicit MA tablets were sampled throughout Thailand by the Drug Dependence Research Center and the Office of Narcotic Control Board (ONCB) in 1983, 1996 and 2000, and brought for analysis in 2005. Each tablet was weighed, ground and dissolved in double deionized water. The sample was centrifuged and the supernatant was analyzed by GC/MS and CE, as described below.

GC/MS apparatus and method

A gas chromatograph (Trace GC Ultra, Thermo Finnigan) equipped with a mass spectrometer (Trace DSQ, Thermo Finnigan) was used with split injection. A capillary column (30 m x 0.25 mm I.D.) with an SGE - BPX5 (5% phenyl 95% dimethyl polysiloxane bonded stationary phase film 0.25 μ m thickness) was used. The inlet temperature was maintained at 180°C. The column oven was held at 80°C for 1 min, then programmed from 80-135°C at 5°C/min, and from 135-250°C at 10°C/min. Helium carrier gas was used at a constant flow-rate of 1 ml/min. The mass selective detector was operated in Selected Ion Monitoring (SIM) mode. The ion source and transfer line temperature were maintained at 200 and 300°C respectively.

The aqueous extract of illicit MA tablets was adjusted to basic pH with 1N NaOH. Liquid-liquid

extraction was performed using ethyl acetate as solvent and phenethylamine as internal standard.

CE apparatus and method

All CE separations were performed on a P/ ACE system 5010 Beckman CE instrument. An uncoated fused silica capillary used was 57 cm in length (50 cm to detector) x 50 μ m I.D., thermostated at 25°C. Voltage was set at 30 kV and UV detection at 200nm. A sample solution was injected by 0.5 psi pressure for 2 s. A new capillary was conditioned with 1 M NaOH for 30 min, water for 30 min, 0.1 M NaOH for 30 min, 0.1 M H_3PO_4 for 30 min and finally with the BGE for 30 min. Prior to analysis each day, the capillary was rinsed with 0.1 M H_3PO_4 for 15 min and then BGE for 15 min. Between consecutive analyses, the capillary was flushed with 0.1 M H_3PO_4 for 5 min and then BGE for 5 min.

The aqueous extract of illicit MA tablet was filtered through 0.45 μ m membrane filter prior to analysis. Each experiment was run in duplicate. Spike standard method was used for confirmation.

Results and Discussion

The study was performed on 263, 192 and 102 tablets of MA sampling in the years of 1983, 1996 and 2000 respectively. The MA tablets were classified by their active ingredients as methamphetamine only (MA), methamphetamine and caffeine (MA,C), ephedrine and caffeine (EP,C), methamphetamine, ephedrine and caffeine (MA,EP,C) and caffeine only (C). In the early period of MA epidemic (1983), 82.8% of MA tablets were EP,C whilst 13.7% were MA,C. The combination of MA and C was popular in the latter period, 74.0% in 1996 and increasing to 99.4% in 2000 (figure 1). The concentrations of MA, EP and C in MA tablets are shown in table 1.

CE has been shown to be an excellent method for chiral separation, typically carried out by addition of a

chiral selector into the BGE. The separation is based on the difference in electrophoretic mobility due to the difference in binding constant between the chiral analyte and the chiral selector. In the case of MA tablets, chiral carbon of MA could be S-MA or R-MA and chiral carbon of EP could be 1*R*,2*S*-EP, 1*S*,2*S*-PE, 1*S*,2*R*-EP or 1*R*,2*R*-PE. One approach to enhance the simultaneous separation of all analytes is the use of dual CDs¹⁶. The BGE containing 6.0 mM β -CD + 10.0 mM DM- β -CD in the triethanol ammonium-phosphate buffer at pH 3.0 was found to achieve resolution of all test analytes (Figure 2). Among 557 MA tablets, ephedrine was found in only the form of 1*R*,2*S*-EP. R-MA was

