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Three-phase molecularly imprinted sol–gel based hollow fiber liquid-phase microextraction combined with liquid chromatography–tandem mass spectrometry for enrichment and selective determination of a tentative lung cancer biomarker

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ABSTRACT

In the present study, the modification of a polysulfone hollow fiber membrane with in situ molecularly imprinted sol–gel process (as a novel and one-step method) was prepared and investigated. 3-(propylmethacrylate)trimethoxysilane (3PMTMOS) as an inorganic precursor was used for preparation of molecularly imprinted sol–gel. The modified molecularly imprinted sol–gel hollow fiber membrane (MSHM) was used for the liquid-phase microextraction (LPME) of hippuric acid (HA) in human plasma and urine samples. MSHM as a selective, robust, and durable tool was used for at least 50 extractions without significant decrease in the extraction efficiency. The non-molecularly imprinted sol–gel hollow fiber membrane (NSHM) as blank hollow fiber membrane was prepared by the same process, only without HA. To achieve the best condition, influential parameters on the extraction efficiency were thoroughly investigated. The capability of this robust, green, and simple method for extraction of HA was successfully accomplished with LC/MS/MS. The limits of detection (LOD) and quantification (LOQ) in human plasma and urine samples were 0.3 and 1.0 nmol L^{-1}, respectively. The standard calibration curves were obtained within the concentration range 1–2000 nmol L^{-1} for HA in human plasma and urine. The coefficients of determination (r^2) were ≥0.998. The obtained data exhibited recoveries were higher than 89% for the extraction of HA in human plasma and urine samples.

1. Introduction

Nowadays, highly selective and sensitive analytical instruments have given us many opportunities for screening of various ranges of analytes in biological fluids. All of these analytical equipments need a valid sample preparation method for better efficiency. Reproducibility, high recovery, fewer operating steps, high throughput, reduction of sample and solvent volume and applicability for automated application are significant indications for a valid sample preparation technique. Due to the variety in range of metabolites and low concentration dosage of drugs in plasma samples, selection of an appropriate sample preparation method is a critical factor for the generation of accurate analytical data. The purpose of sample preparation is to eliminate major interferences from the sample by augmenting the selectivity factor of the method, to improve the enrichment of the analyte and to create a powerful and repeatable way which is independent from changes in the sample media [1].

Hollow fiber based liquid-phase microextraction (HF-LPME) has been accepted as a powerful sample preparation technique [2]. The HF-LPME method is a fast, efficient, sensitive, easy to operate and high enrichment process [3–5]. The efficiency of HF-LPME is related to the mass transfer, and utilizing higher stirring rates can be a useful way to reduce the equilibrium and extraction time [6]. Additionally, the hollow fiber can avoid the interference of biological matrices [7–9]. Because of the robust nature of the hollow fiber membrane, it can solve some of the drawbacks of SPME such as fiber

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fragility, limited availability of fiber coatings, expensive devices, and carry-over between analyses [6].

LPME has been applied in various sample preparation methods such as liquid–liquid microextraction (LLME) [10], liquid–liquid–liquid microextraction (LLLME) [11], carrier mediated [12] and surfactant enhanced methods [13].

In recent years, the uses of molecularly imprinted polymers (MIPs) in analytical chemistry have attained significant interest because of its ability to increase the selectivity of the sample preparation process [14–16]. Several applications of MIP–LPME for the extraction of different analytes have recently been reviewed [17–23]. The poly(vinylidene fluoride) (PVDF) hollow-fiber membranes were modified by a thin layer of molecularly imprinted polymers with thermal polymerization and used for the selective separation of levofloxacin [17]. PVDF with a thin layer of imprinted polymer using water-soluble metal-complex as the template was prepared and the MIP hollow fiber membrane was shown to possess good capacity for the selective permeation of its original imprinting template [18]. The MIP-coated hollow fiber tube was prepared by photo polymerization for the extraction of diethylstilbestrol and its structural analog in milk samples [19]. In a different approach, a two-step modified precipitation polymerization was used and applied to prepare core–shell molecularly imprinted polymeric spheres for recognition and separation of bisphenol A and its derivatives [20]. Recently, hollow fibers modified with MIPs were used for extraction of naproxen enantiomers and as a molecularly imprinted monolithic bar for the microextraction of triazine pesticides [21,22]. In the above mentioned studies, the monomer and cross-linker materials have been based on acrylate or acrylic materials. In all of these works AIBN was used as initiator, and special conditions (UV radiation or thermal bath water) were needed to start and control the polymerization process. It should also be mentioned that the stated methods have some additional disadvantages such as short life span, being time consuming and consisting of multiple steps.

In another approach, an organic–inorganic hybrid method combined with functionalized carbon nanotubes was used for the modification of polypropylene hollow fiber and microextraction of chlorogenic acid in medicinal plants. This was performed through a multi-step process [23].

