A Reliable Method for the Separation and Detection of Synthetic Cannabinoids by Supercritical Fluid Chromatography with Mass Spectrometry, and Its Application to Plant Products

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A reliable method using supercritical fluid chromatography with mass spectrometry (SFC-MS) was developed for cannabinoids using compressed carbon dioxide (CO₂) and methanol as the mobile-phase. The cannabinoids, i.e., cannabicyclohexanol (CCH: cis-isomer), trans-CCH, 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxyxycyclohexyl]-phenol (CP-47497), 5-(1,1-dimethylheptyl)-2-[(1R,2R,5R)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]-phenol (CP-55940), 3-(1,1’-dimethylheptyl)-6aR,7,10,10aR-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol (HU-210), 2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (CBD), (1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone (JWH-018), (1-butyl-1H-indol-3-yl)-1-naphthalenyl-methanone (JWH-073) and 1-(1-pentyl-1H-indol-3-yl)-2-(2-methoxyphenyl)ethanone (JWH-250), were determined within 12 min using a conventional column (2-EP) for SFC. Furthermore, two optical isomers of CCH and trans-CCH were completely and rapidly separated by a chiral stationary phase column (AMY1). A highly sensitive detection (0.002–3.75 ppb) was also obtained by these methods using 2-EP and AMY1 columns. These methods were applied to the qualitative and quantitative determination of cannabinoids in dried plant products. Although the concentration and species were different in the products, JWH-018, JWH-073 and CCH, including the cis-isomer, trans-isomer and the optical isomers, were detected in the products. Therefore, the proposed SFC-MS method seems to be useful as an alternative method to GC-MS and LC-MS for illegal drugs, such as cannabinoids.

Key words cannabinoids; supercritical fluid chromatography; mass spectrometry; plant product; isomer separation

Synthetic and cannabimimetic cyclohexylphenol analogues (CP), e.g., CP-47497, CP-55940 and cannabicyclohexanol (CCH), are currently being sold and distributed worldwide via the Internet and/or the street markets. A great number of synthetic cannabinimetics JWH, which were given their names in honor of the group head, John William Huffman (Clemson Univ., U.S.A.), have also spread around the world. The series of synthetic substances possess a wide structural variability and potent cannabimimetic pharmacological activity, but a low structural selectivity of the cannabinoid receptors. Cannabis derivatives are the most widely abused illicit drugs in the world. The herbal blends have been sold as incense under various brand names such as “Spice” and “Smoke.” There were claimed to be different varieties of a mixture of herbs which should produce cannabis-like effects. However, the analysis found several potent ingredients, such as JWH-018 and JWH-073. From the anxiety of the broad spreading of these products in Japan, psychoactive substances as JWH-018 and JWH-073 and CCH, including the cis-isomer, trans-isomer and the optical isomers, were detected in the products.

Materials and Chemicals Authentic cannabicyclohexanol (CCH: cis-isomer), trans-CCH, 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxyxycyclohexyl]-phenol (CP-47497), 5-(1,1-dimethylheptyl)-2-[(1R,2R,5R)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]-phenol (CP-55940), 3-(1,1’-dimethylheptyl)-6aR,7,10,10aR-

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tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol (HU-210), 2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (cannabidiol, CBD), (1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone (JWH-018), (1-butyl-1H-indol-3-yl)-1-naphthalenyl-methanone (JWH-073) and 1-(1-pentyl-1H-indol-3-yl)-2-(2-methoxyphenyl)-ethanone (JWH-250) (Fig. 1) were donated by the National Institute of Health Science (NIHS, Japan). Acetonitrile (ACN) and methanol (MeOH) of LC-MS grade were obtained from Kanto Chemicals (Tokyo, Japan). Compressed carbon dioxide (CO₂) gas (food additives grade) was used as received from a city gas company. Deionized and distilled water (H₂O) was used throughout the study (PURELAB Flex-3, ELGA, Tokyo, Japan). All other chemicals and solvents were of analytical

