Received: 10 March 2023 | Revised: 12 April 2023 | Accepted: 13 April 2023

DOI: 10.1002/jssc.202300157

JOURNAL OF SEPARATION SCIENCE

REVIEW ARTICLE

Recent advances and future trends in molecularly imprinted polymers-based sample preparation

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Funding information
MCIN/AEI/ 10.13039/501100011033

Molecular imprinting technology is a well-established technique for the obtainment of tailor-made polymers, so-called molecularly imprinted polymers, with a predetermined selectivity towards a target analyte or structurally related compounds. Accordingly, molecularly imprinted polymers are considered excellent materials for sample preparation providing unprecedented selectivity to analytical methods. However, the use of molecularly imprinted polymers in sample preparation still presents some shortcomings derived from the synthesis procedure itself limiting its general applicability. In this regard, molecularly imprinted polymers use to display binding sites heterogeneity and slow diffusion mass transfer of analytes to the imprinted sites affecting their overall performance. Besides, the performance of molecularly imprinted polymers in organic solvents is excellent, but their selective binding ability in aqueous media is considerably reduced. Accordingly, the present review pretends to provide an updated overview of the recent advances and trends of molecularly imprinted polymers-based extraction, focusing on those strategies proposed for the improvement of mass transfer and selective recognition in aqueous media. Besides, with the progressive implementation of Green Chemistry principles, the different steps and strategies for the preparation of molecularly imprinted polymers are reviewed from a green perspective.

KEYWORDS
binding sites, green chemistry, molecular imprinting, sample preparation, water compatibility

Article Related Abbreviations: 4-VP, 4-vinylpyridine; AA, acrylamide; ATRP, atom transfer radical polymerization; DES, deep eutectic solvent; ESOA, epoxidized soybean acrylate; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; HEMA, 2-hydroxyethyl methacrylate; H-MIP, hollow molecularly imprinted polymer; IL, ionic liquid; MAA, methacrylic acid; MIP, molecularly imprinted polymer; MISPE, molecularly imprinted solid-phase extraction; MMIPs, magnetic molecularly imprinted polymers; MOFs, metal-organic frameworks; POSS, methacryl-polyhedral oligomeric silsesquioxanes; RAFT, reversible addition–fragmentation chain transfer; SLM, supported liquid membrane; SSA, specific surface area; TBZ, thiabendazole; TFME, thin film microextraction.

1 | INTRODUCTION

Molecular imprinting technology is a well-established technique for the obtainment of tailor-made polymers, so-called molecularly imprinted polymers (MIPs), with a predetermined selectivity towards a target analyte or structurally related-compounds. Since their introduction by Wulff [1] and Mosbach [2], MIPs have been widely studied and are nowadays considered excellent materials in sample preparation thanks to their ability to perform selective (micro)extractions [3, 4].

MIP synthesis, schematically depicted in Figure 1, is carried out by polymerization of monomers around a template molecule in presence of a large amount of cross-linker in a proper solvent (porogen) able to maximize template:monomer interactions. After polymerization, the template molecule is removed leaving cavities complementary in size, shape, and chemical functionalities within the polymer network. Accordingly, the obtained MIP is able to selectively recognize the template and related compounds in rebinding experiments. Depending upon the kind of interactions taking place between the template (analyte) and monomers during the pre-polymerization and rebinding steps, three different approaches for the synthesis of MIPs have been reported: covalent, semi-covalent, and non-covalent. Wulff and Sarchan [1] introduced the covalent approach consisting of the formation of reversible covalent bonds between the template and monomers during the pre-polymerization step. Then, the template is removed from the polymer by cleavage of the corresponding covalent bonds, which are re-formed during the rebinding step. MIPs prepared according to this approach present a rather homogeneous binding site distribution, minimizing the occurrence of non-specific sites. However, the design of an appropriate template-monomer complex in which covalent bond formation and cleavage are readily reversible under mild conditions is a difficult task making the covalent approach rather restrictive. As an alternative, the semi-covalent approach was proposed [5, 6]. In this approach, the template is also covalently bound to a functional monomer before polymerization, but further template rebinding is based only on non-covalent interactions, thus broadening the template-monomer complex combinations. Finally, the non-covalent approach, proposed by Arshady and Mosbach [2], consists of the formation of non-covalent interactions (i.e., hydrogen bonding, Van der Waals forces, ionic interactions) between the template and selected monomers both during the pre-polymerization and rebinding steps. A wide variety of monomers able to interact with almost any kind of template are commercially available, making the non-covalent approach the most widely used for the preparation of MIPs and their subsequent incorporation into different sample preparation techniques. In this regard, MIPs can be adapted to current micro-extraction techniques and different strategies have been successfully developed for the synthesis of MIP fibers or stir-bars for SPME and stir-bar sorptive extraction, respectively, among other approaches [3, 7], demonstrating in all cases the MIP ability to clean up samples to unprecedented levels.

However, in spite of such success, the use of MIPs in sample preparation still presents some shortcomings derived from the MIP synthesis procedure itself limiting its general applicability. In this regard, when the non-covalent

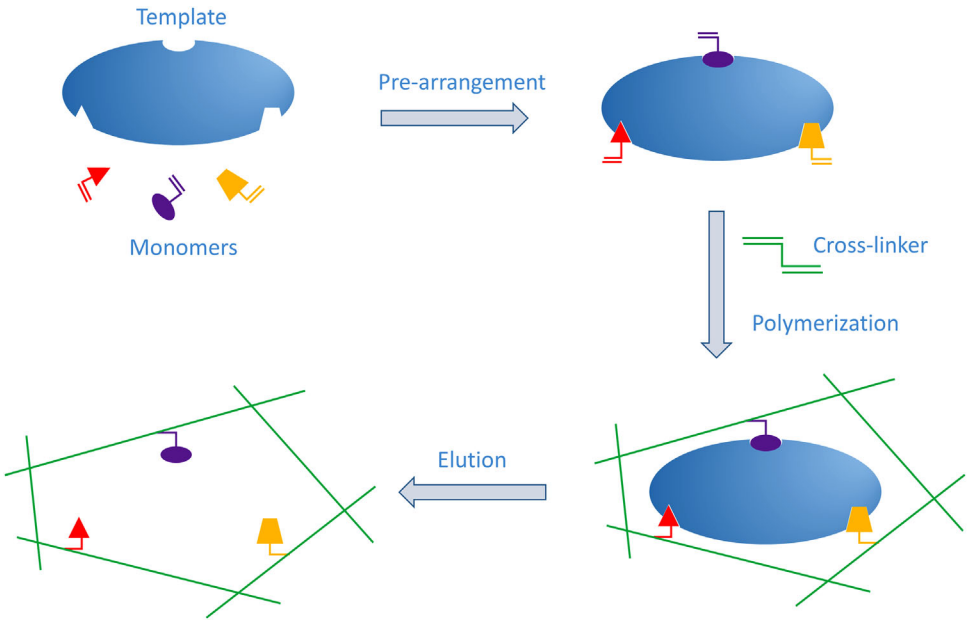

FIGURE 1 Schematic illustration of the preparation of molecularly imprinted polymers following the non-covalent approach.

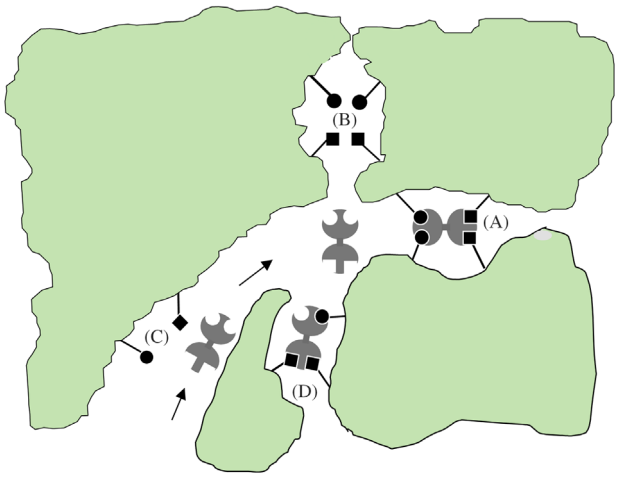

FIGURE 2 Scheme of the different binding sites present in imprinted polymers: (A) High-affinity sites associated with macropores (easy accessibility, fast mass transfer); (B) high-affinity sites associated with micropores (difficult accessibility, slow mass transfer); (C) binding sites with different stoichiometry and affinity. Reproduced [11] with permission from Springer Nature.

approach is used (Figure 1), each template molecule should ideally interact with monomer(s) leading to the formation of a unique pre-polymerization complex with a defined stoichiometry. However, in practice, complexes with different template:monomer stoichiometries are formed, which have different stabilities, depending on the affinity constants between the template and functional monomer(s), thus leading to a rather heterogeneous binding site population [8, 9]. Besides, obtained MIPs have a wide distribution of pore sizes associated with various degrees of diffusional mass transfer limitations. In this sense, Sellergren [10] classified the possible binding sites according to accessibility and suggested that mass transfer would be different if the sites are associated with mesopores or macropores (>20 Å) or with micropores (<20 Å). The number of the latter may be higher since the surface area, for a given pore volume, of micropores, is higher than that of macropores, thus limiting the accessibility of a given analyte to the imprinted sites. Accordingly, as depicted in Figure 2, both binding site heterogeneity and diffusion mass transfer of analytes to the imprinted sites will affect the overall performance of MIPs [11].

