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Preparation and evaluation of magnetic core–shell mesoporous molecularly imprinted polymers for selective adsorption of amitriptyline in biological samples

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ABSTRACT

In this study, preparation of magnetic surface molecular imprinted polymer (MMIP) is employed for sensitive solid phase extraction and measurement of amitriptyline (AMT) by spectrophotometric technique. After polymerization, cavities in the polymer particles corresponding to the AMT were created by leaching the polymer by an appropriate solution. The synthesized nanoparticles of magnetic surface molecular imprinted polymer mesoparticles (Fe_3O_4@SiO_2–MIP) were characterized by transfer electron microscopy (TEM), vibrating sample magnetometer (VSM), Fourier transform infrared spectroscopy (FTIR), X-Ray Diffraction (XRD) and Brunauer–Emmett–Teller (BET). Also, the pH of zero-point charge (pH_{zpc}) for Fe_3O_4@SiO_2–MIP was determined with the pH drift method. The influence of various parameters such as pH, amount of polymer and contact time were investigated by an optimization technique named Box–Behnken design (BBD) and the proposed quadratic model was fitted very well with the experimental data. The validity of optimum parameters and the equation of parameters were investigated by analysis of variance (ANOVA). Also Scatchard isotherm was explored for the equilibrium adsorption investigation and finally, the prepared polymer was successfully applied to the selective identification and the determination of AMT in plasma samples.

1. Introduction

Amitriptyline hydrochloride as an anti-depressant drug, is used for treatment of some psychiatric diseases. Chemically, this drug is a tricyclic dibenzo-cycloheptadiene which acts as an inhibitor for norepinephrine and serotonin uptake. This medication can lead to a balance in behavior, reduction in the amount of stress and abnormal reactions. Abnormal use of this drug causes severe mental and physical problems such as seizure, hyperreflexia, depression and even addiction [1]. Measuring and determining the exact amount of amitriptyline in pharmaceutical and biological samples such as human plasma and urine is important because the maximum daily intake of this drug is between 50 to 200 mg. Analytical separation and preconcentration techniques, such as solid phase extraction, are convenient, simple, and effective solutions to get rid of sample matrix interruptions [2,3]. This technique has been used extensively in recent years to measure accurately and selectively the pharmaceutical [4-6], biological [7,8], environmental [9,10], food [11], forensic [12] and toxin samples. Electrochemical sensors and their combination with nanomaterials caused ultra-high sensitive and eco-friendly methods in designing of novel sensors for detection of specific analytes (drugs and amino acids in pharmaceutical preparation steps and also biologically important materials) [13-17].

One of the areas of development and improvement of the solid phase extraction technique is improvement of adsorption selectivity. In the last decade, molecular imprinting polymers have attracted researcher's attention due to their ability to rapidly and selectively adsorp various analytes [18-21]. This adsorbent is used for extraction and pre-concentration of antidepressants in samples [22-25]. Molecular imprinted polymer mesoparticles (MIP-MPs) are practical materials that make them possible molecular recognition in different fields of analytical sciences such as preconcentration methods [26], solid phase extraction [27], preparation of stationary phase for liquid chromatography [28], drug delivery systems [29], optical and electrochemical sensors [21,30,31], catalytic systems [32] and artificial antibodies [33]. In addition, these mesoparticles have more resistance to antibodies against difficult conditions, such as acid and base environments, high temperatures and organic solvents [34]. Selective cavities of molecular imprinted nanomaterials are formed by non-covalent interaction of amitriptyline as a template and an appropriate functional monomer in the

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presence of cross linker and initiator [35-38]. One of the main problems with the polymers handling in selective extraction is the need to centrifuge and isolate polymer from the solution, which can lead to significant loss of polymer during filtration. Magnetic cores are the most effective and practical solutions. In fact, magnetic nanoparticles are coated with molecular matrix polymers, and hereby the polymer can be simply removed from the solution using a magnet. Fe_3O_4@SiO_2–MIP is prepared by encapsulating Fe_3O_4 magnetite mesoparticles with the polymer [39-41]. Various methods have been proposed for preparation of core–shell magnetic MIPs [42-50]. The surface of metal mesoparticles is coated with different chemical compositions. These coatings give them some special properties, such as oxidation resistance, cluster inhibition, chemical and physical stability and the ease of polymer deposition on the mesoparticles. The influence of parameters and multi-factor interaction effects in extraction and sensitive determination of amitriptyline were explored in detail using response surface methodology (RSM) based on the Box–Behnken design (BBD). Analytical performance, binding properties and selectivity of the polymer were all investigated in the present study.

2. Apparatus

All spectroscopic measurements of this study were performed using a UV–vis spectrophotometer (PerkinElmer's LAMBDA 25). Fourier transform infrared (FT–IR) spectroscopic analysis of the synthesized material was conducted using an infrared spectrometer (Bruker FTIR Vertex 70) over the wavenumber range 400–4000 cm^{-1} in KBr. High angle X-ray diffraction patterns were collected at ambient temperature using Cu-Kα radiation on a Philips-PW 17 C diffractometer. Transmission electron microscopy (TEM) analyses were conducted by a JEM-2010 (HT) microscope at an accelerating voltage of 200 kV. The magnetic property was analyzed by using a vibrating sample magnetometer (VSM) (Meghnatis Daghigh Kavir Co., Kashan, Iran) with a maximum field of 18 kOe at room temperature. N_2 adsorption isotherms were measured on the magnetic MIP by PHS-1020 system (PHSCHINA).

