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Synthesis/characterization of molecular imprinted polymer based on magnetic chitosan/graphene oxide for selective separation/preconcentration of fluoxetine from environmental and biological samples

Asma Barati, Elahe Kazemi, Shayessteh Dadfarnia *, Ali Mohammad Haji Shabani

Department of Chemistry, Yazd University, Safaieh, 89195-741 Yazd, Iran

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ABSTRACT

A novel molecular imprinted polymer (MIP) as a SPE sorbent was synthesized for fluoxetine through a coprecipitation method. The synthesized polymer was characterized by Fourier transform infrared (FT–IR) spectroscopy and scanning electron microscopy (SEM). The kinetic and adsorption equilibrium was studied. Quantification of fluoxetine was done based on the competitive inclusion complex formation of fluoxetine with phenolphthalein-β-cyclodextrin using fiber optic linear array spectrophotometry. The method exhibited a linear dynamic range of 0.8–10.0 $\mu g\,L^{-1}$ with a detection limit of 0.03 $\mu g\,L^{-1}$ and a preconcentration factor of 500. The developed method was successfully applied to determine fluoxetine in various samples.

Introduction

Fluoxetine (FXT), also known by the trade name of 'Prozac' or 'Sarafem', is the most prescribed selective serotonin re-uptake inhibitor (SSRI) antidepressant drug worldwide [1]. It has a long effacing half-life of one to several days, and about 11% of the dose is urinated as unchanged fluoxetine [2]. Thus, due to the high consumption of this drug, there is a risk of dispersing its residue in environmental waters [3]. In view of these considerations, determination of fluoxetine in environmental water samples and human urine is quite essential and can be advantageous for therapeutic and toxicological purposes.

Liquid chromatography [4–10], gas chromatography [11] nuclear magnetic resonance spectrometry [12], capillary electrophoresis [13], potentiometry [14], thin-layer chromatography [15], spectrofluorimetry [16] and spectrophotometry [17] are the most widely used analytical techniques for fluoxetine measurement. Among these techniques, spectrophotometry is the most appropriate one due to its inherent simplicity, low cost, and wide availability in quality control laboratories [18]. However, the spectrophotometric methods developed for the determination of fluoxetine are usually associated with some major drawbacks such as the lack of selectivity [19]. Furthermore, owing to the low concentration of fluoxetine and complexity of matrices of real samples, especially biological fluids, a selective separation and preconcentration step is inevitable prior to its instrumental determination. Different sample preparation techniques including liquid–liquid extraction [5], solid phase extraction (SPE) [6–10], stir bar sorptive extraction (SBSE) [20] and hollow-fiber supported liquid membrane extraction [21] have been used for the separation and preconcentration of fluoxetine in different matrices. Among these methods, solid phase extraction is one of the most attracted sample pretreatment techniques mainly because of low consumption of organic solvents, high recovery, and possibility of trace enrichment and matrix removal in a short time. However, regardless of the mode of SPE, the choice of sorbent is a key factor influencing its performance. To meet the requirements of high selectivity, a novel type of sorbents, namely molecular imprinted polymers (MIPs), have been increasingly utilized for solid phase extraction of different analytes [22]. MIPs are synthetic polymers possessing specific cavities drafted for a target molecule, which is greatly promising in the development of highly selective

* Corresponding author. Tel.: +98 3531232667; fax: +98 3538210644.
E-mail address: sdadfarnia@yazd.ac.ir (S. Dadfarnia).

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SPE methods for trace analysis. They also have an excellent potential for complex sample clean-up. Surface imprinting through grafting the imprinted polymer on the surface of a supporting material such as Fe_3O_4 nanoparticles [23], titanium dioxide [24], carbon nanotubes [25] and graphene oxide [26] has proved to be a promising method for preparation of MIP sorbents. The as-synthesized sorbents enjoy significant features including high selectivity, high sorption capacity, fast sorption/desorption kinetics, high stability, low cost, and relative ease of preparation.

Graphene oxide, with unique mechanical properties, extremely large surface area, and abundant oxygen-containing functional groups (e.g. epoxide, hydroxyl, and carboxylic groups), which allows easy chemical modification of its surface is an excellent supporting material for synthesis of imprinted polymers [27]. The nanoscale size of graphene oxide enables miniaturization of the system and, thereby, lowers the diffusion barrier. Furthermore, its large surface area ensures easy and complete removal of the template molecule and provides a potentially high rebinding capacity [28]. Several researches have been reported the successful application of graphene oxide as a supporting material for synthesis of molecular imprinted polymers [27,29–31].

Chitosan (poly-β-(1,4)-2-amino-2-deoxy-D-glucose), which is an amino-polysaccharide produced by the N-deacetylation of chitin, is another excellent candidate for this purpose. Chitosan possesses some remarkable properties such as high abundance, good hydrophilicity, non-toxicity, biocompatibility, biodegradability, and efficient sorption ability [32]. Additionally, the presence of multi hydroxyl and amino functional groups on its polysaccharide backbone offers the flexibility for its surface modification. However, its high solubility at low pHs ($pH < 4$) and poor mechanical stability limit its practical application in aqueous solutions [33]. The immobilization of chitosan on a solid substrate such as Fe_3O_4 nanoparticles or graphene oxide may be beneficial to overcome these limitations via improving its stability and mechanical strength. A few studies have dealt with the application of chitosan [34,35], magnetic chitosan [36] or combination of chitosan/graphene oxide [29,37,38] as a supporting material in the synthesis of molecular imprinted polymers. However, based on our literature review, there is only one report on the use of mixture of magnetic chitosan/graphene oxide as a supporting material [39]. There is also no report on the synthesis of fluoxetine imprinted polymer on individual or combination of those supporting materials.