Besides, as mentioned above, given the simplicity of the process and the availability of a great variety of functional monomers, most of the MIPs are currently prepared following the non-covalent approach, where the monomer-template complex is stabilized mainly through hydrogen bonding and Van der Waals forces. This synthesis procedure provides excellent performance of MIPs in organic solvents, but their selective binding ability in aqueous media is considerably reduced. Consequently, the development of MIPs showing selective recognition in aqueous media has become an increasingly important research topic and different strategies for preparing so-called water-compatible MIPs have been proposed.

Finally, the scientific community is currently changing the way methods and procedures are designed in an effort to protect the environment according to the 12 Principles of Green Chemistry, introduced by Anastas and Warner in the 90s [12]. In this regard, the reduction of waste, risk, and hazards to prevent side effects for operators and the environment is nowadays considered of paramount importance. It results evident that the synthesis procedures used for the preparation of MIPs are far to be considered green and almost every MIP synthesis step could be improved (i.e., reduction of organic solvents consumption or their replacement by greener solvents, selection of the greener polymerization strategy).

Accordingly, the present review pretends to provide an updated overview of the recent advances and trends of MIPs-based sample extraction procedures, focusing on those strategies proposed for the improvement of mass transfer and selective recognition in aqueous media, as well as on the greener alternatives already available for the synthesis of MIPs. In this regard, it does not pretend to be a collection of related papers but highlights, through relevant examples, the available and expected pathways to the development of the next generation of MIPs to be used in sample preparation.

2 | IMPROVEMENTS OF DIFFUSION MASS TRANSFER OF ANALYTES TO IMPRINTED SITES

As mentioned in Introduction, mass transfer of analytes to imprinted sites in MIPs synthetized by conventional polymerization strategies (bulk polymerization, precipitation polymerization, etc.) is conditioned by the porosity of the material obtained. Imprinted sites are located inside the polymer matrix and analyte diffusion uses to be rather slow. Accordingly, efforts have been directed to generate imprinted sites easily accessible to target analytes through three main approaches: surface imprinting, synthesis of hollow MIP particles, and preparation of MIP thin films on a solid substrate.

2.1 | Surface imprinting

Surface imprinting techniques provide a thin film of imprinted polymer grafted onto the surface of preformed beads and thus may solve some of the drawbacks associated with MIPs (i.e., slow mass transfer). Such a statement

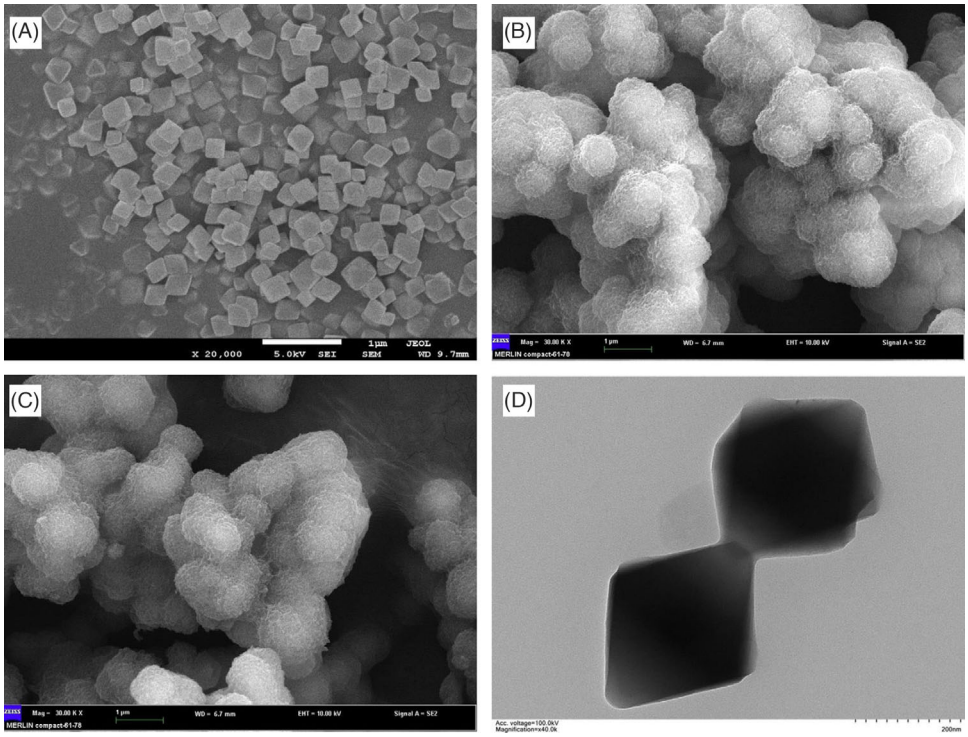

FIGURE 3 Scanning electron microscopy images of (A) UiO-66-NH_2, (B) MIP@UiO-66-NH_2, and (C) NIP@UiO-66-NH_2; (D) Transmission electron microscopy image of UiO-66-NH_2. Reproduced [18] with permission from John Wiley and Sons.

was nicely demonstrated by comparing the chromatographic performance of thiabendazole (TBZ)-imprinted beads prepared by precipitation polymerization [13] with that provided by core-shell imprinted beads synthetized by two-step precipitation polymerization and by an iniferter-type initiator technique on spherical porous silica [14]. Under optimum chromatographic conditions, sharp and well-defined peaks were obtained during the elution of TBZ when core-shell materials were used, demonstrating that the slow mass transfer kinetics associated with conventional MIP stationary phases are clearly improved by surface imprinting techniques. Such study was the basis for the development of an in-line molecularly imprinted SPE (MISPE) method for the determination of TBZ in citrus fruits extracts and fruit juices, allowing the unequivocal determination of TBZ at concentrations pertinent to the Maximum Residue Limits permitted within Europe [15].

Traditionally, porous silica or preformed polymer beads have been used as core material for the preparation of core-shell particles with a thin layer of MIP on their surface. However, in some cases, preformed beads present a relatively small specific surface area (SSA) limiting the capacity of the resulting material. Consequently, new materials possessing larger SSA have been evaluated to be used as core. Among them, metal-organic frameworks (MOFs), porous hybrid materials with periodic three-dimensional networks presenting high porosity and large SSA, are excellent candidates in the development of new core-shell imprinted materials. In this regard, the synthesis of a MIP layer selective for the insecticide metolcarb on MOF-5 as the core was proposed by Qian et al. [16]. The SSA of the obtained hybrid material was 945.05 m^2/g, which was much larger than that of a conventional MIP (610.36 m^2/g). By performing kinetic adsorption experiments, it was observed that binding equilibrium on a conventional MIP was obtained within 2 h [17], whereas it was reduced to 20 min on the MIP@MOF-5 hybrid material.

