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Preparation and study of tramadol imprinted micro-and nanoparticles by precipitation polymerization: Microwave irradiation and conventional heating method

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ABSTRACT

In the present work a series of tramadole imprinted micro- and nanoparticles were prepared and study their recognition properties. Methacrylic acid (MAA), as a functional monomer, ethylene glycol dimethacrylate (EGDMA) as a cross-linker and different solvents (chloroform, toluene and acetonitrile (ACN)) were used for the preparation of molecularly imprinted polymers (MIPs) and non-imprinted polymers (NIPs). Several factors such as template/monomer molar ratio, volume of polymerization solvent, total monomers/solvent volume ratio, polymerization condition (heating or microwave irradiation) were also investigated. Particle size of the polymers, transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FT-IR), rebinding, selectivity tests and release study were applied for evaluation of the polymers. The optimized polymers with smaller particle size and superior binding properties were obtained in acetonitrile under heating method. MIP_{A4} with a size of 42.6 nm and a binding factor (BF) of 6.79 was selected for selectivity and release tests. The polymerization was not successful in acetonitrile and toluene under microwave irradiation. The MIP_{A4} could selectively adsorb tramadol, compared to imipramine, naltrexone and gabapentin. The data showed that tramadol release from MIP_{A4} was significantly slower than that of its non-imprinted polymer. Therefore, MIP nanoparticles with high selectivity, binding capacity and ability to control tramadol release could be obtained in precipitation polymerization with optimized condition.

1. Introduction

Molecular imprinting technique is one of the most attractive and promising method to create template-shaped cavities in polymeric network with memory of the template molecule to be used in molecular recognition. The active binding site in a molecularly imprinted polymer (MIP) has a unique geometric structure which is particularly selective for a template molecule (Beltran et al., 2007; Haginaka, 2009; Kan et al., 2009; Mohajeri and Ebrahimi, 2008; Mohajeri et al., 2011). Several factors (e.g. template–monomer interactions, the stoichiometry and concentration of the template and monomers, the kind and polarity of the porogen and the temperature of polymerization) influence the selectivity performance of MIPs (Batra and Shea, 2003; Mijangos et al., 2006). Many efforts have been done over the years to develop MIPs for different applications (Malaekeh-Nikouei et al., 2012; Mohajeri and Ebrahimi, 2008; Mohajeri et al., 2010, 2012; Pérez-Moral and Mayes, 2004). The MIPs have been evaluated recently as the new drug delivery systems to increase the drug loading capacity and sustain the drug release in aqueous media (Cirillo et al., 2004; Mohajeri et al., 2012). Typically, MIPs were prepared by bulk polymerization as brittle monoliths which are then ground and sieved to create a large surface area and appropriate size of particles (Esfandyari-Manesh et al., 2011; Luliński et al., 2012). Unfortunately, this procedure is time-consuming, causes loss of materials, the cavities of the MIPs may be destroyed, reduced the efficiency of binding assay due to difficult access to the depth of the polymer matrix (Yoshimatsu et al., 2007) and also the irregular shape of such MIP particles generally give