Fig. 1. Structures of Tested Cannabinoids

| Table 1. SFC-MS/MS Conditions Using 2-EP Column |
|-----------------------------------------------|
| SFC condition                     | UPC²         |
| Column                           | 2-EP, 1.7 µm, 3.0 mm×100 mm |
| Column temp.                     | 40°C         |
| Injection                        | 1 µL         |
| Mobile phase A                   | CO₂          |
| Mobile phase B                   | MeOH         |
| Elution                          | Time (min)   | Flow rate | %A | %B | Profile       |
| 0                               | 2.5          | 99.5      | 0.5 | Hold          |
| 5.0                             | 2.5          | 99.5      | 0.5 | Hold          |
| 10.0                            | 2.5          | 90        | 10  | Linear GR     |
| 12.0                            | 2.5          | 90        | 10  | Hold          |
| MS interface                    | Splitter/make-up: MeOH 0.2 mL/min |
| ABPR pressure                   | 2500 psi     |
| MS/MS condition                 | Xevo TQD tandem quadupole MS |
| Ion mode:                       | ESI⁺ and ESI⁻ |
| Capillary voltage               | 2.5 kV       |
| Des. temp.:                     | 550°C        |
| Ion source temp.                | 150°C        |
| Cone voltage:                   | 20 V         |
| Desolvation gas flow:           | 1000 L/h     |
| Cone gas flow:                  | 50 L/h       |
| Collision gas flow:             | on           |

Table 1. SFC-MS/MS Conditions Using 2-EP Column
**SFC-ESI-MS/MS Analysis**
The SFC-ESI-MS/MS analysis was performed using an Ultra-Performance Convergence Chromatograph (ACQUITY UPC²) connected to a Xevo³ TQD triple quadrupole-mass spectrometer (Waters Co., Milford, MA, U.S.A.). The ACQUITY UPC² BEH 2-EP column (1.7 µm, 100×3.0 mm i.d.; Waters) and ACQUITY UPC² Trefoil AMY1 column (2.5 µm, 150×3.0 mm i.d.; Waters) were used for the determination by SFC. The AMY1 column is filled with amyllose tris-(3,5-dimethyl-
phenylcarbamate) coated chiral stationary phase on 2.5 μm spherical porous silica particles, whereas the stuff of 2-EP column is 2-ethylpyridine bonded stationary phase on 1.7 μm spherical porous BEH (ethylene bridged hybrid) particles. The cannabinoids were analyzed by SFC-MS/MS in the positive-ion (ESI+) and negative-ion (ESI−) modes. The separation and detection conditions by the 2-EP column and Trefoil AMY1 column are shown in Tables 1 and 2, respectively. Analytical software (MassLynx, version 4.1: Waters Co.) was used for the system control and data processing.

**Separation and Detection of Cannabinoids by SFC-ESI-MS/MS**

One mg/mL of each cannabinoid (CCH, trans-CCH, CP-47497, CP-55940, HU-210, CBD, JWH-018, JWH-073, and JWH-250) in MeOH were prepared as the stock solutions. An aliquot of the solution was injected into the 2-EP (achiral conventional column) and the AMY1 (chiral stationary phase (CSP) column), connected to the SFC-ESI-MS/MS system.

**Table 3. Detection Conditions of SFC-MS/MS of Cannabinoids Using Different Columns**

| Drug          | Formula | MW     | ESI  | Precursor ion (m/z) | Product ion (m/z) | CE (eV) |
|---------------|---------|--------|------|--------------------|-------------------|---------|
| CCH (trans)   | C22H36O2 | 332.52 | −    | 331.5              | 313.4             | 30      |
| CCH (cis)     | C22H36O2 | 332.52 | −    | 331.5              | 313.4             | 30      |
| CP-47497      | C21H34O2 | 318.49 | −    | 317.5              | 299.2             | 30      |
| CP-55940      | C24H40O3 | 376.57 | −    | 375.5              | 357.7             | 30      |
| JWH-073       | C21H3NO  | 327.40 | +    | 328.5              | 155.1             | 30      |
| JWH-018       | C21H3NO  | 341.44 | +    | 342.4              | 155.1             | 28      |
| JWH-250       | C21H3NO  | 334.20 | +    | 336.2              | 121.1             | 20      |
| HU210         | C21H3O2  | 386.56 | +    | 387.6              | 71.1              | 20      |
| CBD           | C21H30O2 | 314.46 | +    | 315.5              | 193.1             | 20      |