Similarly, and in order to improve the stability of MOFs in water, mesoporous UiO-66-NH_2 (a popular MOF with good thermal and chemical stability) was used as a core on the synthesis of a MIP@UiO-66-NH_2 hybrid material to be used for the MISPE of fluoroquinolones in lake water [18]. As shown in Figure 3, UiO-66-NH_2 is an octahedron with a smooth surface and a narrow size distribution (Figure 3A,D). However, after the grafting of polymer layers, the sharp edges and corners of the crystal disappeared (Figure 3B,C). The SSA of UiO-66-NH_2 and MIP@UiO-66-NH_2 were 325.8 and 217.7 m^2/g, respectively, high enough to facilitate the mass transfer of target analytes. In this regard, it is remarkable that only 65 s were necessary to reach the equilibrium in kinetic adsorption experiments. From these studies, it results evident that the larger SSA of MIP@MOF hybrid materials has a positive influence on the mass-transfer of target analytes to the binding sites

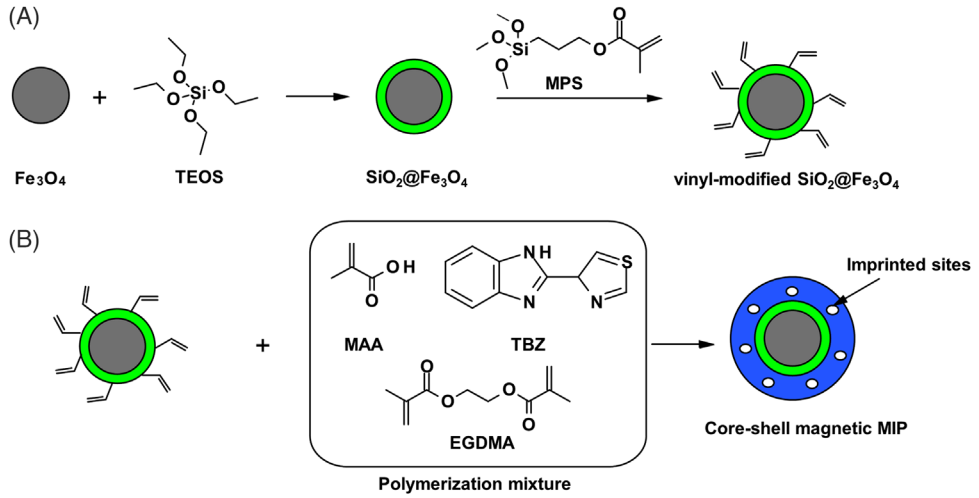

FIGURE 4 Schematic representation of the preparation of magnetic molecularly imprinted polymers (MIPs). Reproduced [21] with permission from John Wiley and Sons.

and further studies in this field are expected in the coming years.

Other nanostructured materials presenting large SSA have been used as supports in the preparation of imprinted polymers, including carbon nanotubes, magnetic nanoparticles, multi-walled carbon particles, and TiO_2 nanotubes, among others [19]. From them, the combination of magnetic nanoparticles and MIPs has attracted considerable attention in recent years. Core-shell magnetic MIPs (MMIPs) are easy to prepare and chemically stable and possess a small size and high surface-to-volume ratio leading to rapid binding kinetics [20].

Typically, the preparation of core-shell MMIPs involved three different steps easy to perform which are schematically shown in Figure 4. The first step consists of the silylation of magnetite nanoparticles through a conventional sol-gel reaction using tetraethyl orthosilicate leading to the obtainment of hybrid $SiO_2@Fe_3O_4$ particles. Subsequently, obtained particles are further treated with 3-methacryloyloxypropyltrimethoxysilane in order to introduce the vinyl groups on the particle surface necessary for the subsequent surface imprinting. Finally, a layer of MIP is formed onto the surface of the particles by the copolymerization of vinyl end groups with methacrylic acid (MAA) and ethyleneglycol dimethacrylate in the presence of the template molecule (TBZ in this case) [21]. Such materials not only can selectively recognize the target analytes but also can be quickly isolated from the complex matrix with an external magnetic field avoiding additional centrifugation or filtration procedures. Such valuable properties make core-shell MMIPs ideal materials to be used in dispersive SPE in food and environmental analysis fields and further developments (i.e., improving the control of the thickness of MIP layer by controlled radical polymerization strategies such as atom transfer radical polymerization) are expected in the near future [22, 23].

2.2 | Hollow MIPs

In order to improve the accessibility of target analytes to the imprinted sites, hollow MIP beads (H-MIPs) have been proposed. In this manner, target analytes can reach both the inner and outer surface of the hollow particles increasing particle capacity and improving mass transfer kinetics compared to conventional MIPs, or even to core-shell MIPs, prepared by surface imprinting. Figure 5 shows schematically the synthesis procedure of single-hole H-MIPs. Firstly, carboxylated polystyrene particles are synthetized to be used as seeds in a multi-step swelling and polymerization procedure. The strong hydrogen-bond interactions between the carboxyl groups at the surface of the polystyrene seeds and acrylamide (AA), used as a functional monomer, allow the subsequent polymerization at the surface of the polystyrene seeds. Then, a consecutive two-step procedure including swelling and polymerization followed by dissolving polystyrene seeds with dichloromethane leads to the obtainment of a single hole in the highly cross-linked polymer shell. The formation of the hole is attributed to the symmetrical shrinkage of shell material along the surface of the rigid polystyrene particles during the cross-linkage of the shells [24]. Such synthesis procedure of single-hole H-MIPs was first proposed by Guan et al. in 2007 [24] and evaluated in rebinding experiments toward 2,4,6,-trinitrotoluene, although it was not applied to the extraction of 2,4,6,-trinitrotoluene from real samples. Later, following the same synthesis procedure, H-MIPs have been successfully prepared and

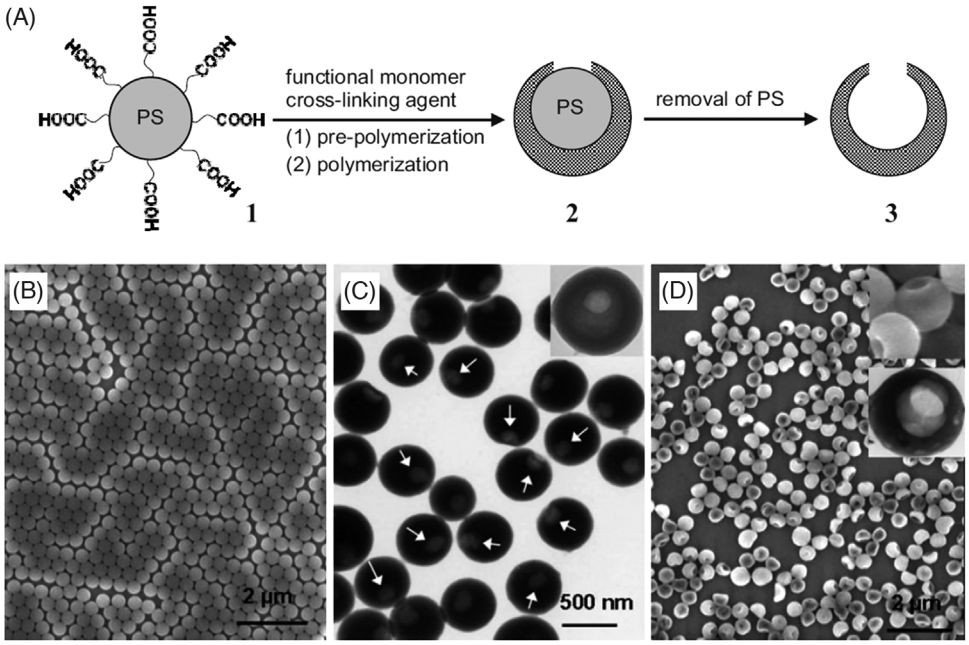

FIGURE 5 Schematic illustration of the preparation of single-hole hollow molecularly imprinted polymers (H-MIPs): (A) Single-hole hollow polymer microspheres were synthesized by a consecutive two-step polymerization at the surface of carboxyl-capping polystyrene (PS) beads, followed by the dissolution of the PS cores with tetrahydrofuran. (B–D) SEM and TEM images of experimental samples: (B) SEM image of original carboxyl-capping PS beads, (C) TEM image of PS@poly(AA-EGDMA) microspheres (inset is a high-magnification TEM image), (D) SEM image of poly(AA-EGDMA) hollow microspheres with a single hole (the upper and bottom insets are high magnification SEM and TEM images, respectively). Reproduced[24] with permission from John Wiley and Sons.

applied to the SPE of triazines in soil [25] and Sudan I in chili sauce [26] samples. After these seminal works, other strategies have been studied for the obtainment of H-MIPs, including Pickering emulsion polymerization, suspension polymerization, and surface imprinting on hollow cores. The detailed description of the different polymerization strategies for the obtainment of H-MIPs is out of the scope of the present paper and thus, for interested readers, the review by Hua et al. is highly recommended [27].

Regardless of the polymerization strategy, the obtained H-MIPs present higher capacity and improved binding kinetics compared to traditional MIPs. For instance, H-MIP beads for the SPE of triazines from cereals samples [28] exhibited a much higher binding capacity for prometryn (124.78 mg/g) than the MIPs prepared by precipitation polymerization (86.41 mg/g) or surface polymerization (65.65 mg/g). Besides, H-MIP displayed a faster equilibrium adsorption time for prometryn (230 min) than those of MIPs prepared by precipitation polymerization (320 min) or surface imprinting (420 min).

