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Molecularly imprinted macroporous monoliths for solid-phase extraction: Effect of pore size and column length on recognition properties

E.G. Vlakh[a], M.A. Stepanova[a,b], Yu.M. Korneeva[a], T.B. Tennikova[a,*]

[a] Institute of Macromolecular Compounds, Russian Academy of Sciences, St. Petersburg, Russia
[b] Institute of Chemistry, Saint-Petersburg State University, St. Petersburg, Russia

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ABSTRACT

The series of macroporous monolithic molecularly imprinted monoliths differed by pore size, column length (volume) and amount of template used for imprinting was synthesized using methacrylic acid and glycerol dimethacrylate as co-monomers and antibiotic ciprofloxacin as a template. The prepared monoliths were characterized regarding to their permeability, pore size, porosity, and resistance to the flow of a mobile phase. The surface morphology was also analyzed. The slight dependence of imprinting factor on flow rate, as well as its independence on pore size of macroporous molecularly imprinted monolithic media was observed. The column obtained at different conditions exhibited different affinity of ciprofloxacin to the imprinted sites that was characterized with K_{diss} values in the range of 10^{-5}–10^{-4} M. The solid-phase extraction of ciprofloxacin from such biological liquids as human blood serum, human urine and cow milk serum was performed using the developed monolithic columns. In all cases, the extraction was found to be 95.0–98.6%. Additionally, the comparison of extraction of three fluoroqinolone analogues, e.g. ciprofloxacin, levofloxacin and moxifloxacin, from human blood plasma was carried out. Contrary to ciprofloxacin extracted with more than 95%, this parameter did not exceed 40% for its analogues.

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1. Introduction

Molecular imprinting represents a technique widely used for preparation of polymer materials that are capable to the specific molecular recognition of previously imprinted target molecule [1]. So called “artificial receptors” are generated due to the self-assembly of a template with monomer followed by a cross-linked copolymerization and template removal from bulk or dispersed polymer material after the polymerization process.

The molecularly imprinted rigid polymers (MIPs) find the application in different analytical, semi-preparative and preparative fields such as liquid chromatography, solid-phase extraction, capillary electrochromatography, biosensors, etc. The conventional MIP sorbents for chromatography and sold-phase extraction represent the particular packing solid phase [2–6]. The MIP beads for column preparation can be obtained by different methods, among which the bulk polymerization followed by grinding and sieving of polymer material is the most popular.

Macroporous monolithic MIPs are the modern forms of sorbents intended to the separation processes based on biorecognition. These materials combine the advantages of widely used monolithic columns and MIP technology. As the preferences of monolithic materials, the simplicity of synthesis, versatile surface chemistries, high reproducibility, as well as fast mass transport predominantly controlled by convection can be counted [7,8]. In turn, MIP technology allows the formation of receptor-like binding sites with a ‘memory’ of a shape and functional group position of applied template molecule [1].

Obviously, the mentioned advantages of macroporous sorbents are undoubtedly useful for their application in MIP-based separations. Since the macroporous monoliths have practically no dead volume, the surface of flow-through macropores is dominantly involved in adsorption/desorption process [9]. It means that the removal of a template from macroporous monolithic matrix occurs significantly faster comparatively to the case of packed columns. At the same time, due to better accessibility of imprinted sites the

* Corresponding author at: Institute of Macromolecular Compounds, Bolshoy pr. 31, 199004, St. Petersburg, Russia.
E-mail address: tennikova@mail.ru (T.B. Tennikova).

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specific sorption kinetics have to positively differ comparing to the bead-based MIP devices.

Contrary to conventional MIP polymerization mixture, in the case of monoliths it includes also chemically inert porogenic solvents necessary for macroporous structure formation. In most cases, a template used for imprinting represents a solid compound, which has to be dissolved before the polymerization. Ideally, it could be dissolved in functional monomer. If not, the template has to be introduced into appropriate solvent, which inevitably becomes one of the components of porogenic mixture and can affect the formation of desired pore size. Thus, the optimal monolithic MIP must combine both highly selective imprinted sites and good flow-through properties. Sometimes, the synthesis of these materials represents a "bottle-neck" task. However, a range of successful examples on preparation and application of MIP monoliths can be found in several recent reviews [10,11].

Despite the existing data on MIP monoliths preparation, the most of works suffer from poor sorbent characterization that is very important for understanding of features MIP applications. Usually, the surface morphology determined by SEM but no pore characteristics for NIP and MIP were described [12–15]. At the same time, the introduction of a template into polymerization mixture used for MIP preparation, as well as an increase of its amount, sometimes may influence the phase separation process and, in turn, change the pore properties of final monolith [16,17]. Thus, it seems to be very important to use for comparison the sorbents with close structure and pore characteristics since these parameters may affect the mass transfer inside the sorbent and as a result separation/extraction efficiency.