**Table 4. Retention Time and Sensitivity of Cannabinoids by SFC-MS/MS Analysis**

| Drug          | 2-EP | AMY1 |
|---------------|------|------|
|               | RT (min) | LOD (S/N=3) ppb | RT (min) | LOD (S/N=3) ppb |
| CCH (trans)   | 8.12 | 0.200 | 2.24 | 0.116 (trans-1)* |
| CCH (cis)     | 8.64 | 0.750 | 3.53 | 0.188 (trans-2)* |
| CP-47497      | 8.61 | 0.370 | 2.10 | 0.137 (cis-1)* |
| JWH-073       | 4.17 | 0.004 | 2.87 | 0.188 (cis-2)* |
| JWH-250       | 3.64 | 0.012 | 2.65 | 0.750           |
| HU210         | 9.19 | 0.300 | 2.78 | 0.002           |
| CP-55940      | 10.24 | 3.750 | 1.65 | 0.075           |
| CBD           | 4.21 | 1.500 | 1.96 | 2.000           |
| JWH-018       | 3.92 | 0.012 | 1.45 | 0.091           |

*Calculated as 1:1 mixture of trans-1 (cis-1) and trans-2 (cis-2).

**Table 5. Calibration Curves of Tested Cannabinoids**

| Drug          | Range (ppb) | Linear equation | r   |
|---------------|-------------|-----------------|-----|
| CCH (trans)   | 1–100       | y=10.17x−2.442  | 0.9999 |
| CCH (cis)     | 1–100       | y=7.69x−5.951   | 0.9996 |
| CP-47497      | 1–100       | y=3.824x−2.220  | 0.9995 |
| JWH-073       | 1–100       | y=257.9x+223.0  | 0.9966 |
| JWH-018       | 1–100       | y=128.0x+78.57  | 0.9998 |
| JWH-250       | 1–100       | y=220.9x+16.80  | 0.9998 |
| HU210         | 1–100       | y=50.34x−13.25  | 0.9999 |
| CP-55940      | 1–100       | y=1.370x−4.585  | 0.9996 |
| CBD           | 1–100       | y=1.655x+0.1013 | 0.9983 |

**Table 6. Recovery of Cannabinoids from Herb by SFC-MS/MS Using 2-EP Column**

| Std concn. (ppb) | Recovery (%) (mean, n=3) |
|------------------|-------------------------|
| trans-CCH        | 98.5                    |
| cis-CCH          | 101.9                   |
| JWH-073          | 105.3                   |
| JWH-018          | 90.5                    |
| JWH-250          | 106.7                   |
| HU210            | 102.7                   |
| CP-55940         | 98.8                    |
| CBD              | 87.8                    |
| JWH-018          | 96.8                    |
| JWH-250          | 97.0                    |
calculated from the peak intensity of the low concentration of each cannabinoid versus the baseline noise.

**Determination of Cannabinoids in Dried Plant Products**

To 10 mg of the dried plant pieces (Products A, Y and G), which were obtained from a street market in 2009, 1 mL of ACN was added and vigorously mixed for 1 min. The solution was then filtered through a 0.2 µm membrane (Millex, MILLIPORE), then an aliquot of the supernatant was subjected to the SFC-ESI-MS/MS system. The amounts of the cannabinoids in three plant products were represented as part-per-million (ppm) concentrations. The determination was repeated six times and the precision was defined as relative standard deviation (R.S.D.) (%).