In spite of the aforementioned advantages of H-MIPs over conventional MIPs, there are some limitations that need to be tackled in the coming years. In this regard, H-MIPs are brittle materials in nature due to their hollow structures and thus can be deteriorated after several uses. Reducing the size of the sacrificial core could allow for increasing the thickness of the imprinted shell preventing its breakage with use. However, in contrast, a too thick imprinted shell would negatively affect mass transfer kinetics, thus reducing the inherent advantages of H-MIPs.

2.3 | Molecularly imprinted thin-films on a solid substrate

With the same aim of improving MIP performance, the in-situ synthesis of MIPs on the surface of microfiltration glass fiber membranes in multi-well filter plates [29] or onto polyethylene frits [30, 31] has been proposed. In general, the obtained MIP composites allowed high throughput analysis and remarkably lower volume consumption of organic solvents compared to that used in conventional SPE cartridges.

Besides, the developed surface imprinting methodologies, described in section 2.1, have been also adapted to the synthesis of MIP-coated fibers and stir bars to be used in SPME and stir-bar sorptive extraction, respectively [32]. Typically, silica fibers or glass magnets are firstly activated by silylation and subsequently immersed in the pre-polymer solution to carry out the polymerization. Such an approach was originally proposed by Koster et al. [33] in 2001 for the preparation of imprinted fibers for the

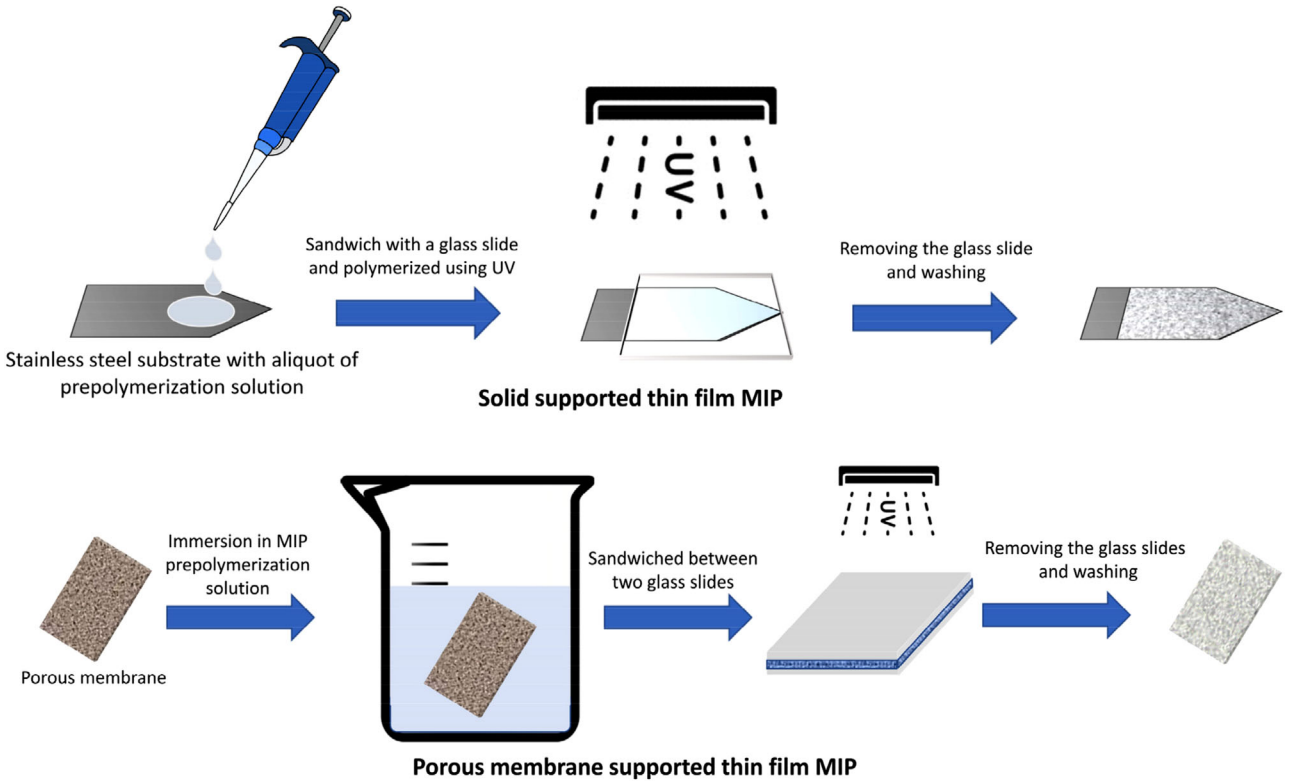

FIGURE 6 Molecularly imprinted polymer (MIP) thin film microextraction devices preparation. Reproduced [32] with permission from Elsevier.

SPME of brombuterol from urine samples and has been widely used for the preparation of MIP-coated fibers. Key parameters affecting the synthesis and subsequent performance of the imprinted fibers have been identified, including polymerization time and used porogen, both affecting the coating thickness and porosity of the final imprinted fiber. Nevertheless, even after careful optimization, controlling polymeric film thickness is a difficult task, since the desired graft polymerization is invariably accompanied by polymerization in solution when traditional azo-initiators are used. Other approaches such as surface reversible addition–fragmentation chain transfer polymerization (RAFT), where a RAFT agent is linked to the silylated fiber [34], or electropolymerization of suitable monomers (i.e., pyrrole) onto proper support (i.e., platinum or stainless steel) [35] have been proposed as alternatives since both synthesis procedures allow to control the thickness of the polymer layer by varying the polymerization conditions. Unfortunately, and in spite of their excellent outcome and performance such approaches have not been further explored likely due to experienced staff and/or specific equipment being required in both cases.

As an alternative, a molding technique has been proposed to control the final dimensions of the imprinted device obtained. Typically, silanized fiber [36] or stir bar [37] is inserted into a glass mold filled with pre-polymer solution. After polymerization, the glass mold is removed leading to a MIP monolith whose thickness can be determined by the inner diameter of the glass mold capillary used. This technology has been further simplified by the direct synthesis of MIP monoliths avoiding the use of pretreated glass fibers or stir bars [38, 39]. Regardless of the technique used, imprinted fibers show good performance in terms of selectivity and reusability, although the binding capacity uses to be rather low. On the contrary, imprinted stir bars present higher capacity and extraction efficiency but are accompanied by a restricted diffusion into the binding sites leading to long extraction times.

The incorporation of MIPs into the so-called thin film microextraction (TFME) technique appears as a promising alternative since it provides a large surface area and improved binding site accessibility. Such an approach was proposed and further evaluated in subsequent papers, by Bottaro's group for the selective extraction of phenol, alkylphenols, and polycyclic aromatic sulfur heterocycles in waters, among others [40–45]. Typically, MIP TFME devices are prepared by drop-casting a few microliters of pre-polymer solution between a silanized glass microscope slide and a glass cover slide and then exposed to UV light to initiate polymerization. The obtained thin films are then washed with an appropriated solvent to remove the template. As shown in Figure 6, MIP TFME devices have been

also fabricated using more robust support such as stainless steel, which does not need any treatment or modification prior to deposition of the pre-polymer solution and can be easily cut-to-fit [46]. Alternatively, as also depicted in Figure 6, membrane-supported MIP-TFME devices can be also fabricated just by immersing a porous membrane into the MIP pre-polymerization solution. Then, the membrane is sandwiched between two glass slides and polymerized under UV light [47]. Although extraction times are still generally long (30–60 min), the simplicity of preparation and use makes MIP TFME to be considered a relevant advance in the field. Further research in this area is expected in the coming years extending its use to the extraction of target analytes in complex samples where a high degree of selectivity is required.

2.4 | Other approaches

The use of liquid crystal monomers has been proposed for the synthesis of MIPs allowing a significant reduction of cross-linking. In such systems, the pendant rigid or mesogenic groups form physical cross-linking through non-covalent reversible interactions, thus allowing a reduction in the chemical cross-liking and an improvement in the mass transfer kinetics of the resulting MIP. Liquid crystal monomers-based MIPs have been mainly evaluated as selective stationary phases in liquid chromatography and capillary electrophoresis achieving a clear improvement in resolution and column efficiency [48, 49]. Although such new materials have not been used in sample preparation, they might represent a relevant alternative to the above-mentioned strategies.