3. Materials

Amitriptyline (AMT), ethyl glycol dimethacrylate (EGDMA, 98%), methacrylic acid (MAA) and azobisisobutyronitrile (AIBN) were purchased from Sigma–Aldrich, USA. Iron (II) chloride tetrahydrate ($FeCl_2{\cdot}4H_2O$), iron (III) chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), methanol (MeOH), acetonitrile (MeCN), acetic acid (HOAc) and tetraethoxysilane (TEOS), were purchased from Merck (Darmsctat, Germany). Deionized water was used in all experiments.

3.1. Preparation of mesostructured Fe_3O_4@SiO_2

Magnetic mesoparticles were prepared according to a conventional chemical treatment method with minor modifications, and then they were covered by silica layers [51]. Iron (III) chloride hexahydrate (6.84 g) and iron (II) chloride tetrahydrate (2.15 g) were dissolved in 100 mL ultra-pure water with vigorous mechanical stirring (at 85 °C under nitrogen purging) to get solution. Then, 13.15 mL of 28% aqueous NH_4OH was added dropwise from a burette to the solution. The color of the solution changed from orange to black by adding ammonia. After 30 min stirring at 25 °C, the black magnetic precipitates were washed twice with pure water and once with 0.1 molar sodium chloride by magnetic decantation.

Then, 40 mL of tetraethoxysilane (TEOS, 10% (v/v), 40 mL) was dropped into the magnetite mesoparticles prepared above, followed by glycerol (30 mL). The pH of the mixture was adjusted to 5.5 using glacial acetic acid, and the suspension was then stirred and heated (90 °C for 2 h) under nitrogen atmosphere. After cooling, the suspension was washed with ultra-pure water and methanol. During washing steps, a permanent magnet was used to assist collection of the magnetic black precipitate. The obtained Fe_3O_4 mesoparticles were dried at 55 °C under vacuum for 14 h.

3.2. Preparation of Fe_3O_4@SiO_2–MIP

Synthesis of AMT imprinted polymer on the surface of Fe_3O_4@SiO_2–MIP was carried out through surface initiated atom transfer radical polymerization (SI-ATRP). Therefore, AMT (3 mmol) as the template molecule, MAA (6 mmol) as the functional monomer, EGDMA, (20 mmol) as the crosslinking agent and SiO_2 coated magnetic surface mesoparticles (SCMMPs, 400.0 mg) as the core were dispersed into acetonitrile solution (degassed, 45 mL) in a 50 mL Schlenk flask. After sealing, shaking, and purging the mixture with nitrogen, a 5.0 mL acetonitrile solution with 50.0 mg of AIBN as the initiator was added into the suspension with a sample injector. The resultant mixture was ultrasonicated (60 °C for 4 h) under nitrogen protection and then stirred for 15 h. The product was washed with ethanol until no AMT was detected spectrophotometrically in the washing solution [32].

3.3. Batch adsorption experiments

An appropriate aliquot of AMT solution (20 mL in concentration ranges from 0.01 to 50 µg/mL) was treated with 117.5 mg of MIP and NIP sorbents. The pH of the suspensions was maintained to 8.02 by adding sodium hydroxide or hydrochloric acid. The samples were incubated for 19.87 min with continuous stirring at room temperature. After centrifugation (5.0 min, 4300 rpm), the supernatant solution was removed and the AMT preconcentrated onto MIP nanoparticles was then eluted by 5.0 mL of methanol (elution solvent) during 5 min stirring. The suspensions were centrifuged and then eluent solutions containing AMT were separated from the nano-MIP. The AMT contents of the solutions were determined by UV spectrophotometry detection at 245 nm. The percent adsorption, i.e., the drug recovery, was determined using the following equation:

$$\%R = \left[\frac{(C_t)}{C_0}\right] \times 100\% \quad (1)$$

where C_0 and C_t represent the initial and final (after adsorption) concentrations of the drug in mg/L, respectively.

The adsorption capacity of Fe_3O_4@SiO_2–MIP or Fe_3O_4@SiO_2–NIP can be computed from the initial and equilibrium concentrations of AMT as Eq. (2)

$$Q = \frac{(C_0 - C_e)v}{w} \quad (2)$$

C_o and C_e are the initial and equilibrium concentrations of AMT (from 0.5 to 50 ppm) respectively, v is the solution volume in L, and w is the amount of sorbent in g.

3.4. Pharmaceutical and serum sample analysis

For AMT determination in pharmaceutical preparations, an average mass of 5 tablets of amitriptyline (50.00 mg, Arasto Pharmaceutical Company) from the same batch were selected, then finely ground and homogenized in a mortar. A portion of powder, equivalent to 50.00 mg of AMT, was accurately weighed and dissolved in 50 mL of ultra-pure water in pH of 8.0. The mixture was then sonicated for 19.87 min and allowed to rest for 10 min before bringing it up to volume. The mixture was filtered into a 100 mL volumetric calibrated flask. Further dilutions were made up with ultra-pure water to obtain appropriate concentrations of AMT.

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