**Recovery of Cannabinoids from Herb Product**

One-milliliter of diluted solution of several cannabinoids in acetonitrile (1–100 ppb) was added to the vial containing 10 mg of dried herb tea product (rose hip) which was purchased from a city market. The vial was vigorously mixed for 1 min, then the solution was filtered through 0.2 µm membrane (Millex, MILLIPORE). An aliquot of the filtrate was subjected to SFC-ESI-MS/MS system. The concentration of each cannabinoid was determined from the corresponding calibration curve. The recovery (%) was defined as \((F/A) \times 100\) (%), where \(F\) is the detection amount of the cannabinoid in the sample and \(A\) is the spiked amount.

**Results and Discussion**

LC-ESI-MS is an efficient technique for the separation and detection of relatively low molecular mass compounds in terms of the qualitative and quantitative analysis. However, the separation of hydrophobic compounds, such as aromatic hydrocarbons and long-chain fatty acids, generally requires a long elution time by reversed-phase chromatography under a higher ratio of water-miscible organic solvents, such as ACN and MeOH. For analysis of the cannabinoids, a high organic solvent ratio in the mobile-phase and/or a relatively long run time was also required. In such a situation, hydroxyl interaction liquid chromatography (HILIC) using a

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**Table 7. Determination of Dried Plant Products by SFC-MS/MS Using 2-EP Column**

| Product | Conc. (n=6) (mean, ppm) | R.S.D. (%) | Conc. (n=6) (mean, ppm) | R.S.D. (%) | Conc. (n=6) (mean, ppm) | R.S.D. (%) |
|---------|------------------------|------------|------------------------|------------|------------------------|------------|
| JWH-073 | 7.78                   | 11.79      | N.D.                  |            | N.D.                  |            |
| JWH-018 | N.D.                   |            | 3906                  | 13.94      | 17686                  | 13.69      |
| trans-CCH | 1065                  | 8.51       | 388.0                 | 5.44       | 41.64                  | 5.34       |
| cis-CCH | 4301                  | 9.58       | 4927                  | 4.65       | N.D.                  |            |
| cis/trans-CCH | 4.04                  | 12.7      |                        |            |                        |            |

N.D.: not detected.
normal-phase column is adopted to decrease the run time. The SFC using compressed CO\(_2\) can also possibly be used for the same purpose. Thus, we tried to determine the synthetic cannabinoids by SFC-ESI-MS/MS method.

The separation efficiency was first investigated using a conventional 2-EP column which was filled with 2-ethylpyridine bonded silica particles. Figure 2 shows a typical separation example of 8 cannabinoids by the 2-EP column. The cannabinoids including cis-CCH and trans-CCH were separated within 12 min by the column. The JWH compounds (e.g., JWH-018 and JWH-073) tended to elute faster than those of the CP analogues (e.g., CCH and CP-47497) which have no nitrogen atom in their structures, but contain an oxygen atom.

The mass spectrometric feature of the cannabinoids was next tested by tandem triple quadrupole MS. Table 3 shows the MS transitions (precursor and product ions) and the effective detection mode (positive or negative) of the tested cannabinoids. The recommended detection mode was dependent on the structure of the cannabinoids. The cannabinoids, i.e., CCH, CP-47497, CP-55940, which have no amine group in their structures, were higher in the negative ion mode (ESI\(^−\)) than the positive ion mode (ESI\(^+\)), whereas the detection by ESI\(^+\) was suitable for the JWH analogues such as JWH-073 and JWH-250. The cleavage position was different in each cannabinoid (Table 3). The sensitivity difference was also observed in the tested cannabinoids (Table 4). Under these separation and detection conditions, a good linearity of the calibration curves was obtained from all tested cannabinoids (Table 5). The recovery (%) of several cannabinoids from dried plant product was next determined. A commercially available herb tea product (i.e., rose hip) was used for the recovery study, because we have no enough real products for recovery experiment. As shown in Table 6, a good recovery (82.8–106.7%) was obtained from the tested cannabinoids. Based on the results of the separation and detection of the authentic cannabinoids, the present method seems to be applicable for the determination of real samples. The qualitative and quantitative determinations of cannabinoids in dried plant products were thus performed by the proposed method using SFC-ESI-MS/MS. Figure 3 shows the multiple reaction monitoring (MRM) chromatograms of the ACN extracts of the plant pieces (Products: A, Y and G). Although the concentration was different in each product, CCH (cis-isomer) was contained in all the products. Furthermore, the relatively low concentration of the trans-CCH was identified in these products (Table 7). However, the ratios of CCH (cis-isomer) versus trans-CCH were different in each product (e.g., A=4.04 and Y=12.7) (Table 7). Products Y and G also contained a high concentration of JWH-018, and a low concentration of JWH-073 was only detected in Product A (Table 7).