Similarly, the incorporation of methacryl-polyhedral oligomeric silsesquioxanes (POSS) into the pre-polymerization mixture has been proposed in order to improve target analyte accessibility and selectivity. POSSs, composed of an inorganic–organic hybridized cage architecture at the nanoscale, can reinforce the physical and chemical properties after being incorporated into a polymer structure as a building block. Such nano-cage units alter the polymer structure at the molecular level and have been found to exhibit enhanced selective recognition in separation while increasing the mesoporous structure of the resulting MIPs [50]. Although its application in sample preparation is scarce, it is important to highlight the work by Bi et al. on the incorporation of POSS into the structure of a baicalin-imprinted monolith [51]. The prepared in-capillary MIP monolith was used for in-tube SPME-HPLC to analyze baicalin in *Scutellaria baicalensis* (a traditional Chinese medicine). According to the authors, the enhanced recognition capacity of the obtained MIP incorporating POSS in its structure allows a highly effective enrichment of baicalin out of a complex matrix by the proposed on-line MIP-SPME-HPLC, allowing it to reach a limit of detection as low as 1 ng/ml.

3 | WATER-COMPATIBLE MIPs

The development of MIPs showing selective recognition in aqueous media, so-called water-compatible MIPs, has become an increasingly important research topic. As indicated in the Introduction, MIPs perform well in aprotic organic solvents since, in most cases, selective recognition of target analytes is mainly based on hydrogen bonding. However, the presence of water disrupts such interactions preventing MIPs' applicability to aqueous samples. Besides, MIPs are traditionally prepared by using hydrophobic raw materials leading to hydrophobic polymer networks. Such hydrophobicity favors the retention of target analytes from water samples through non-specific interactions with the polymer matrix masking the selective interaction taking place in the binding sites. Besides, biological macromolecules (proteins, lipids, etc.) tend to attach on the surface of hydrophobic MIPs through non-specific interactions blocking imprinted sites and reducing the inherent MIP selectivity.

Several strategies for the obtainment of water-compatible MIPs have been proposed in last years, including free radical polymerization approaches regulating the preparation environment, introducing non-hydrogen bonding interactions, and utilizing hydrophilic monomer or cross-linker and surface modification, among others. Also, non-free radical polymerization strategies such as the sol-gel route, chemical/natural polymer assembly, or hydrophilic molecularly imprinted resin have been proposed [52]. From the authors' point of view, the use of hydrophilic monomers and cross-linkers is the most relevant and useful strategy. It can be easily incorporated into the synthesis of any MIP and thus such an approach can be considered of general applicability.

The use of 2-hydroxyethyl methacrylate (HEMA) as a hydrophilic co-monomer for the synthesis of water-compatible MIPs for the extraction of bupivacaine from blood plasma samples was proposed by Dirion et al. [53]. It was observed that the presence of HEMA in the polymerization mixture led to the obtainment of MIPs with improved selective recognition in aqueous samples. In this regard, a significant difference in the amount of bupivacaine present in the breakthrough aliquots of MIP and NIP cartridges was found (only 15% in MIP vs. 60 % in NIP) after loading plasma samples spiked with a known amount of labeled bupivacaine. Obtained results suggested that the inclusion of HEMA contributed to defining the imprinted sites and, in parallel, to create a more

hydrophilic polymer matrix leading to the reduction of hydrophobic non-specific interactions. Such conclusions were recently confirmed by the synthesis of a water-compatible MIP, using HEMA as a co-monomer, for the extraction of triazines from environmental waters [54]. By careful optimization of the HEMA:MAA ratio, a water-compatible MIP is able to selectively extract 7 triazines from environmental waters with quantitative recoveries (>80%), whereas they drop to about 20% (depending upon the triazine under study) for conventional MIP using only MAA as functional monomer. Such high recoveries allowed to increase water sample volumes up to 50 ml, achieving high pre-concentration factors with excellent selectivity. Figure 7 shows the HPLC-UV chromatograms obtained for surface and well water samples after MISPE together with that obtained for well water samples after SPE using a conventional C18 cartridge. As it can be observed, all selected triazines can be determined at low concentration levels (detection limits below 0.5 μg/L were reached) thanks to the high selectivity provided by the water-compatible MIP. On the contrary, chromatograms obtained after SPE using C18 cartridges showed a big hump of interferences that completely prevents an accurate and selective determination of the selected triazines in these samples.

Other hydrophilic monomers such as 2-acrylamido-2-methylpropanesulfonic acid or alkenyl glycosides glucose, and cross-linkers such as *N*,*N*-methylene diacrylamide or divinyl galactose have been also exploited to confer water-compatibility to MIPs, but none has shown superior performance to the others. In general, such monomers and cross-linkers are expensive and require a complex synthesis to be obtained, thus limiting their general applicability [52].

The modification of surface MIP particles with hydrophilic polymer brushes by RAFT polymerization and surface atom transfer radical polymerization have been proposed and mainly exploited by Zhang's group [55–57]. In this case, the hydrophilic polymer brush has a double effect as it is schematically illustrated in Figure 8. It enhances the hydrophilicity of the MIPs and, in addition, behaves as a typically restricted access media by blocking the access of macromolecules. In spite of the success of this approach, it results evident that it requires specialized skills in polymer synthesis, and thus its implementation in general laboratories is rather limited.

As an alternative, the combination of supported liquid membrane (SLM) with conventional MIPs allows for circumventing their lack of selective recognition in aqueous media [58]. SLM liquid-phase microextraction is based on the extraction of target analytes from an aqueous sample (donor phase) to a water-immiscible organic solvent immobilized onto the pores of a membrane (SLM). Then, analytes are re-extracted from the liquid membrane to a proper solvent (acceptor phase) for subsequent final analysis. Figure 9 schematically shows the different formats proposed for the combination of SLM and MIPs. In all of them, MIP is placed at the acceptor phase constituted by an appropriated organic solvent and thus target analytes able to reach the acceptor phase would be retained by the MIP. Regardless of the used device, this methodology provides selectivity to the extraction process both by the membrane itself, acting as a barrier preventing the diffusion of high molecular weight compounds and suspended particulate matter, and by the used MIP. This technique has been successfully used for the determination of polycyclic aromatic hydrocarbons in wastewater [59], triazines in sludge water, water melon, milk, and urine samples [44, 60], thiabendazole in citrus-juice samples [61], sulfonamides in environmental waters [62], and biochanin A from urine samples [63], among others. Nevertheless, it is important to point out that MIP performance is conditioned by the success of the previous liquid-liquid extraction process, and thus better extraction efficiencies will be observed for analytes with high octanol-water partition coefficients. Besides, the diffusion of target analytes through the membrane might be also a limiting factor and long extraction times might be required for high molecular weight target analytes.

4 | GREEN MIPs

According to the Principles of Green Chemistry [64, 65], the synthesis of MIPs is far from ideal. In this regard, the sustainable development of MIPs should adopt a life cycle perspective covering all the stages, including the used reagents, the synthesis procedure, the final use, and how MIP residues are disposed of. As shown in Figure 10, several sustainable goals can be established together with the proposed strategies to achieve such objectives. It is clear that almost every MIP synthesis step could be improved, including the proper selection of the template to be used, the implementation of computational approaches for polymerization reagent selection, the selection of the right polymerization strategy, and the reduction of organic solvents consumption or their replacement by greener solvents. In this regard, Arabi at al. [66] proposed the fourteen principles of green molecular imprinting technology, represented by the acronym GREENIFICATION (Figure 11), which could serve as a guide for the green synthesis and subsequent use of MIPs in sample preparation.