The aim of this study was to develop a novel, reliable method for selective separation and simple determination of fluoxetine. For this purpose, a sorbent of MIP was synthesized using magnetic chitosan/graphene oxide as a supporting material to provide multi imprinting sites, large surface area, and ease of separation of magnetic nanocomposites. The synthesized polymer was thoroughly characterized, and its capability as a selective sorbent in magnetic solid phase extraction of fluoxetine was investigated. Determination of the extracted fluoxetine was done using a simple, fast and sensitive spectrophotometric method based on the competitive inclusion complex formation of fluoxetine with phenolphthalein-β-cyclodextrin (PHP-β-CD) [40]. All the parameters affecting the extraction and determination of fluoxetine were investigated and optimized. The developed method was successfully applied to the separation, preconcentration and determination of fluoxetine in pharmaceutical formulation, human urine and environmental water samples.

Experimental

Materials and reagents

All the reagents used were of at least analytical grade and the standard solutions were of high purity grade (>90%). Ferric chloride ($FeCl_3.6H_2O$), ferrous chloride ($FeCl_2.4H_2O$), ethylene glycol dimethacrylate (EGDMA), acetonitrile (ACN), glutaraldehyde (25 wt.%), methacrylic acid (MAA) acrylic acid (AA), sodium hydroxide (NaOH), methanol, acetic acid, graphite powder, phenolphthalein (PHP), β-cyclodextrin (β-CD), and high molecular weight chitosan were purchased from Merck Company (Darmstadt, Germany). Chitosan with an average molecular weight of 350 kDa and deacetylation degree of >75% was purchased from Sigma-Aldrich (Missouri, USA). 2,2 Azobisisobutyronitrile (AIBN) was purchased from ACROS Company (New Jersey, USA), and pure fluoxetine hydrochloride was obtained from Tehran Chemie (Tehran, Iran). Double distilled water was used in the preparation of all the solutions. A stock standard solution of 1000 mg L^{-1} of fluoxetine was prepared by dissolving an appropriate amount of fluoxetine hydrochloride in a minimum volume of ethanol and diluting it with distilled water. The solutions of PHP used in the UV–visible spectral measurements were freshly prepared on a daily basis by dissolving a weighed amount of it in a small volume of NaOH solution and diluting the solution with double distilled water.

Instruments

All the absorbance spectra were recorded using an Avantes photodiode array spectrophotometer model AvaSpec-2048 equipped with a source model of Ava Light-DH-S-BAL. The pH measurements were done using a Metrohm pH meter (model 827, Switzerland) with a combined glass calomel electrode. A Haiddolph heater-stirrer (model MR 3200, Germany) was utilized for polymer synthesis. The magnetic phase separation was carried out by means of a strong magnet (1.2 T, 10 cm × 5 cm × 2 cm).

Synthesis of the sorbent

Synthesis of magnetic nanoparticles

Magnetic Fe_3O_4 nanoparticles were synthesized by dissolving 2.25 g of $FeCl_2{\cdot}4H_2O$ and 8.4 g of $FeCl_3{\cdot}6H_2O$ in 400.0 mL of doubly distilled water under nitrogen atmosphere and vigorous stirring. The temperature was then raised to 80 °C, and 20.0 mL of ammonia solution was added rapidly to the mixture. Then, a black precipitate was formed which was collected with an external magnet after 5 min, washed several times with ethanol and distilled water, and dried in vacuum at 60 °C [41].

Synthesis of graphene oxide (GO)

Graphene oxide was synthesized based on the modified Hummers method [42,43]. For this purpose, graphite powder (5.0 g) and $NaNO_3$ (2.5 g) were added to concentrated sulfuric acid (120.0 mL, 0 °C) under vigorous stirring. Then, potassium permanganate (15.0 g) was slowly added to the suspension, the ice bath was removed, and the mixture was stirred at room temperature overnight; thereby, the solution mixture turned into a brown pulp. Subsequently, 150.0 mL of H_2O was added under vigorous stirring, followed by slow addition of 50.0 mL of H_2O_2. The solution was centrifuged, and the resultant precipitate was washed with distilled water several times to remove the excess acid. At this stage, a gray powder of graphite oxide was obtained. Finally, the graphite oxide powder was dispersed in deionized water under ultrasonication for 30 min to exfoliate graphite oxide to graphene oxide. The mixture was centrifuged, and the final product was dried in vacuum at 60 °C.

Synthesis of graphene oxide/magnetic chitosan composite (GO/Chm)

Two grams of pure chitosan was dissolved in 100.0 mL of acetic acid solution (2% v/v), and the solution was subjected to sonication for 30 min. Afterwards, 0.75 g of previously synthesized magnetic nanoparticles was added to the solution, and it was stirred for

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