Analytica Chimica Acta 898 (2015) 50–59

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Porous membrane-protected molecularly imprinted polymer micro-solid-phase extraction for analysis of urinary cocaine and its metabolites using liquid chromatography – Tandem mass spectrometry

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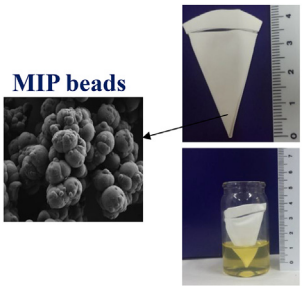
HIGHLIGHTS

- Molecularly imprinted polymer (MIP) for cocaine recognition in urine samples.
- μ-SPE device based on porous membrane-protected containing MIP.
- Fast cocaine and metabolites determination by reverse phase HPLC-MS/MS.
- Limit of quantification lower than the cut-off values for cocaine abuse confirmation.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 31 July 2015
Received in revised form
30 September 2015
Accepted 7 October 2015
Available online 21 October 2015

Keywords:
Porous membrane-protected
Molecularly imprinted polymer
Micro-solid phase extraction
Human urine
Cocaine
High performance liquid chromatography
tandem mass spectrometry

ABSTRACT

Porous membrane-protected micro-solid phase extraction (μ-SPE) using a molecularly imprinted polymer (MIP) as an adsorbent has been proposed as an integrated extraction-cleanup procedure for isolating cocaine (COC) and its metabolites [benzoylecgonine (BZE), ecgonine methyl ester (EME), and cocaethylene (CE)] from human urine. MIP beads have been synthesized using COC as a template molecule, ethylene dimethacrylate (EDMA) as a functional monomer, divinylbenzene (DVB) as a cross-linker, and 2,2′-azobisisobutyronitrile (AIBN) as an initiator. High performance liquid chromatography – tandem mass spectrometry (HPLC-MS/MS) has been used for quantifying the analytes after MIP-μ-SPE. Variables such as urine pH, adsorption temperature and time, mechanical (orbital-horizontal) stirring; and composition of the eluting solution and eluting time, were evaluated. The proposed method was shown to be precise and accurate [relative standard deviations (RSDs) of intra- and inter-day tests ranging from 3 to 8% and from 2 to 10%, respectively]; and analytical recoveries in the range of 89–100%). In addition, excellent accuracy was also verified after analyzing a FDT +25% control material for BZE. The detection limits were in the range of 0.16–1.7 ng L^{-1}, low enough for confirmative conclusions regarding cocaine

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http://dx.doi.org/10.1016/j.aca.2015.10.002
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abuse. The method was finally applied for screening/quantifying cocaine and metabolites in urine samples from poly-drug abusers.

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1. Introduction

Despite the remarkable advances in the development of reliable analytical instruments, sample preparation is still a necessary stage in analytical procedures. This is especially important when analyzing urine and blood/serum due to the high concentration of salts and large biomolecules. Improvements in extraction techniques involve the use of a small volume/mass of the extracting phase (microextraction techniques), and also a small amount of sample, and these techniques are therefore appealing methodologies in the toxicological laboratory where the available sample amount is low. Sample pre-treatments based on solid phase extraction (SPE) have been reported to offer high extraction efficiency for analyte separation/pre-concentration and also for clean-up purposes. As reviewed by Janicka et al. [1], SPE is widely used when assessing cocaine and its metabolites in biological samples. Regarding miniaturization of SPE techniques, solid phase microextraction (SPME) is the most popular and successful sorbent-based (solvent-free) micro-extraction technique. However, some drawbacks concerning SPME (high price of fibers, fiber breakage, long sampling/adsorption times, etc.) are commonly reported [2].

Other miniaturization approaches, such as micro-solid-phase extraction (μ-SPE), have been recently developed. μ-SPE, first proposed by Basheer et al. [3], consists on holding the adsorbent material [3] (or an acceptor liquid phase [4]) in a polypropylene (PP) membrane. Analytes diffuse freely through the membranes's porous and are retained by the solid sorbent/acceptor phase; whereas, the diffusion of other components in the sample is hampered by the membrane. This is especially important in biological/clinical samples which exhibit high amounts of large biomolecules. The PP membranes are typically rectangular (2.0 × 1.5 cm) in shape, and the edges of the PP membrane are heat-sealed after each successive fold and finally after packaging the adsorbent/liquid acceptor phase. The μ-SPE device (5–20 mg of adsorbent) is placed into the vial containing the sample, and it is magnetically stirred (with a magnetic stirring bar) allowing the μ-SPE to tumble freely. The use of solid adsorbent, however, is better than the use of liquid phases in terms of practical operation because the adsorbed analytes can be easily desorbed with an appropriate solvent; whereas, the membrane containing the liquid phase must be chopped off with a sharp blade to allow the analyte-enriched acceptor solvent to be withdrawn with a microsyringe.

