



Contents lists available at ScienceDirect

Journal of Chromatography B

journal homepage: www.elsevier.com/locate/chromb



Molecularly imprinted polymers for bioanalytical sample preparation

Mariana Roberto Gama, Carla Beatriz Grespan Bottoli*

Institute of Chemistry – State University of Campinas, Unicamp, Brazil

ARTICLE INFO

Article history:

Received 28 June 2016
Received in revised form
20 September 2016
Accepted 23 September 2016
Available online xxx

Keywords:

Molecularly imprinted polymers
Sorbents
Biomarkers
Metabolites
Bioanalysis

ABSTRACT

Molecularly imprinted polymers (MIP) are stable polymers with molecular recognition abilities, provided by the presence of a template during their synthesis, and are excellent materials with high selectivity for sample preparation in bioanalytical methods. This short review discusses aspects of MIP preparation and its applications as a sorbent material in pharmaceutical and biomedical analysis. MIP in different extraction configurations, including classical solid-phase extraction, solid-phase microextraction, magnetic molecularly imprinted solid-phase extraction, microextraction by packed sorbent and solid-phase extraction in pipette tips, are used to illustrate the good performance of this type of sorbent for sample preparation procedures of complex matrices, especially prior to bioanalytical approaches.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

High-throughput bioanalyses are essential to support drug discovery and are used for analysis for metabolites and biomarkers, while plasma, urine and cerebrospinal fluid are the most common biological sample matrices. Despite the high detectability and selectivity of current analytical techniques for quantifying target analytes in biological fluids, biological samples are not usually directly introduced into a chromatographic system without a pre-treatment step.

Abbreviations: MIP, molecularly imprinted polymer; LLE, liquid–liquid extraction; SPE, solid-phase extraction; SPME, solid-phase microextraction; MISPE, molecularly imprinted solid-phase extraction; MMISPE, magnetic molecularly imprinted solid-phase extraction; MSPD, matrix solid-phase dispersion; MEPS, microextraction by packed sorbent; RAMIP-BSA, restricted access molecularly imprinted polymer coated with bovine serum albumin; SBSE, stir-bar sorptive extraction; PT-SPE, solid-phase extraction in pipette tips; MAA, methacrylic acid; EGDMA, ethylene glycol dimethacrylate; DVB, divinyl benzene; TRIM, trimethylol propane trimethacrylate; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; NOBE, *N,O*-bismethacryloylethanolamine; PETA, pentaerythrol triacrylate; PETEA, pentaerythrol tetraacrylate; CEC, capillary electrochromatography; DAD, diode array detector; FL, fluorescence; LOD, limit of detection; LOQ, limit of quantification; RAM, restricted access material; BSA, bovine serum albumin; CSF, cerebrospinal fluid; MALDI, matrix-assisted laser desorption/ionization; TOF, time-of-flight; MS, mass spectrometry; MS/MS, tandem mass spectrometry; UHPLC, ultra high performance liquid chromatography.

* Corresponding author.

E-mail address: carlab@iqm.unicamp.br (C.B.G. Bottoli).

The goals of sample preparation in bioanalytical methods are to: (i) minimize matrix effects, by the reduction of ion suppression; (ii) eliminate sample variability, to achieve more reproducible quantitation even from different sources and to improve method robustness; (iii) increase detectivity, through analyte concentration and removal of interferences from the biological matrices; and (iv) clean samples, in order to increase both instrument uptime and system performance.

Liquid-liquid extraction (LLE), protein precipitation and solid-phase extraction (SPE) are used to isolate and concentrate analytes from biological matrices. Protein precipitation is fast, requires little method development and is cost-effective. However, this method only removes proteins from samples, leaving behind other interferences that can negatively affect the analysis and column lifetime. Traditional LLE removes proteins, phospholipids and salts, but it is time-consuming and difficult to automate, which limits its throughput capability [1–3].

Sample extraction by SPE has gained in popularity because of its compatibility with automation, especially with sorbent material packed into a 96-well format plate. Advances in SPE include the development of on-line procedures, polymeric sorbents that no longer suffer from sorbent drying problems while enjoying extended working pH ranges, and high affinity sorbents, such as molecularly imprinted polymers (MIP).

This short review describes the MIP, discussing aspects of its preparation and its applications as sorbent material for sample preparation routines in bioanalytical methods. Recent pharmaceutical and biomedical applications of MIP in different SPE configurations are also presented to illustrate the good perfor-

mance of this sample preparation procedure for complex matrices, especially for bioanalysis.

2. Molecular imprinting processes

2.1. Synthesis of molecularly imprinted polymers

Molecular imprinting is a process by which selected functional monomers are self-assembled around a template molecule, and subsequently polymerized in the presence of a cross-linker. Once the template molecule is removed from the polymeric structure, a cavity complementary in shape and chemical properties is present in the structure, and becomes available to bind molecules identical to or closely related to the template [4]. Fig. 1 shows a typical MIP synthesis, with the interactions between the template and the functional polymer during the polymerization.

Thus, a MIP is a polymer with a memory of the shape and the functional groups of one or more template molecules. Each MIP has high molecular recognition properties, achieved by using a wide variety of molecules that act as templates. Usually, non-covalent interactions like hydrogen bonds, dipole–dipole and ionic interactions between the template molecule and functional groups present in the polymer matrix drive the molecular recognition phenomena.

