Journal of Colloid and Interface Science 531 (2018) 654–663

Contents lists available at ScienceDirect

Journal of Colloid and Interface Science

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

Chiral separation of (±)-methamphetamine racemate using molecularly imprinted sulfonic acid functionalized resin

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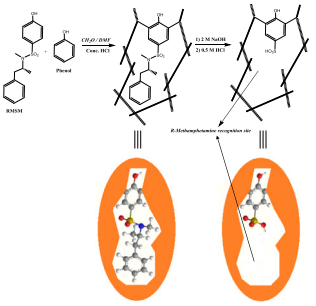
GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 12 June 2018
Revised 14 July 2018
Accepted 17 July 2018
Available online 18 July 2018

Keywords:
Molecular-imprinting
Methamphetamine
Sulfonic acid resin
Chiral resolution

ABSTRACT

In the present study, a sulfonic acid functionalized enantio-selective resinous material was developed for effective chiral separation of (±)-methamphetamine racemate. R-methamphetamine-sulfonamide phenolic derivative was first prepared and fully characterized utilizing instrumental and spectroscopic techniques, then the sulfonamide was implemented in an acid catalyzed condensation copolymerization with phenol and formaldehyde. The resulted resinous material was then exposed to successive alkaline and acidic treatments in order to remove the R-methamphetamine enantiomer out of the resin matrix and obtaining the molecularly imprinted enantio-selective material, which was also investigated by scanning electron microscope, FTIR and XPS spectroscopy. The maximum selective extraction of the R-methamphetamine enantiomer was achieved at pH 7. The adsorption isotherms indicated an adsorption capacity of 233 ± 1 mg/g and followed the well-known Langmuir model. Also, the enantio-separation experiment of the racemic mixture was performed by column technique and both the supernatant loading and the eluant recovery solutions indicated an enantiomeric excess of 80% and 67% related to S- and R-methamphetamine, respectively.

1. Introduction

The majority of biologically active organic molecules and drugs are chiral due to the lack of symmetry elements or presence of one or more asymmetric carbon atoms. In this case, the chiral molecule will not superimpose on its mirror image and both the molecule and its mirror image form is called enantiomers [1,2]. As a result of the different, and sometimes opposite, biological and toxicological behavior that usually displayed by many enantiomer pairs, the chiral separation of chiral molecules into its enantiomers is a major challenge facing many fields such as pharmaceutical and

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https://doi.org/10.1016/j.jcis.2018.07.070
0021-9797/

biomedical industries besides the forensic chemistry [3,4]. In one of the tragic events of the late last century called the thalidomide disaster where thousands of embryos were deformed due to misuse of S-thalidomide instead of the sedative-hypnotic R-thalidomide by some women during the pregnancy [5].

Methamphetamine (*N*-methylamphetamine) is a central nervous system (CNS) stimulant, which is medically prescribed for some cases associated with mental disorders such as attention deficit hyperactivity disorder. However, because of the impact of methamphetamine on mental and psychological health, it was classified as an illegal product that can only be traded through medical prescriptions [6]. The structural formula of methamphetamine containing a single chiral carbon, resulting in two enantiomeric forms, which are S(+)- and R(-)-methamphetamine [7]. Both enantiomeric forms are stimulant to the CNS but S-methamphetamine displayed a comparatively higher pharmacological activity and consequently, the risk of addiction is considerably higher in the formulation containing the S-enantiomer or a mixture of R- and S-enantiomers compared to that containing only R-methamphetamine enantiomer [8].

Besides the great importance of methamphetamine chiral discrimination process in the pharmaceutical, biomedical and forensic applications, this process is also important from the legal point of view [9]. According to US federal law, the charge of possession of methamphetamine is in case if the percentage of S-enantiomer exceeded 80% in the sample that criminalized by the authorities [10,11].

Until the 1980s, there were no effective techniques to prepare or separate biologically active drugs with a considerable enantiomeric purity [12–16]. However, recently various techniques that based on liquid chromatography have become remarkably effective in enantiomeric chiral discrimination of many optically active compounds [17–21]. All chromatographic separation methods are based primarily on the presence of chiral stationary phases (CSPs), which can be obtained by fixing certain chiral species such as nucleic acid, polysaccharides or protein onto suitable solid supports [22,23]. Among various CSPs, those that are manufactured based on molecularly imprinted polymers (MIPs) displayed remarkably higher efficiency compared to the other previously mentioned types concerning the lower cost, higher affinity, selectivity, and ease of preparation [24,25]. These important features have expanded the utility of MIPs not only in the enantiomeric chiral purification but also in some biotechnical applications including drug delivery systems [26,27], biosensors [28–30], and artificial antibodies [31,32].