The tested cannabinoids was efficiently determined by the SFC-MS/MS, the same as the LC-MS/MS method. However, the separation of the optical isomers of the cannabinoids (e.g., CCH), possessing the isomers of (+)-cis, (−)-cis, (+)-trans and (−)-trans, was theoretically impossible by the 2-EP because the column could not distinguish the difference in the three-dimensional structures of the optical isomers. Moreover, the run time (ca. 12 min) was relatively long for a high-throughput analysis (Fig. 2). To alleviate these drawbacks, the separation using a chiral stationary phase (CSP) column was tried.
Figure 4 shows the optimized MRM chromatograms obtained from the cannabinoids including cis-CCH and trans-CCH. As shown in the chromatograms of the authentic (±)-trans-CCH and (±)-cis-CCH, two optical isomers were completely separated by the AMY1 CSP column. Based on the chromatogram in Fig. 4, the optical separation seemed to be performed in CP-47497. Other achiral cannabinoids were also separated in a short run time of less than 4 min by the SFC method using the AMY1 column. The sensitivity of the methods using the AMY1 and 2-EP columns was next compared in terms of the LOD (S/N=3). Although the LOD values were different from drug-to-drug, the detection sensitivity was essentially the same for both methods (Table 4). Thus, these methods using the chiral and achiral columns seem to be applicable for the analysis of cannabinoids. However, the method using chiral column is predominant for the determination of cannabinoids, because not only stereo isomer, but also optical isomers are separated by the AMY1 column (Fig. 4). The ratios (peak-1/peak-2) of the optical isomers in Product A were 0.948 for trans-CCH and 1.068 for CCH (cis-isomer), whereas those of Product Y were 1.147 (trans-CCH) and 1.032 (cis-CCH) (Fig. 5). In contrast, the concentration of the trans-CCH isomer was negligible in Product G. These results suggest that the products were prepared in a different place and/or different shop. Therefore, the identification of the synthesized lot and preparation place may be possible, based on the concentration difference.

Conclusion

The cannabinoids tested in this study were determined in a short run time by the SFC-ESI-MS/MS method. The optical isomers, such as (±)-trans-CCH and (±)-cis-CCH, were also clearly separated using a CSP column (AMY1). Because compressed CO₂ and a small amount of organic solvents, such as MeOH, are generally used for the mobile-phase in the SFC analysis, the affect on the environment is more reduced than for the LC analysis. In addition, a rapid separation is possible by a high flow rate of the mobile-phase due to the low viscosity of the mobile-phase (Tables 1, 2). The liquid CO₂-based mobile-phase in SFC has made versatility enough to separate a much wider range of compounds than GC and LC, because liquid CO₂ is miscible polar, non-polar, basic and acidic solvents. The other superiority of SFC analysis seems to be wide choice of stationary phases including chiral and achiral columns, reduction of toxic solvent use, saving solvent and short run time. The sensitivity and specificity of the present method using MRM were good enough for the real sample analysis, as demonstrated by the determination of the dried plant products. When a further high sensitivity is required (e.g., biological sample analysis such as blood and urine), the sensitivity seems to be increased by a change in the species and/or the additive of the make-up solution for the MS/MS detection. The proposed SFC-ESI-MS/MS method could be adopted as an alternative method for illegal drugs, such as cannabinoids, the same as GC-MS and LC-MS.

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Conflict of Interest

The authors declare no conflict of interest.

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