Different approaches may be employed for MIP syntheses. In the first strategy, there is the formation of reversible covalent bonds between the monomers and the template. However, after the MIP synthesis, template removal requires the cleavage of the covalent bonds that can affect cavity functionality [6]. The second approach involves the preparation of non-covalent interactions between the monomer and template, such as ionic, hydrophobic or hydrogen-bond interactions. This method for preparing MIP has been the most used due to the ease of template removal without the need for formation and subsequent cleavage of chemical bonds, preventing the collapse of the polymeric structure [7]. The semi-covalent method involves the both processes mentioned above; covalent bonds are formed during the molecular imprinting, however, the target molecule binds with the monomer via non-covalent interactions [8].

Several polymerization techniques can be applied for the production of MIP particles including bulk, precipitation, suspension and emulsion polymerizations. The method most frequently applied is bulk polymerization, which requires the milling of the MIP after the polymerization step and prior to use [9]. However, irregularly shaped particles can be produced after the milling and binding sites might be destroyed during the MIP pulverization [10].

If regularly-shaped particles are required, precipitation or suspension polymerization should be used. The precipitation polymerization method is based on the growing of polymer chains, which precipitate during the reaction when a certain polymer chain length is reached. In suspension polymerization, the reaction occurs in two phases – aqueous and organic phases, helped by micelles. With both preparation techniques, it is possible to obtain spherical particles that are highly interesting for MIP applications. In addition, spherical MIP particles are necessary to obtain an optimal contact surface with the target molecules, since irregular particles are less effective for extraction of analytes [11,12].

Mayes and Whitcombe [13] have presented a comprehensive description of all the aspects of MIP synthesis and post-polymerization processing, while Vasapollo et al. [14] have discussed some significant aspects about the synthesis of MIP. Both authors presented common chemical reagents, reaction singularities, and optimization of the MIP synthesis.

In the synthesis of MIP, the choice of the chemical reagents is of primary importance in order to obtain an efficient and functional

MIP. A wide range of template biomolecules such as drugs, amino acids, carbohydrates, proteins, nucleotide bases, hormones, and co-enzymes have been successfully used. One or more templates can be employed for MIP synthesis; the double-template approach can simultaneously produce a MIP that catches more target analytes and resolves some limitations of single-template MIP for processing complex samples, especially when a long time is spent for the extraction process. Tang et al. [15] described a double-template MIP preparation for SPE extraction of theophylline and chlorogenic acid from green tea. The adsorption capacity of the double-template MIP was higher than with the single-template one, attesting to the higher binding properties for both analytes. The authors also confirmed a higher adsorption capacity with increases of analyte concentration, and the reduction of experimental steps compared to the conventional single-template technique.

Using small molecules as templates is well-consolidated and MIP syntheses using these targets are widely described in the literature. New approaches to syntheses show a tendency to move towards MIP that are selective for larger and more complex molecules, as reviewed by Li et al. [16] and Lv et al. [17].

Monomer selection is very important in order to create highly specific cavities designed for the template molecule. Typical functional monomers (Table 1) are carboxylic acids [acrylic acid, methacrylic acid (MAA), vinylbenzoic acid], sulphonic acids (2-acrylamido-2-methylpropane sulphonic acid), and heteroaromatic bases (vinylpyridine, vinylimidazole). The best monomers for synthesizing imprinted materials are chosen considering the strength and the nature of template-monomer interactions [13].

The cross-linker is also important to control the morphology of the MIP matrix, to stabilize the imprinted binding sites and to give mechanical stability to the polymer matrix in order to retain its molecular recognition capability. Different cross-linker reagents can be used in MIP synthesis, as is shown in Table 2.

High cross-linking ratios are generally used in order to obtain permanently porous (macroporous) materials with good mechanical stability. The most employed cross-linkers are ethylene glycol dimethacrylate (EGDMA), divinylbenzene (DVB) and trimethylol propane trimethacrylate (TRIM). Using TRIM as cross-linker gives polymers with more rigidity, structure order and effective binding sites than EGDMA [14]. Typically, the cross-linker promotes a larger impact on the physical characteristics of the polymers and much less specific interactions, especially for those between the template and functional monomers [51]. The type of cross-linker can strongly influence the final size and yield of MIP particles; as an example, when DVB was used as the cross-linker, MIP particles were obtained in low yield, whereas TRIM led to uniform particles in high yield (90%) [52,53].

The molecular imprinting process also depends on the solvent used. The main function of the solvent is to create the pores in the polymeric structure and, for this reason, it is quite common to refer to the solvent as the “porogen”. Common porogens used in MIP synthesis are toluene, chloroform, dichloromethane or acetonitrile. In non-covalent imprinting, the porogen must be chosen considering its role in promoting template-functional monomer complex formation: less polar solvents, such as chloroform or toluene, increase complex formation, facilitating polar non-covalent interactions such as hydrogen bonds. On the other hand, more polar solvents (e.g., acetonitrile, methanol or water) tend to dissociate the non-covalent interactions in the polymerization mixture, especially the protic solvents that give a high degree of disruption of the hydrogen bonds [14]. If strong template-monomer interactions are observed, polar porogens can be used to prepare efficient MIP without any limitation [54].

After the polymerization, the rebinding performance is increased when carried out in the same solvent used for the imprinting, suggesting that the optimized rebinding conditions

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات