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Review

Review: LC coupled to low- and high-resolution mass spectrometry for new psychoactive substance screening in biological matrices – Where do we stand today?

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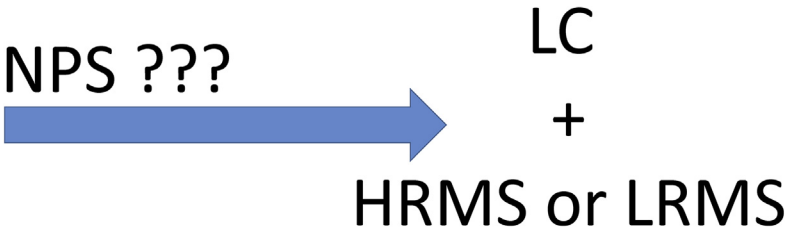
HIGHLIGHTS

- Application of LC coupled to low- and high-resolution MS are reviewed.
- Only articles considered for new psychoactive substances screening.
- Latest developments and applications are highlighted.
- Selected papers critically discussed.

GRAPHICAL ABSTRACT



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ABSTRACT

The field of new psychoactive substances (NPS) is highly dynamic and the situation changes from year to year. Therefore, the current review provides a timely update about the latest developments to help analysts keep the pace with NPS distribution. It covers PubMed-listed studies published between January 2014 and January 2016 dealing with the application of liquid chromatography (LC) coupled low- and high-resolution mass spectrometry (MS) for broad screenings for NPS in clinical (CT) and forensic (FT) toxicology. Latest developments and applications are highlighted and selected papers critically discussed. Comprehensive tables summarizing all discussed articles complete the overview. Finally, an outlook on the future of LC coupled MS in CT and FT is provided and readers will learn why low-resolution mass spectrometry might remain the standard for the next couple of years at least for easy-to-use quantitative screening procedures.

Contents

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1. Introduction

New psychoactive substances (NPS) are usually sold via Internet websites but also via head shops and are expected to mimic the effects of known illegal drugs such as cannabis or amphetamine. Other terms used for novel stimulants are 'research chemicals', 'bath salts', or 'legal highs' [1]. One of the biggest issues with NPS is the ever increasing number since new derivatives are expected to be sold as soon as NPS are scheduled. This is also reflected by the number of compounds annually reported by the European Monitoring Centre for Drugs and Drug Addiction and the United Nations Office on Drugs and Crime [2,3].

Some review articles were published since 2014 in part covering the discussed topic but each with individual and specific focuses. Peters aimed in his review article on literature about the urinalysis of NPS metabolites published after 2008 [4]. Znaleziona et al. summarized in 2015 sample preparations and determination strategies for synthetic cannabinoids in different matrices (serum, urine, herbal blends, oral fluid, hair) [5]. Techniques covered were thin layer chromatography, gas chromatography (GC), liquid chromatography (LC), and capillary electrophoresis, mostly hyphenated to mass spectrometry (MS). The review by Znaleziona et al. also included spectral methods such as infrared spectroscopy and nuclear magnetic resonance but also direct-injection MS. Finally, Castaneto et al. reviewed in 2015 literature published since October 2014 addressing *in vivo* and *in vitro* synthetic cannabinoid pharmacokinetics and analytical methods for their detection and quantification in biological matrices [6]. A review summarizing colorimetric detections, immunochemical assays, GC-MS, and LC-MS methods for the analysis of synthetic cannabinoids and cathinones was published by Namera et al. in 2015 [7].

The present review will not describe basic methodology and principles because such details can be found for instance in Refs. [8–17]. There will also be no exhaustive list of published work but a critical and comprehensive view on the field and expert opinion on selected publications to the topic under review. The present article will cover PubMed-listed studies published between January 2014 and January 2016 dealing with the application of LC coupled low- and high-resolution mass spectrometry (LRMS and HRMS, respectively) for the broad screening of NPS in clinical (CT) and forensic (FT) toxicology. As the field of NPS is highly dynamic and the situation changes from year to year, the current review provides a timely update about the latest developments to help analysts keep the pace with NPS distribution. Latest developments in doping control are not considered but interested readers may refer to the annual reports by Thevis et al. [18–20].

2. Methods

A search of PubMed for English-written literature published between 01 January 2014 and 31 January 2016 was done using combinations of the search terms "mass spectrometry", "new psychoactive substances", "novel psychoactive substances", "psychoactive", and "screening", in the title or the abstract. We identified a total of 88 articles but only 34 were topic-related and considered for this review.

3. Results and discussion

3.1. LRMS for NPS screening

Screening procedures presented using LRMS were all so-called "targeted screening procedures". These procedures were focused on the usually quantitative determination of a predefined set of analytes in biological matrices such as blood [21–23], dried blood spots [24], hair [25,26], or urine [27]. The instrument of choice was always a triple MS coupled to LC. A summary of the key parameters of all mentioned methods within this section can be found in Table 1.

The methods mostly covered parent compounds but also a few metabolites [21–24]. A screening based on parent compounds might be acceptable for methods developed for blood [21–24] or hair [25,26] but not for urine [27]. As nearly all compounds are at least in part metabolized before renal excretion, the main urinary metabolites should be included. However, also complete metabolism was observed e.g. in the case of synthetic cannabinoids [6].

The main focus of the LRMS-based screening procedures was on synthetic cannabinoids (analyzed 131 times), followed by synthetic cathinones (100 times), and phenethylamines and amphetamines (86 times). This also reflects the current situation on the European NPS market, where the synthetic cannabinoids and the synthetic cathinones were the most frequently reported classes [2].

3.1.1. LRMS for NPS screening in whole blood and dried blood spots

The used sample preparations for whole blood and dried blood spots were either extraction [22–24] or just precipitation [21]. An interesting procedure was described by Odoardi et al. who used dispersive liquid/liquid microextraction (DLLME) [22]. DLLME is based on a mixture of extraction solvent (e.g. C_2Cl_4) and disperser solvent (e.g. acetone), which are rapidly injected into an aqueous sample [28]. Odoardi et al. used methanol-deproteinized blood samples and mixed them after centrifugation with water, NaCl, and carbonate buffer (pH 9). A mixture of chloroform/methanol was used as extractant and disperser solvent. The samples were sonicated, centrifuged, and afterwards the sediment phases transferred into vials, evaporated, and reconstituted in methanol/water.

The screening limit of detection (LOD) for most NPS in whole blood were between 0.01 and 2 ng/mL and in dried blood spots between 1 and 10 ng/mL [21,22,24]. The paper published by Tuv et al. reported no limits [23]. If those LODs are sufficient for routine screening is often hard to say as only limited data are available about the antemortem concentration of NPS after recreational use.