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Fabrication of new drug imprinting polymer beads for selective extraction of naproxen in human urine and pharmaceutical samples

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ABSTRACT

A drug imprinting polymer based on suspension polymerization was prepared with N,N-dimethylacrylamide and 1-(N,N-*bis*-carboxymethyl) amino-3-allylglycerol as functional monomers, N,N methylene diacrylamid as the cross-linker, naproxen as the template and 2,2′-azobis (2-methylbutyronitrile) as the initiator. The drug imprinted polymer was characterized by Fourier transform infrared spectroscopy, elemental analysis, thermogravimetric analysis and transmission electron microscopy. The imprinted polymer of agglomerated micro-particles with multi-pores was used for solid phase extraction. The drug imprinted polymer sorbent was selective for naproxen. The profile of the naproxen uptake by the sorbent reflects good accessibility of the active sites in the imprinted polymer sorbent. In addition, the equilibrium adsorption data of naproxen by imprinted polymer were analyzed by Langmuir isotherm models. The developed method was utilized for determination of naproxen in pharmaceutical and human urine samples by high performance liquid chromatography with satisfactory results.

1. Introduction

Naproxen, (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid, is poor water soluble and a non-steroidal anti-inflammatory drug commonly used for the reduction of moderate inflammation, pain, and fever. This drug is rate-limited by its dissolution. It has been reported that naproxen exists in one crystal form and its crystallographic structure has been described as monoclinic (Song and Sohn, 2011). The potential benefits and risks of naproxen therapy as well as alternative therapies should be considered prior to initiating naproxen therapy. The lowest possible effective dosage and shortest duration of therapy consistent with treatment goals of the patient should be employed. The analysis of naproxen has been basically based on a preconcentration step followed by chromatographic separation and detection. Several methods have been reported for the determination of this drug, including solid-phase extraction-chromatographic/photometric determination (María Costi et al., 2008), solid-phase microextraction coupled to liquid chromatography (Aresta et al., 2005), fluorimetric determination (Ibanez and Escandar, 2005), solid-phase microextraction based sol–gel technique (Sarafraz-Yazdi et al., 2012), monolithic molecularly imprinted stationary phase (Chent et al., 2011), of affinity chromatography model using molecular imprinting (Lei and Tan, 2002) and liquid chromatography–mass spectrometry (Farre et al., 2001).

The molecularly imprinting polymer (MIP) involving the formation of cavities in a synthetic polymer for a template drug is useful for selective extraction. This analytical method is a rapidly developing technique for preparation polymeric materials that are capable of high molecular recognition (Rimmer, 2008; Wang et al., 2003; Nicholls and Rosengren, 2002; Dmitrienko et al., 2004). Radical polymerization usually used for cross-linking of the functional monomers in the presence of template structures and then removing the target. Imprinting polymer preparation has generally been based on hydrogen bonding interactions for small compounds. The scientists always try to prepare imprinting polymers for high affinity toward the template compounds. For this purpose the type of monomers and polymerization were designed for better selectivity. The method presented in this paper employs a new synthetic monomer for the preparation of naproxen-imprinted polymer based on suspension polymerization. To the best of our knowledge suspension polymerization is an established process of the polymer industry for the manufacturing of polymer particles. Naproxen with etheric oxygen and also carboxylic acid group, was selected as candidate template. Therefore, the choice of the functional monomer making up the polymer must be judicious in order to create highly specific cavities with suitable size designed for the template drug. Our synthesized monomer 1-(N,N-*bis*-carboxymethyl)amino-3-allylglycerol (AGE/IDA) shows

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high affinity toward the naproxen via hydrogen bonding and produce non-covalent imprinting polymer with specific recognition sites. The imprinted polymer in batch-wise mode as the solid-phase extractant, was used for the pretreatment of trace naproxen in human urine and tablet prior to the determination of concentration of naproxen by high performance liquid chromatography (HPLC).

2. Experiment

2.1. Instruments

Elemental analysis was carried out on a Thermo-Finnigan (Milan, Italy) model Flash EA elemental analyzer. In addition, thermogravimetric analysis (TGA) was carried out using a TGA-50H (Shimadzu Corporation, Kyoto, Japan). Fourier transform infrared spectra were recorded on a Jasco Fourier transform infrared spectrometer (FT-IR-410, Jasco Inc., Easton, Maryland). The transmission electron microscopy (TEM) images were obtained in on a TEM-PHILIPS model CM 120 Netherlands.

2.2. Reagents and solutions

N,N-dimethylacrylamide (DMAA) and aluminum oxide were acquired from Aldrich (Steinheim, Germany). 2,2′-azobis (2-methylbutyronitrile) (AIBN) was purchased from Across (New Jersey, USA). Divinyl benzene (DVB), N,N methylene diacrylamid (MDAA), iminodiacetic acid (IDA), acetonitrile, hydrogen disodium phosphate, dihydrogen sodium phosphate, phosphoric acid, potassium hydroxide, acetic acid and methanol were products of Merck (Darmstadt, Germany). Polyvinyl alcohol, allyl glycidyl ether (AGE) was purchased from Fluka Chemica (Buchs Switzerland).

DMAA was purified with Aluminum oxide to remove the impurities from DMAA. The stock solution (100 mg L^{-1}) of naproxen was prepared by dissolving appropriate amounts of naproxen in methanol. To adjust the pH of the solution, 0.01 M acetic acid-acetate buffer or 0.01 M phosphate buffer were used wherever suitable.

