Automatic Screening of Major Impurities in Methamphetamine Samples Synthesized by Emde Method Using Accurate Mass Spectrometry

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Abstract
An ultra-fast liquid chromatography coupled with high-precision time of flight tandem mass spectrometry method was developed to screen major impurities in methamphetamine samples synthesized by Emde method. In this study, mass spectrometry isolation in positive mode was coupled with TOF/TOF MS-EMRMS was used to determine impurities. After analysis of two hundred samples, some impurities were detected by MarkerView® software based on the criterion of df (p) present in at least 90% samples. Impurities were determined by correlation analysis for sample to sample comparison. The chemical formulas of these markers were determined by ICP-MS and MS/MS spectra. Sixteen markers were finally selected for further verification. The chemical identification of these markers was confirmed to be based on the fragment mass spectra. The 16 markers are closely related to the raw material, ephedrine, and pseudoephedrine. These impurities could be detected by GC and trace impurities could be detected by LC-MS. Therefore, this method is essential for law enforcement agencies for both evidential and strategic intelligence purposes.

INTRODUCTION
Methamphetamine is one of the most widely abused drugs in China. Ephedrine and pseudoephedrine are main raw materials for methamphetamine synthesis. Therefore, accurate mass spectrometry methods were developed to screen major impurities in methamphetamine. 200 samples, whose synthetic routes were confirmed to be Emde, were analyzed to determine major impurities in methamphetamine. The ultra-fast liquid chromatography coupled with hybrid quadrupole time of flight mass spectrometry method, which featured high resolution, mass accuracy and sensitivity, was developed to detect impurities for profiling in methamphetamine samples synthesized by Emde method. In this study, mass spectrometry isolation in positive mode was coupled with TOF/TOF MS-EMRMS was used to determine impurities. After analysis of two hundred samples, some impurities were detected by MarkerView® software based on the criterion of df (p) present in at least 90% samples. Impurities were determined by correlation analysis for sample to sample comparison. The chemical formulas of these markers were determined by ICP-MS and MS/MS spectra. Sixteen markers were finally selected for further verification. The chemical identification of these markers was confirmed to be based on the fragment mass spectra. The 16 markers are closely related to the raw material, ephedrine, and pseudoephedrine. These impurities could be detected by GC and trace impurities could be detected by LC-MS. Therefore, this method is essential for law enforcement agencies for both evidential and strategic intelligence purposes.

MATERIALS AND METHODS
Sample Preparation: Sample preparation method was from ‘Collaborative measurement of Method for Profiling of Amphetamine Type Stimulants’ (CMTAMS) with some modifications were focused on basis impurities in the sample. Organic Impurity was prepared by liquid-liquid extraction.

LC-MS Experiment and Workforce
AB SCIEX™ Triple Quad® 6500 with a TOF/TOF MS EMR® 6000 System
An Agilent Eclipse Plus C18 (150 x 4.6 mm, 5 µm) Column was set at 45°C. Mobile phases were aqueous H2O and acetonitrile (ACN), 40:60 v/v, 1% formic acid and 0.1% formic acid, respectively, pH 2.0.

Table 1: Showing all markers in 3 samples

<table>
<thead>
<tr>
<th>Marker</th>
<th>Formula</th>
<th>Bconc</th>
<th>Bvar</th>
<th>Bstd</th>
<th>DP</th>
<th>GS1</th>
<th>GS2</th>
<th>Bconc</th>
<th>Bvar</th>
<th>Bstd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marker 1</td>
<td>C20H28N2O</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Marker 2</td>
<td>C20H28N2</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Marker 3</td>
<td>C11H17NO</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Marker 4</td>
<td>C11H17N</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>15</td>
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REFERENCES

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