Introduction

Tetrahydrocannabinol (Δ9-THC) is a psychoactive substance found in cannabis plants ("Medical Marijuana"). Synthetic Δ9-THC, also called Dronabinol, was approved by US FDA as a drug to treat pain, anorexia and nausea related to chemotherapy and other disorders.

Dronabinol is a light yellow to amber glassy material. It is sensitive to light, heat, and oxygen (air). The impurities in commercial Dronabinol drugs may come from either the synthetic process or through product degradation. Identification of these impurities is required by FDA and ICH guidelines for pharmaceuticals.

A comparison of impurities in Dronabinol from a variety of sources was performed by HPLC and LCMS.

Materials and Methods

Materials

- Austin Pharma API, Dronabinol, USP
- Capsules manufactured from Austin Pharma API
- Marion® @ (RLD)
- Generic Dronabinol manufactured by Par Pharmaceuticals

Methods

HPLC method conditions are based on USP 29 monograph for Dronabinol. LCMS run conditions were adapted from the HPLC method using ammonium formate as the mobile phase additive for MS detection. Capsules were extracted based on USP Dronabinol capsule monograph.

Instrument

Agilent G6410 Series Triple Quad (GQQQ) LC/MS/MS

Column

Phenomenex Luna 3u C18(2) 1.50x4.6 mm

Column Temperature

20°C

Mobile Phase

71:24:5 v/v MeOH/H2O/THF, with 5 mM ammonium formate

Gradient

Isocratic

Flow Rate

1 mL/min

Injection Volume

5-20 µL

UV wavelength

228 nm

Polarity

Positive scan

Ionization Source

Electrospray Ionization [ESI]

Mass scan range

300-4000 Da

Conclusions

- Impurities in Dronabinol Samples were identified.
- Specified impurities were Cannabinol, cis Δ9-THC and Δ9-THC.
- Unspecified impurities were typically oxidative in nature. Structures were proposed for the observed unspecified impurities based on LCMS results.
- Similar impurity profiles were observed in all three capsules and stressed API. With an increase in number and amount of impurities.

Investigation of the Impurities in Dronabinol Samples by LC/MS

Authors: Huahua Jian, Isil Dilek, Uma Sreenivasan, Kenan Yaser

Comparison of Impurity Profiles of Dronabinol

<table>
<thead>
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<th>RRT</th>
<th>m/z</th>
<th>M.W.</th>
<th>Generic Brand</th>
<th>Capsule Made from Austin Pharma API</th>
<th>Marion® API</th>
<th>Par General</th>
<th>Austin Pharma API Sample Enriched with Impurities</th>
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</table>

• Present in sample
• Not detected in sample or peak is too small to be extracted.

- Mass spectrum is compromised because the impurity is low in the sample.
- The mass spectra of RRT 0.23 for fresh API sample is 312. For the other four samples, it is a mixture of two compounds, with molecular weights 312 and 328. The ratio of the two peaks varies, but m/z 313 (M+H+) and m/z 329 (M+1+H+) are all evident. The m/z 329 peaks is oxygen adduct of m/z 313 peak. The structure of this impurity is proposed to be an isomer of Dihydrocannabinol and its oxygen adduct.

Mass Spectra of Selected Impurities

RRT 0.30 – Hydroxydihydrocannabinol

RRT 0.78 – Cannabinol

RRT 0.91 – cis Δ9-THC

RRT 1.06 – Dihydrocannabinol

Structures of Dronabinol Impurities

- Identification of the specified impurities were confirmed by comparison to authentic references: RRT 0.78 – Cannabinol; RRT 0.91 – cis Δ9-THC; RRT 1.15 – Δ9-THC.
- The proposed structures of other impurities were based on LCMS results. Extracted ion Chromatogram (EIC) confirmed the relative retention time of these impurities. MRM studies did not provide additional information as the impurities are similar in structure.