Investigation of the Impurities in Dronabinol Samples by LC/MS

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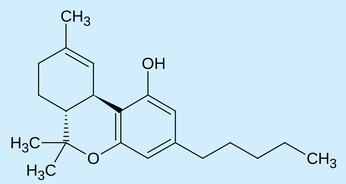
Introduction

Tetrahydrocannabinol (Δ^9-THC) is a psychoactive substance found in cannabis plants ("Medical Marijuana"). Synthetic Δ^9-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.

Dronabinol



Materials and Methods

Materials

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

Methods

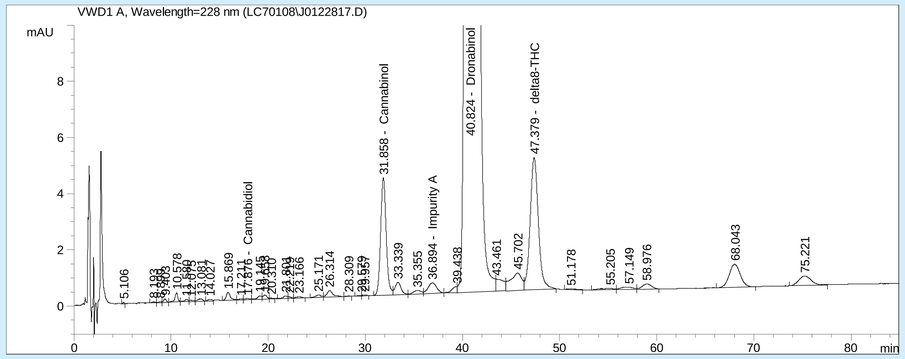
HPLC method conditions are based on USP 29 monograph for Dronabinol. LCMS run conditions were adapted from the HPLC method using ammonium formate as the mobile phase additive for MS detection.

Capsules were extracted based on USP Dronabinol capsule monograph.

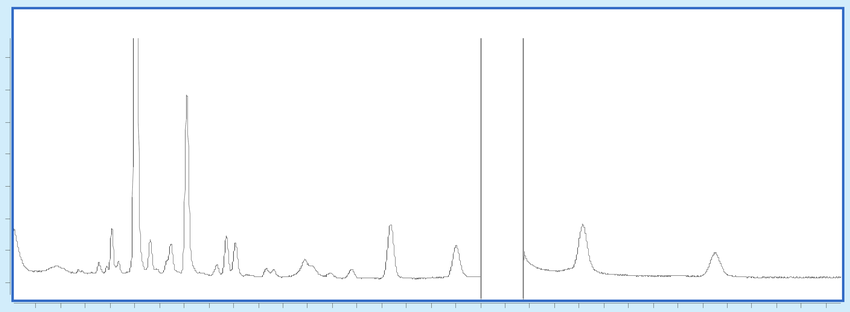
Instrument	Agilent G6410 Series Triple Quad (QQQ) LC/MS/MS
Column	Phenomenex Luna 3u C18(2) 150x4.6 mm
Column Temperature	20°C
Mobile Phase	71:24:5 v./v. MeOH/H_2O/THF, with 5 mM ammonium formate
Gradient	Isocratic
Flow Rate	1 mL/min
Injection Volume	5-20 µL
UV wavelength	228 nm
Polarity, scan type	Positive scan
Ionization Source	Electrospray Ionizaion (ESI)
Mass scan range	300-400 Da

Chromatograms

HPLC Chromatogram:



TIC Chromatogram:



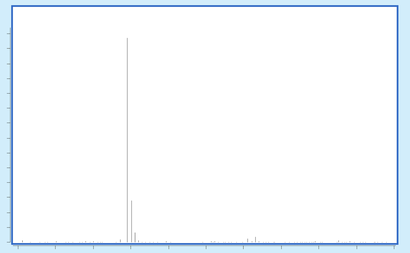
Comparison of Impurity Profiles of Dronabinol