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less binding recognition in adsorption procedure (Abouzarzadeh et al., 2012; Esfandyari-Manesh et al., 2011; Poma et al., 2010). To simplify and optimize the synthesis procedure and to enhance the performance of MIP particles, alternative synthetic tactics have been applied to avoid the need for grinding the polymer monolith, sieving and separating the imprinted particles (Abouzarzadeh et al., 2012; Mohajeri et al., 2011). Several methods such as suspension polymerization (Zhang et al., 2009), core–shell emulsion polymerization (Gao et al., 2011) and mini-emulsion polymerization (Curcio et al., 2009) have been reported for preparation of polymeric imprinted micro- and nanoparticles. Although, these methods have clear value, optimization of dependable experimental protocols can be lengthful, the general enforceability is suspicious in some cases, and the residual emulsifier or stabilizer, remain in polymerization media, potentially affect the selectivity of the final imprinted polymer. The precipitation polymerization, as an alternative to above mentioned methods, is a marvelous and simple approach which could be applied as a general method for producing high-quality spherical imprinted particles. Precipitation polymerization is a surfactant-free method that involves polymerization of monomers in an excess of solvent (Wang et al., 2007). This method has been also used for preparation of MIP nanoparticles. Due to the higher surface area-to-volume ratios in nanoparticles, the imprinted cavities are more easily accessible for the templates, and the binding kinetics are improved (Gao et al., 2011; Poma et al., 2010). MIPs are stable under different conditions such as heating, organic solvents and different pH values. Their stability and other beneficial properties, make them attractive for numerous applications such as chemosensor (Guan et al., 2008), surface plasmon resonance (SPR) sensor (Matsui et al., 2005), water treatment (Caro et al., 2005), artificial antibodies (Ramstrom et al., 1996a), separation of enantiomers from a chiral compound (Ramstrom et al., 1996b; Schweitz et al., 1997a, 1998), based stationary phases for capillary electro chromatography (Schweitz et al., 1997a,b), solid-phase extraction (Andersson, 2000) and high performance liquid chromatography (HPLC) stationary phase (Lai et al., 2007). Previous studies indicated that the MIP nanoparticles have a good potential for the controlled delivery of drugs and can increase the time of drug release (Ciardelli et al., 2004; Kryscio and Peppas, 2009; Puoci et al., 2004). Also, MIP nanoparticles can enhanced the capacity of template loading versus the monolith polymers that synthesized by bulk polymerization (Cacho et al., 2004). The present research was focused on the synthesis of tramadol {(1R, 2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol} imprinted micro- and nanoparticles with high loading capacity and selectivity. Tramadol is a centrally acting synthetic analgesic compound that is not derived from natural sources (Sindrup et al., 1999). Tramadol overdose and poisoning has been increased recently especially in young adults with a history of drug abuse and mental disorders (Shadnia et al., 2008). Nausea and vomiting, depression, tachycardia, seizures and prolonged hypoglycemia are the most common symptoms of tramadol poisoning (Marquardt et al., 2005; Mugunthan and Davoren, 2012; Taghadosinejad et al., 2011). Also, this toxic molecule is a potent water pollutant chemical agent which should be detected and removed from waste water in a water treatment process (Rúa-Gómez and Püttmann, 2012). Therefore, preparation of molecularly imprinted polymeric beads is valuable for application in HPLC column and chemical sensor design for analysis of tramadol in water and biological fluid. Also, the molecularly imprinted polymeric beads could be evaluated as a drug delivery system for sustaining the tramadol release and thereby decreasing its toxicity and adverse effects following oral administration. In this work, a series of tramadol imprinted polymers were prepared using MAA and EGDMA as monomers and ACN, toluene and chloroform as polymerization solvent. The polymerization was initiated and continued under microwave irradiation or conventional heating method and the performance of the final MIP particles was studied in different experiments.

2. Materials and methods

2.1. Chemicals

Methacrylic acid (MAA, purity: 98%) and ethylene glycol dimethacrylate (EGDMA, purity: 98%) were purchased from Sigma–Aldrich (Steinheim, Germany); chloroform, toluene, acetonitrile (ACN), methanol and acetic acid were of high purity or HPLC grade and obtained from Merck (Darmstadt, Germany). 2,2′-Azobisisobutyronitrile (AIBN, purity: 98%) was obtained from ACROS (Geel, Belgium). All other chemicals and reagents were of the highest available purity and used as purchased. Tramadol hydrochloride and gabapentin were provided by Daru Pakhsh Company (Tehran, Iran), imipramine hydrochloride by Sobhan Darou Company (Rasht, Iran) and naltrexone hydrochloride by Iran Daru Company (Tehran, Iran) (Fig. 1). Tramadol base (as the template for imprinting process) was prepared by alkalinization of

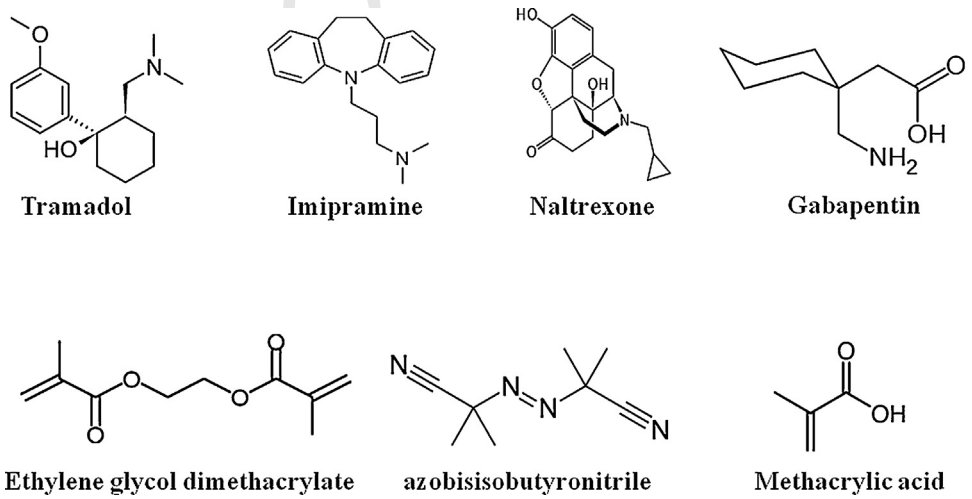

Fig. 1. Structures of chemicals used in this study.

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