Molecularly imprinted solid-phase extraction in combination with dispersive liquid–liquid microextraction (MISPE–DLLME) and microextraction (MIP SPME–DLLME) are new strategies in sample preparation for extraction and screening of various ranges of analytes in biological, environmental and food analysis [24–29]. It seems that development of a simple, single-step, selective, stable method with a longer lifetime for the modification of hollow fiber membrane is a crucial issue.

In our group, MIPs as artificial receptors have been successfully applied for the off-line and on-line solid phase extraction of different analytes in biological fluids and pharmaceutical samples [14–16,30–33]. In this study, a novel and one-step inorganic MIP sol–gel process for the modification of polysulfone hollow fiber membrane is presented. This modified MIP sol–gel hollow fiber membrane (MSHM) was applied for the selective extraction of hippuric acid (HA) as a lung cancer biomarker in human plasma and urine samples [34]. The results of this work were supported by LC/MS/MS and some effective parameters in the extraction process were investigated and optimized. To the best of our knowledge no report can be found of the modification of hollow fiber membrane surface with in situ inorganic molecularly imprinted sol–gel method. Apart from the MSHM, non-molecularly imprinted sol–gel hollow fiber membrane (NSHM) was also synthesized under the same conditions but in the absence of the template for comparison.

2. Experimental

2.1. Reagents and apparatus

Polysulfone hollow-fiber membranes (PSH) (self-made: 30.0 × 0.8 i.d. mm, porosity = 75%, pure water flux = 12 L/(m^2 h Bar), Huppuric acid (HA), L-tyrosine (Tyr), L-tryptophan (Trp), kynurenine (Kyn), and 3-(propylmethacrylate) trimethoxysilane (3PMTMOS) with purity higher than 97% were purchased from Alfa Aesar (Karlsruhe, Germany). Methanol (MeOH), acetone (ACT), acetonitrile (ACN), toluene, n-hexane, benzene, cyclohexane, trifluoroacetic acid (TFA), ammonium hydroxide, and acetic acid were supplied from Merck (Darmstadt, Germany). HA was dissolved in ACN at 1.0 mmol L^{-1} and stored at 4 °C and it was found to be stable for more than one month. For different HA solutions, it was diluted with ultra-pure water. Mefenamic acid was used as internal standard for all experiments.

All experiments were performed using a triple quadrupole mass spectrometer (Micromass Ultima, Waters, Manchester, UK), equipped with an electrospray ionization source (ESI) and operated in negative ion mode. For data handling and quantification, MassLynx (version 4.1) was used. The liquid chromatography (LC) instrument included two pumps, Shimadzu (Kyoto, Japan), an autosampler, CTC-Pal (Analytics AG, Zwingen, Switzerland) and a 50 mL sample loop. The analytical column was a ZORBAX SB-C18 (150 × 3.9 mm, 4.0 μm particle size).

Mobile phase A was 0.01 mol L^{-1} ammonium acetate at pH 9.8, and mobile phase B was 0.01 mol L^{-1} ammonium acetate: methanol (20:80). The starting gradient was 30.0% of mobile phase B with a hold of 3.0 min and then increased to 90 % at 3.0 min with a hold of 3 min and then to 30% again. The column oven temperature was set at 40 °C and the CTC-Pal tray temperature was set at 8 °C. The automatic switch valve in the mass detector was set to divert the first 3.0 min of the gradient program. The MS source block temperature and desolvation temperature were 150 and 350 °C, respectively. Nitrogen was used as both drying and nebulizing gas and argon was used as collision gas (collision energy 15 eV). The scan mode was multiple reaction monitoring using the precursor ion at m/z (M + 1; m/z: 177.94), and after collisional dissociation the product ion 133.96 was used for quantification of HA.

2.2. Preparation of MSHM and NSHM

In the first step, for removing any pollutants, the polysulfone hollow fiber (PHF) was washed with MeOH, followed with water and ACT. To prepare the sol solution 0.8 mL of 3PMTMOS as the precursor and 0.7 mL of HA (0.3 mmol L^{-1} in ACN) as the template molecule were mixed and sonicated for 30 min to create maximum binding possibility. Then 0.45 mL TFA (100%) as the catalyst was slowly added in three steps (each time 0.15 mL) and the solution was sonicated for 10 min. Subsequently, drop by drop 0.15 mL distillate water was added to start the hydrolysis process and the solution was kept in this state for 30 min. In the following, PHF was immersed in the sol solution for 15 min. The modified MIP sol–gel hollow fiber membrane (MSHM) was then placed into a desiccator for 24 h for further aging. Finally, to complete the polycondensation process, the prepared MSHM was kept at a temperature gradient between 50 and 150 °C for 4 h. After completing these steps, to remove the trapped template and create a porous selective surface, the MSHM was washed with a mixture of MeOH: acetic acid (80:20) for 4 h. Apart from the MSHM, non-molecularly imprinted (NSHM) was prepared at the same conditions as MSHM, only without the template to be used as a control polymer. The process of preparation is shown in Fig. 1.