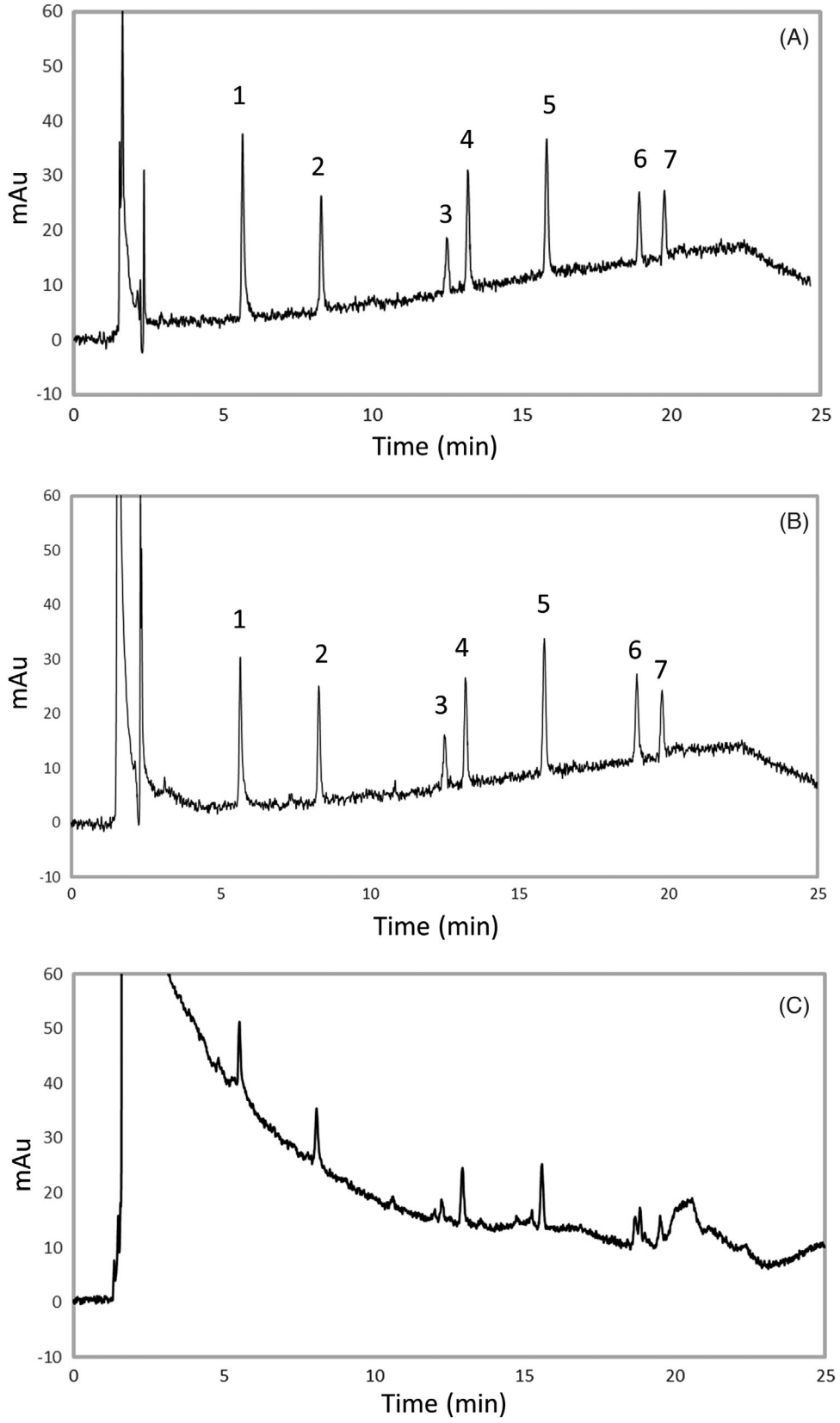

FIGURE 7 UV–Vis chromatograms obtained at 220 nm for a well (A) and surface (B) water samples spiked at 1 μg/L concentration level after molecularly imprinted SPE (MISPE) onto a water-compatible molecularly imprinted polymer (MIP), and for well water samples spiked at the same level after SPE in conventional C18 cartridge (c). Peak assignment: (1) desisopropylatrazine; (2) desethylatrazine; (3) simazine; (4) cyanazine; (5) atrazine; (6) propazine; (7) terbuthylazine. Reproduced [54] with permission from John Wiley and Sons.

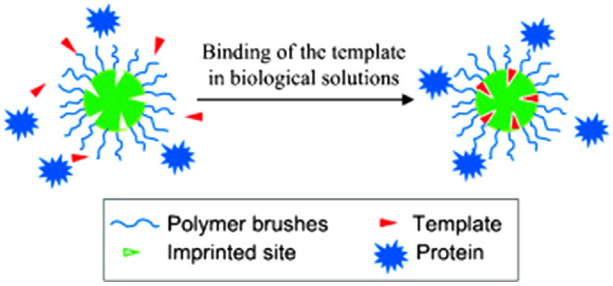

FIGURE 8 Scheme of recognition of target analytes by a water-compatible molecularly imprinted polymer (MIP) whereas large bio-macromolecules are blocked by hydrophilic polymer brushes. Reproduced [56] with permission from John Wiley and Sons.

4.1 | Greener reagents for the synthesis of MIPs

4.1.1 | Ionic liquids

Typically used monomers (i.e., acrylic acid and methacrylic acid) for the synthesis of MIPs are considered toxics and thus their use should be minimized or ideally replaced by other greener alternatives. In this regard, ionic liquids (ILs), molten salts with melting points close to room temperature, have been considered a class of green reagents due to their tunable properties, negligible vapor pressure, and non-flammability. In addition, ILs are able to interact with organic compounds by hydrogen bonding, anion-exchange, electrostatic, hydrophobic, and π-π interactions, thus making them ideal monomers in molecular imprinting as an alternative to conventional above-mentioned monomers [67]. In this regard, Xiang et al. studied the recognition capabilities of MIPs prepared using 1-vinyl-3-methylimidazolium chloride or 4-vinylpyridine (4-VP) as functional monomers and salicylic acid as a template [68]. From this study, it was concluded that the adsorption capacity of MIPs was higher when 1-vinyl-3-methylimidazolium chloride was used as a functional monomer (29.75 mg/g), than when 4-VP was employed (22.61 mg/g), thus demonstrating that the use of ILs as monomers could be more efficient than typically used functional monomers.

Besides, ILs properties can be easily tuned by modifying their chemical structure in order to maximize interactions with the target template molecule. For instance, it was demonstrated that the length of the side-chain (methyl-, ethyl-, butyl-, and pentyl- carboxylic acid group) of acidic imidazolium ILs has a direct influence on the performance of synephrine-imprinted polymers. The results showed that MIP prepared using 1-vinyl-3-carboxybutylimidazolium bromide as a functional monomer presented the best adsorption capacity (38.7 μmol/g), suggesting that such side chain (butyl-) favored hydrogen bond interactions between the amine/hydroxyl group of synephrine and the carboxylic acid group of IL [69]. The highlighted examples clearly indicate that functional groups on ILs have a remarkable influence on the formation of template-functional monomer complex and that it is possible the obtainment of MIPs with improved performance by clever modifications of IL chemical structure.

The use of ILs as porogen was proposed for the synthesis of the *trans*-aconitic acid-imprinted polymer [70]. In this work, 1-butyl-3-methylimidazolium tetrafluoroborate and 1-butyl-3-methylimidazolium hexafluorophosphate were evaluated as porogen in the preparation of MIPs by bulk and precipitation polymerization under photochemical and thermal conditions. The performance of new ILs-based MIPs was compared to that provided by a conventional MIP prepared by precipitation polymerization using acetonitrile as porogen. According to the obtained results, it was concluded that the presence of ILs allowed the rapid synthesis of polymer microspheres with improved selectivity. In this regard, the MIP prepared using 1-butyl-3-methylimidazolium tetrafluoroborate under thermal conditions displayed a selectivity two times higher than the corresponding MIP prepared under traditional precipitation polymerization conditions. Besides, it has been demonstrated that ILs-based MIPs provide superior performance under polar conditions [71], and reduce the shrinking or swelling of MIPs [72] making ILs an attractive alternative to traditional solvents used in the molecular imprinting field.

4.1.2 | Deep eutectic solvents

Although ILs were initially considered green solvents, some reports have alerted about their toxicity and poor biodegradability [73, 74]. As an alternative, deep eutectic solvents (DESs) have been proposed as a new generation of green solvents and nowadays are widely used in different fields [75]. DESs are composed of at least two components, a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD), interacting with each other through hydrogen bonding. DES has been used in the molecular imprinting field as functional monomers, cross-linkers, and porogen [76].