Among the known applications, MIP materials are widely considered as stationary phases for isolation and highly specific detection of antibiotics [18,19]. Such interest to the development of the effective methods for discovery of these medicines in complex natural mixtures is closely connected with their growing application in agriculture, animal aquaculture and food industry that leads to the environment pollutions. There are excessive amounts of publications devoted to the development of bead-based MIPs [20–28] and only several works concerning the preparation of MIP monoliths imprinted with antibiotics can be found in current literature [29–33]. Among latter's there are a few publications focused on imprinting of fluoroquinolone antibiotics into monolithic materials. Particularly, Yan et al. reported the results on synthesis of MIP monolithic column based on copolymer of methacrylic acid (MAA) and ethylene glycol dimethacrylate (EDMA) imprinted with ciprofloxacin (CIP), as well as the data on evaluation of binding constant of CIP with imprinted cites and CIP recovery from urine samples [30]. Sun et al. and Yan et al. described the preparation of MIP monolithic columns based on MAA-EDMA copolymer imprinted with norfloxacin and the application of developed sorbents for analysis of analogous antibiotics in pork meat [31] and human urine [32]. Zheng et al. corresponded the synthesis of pefloxacin imprinted capillary column for determination of flouroquinolones in milk samples [33]. However, neither the characteristics of MIP materials obtained, nor the correlation between material properties and column behavior were discussed.

In present work, we concerned the synthesis of macroporous MIP monolithic columns with different pore size and column length to evaluate the impact of these parameters on molecular recognition of imprinted molecule. The antibiotic ciprofloxacin (CIP) was chosen as a model compound. The macroporous MIP columns were synthesized in situ by polymerization of methacrylic acid (MAA) and glycerol dimethacrylate (GDMA) as monomers and ciprofloxacin as a template. The porogenic system was optimized to reach similar macroporous structure for both MIP and control non-imprinted polymer (NIP). Such important parameters as imprinting factors, dissociation constants and adsorption capacity were determined. Moreover, the possibility to isolate ciprofloxacin from different biological liquids (human blood plasma, human urine and cow milk serum) was also demonstrated.

2. Experimental part

2.1. Materials

Methacrylic acid (99% pure), ethylene glycol dimethacrylate (98% pure), glycerol dimethacrylate (75% pure), ciprofloxacin (CIP, 98% pure), 1-dodecanol (98% pure) and 1,4-butanediol (99% pure) were purchased from Sigma-Aldrich (Darmstadt, Germany). 2,2′-azo-bis-izobutyronitrile (AIBN) was a product of Acros Organics (New Jersey, USA) recrystallized prior to use. Levofloxacin (LEV, 98.5% pure) and moxifloxcin (MOX, 98.5% pure) were the products of Zhejiang Apeloa Pharm. Co Ltd (Hangzhou, China) and Fabbrica Italiana Sintetici SpA (Montecchio Maggiore, Italy), respectively.

Acetonitrile (HPLC-grade) was purchased from JTBaker (Phillipsburg,USA). Toluene (99.5% pure), isooctane (99.9% pure) and *n*-nonane (99.5% pure) were received from Vecton (St. Petersburg, Russia). Methanol (HPLC-grade) was a product of JTBaker (Phillipsburg, USA). All other reagents used in the experiments were of the highest grade of purity. All solvents were filtered with a 0.22 μm SPE filter membrane Jet Biofil (Guangzhou, China). The empty stainless steel columns of 4.6 mm i.d. ×50 mm purchased from Supelco (Bellefonte, USA) were used as the molds for in situ preparation of monolithic columns.

2.2. Instruments

The monolithic sorbents were synthesized using MLW U2 water thermostat (VEB, Germany). The morphology of resulting materials was studied with a JSM35 CF scanning electron microscope JEOL (Tokyo, Japan). HPLC experiments were performed on Shimadzu Liquid Chromatographic System equipped with two pumps LC-20AD, system controller SCL-10A VP, scanning UV detector SPD-10AV, degasser and pump DGU-14A (Canby, USA). Column temperature was maintained at 25 ± 1 °C using column thermostat Eppendorf TC-50 (Hamburg, Germany). Data acquisition and processing was performed using LC Solution software (Shimadzu Corporation, Tokyo, Japan). The morphology of monolithic columns was investigated with scanning electron microscopy using cathode sputtering of platinum (50–100 Å thick layer) performed with a Polaron Instruments SEM setup (London, United Kingdom).

2.3. Methods

2.3.1. Synthesis of macroporous molecularly imprinted polymer monoliths

Macroporous monolithic columns were synthesized by free radical copolymerization of MAA (31 mol%) and GDMA (69 mol%) inside the stainless steel housing. The amount of CIP was 1.5 and 3.5 mol%. The polymerization was carried out with 1 mass% (from mass of monomers) of AIBN. The system of porogens consisted of 1,4-butanediol, 1-dodecanol (DoOH) and *n*-nonane. The volume monomers/porogens ratio was 1/3. The pre-polymerization complexes were prepared by dissolution of CIP in a mixture of monomers and stored at 22 °C for 1 h. After that, porogens and initiator were added and the mixture was vortexed and purged with argon for 5 min. Finally, the column housing was filled up with polymerization mixture and placed in water thermostat at 70 °C for 4 h.

After the synthesis was finished each monolithic column was washed with warm (45 °C) mixture, consisting of 19.5 vol% of acetic acid, 0.5 vol% of trifluoracetic acid and 80 vol% methanol until the

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