2.3. Synthesis of the functional monomer 1-(N,N-bis-carboxymethyl) amino-3-allylglycerol (AGE/IDA)

Details of the preparation and characterization of the functional monomer, coupling of AGE/IDA, was reported in the previous work (Ahmad Panahi et al., 2010). The monomer was purified and used for polymeric sorption in next step.

2.4. Preparation of naproxen imprinted poly[1-(N,N-bis-carboxymethyl)amino-3-allylglycerol-codimethylacrylamide] (poly(AGE/IDA-co-DMAA)) by suspension copolymerization

A 200 mL three-neck round-bottom flask was equipped with a reflux condenser, thermometer and a nitrogen gas inlet and outlet. The flask was initially charged with 60 mL of 3.33 mg L^{-1} of water solution of polyvinyl alcohol. Then the template and monomer phase containing 100 mg of naproxen as template, 1 mL of DMAA, 8.76 mmol of AGE/IDA, 8 mL of ethyleneglycoldimethacrylate as cross-linker, and 12 mL of toluene was dispersed in water solution of polyvinyl alcohol. The mentioned mixture was stirred for 10 min and then the 0.1 g of AIBN was added to the flask. The polymerization reaction was carried out at 70 °C for 6 h and then at 90 °C for 3 h with vigorous stirring under a nitrogen atmosphere. After complete polymerization, the polymer was filtered immediately and washed with 250 mL of water and dried in the oven at 45 °C. The resultant bulk polymers were ground in a mechanical mortar and sieved through a 100 μm sieve and washed again with

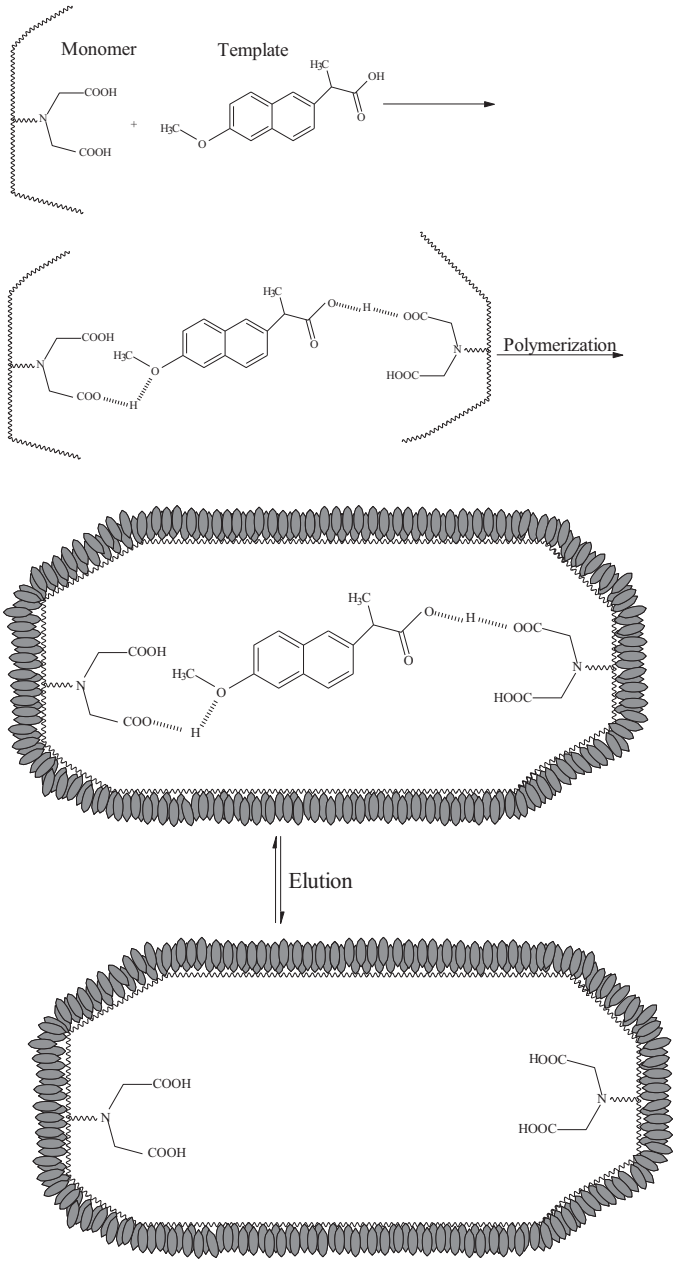

Fig. 1. Schematic presentation of synthesis process of poly(AGE/IDA-co-DMAA).

methanol/water (90:10) for 48 h. The product was recovered by filtration and was washed with ultra pure methanol. Ultimately, the imprinted polymer was dried under vacuum and stored at 4 °C. The methodology used to synthesize MIP is summarized in Fig. 1. The MIP was characterized by Fourier transform infrared spectroscopy (FT-IR), elemental analysis, TEM and TGA. FT-IR (NaCl, cm^{-1}) 3386 (OH), 1651 (C=O), 2936 bending (CH_2), 1208 (C—O). Elemental analysis for imprinted polymer revealed that the percentage of carbon, hydrogen, and nitrogen were (C: 60.36; H: 7.12; N: 2.17%).

The non-imprinted polymer (NIP) was also prepared in the same way but without the template. The FT-IR and elemental analysis of NIP is like the MIP (C: 59.35; H: 7.13; N: 2.39%).

2.5. HPLC system

Chromatographic separations were carried out on an Agilent HPLC, 1200 series, equipped with UV/Vis detector. Separations were carried out on a Zorbax Extend C18 column (15 cm – 4.6 mm,