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Determination of selected synthetic cannabinoids and their metabolites by micellar electrokinetic chromatography – mass spectrometry employing perfluoroheptanoic acid-based micellar phase

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ABSTRACT

Perfluoroheptanoic acid was employed as a volatile micellar phase in background electrolyte for micellar electrokinetic chromatography–tandem mass spectrometry separation and determination of 15 selected naphthoyl- and phenylacetylindole- synthetic cannabinoids and main metabolites derived from JWH-018, JWH-019, JWH-073, JWH-200 and JWH-250. The influence of concentration of perfluoroheptanoic acid in background electrolytes on the separation was studied as well as the influence of perfluoroheptanoic acid on mass spectrometry detection. The background electrolyte consisted of 75 mM perfluoroheptanoic acid, 150 mM ammonium hydroxide pH 9.2 with 10% (v/v) propane-2-ol allowed micellar electrokinetic chromatography separation together with mass spectrometry identification of the studied parent synthetic cannabinoids and their metabolites. The limits of detection of studied synthetic cannabinoids and metabolites were in the range from 0.9 ng/mL for JWH-073 to 3.0 ng/mL for JWH-200 employing liquid–liquid extraction. The developed method was applied on the separation and identification of studied analytes after liquid–liquid extraction of spiked urine and serum samples to demonstrate the potential of the method applicability for forensic and toxicological purposes.

1. Introduction

Syntheses of new psychoactive substances have been developing over the time and many new drugs have been synthesized so far. One of the group of so-called “designer drugs” are synthetic cannabinoids (SCs), which possess similar physiological effects to naturally occurring cannabinoids while their chemical structures are different. Despite the huge structural diversity, SCs bind to one of the both cannabinoid receptors, which is a common physiological property for all SCs [1].

SCs are currently one of the major abusing designer drugs that are distributed, both legal and illegal, as non-drugs products with a label stating “not for human consumptions” (e.g. herbal products (spices), room deodorizers, air fresheners and also as collectibles). SCs exhibit numbers of clinical responses after abusing (namely by smoking) including e.g. nausea, vomiting, blurred visions, ataxia, tremors, confusion, irritability, paranoia, hallucination, mydriasis, hypertension and tachycardia. Several case reports have been published recently [2–6]. SCs are extensively metabolized after administration and some of the metabolites are also physiologically active compounds. There is still a lack of knowledge in their metabolism, however, several works scope on the study of selected SCs metabolism in humans have been published [7–9]. The objective diagnosis of intoxication by SCs for clinical and forensic purposes can be difficult namely in case of the new synthesized SCs for which the metabolites are not commercially available. It is necessary to develop fast and efficient analytical methods to reveal the intoxication as well as quantification of SCs and their metabolites in biological fluids.

The most used method for the separation and identification of SCs and their metabolites in biological fluids (namely in urine) are LC and GC with (tandem) mass spectrometry. Elsohly et al. and Znaleziona et al. published reviews on chemical structure of SCs and related metabolites connected with previously published analytical methods for their identification and determination in herbal blends and biological fluids [10,11]. Generally, reversed phase stationary phases (C8 and C18) are used for LC/MS for SCs analysis employed ESI or APCI ionization [12–14].

SCs are extensively metabolized in human organism and the objective diagnosis of intoxication by SCs is not possible by identification and determination of the parent compound in blood

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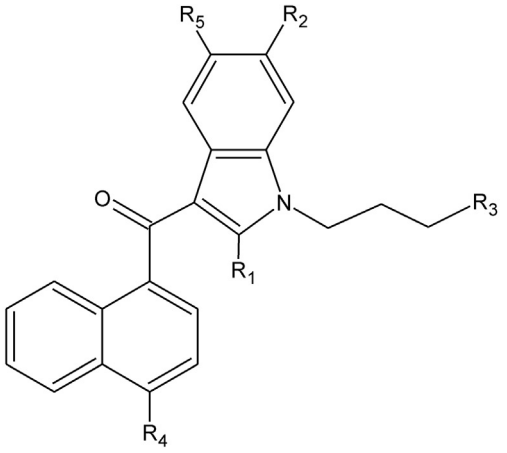
samples only [15,16]. Simultaneous quantification of 20 SCs and 21 metabolites and semi-quantification of 12 alkyl hydroxyl metabolites in human urine by LC–MS/MS was published by Scheidweiler et al. [17]. Sobolevsky et al. identified two main hydroxylated metabolites of JWH-018 by GC–MS and LC–MS methods [18].