Several solid sorbents have been proposed for μ-SPE; such as multiwalled carbon nanotubes (MWCNTs) [3], reverse phase sorbents such as C18 [5–7], and ethylsilane (C2) modified silica [8], rice husk modified to silica–Fe [9], amino and urea-grafted silica gel [10], and synthetic zeolite imidazolate framework 8 (ZIF-8) [11–13]. Selectivity enhancement is one of the greatest challenges of modern SPE developments, and molecularly imprinted polymers (MIPs) have attracted the attention of the scientific community due to the excellent selectivity for those molecules used as templates when performing the MIP synthesis [14]. The high selectivity of MIPs is attributed to the recognition cavities obtained in the highly cross-linked polymer matrix after template removal, which are complementary to the template molecule (and to other structurally similar molecules) in shape, size and chemical functionality. Packaging MIP beads in the μ-SPE format offers as an advantage the possibility of using molecularly imprinted polymer solid phase extraction (MISPE) in batch mode, which results advantageous when dealing with clinical samples (small volumes of sample). The μ-SPE device can be easily removed from the bulk sample after the loading and elution stages without loss of the sorbent (filtration/centrifugation is not needed). As reviewed by Martín-Esteban [15], μ-SPE formats have renewed the interest for batch MISPE approaches. The first attempts have been performed by using MWCNTs coated with MIPs [16], and commercial [17] and lab-prepared [18] MIPs.

The aim of the current work has been the synthesis and characterization of an MIP for cocaine (COC) and metabolites (BZE, EME, and CE) recognition, and the development of a suitable μ-SPE for urine analysis. Most μ-SPE developments use the adsorbent packaged in a PP rectangular envelope (2.0 × 1.5 cm) which is allowed to freely tumble under magnetic stirring. However, since the dichloromethane used for analyte desorption deteriorates the heat-sealing, leading to the loss of MIP beads, we have devised a cone-shape PP membrane for containing the MIP beads. The deterioration of the heat-sealing has not been reported in published methods when using other solvents such as hexane [3,12], acetonitrile [5–7], acetone [8,13], toluene [11], and methanol [9,10,16,17]. The excellent pre-concentration factor achieved and the use of HPLC-MS/MS lead to limits of detection lower than the cut-off values of BZE in urine for confirmation analysis of cocaine abuse [19,20].

2. Materials and methods

2.1. Instrumentation

COC, BZE, EME and CE determination was performed with a 3200 Q TRAP LC/MS/MS system (ABSciex, Concord, Canada), equipped with a Kinetex 5μ C18 100 Å reverse phase column (100 mm length × 2.10 mm i.d., 5.0 μm particle diameter) from Phenomenex (Torrance, CA, USA) connected to a Phenomenex C8 guard column (4 mm length × 3.0 mm i.d), a Flexar FX-15 UHPLC binary chromatographic pump (Perkin Elmer, Waltham, MA, USA), and a Flexar UHPLC autosampler (Perkin Elmer). A Boxcult temperature-controlled incubation camera (Stuart Scientific, Surrey, UK) equipped with Rotabit orbital-rocking platform shaker from J.P. Selecta (Barcelona, Spain) or a low-profile roller (Stovall, Greensboro, NC, USA) was used for MIP-μ-SPE (loading stage) or for MIP synthesis, respectively. The cone-shape PP envelope containing MIP beads was heat-sealed with a TN1010 heat-sealer from Siemens (Munich, Germany). A Raypa® Model UCI-150 ultrasonic cleaner bath from R. Espinar S.L. (Barcelona, Spain) programmable for temperature and time, frequency of 35 kHz for the ultrasound energy, was used for analyte elution from the μ-SPE device. Other laboratory devices were: a field emission scanning electron microscope Ultra Plus (Zeiss Oberkochem, Germany), a Basic20 pH–meter with a glass–calomel electrode (Crison, Barcelona, Spain), a Reax 2000 mechanical stirrer (Heidolph, Kelheim, Germany), a vacuum pump (Millipore Co., Bedford, MA, USA), an oven model 207 from Selecta (Barcelona, Spain), a VLM EC1 metal block thermostat and N_2 sample concentrator from VLM (Leopoldshöhe-Greste, Germany), and a R-210 rotavapor equipped with a B-491

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