For instance, the use of a DES as an auxiliary solvent (porogen) to enhance the affinity and selectivity of MIPs towards chlorogenic acid was reported by Li et al. [77]. DES was prepared using choline chloride as HBA and glycerol as HBD. The obtained DES-MIP displayed a recovery of 72.56%, higher than that provided by the corresponding

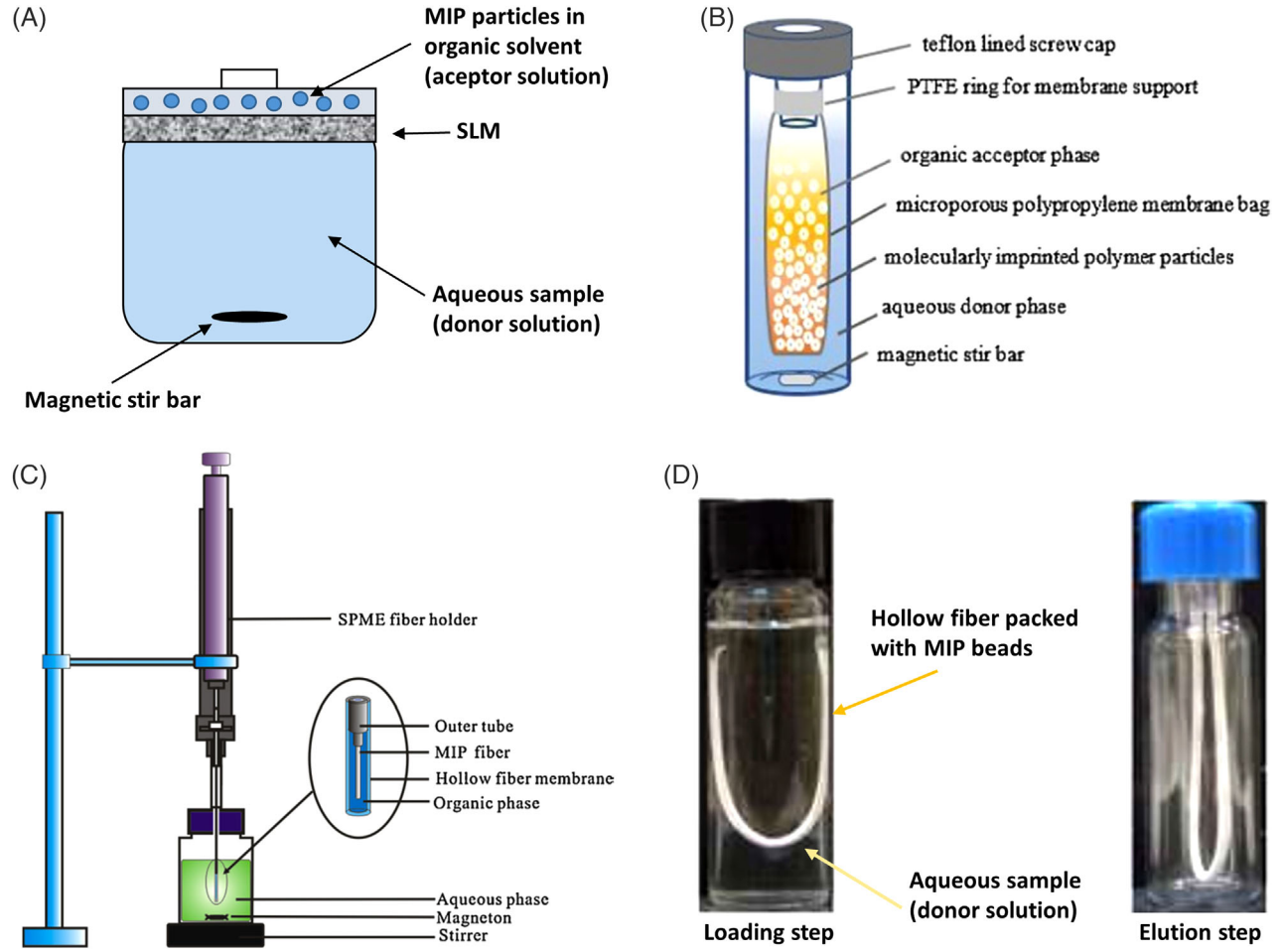

FIGURE 9 Different devices and set-ups used for combining supported liquid membrane (SLM) and molecularly imprinted polymers (MIPs). (A) Flat membrane; (B) Membrane bag; (C) Device for the insertion of an imprinted fiber into the lumen of a hollow fiber; (D) Packed beads inside a hollow fiber. Reproduced [58] with permission of Elsevier.

MIP without the presence of DES (69.34%). The selectivity provided by the DES-MIP was good enough to allow the purification of chlorogenic acid from honeysuckle. Similarly, Tang et al. [47] evaluated three different DES as an auxiliary solvent in the synthesis of chloramphenicol-imprinted polymers. Three different HBDs were tested (ethylene glycol, glycerol, or propylene glycol) combined with choline chloride as HBA. From both static and dynamic absorption experiments, it was concluded that DES-MIP prepared in presence of ethylene glycol provided a higher absorption capacity and improved mass transfer, and was successfully used for the selective pipette-tip SPE of chloramphenicol from milk samples. From this study, it results evident that the kind of HBA and HBD used for the preparation of DES have a significant influence on the final performance of the obtained DES-MIP. In this regard, different compounds and combinations have been reported for the synthesis of DES-MIPs, including even the use of ternary DES, to be used not only as a porogen but also as a template or as a functional monomer [76]. Although, in general, the performance of the new DES-MIPs is improved when compared to the corresponding conventional MIPs, the relevant mechanisms behind such improvements are still unclear and further research is needed in this field in order to clearly demonstrate that DES can be a real alternative for replacing conventional solvents.

4.1.3 | Biopolymers and natural monomers

The use of natural polymers (biopolymers) for the preparation of non-toxic, biodegradable, and biocompatible MIPs might progressively replace traditional monomers with biomaterials such as chitosan and cellulose. These green biomaterials are widely available in nature and some of them can even be obtained from biomass waste thus their use appears as a hot topic for the coming years [78]. Chitosan has been the most studied in molecular imprinting technology due to its excellent biological

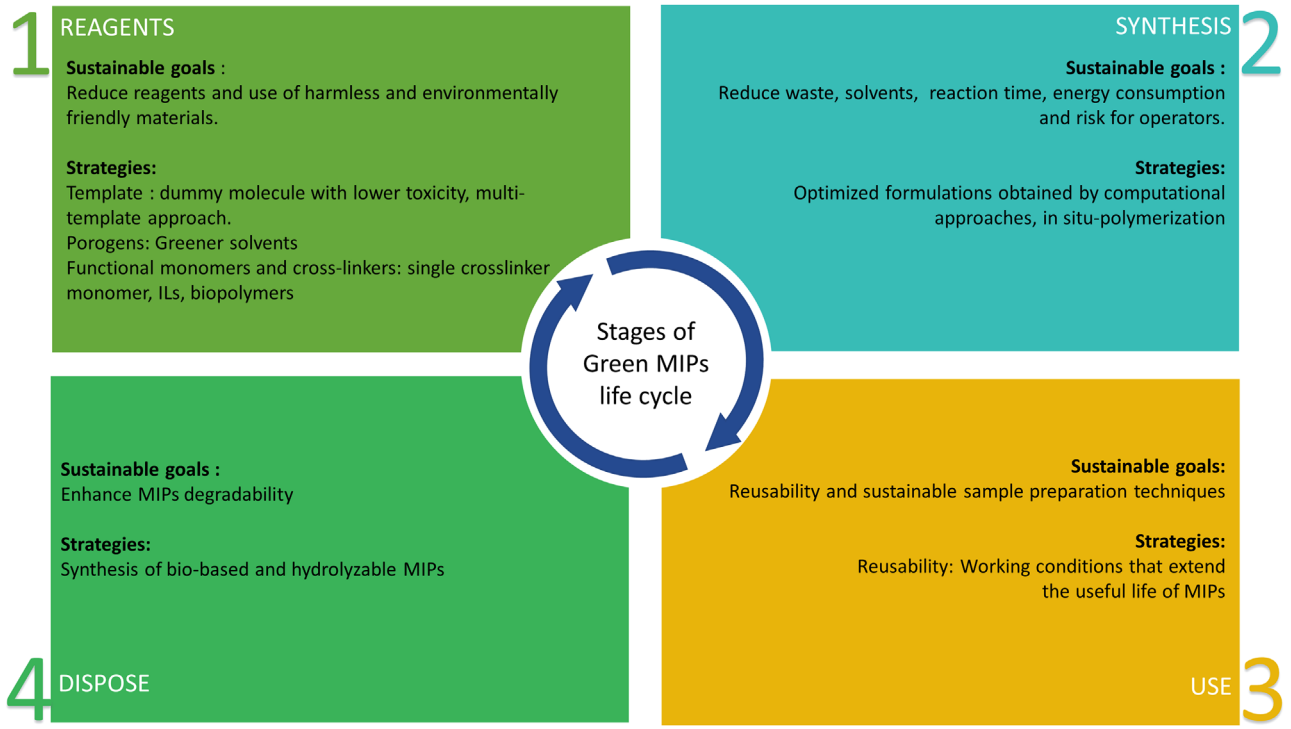

FIGURE 10 General phases of a life cycle of Green molecularly imprinted polymers (MIPs).