GC–MS as one of the most frequently used analytical method for toxicology analyses has one drawback in case of separation and identification of SCs and their metabolites – derivatization is necessary. Silylation is the most common derivatization method for SCs metabolites providing the highest sensitivity and lowest retention [19,20].

Only two works have been published on separation and determination of SCs by electrodriven methods. Gottardo et al. published a MEKC separation of SCs in herbal blends employing UV detection [21]. Sodium borate pH 8.0 with 30 mM sodium dodecyl sulfate (SDS) and the addition of 20% (v/v) propane-1-ol was used as the running electrolyte for the separation of twelve SCs. The developed method was applied on determination of SCs in herbal blends and also octanol/water partition coefficients were estimated as a crucial parameter of their hydrophobicity, bioavailability, absorption and toxicity information.

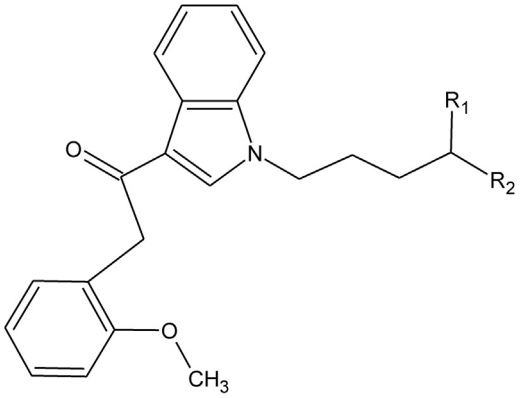
Twelve SCs were separated and determined by MEKC–MS/MS [22]. The MEKC–MS/MS method was applied on the identification and determination of SCs in illegal herbal blends. 50 mM ammonium perfluorooctanoate in 20% (v/v) acetonitrile/water (apparent



JWH-018, 019, 073 and their metabolites

Compound	R_1	R_2	R_3	R_4	R_5
JWH-018	H	H	Et	H	H
JWH-018 2-hydroxyindole metabolite	OH	H	Et	H	H
JWH-018 6-hydroxyindole metabolite	H	OH	Et	H	H
JWH-018 *N*-(4-hydroxypentyl) metabolite	H	H	CH_2-OH-CH_3	H	H
JWH-018 *N*-pentanoic acid metabolite	H	H	CH_2-COOH	H	H
JWH 019 5-hydroxyindole metabolite	H	H	Pr	H	OH
JWH 019 *N*-(6-hydroxyhexyl) metabolite	H	H	PrOH	H	H
JWH-073	H	H	Me	H	H
JWH-073 5-hydroxyindole metabolite	H	H	Me	H	OH
JWH-073 6-hydroxyindole metabolite	H	OH	Me	H	H

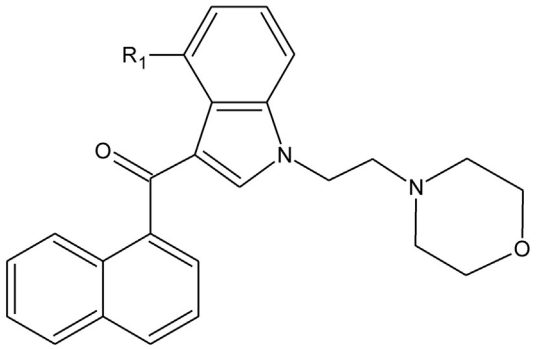
Abbreviations: OH - *hydroxyl;* Me - *methyl;* Et - *ethyl;* Pr - *propyl;* PrOH - *hydroxypropyl;* COOH - *carboxyl*



JWH-250 and its metabolites

Compound	R_1	R_2
JWH-250	H	Me
JWH-250 *N*-(5-carboxypentyl) metabolite	H	COOH
JWH-250 *N*-(5-hydroxypentyl) metabolite	OH	Me

Abbreviations: OH - *hydroxyl;* Me - *methyl;* COOH - *carboxyl*



JWH-200 and its metabolites

Compound	R_1
JWH-200	H
JWH-200 4-hydroxyindole metabolite	OH

Abbreviations: OH - *hydroxyl*

Fig. 1. The scheme of chemical structures of studied synthetic cannabinoids and their metabolites.