RRT	m/z	M.W.	Generic Brand Capsule Made from AustinPharma API	Marinol®	Par Generic	Austin Pharma API Sample	Stressed API Sample Enriched with Impurities	Identification
0.23	329	328	+	+	+	+, a	+	Hydroxydihydrocannabinol
0.25	361	360	+	+	+	+	+	Trihydroxydihydrocannabinol
0.26	345	344	+	+	+	–	+	Dihydroxydihydrocannabinol
0.28	329	328	+, a	+, a	+, a	–	+, a	Hydroxydihydrocannabinol
0.30	329	328	+	+	+	+	+	Hydroxydihydrocannabinol
0.36	345	344	+	+	+	–	+, a	Dihydroxydihydrocannabinol
0.38	345	344	+	+	+	+	+	Dihydroxydihydrocannabinol
0.45	315	314	–	–	–	–	–	Cannabidiol
0.47	327	326	–	+	+	+	+	Hydroxycannabinol
0.63	313	312	+	+	+	+	+	Dihydrocannabinol
0.68	329	328	+	+	+	–	–	Hydroxydihydrocannabinol
0.71	313	312	+	+	+	+	+	Dihydrocannabinol
0.78	311	310	+	+	b	+	+	Cannabinol
0.82	313	312	+, b	+, b	+, b	+	+, b	Dihydrocannabinol
0.91	315	314	+	+	+	+	+	Cis Δ^9-THC
1.00	315	314	NA	NA	NA	NA	NA	Dronabinol, API
1.06	313	312	+	+	+	–	+	Dihydrocannabinol
1.10	313	312	+	+	+	+, a	+	Dihydrocannabinol
1.15	315	314	+	+	–	+	+	Δ^8-THC

+: Present in sample.
–: Not detected in sample or peak is too small to be extracted.
a: Mass spectrum is compromised because the impurity is low in the sample.
b: The mass spectra of RRT 0.82 for fresh API sample is 312. For the other four samples, it is a mixture of two components, with molecular weights 312 and 328. The ratio of the two peaks varies, but m/z 313 (M+H+) and m/z 329 (M+16+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.

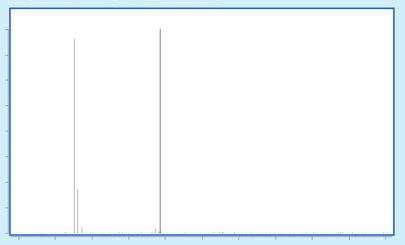
Mass Spectra of Selected Impurities

RRT 0.30 – Hydroxydihydrocannabinol

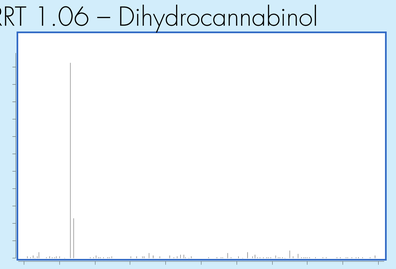


RRT 0.78 - Cannabinol

RRT 0.91 – *Cis* Δ^9-THC

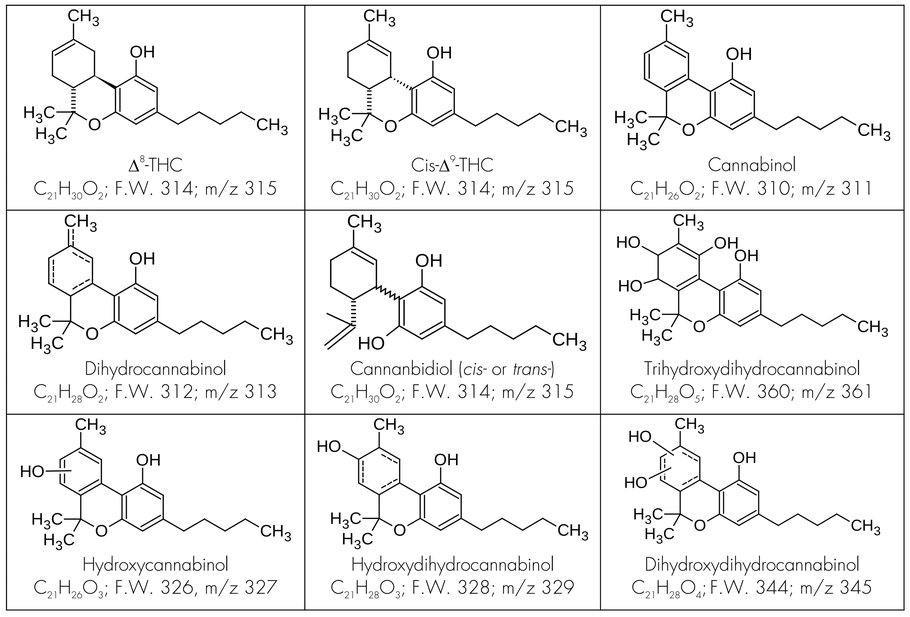


RRT 1.06 – Dihydrocannabinol



Structures of Dronabinol Impurities

- Identification of the specified impurities were confirmed by comparison to authentic references: RRT 0.78 – Cannabinol; RRT 0.91 – *Cis* Δ^9-THC; RRT 1.15 – Δ^8-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.



Conclusions

- Impurities in Dronabinol Samples were identified.
- Specified impurities were Cannabinol, *cis*- Δ^9-THC and Δ^8-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.

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