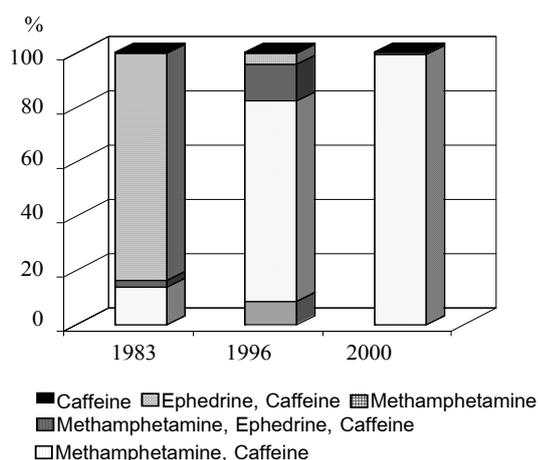


Figure 1 Chemical characteristics of active substances in MA tablets from different periods

Table 1 Concentrations in mg% of active substances in MA tablets from different periods

	1983	1996	2000
Methamphetamine	9.1 ± 4.4	19.7 ± 4.1	22.2 ± 4.7
Ephedrine	65.1 ± 16.5	9.3 ± 9.9	-
Caffeine	18.2 ± 15.0	51.9 ± 12.0	60.8 ± 5.1

Table 2 The percentage of enantiomeric forms of active substances in MA tablets from different periods

	1983	1996	2000
S-MA	96.6	100.0	100.0
R-MA + S-MA	3.4	-	-
1 <i>R</i> ,2 <i>S</i> -EP	100.0	100.0	100.0

found in 1982 MA tablets (3.4%) as racemic methamphetamine (the mixture of S-MA and R-MA). S-MA constituted 100% of the methamphetamine tablets from 1996 (Table 2). Enantiomeric characterization can disclose more detail of the chemical structures and give beneficial information for monitoring study in dynamic change in chemical composition of amphetamine type stimulants in Thailand.

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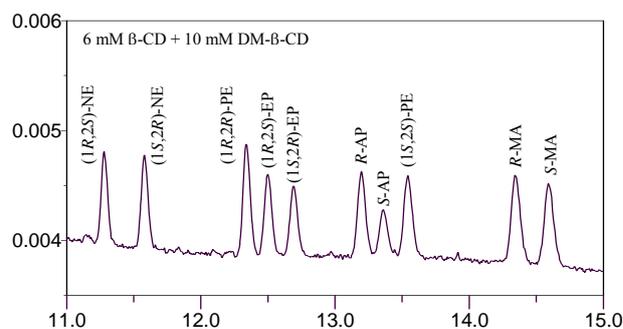


Figure 2 Electropherograms of enantiomeric separation of AP, MA, PE, EP and NE using dual CDs (6.0 mM- β -CD + 10.0 mM DM- β -CD) as chiral selectors

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อิแนนทิโอเมอร์ของยาบ้าในประเทศไทย

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บทคัดย่อ

วิเคราะห์อิแนนทิโอเมอร์ของสารกระตุ้นประสาทกลุ่มแอมเฟตามีนในยาบ้า 557 ตัวอย่าง ที่ระบอบในช่วง พ.ศ. 2526 – 2543 ด้วยเทคนิคอะลลิเลอิกโทรฟอริซิสโดยใช้ตัวเลือกไครัลเป็นเบตาไซโคลเดกซ์ทรินและไดเมทิลเบตาไซโคลเดกซ์ทริน ร่วมกับเทคนิคแกสโครมาโทกราฟี – แมสสเปกโตรเมตรี สารออกฤทธิ์ที่พบในตัวอย่างเม็ดยาบ้าเป็นเมทแอมเฟตามีน อีเฟดรีน คาเฟอีน หรือ สารผสมของสารดังกล่าว การแยกอิแนนทิโอเมอร์พบว่าอีเฟดรีนเป็นชนิด 1R,2S-ephedrine ไม่พบซุโดอีเฟดรีน เมทแอมเฟตามีนทั้งหมดในปัจจุบันเป็น S-methamphetamine อย่างไรก็ตามในช่วงแรกของกระบวนพบ R-methamphetamine ด้วย

คำสำคัญ: สารกระตุ้นประสาทกลุ่มแอมเฟตามีน เมทแอมเฟตามีน อิแนนทิโอเมอร์ อะลลิเลอิกโทรฟอริซิส ตัวเลือกไครัล

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