The basic procedures in the preparation of MIPs include the synthesis of a template-monomer complex that could be copolymerized with a cross-linker. The targeted template molecules are contained within the obtained three-dimensional polymeric network, which can be liberated out of the polymeric matrix leaving selective active binding sites to match the molecular shape, configuration, and size of the removed template [33].

In the current work, R-methamphetamine molecularly imprinted sulfonic acid functionalized phenolic resin (RM-SP) was synthesized and examined for chiral resolution of (±)-methamphetamine racemic mixture. Various methods such as elemental analysis, mass spectra, FTIR and NMR spectra were utilized to extensively investigate the performed synthetic procedures. In addition, the surfaces of the prepared adsorbent particles were visualized using scanning electron microscopy and the surface elemental analysis was examined by EDX spectra. The enantio-selective extraction of the targeted R-methamphetamine enantiomer by the fabricated resin was tested in batches for optimizing the conditions by which the chiral separation could be carried out.

2. Materials and methods

2.1. Materials

R- and S-methamphetamine (95%) were provided from Aurora Fine Chemicals LLC (USA), 4-hydroxybenzenesulfonyl chloride (HBSC) (95%) was obtained from BOC Sciences Inc. (USA), phenol and formaldehyde were purchased from Sigma-Aldrich (USA). The other reagents and solvents were supplied from different companies and used as received without any treatments.

2.2. Synthesis of R-methamphetamine-sulfonamide derivative (RMSM)

The sulfonamide derivative was prepared following the synthetic steps of a previous report [34] and schematically displayed in Scheme 1. In 250 mL round-bottomed flask 2 g R-methamphetamine was completely dissolved in 20 mL pyridine. The flask was heated in a water bath at 50 °C under magnetic stirring. In another vial, 2.6 g HBSC was mixed with 20 mL pyridine and strongly shaken till complete dissolution, then gradually injected into the first R-methamphetamine solution. The stirring was then continued at 50 °C and TLC was utilized to hit upon the synthesis process. After 3 h, the product crude precipitate was obtained by pouring the contents of the reaction flask on a beaker containing crushed ice. The product crude was precipitated, filtered and washed with distilled water then the sulfonamide (RMSM) derivative was purified by recrystallization using a water/ethanol (50/50) solvent mixture.

2.3. Synthesis of imprinted resin (RM-SP)

The imprinting process is schematically displayed in Scheme 2. In 500 mL beaker 3 g of the previously prepared RMSM was mixed with 3 g phenol and the mixture was dissolved in 20 mL dry DMF. 15 mL, 37% (wt/v) formaldehyde solution was then added followed by 5 mL glacial acetic acid and the contents were homogenized by magnetic stirring. 2 mL, 5 M HCl solution was then dropped gradually within approximately 10 min. A solid pink resin mass was suddenly formed, which was separated and continuously heated in a microwave oven at about 80 °C for 1 h to complete the set and cross-linking of the formed polymeric network. The dry polymeric resin mass was then crushed using a mortar and the resin particles with an average size of 200 μm were obtained by passing the smashed particles through 50 mesh sieve. The R-methamphetamine enantiomer was then got out of the resinous network by placing the obtained dry resin particles in 100 mL, 2 M NaOH solution at 100 °C under magnetic stirring for 6 h followed by acidification by placing the particles in 100 mL aqueous HCl solution (0.5 M) for 1 h at 30 °C. The resin particles were then collected and stored in a desiccator till performing the subsequent experiments. In order to evaluate the performed enantio-selective molecular imprinting process, another non-imprinted blank adsorbent (NI-SP) was synthesized by using an equivalent amount of 4-hydroxybenzenesulfonic acid instead of RMSM.

2.4. Characterization

The percentages of carbon, hydrogen, and nitrogen in the synthesized RMSM were determined by Elemental Analytical Instrument (Perkin–Elmer 240 C, USA). A Perkin–Elmer Fourier-Transform Infrared (FT-IR) spectrometer supported with Attenuated total reflectance (ATR) unit was employed to investigate the sulfonamide derivative RMSM along with the fabricated resins NI-SP and RM-SP within scan ranged between 500 and 4000 cm^{-1}. The mass spectrum of RSMS was recorded by ICP-MS