FIGURE 11 The fourteen principles of green molecular imprinting expressed as the mnemonic device "GREENIFICATION". Reproduced [66] with permission of John Wiley & Sons.

properties (non-toxic, biodegradable, biocompatible, anti-allergic, anticoagulant, antifungal, and antimicrobial) as well as to the presence of hydroxyl and amine groups in its structure, allowing interaction with a wide variety of template molecules through hydrogen-bonding, even in aqueous media. Besides, the preparation of chitosan-based MIPs can easily be adapted to microextraction techniques such as pipette-tip microextraction [79], dispersive magnetic SPE [80], or ultrasound-assisted dispersive SPE [81], among others. However, despite the above advantages, the effect of several experimental factors, such as chitosan concentration, polymerization temperature and time, polymerization mixture volume, and cross-linker type, is still rather unclear limiting its general use [82].

Cellulose is biodegradable, biocompatible, inexpensive, and chemically and thermally stable and thus it appears

as an ideal candidate for the preparation of sustainable MIPs. Cellulose-based MIPs can be prepared with commercially available pure cellulose, natural cotton fibers, porous cellulose microspheres, or cellulose nanocrystals providing high specific surface area. Although cellulose-based MIPs have not been extensively studied, some promising results using them as selective sorbents for SPE [83, 84] and magnetic SPE [85] have been reported.

The use of silk fibroin for the preparation of MIP nanoparticles for the selective recognition of human serum albumin and hepcidin was recently proposed [86, 87]. Such MIP nanoparticles were in addition successfully coupled to silk microfibers and to silk electrospun nanofibers leading to all-silk MIP-nanoparticles fiber superstructures. Imprinting silk fibroin involves the whole range of amino acid side chains present on the fibroin backbone maximizing eventual interactions with complex template molecules (i.e., peptides/proteins). In contrast, the use of other natural polymers (i.e., chitosan), whose structures are composed of repetitions of the same monomer unit, strongly restricts the portfolio of functional groups available for the imprinting of complex molecules.

Recently, epoxidized soybean acrylate (ESOA), a vegetable oil-derived cross-linker, was proposed for the synthesis of bio-based MIPs using common functional monomers (i.e., 4-VP and 1-vinylimidazole) [88]. ESOA-based MIPs showed high affinity and selectivity for resveratrol (template molecule) when compared to MIPs prepared with the traditional cross-linker ethyleneglycol dimethacrylate. Besides, ESOA-based MIPs exhibited sensitivity to a fungal lipase, showing that bio-based MIP can be degraded by enzymes. This is a very interesting result for the future application of MIPs since it opens the possibility of using natural monomers and cross-linkers for the preparation of eco-friendly MIPs.

4.1.4 | Fragment imprinting and multi-template approaches

Template molecule is responsible for producing selective binding sites and thus its use is unavoidable in molecular imprinting. Template molecules must fulfill some requirements, such as solubility in the reaction media, stability under polymerization conditions, presence of appropriated functional groups, inexpensive and, from a green chemistry perspective, the template must be non-toxic both for the operator and the environment. In this regard, the use of a dummy molecule with similar functionality, shape, and size but with lower toxicity is widely extended in molecular imprinting. In this regard, if a compound cannot be readily imprinted because of its toxicity, cost, or low stability, a specific segment or part of its structure can be alternatively used as a template leading to the so-called fragment (or segment) imprinting. Such an approach has been successfully used for the synthesis of MIPs to be used in matrix solid-phase dispersion extraction of three azole fungicides from fish samples [89] and SPE of pyrethroids in honey samples [90].

The preparation of MIPs using (bio)macromolecules or entire biological species such as proteins presents difficulties due to their size and structure delicacy. In this regard, the epitope-imprinting approach is widely used for the synthesis of MIPs for selectively recognizing proteins. In this case, a part (i.e., peptide sequence) of the target protein is used as a dummy template, leading to MIPs presenting lower non-specific binding. Furthermore, the peptides can be obtained in pure form, are cheaper than the complete proteins, and are stable in organic solvents [91, 92].

One of the main advantages of MIPs is their ability to rebind selectively not only target analyte but also related compounds, thus allowing the simultaneous extraction of a family of compounds. However, from a green chemistry perspective, such ability can be considered a drawback since it would be necessary to prepare a different MIP for each family of compounds. Alternatively, the multi-template approach (the simultaneous use of more than one template) allows the obtainment of MIPs with selective recognition ability for more than one single family of compounds. In this regard, the preparation of a dual dummy template imprinted polymer using simultaneously pipemidic acid (a fluoroquinolone) and sulfabenzamide (a sulfonamide) was proposed by Song et al. [93]. The obtained MIP was able to simultaneously extract eight fluoroquinolones and eight sulfonamides from pork and chicken muscle samples. Later, a third template, chlortetracycline (a tetracycline), was included during the synthesis making the obtained MIP able to additionally extract four tetracyclines from meat samples by matrix solid-phase dispersion [94]. However, in spite of such relevant results, some templates might interact with each other producing synergistic/antagonistic effects in the presence/absence of any of them, thus affecting the MIP recognition ability. In this regard, the multi-template approach should be further studied in order to demonstrate its general applicability.

4.2 | Polymerization strategies and template removal

Bulk, precipitation, and suspension polymerization are the polymerization strategies most used in the synthesis of MIPs, however, all of them are far from being considered green. In bulk polymerization, a small volume of organic solvent is required but the obtained solid polymer has to be grounded and sieved to the desired particle size. This

process is not only tedious and time-consuming but also might be harmful to the operator due to the generation of dust particles. Besides, it is estimated that about 50% of solid material is discarded as solid waste. On the contrary, the alternative polymerization strategies, namely precipitation and suspension polymerization, which allows the obtainment of MIP beads, require a large amount of organic solvents (porogens), thus producing a large amount of liquid waste. As mentioned above, the use of greener solvents (ILs and DESs) as porogens in precipitation and suspension polymerization might help to transform polymerization strategies into greener processes, and research in this area is expected in the coming years. Alternatively, in-situ polymerization, where the whole polymerization mixture is used and thus waste generation is minimized, is recommended. In-situ polymerization involves the MIP synthesis on an appropriated support or inside a column, capillary, or micropipette leading to well-suited microextraction devices for sample preparation.

Regardless of the polymerization strategy used, the template molecule has to be removed from the polymer network by exhaustive washing of the polymers with a large amount of organic solvents (i.e., Soxhlet extraction). It is clear that such a procedure is far to be ideal from a green chemistry perspective. Although different strategies/techniques have been studied for the quantitative removal of the template molecule, the replacement of solvents has not been objective of them. A relevant exception was the use of pressurized hot water extraction as the optimum technique for template removal proposed by Batlokwa et al. [95]. It results evident that water is environmental-friendly and readily available and thus it would be the ideal solvent from a green chemistry perspective. However, the current cost associated with the required instrumentation has prevented its widespread use.

5 | CONCLUDING REMARKS

The synthesis and further use of MIPs in sample preparation have been reviewed considering not only traditional limitations related to binding sites heterogeneity, slow mass transfer, and water compatibility but also regarding the recent trends in the synthesis and further use of MIPs from a green chemistry perspective. In this regard, the combination of MIPs with other high porosity materials (i.e., MOFs) and formats (i.e., thin film microextraction) appears as an interesting alternative for increasing the surface area and porosity of MIPs, facilitating the mass transfer of target analytes to the binding sites. Besides, by slight modifications to the synthesis procedure including hydrophilic monomers in the polymerization mixture, it is possible the obtainment of water-compatible MIPs, and further research in this area is expected. Finally, research on the use of environmentally friendly monomers and porogens (i.e., DESs) will be an important research area in the coming years leading to a green improvement in terms of MIP synthesis and performance.

ACKNOWLEDGMENTS

The Grant PID2021-122327OB-I00 funded by MCIN/AEI/10.13039/501100011033 and by "ERDF A way of making Europe" is gratefully acknowledged. This article is based upon work from the Sample Preparation Study Group and Network, supported by the Division of Analytical Chemistry of the European Chemical Society.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Díaz-Álvarez M, Turiel E, Martín-Esteban A. Recent advances and future trends in molecularly imprinted polymers-based sample preparation. J Sep Sci. 2023;2300157. https://doi.org/10.1002/jssc.202300157