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Application of molecularly imprinted polymers in an analytical chiral separation and analysis

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ABSTRACT

Over the last two decades the process of development and application of a new types of molecular imprinted polymer (MIP) sorbents in the field of analytical chemistry have been widely described in the literature. One of the new trends in analytical chemistry practice is the use of new types of MIP sorbents as specific sorption materials constituting the stationary phase in advanced separation techniques. The following review paper contains comprehensive information about the application of a specific and well defined MIP sorbents (with the data base in the paper about the reagents used in MIP preparation process) as stationary phases in separation techniques including high performance liquid chromatography and capillary electrochromatography. Coverage includes newly created types of stationary phases (MIP sorbents) used for chiral recognition, with the focus on applications in enantioselective separation.

1. Introduction

It is widely known that almost every biochemical process occurring in the cells of living organisms is based on the specific, stereoselective interactions between reacting molecules and catalysts. Therefore, the stereochemistry of molecules involved or affecting those processes should be considered. A rapid growth of the branches of scientific activity dealing with the stereochemistry occurred with these considerations. As a consequence, almost all newly designed, biologically active substances such as drugs or pesticides are compounds with strictly defined stereochemistry. There is great interest in obtaining enantiomerically pure biologically active compounds with this being achieved by different approaches for example stereoselective synthesis and/or crystallization, biotransformation or chiral separation of isomeric mixtures.

The separation of isomeric mixtures is a complex process requiring enantiomer to diastereoisomer formation to create differences in physicochemical properties. The key problem for the modern analytical chemistry is to develop procedures using appropriate techniques to conduct separation processes in an effective way. In most cases enantiomers might be separated applying the wide spectrum of methods such as: crystallization, extraction, chromatographic techniques, membrane techniques and electromigration techniques. For the assessment of optical purity of particular enantiomers the following analytical techniques have been successfully applied: NMR, polarimetry, immunoanalytical methods, chiral sensors, isotopes dilution, chromatographic techniques and capillary electrophoresis (CE) [1,2].

The separation of enantiomers for chiral molecules is crucial, particularly in the pharmaceutical industry, since enantiomers can present different, and even opposite pharmacological and toxicological properties. The development of effective methods and techniques to prepare drugs with highly enantiomeric purity taken places at the beginning of 1980s. Since this time, high performance liquid chromatography (HPLC) has become the most extensively applied approach for chiral separation, while capillary electrochromatography (CEC) is attracting increasing interest recently [3]. Generally, the enantiomers resolution may be carried out by chromatography of the racemic mixture on a chiral stationary phase (CSP). These commonly includes cyclodextrins (CDs), crown ether, several types of derivatives of cellulose and amylose, pirkle type phases, macrocyclic antibiotics and cyclofructans. Recently a common course of action is the use of molecularly imprinted polymers (MIPs) as the stationary phase for the separation of racemates. This type of stationary phase can be classified as a specific group of CSP [4]. Molecular imprinting is a promising technique for the preparation of polymers which possess highly selective recognition properties and serve as separation media, especially for chiral molecules. In comparison to traditional stereoselective selector systems, chiral imprinting of polymers has several advantages, for example low material costs, ease of preparation, scalability, and flexibility to design various self-supporting formats. Moreover, these polymers have demonstrated improved stability toward mechanical and thermal stress and to tolerate a broad

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range of solvents, bases, acids, and salts, making them particularly well-suited to operation in challenging environments [5].

Taking into account the chemical nature of the interactions between the templating molecule and the interactive functional groups, molecular imprinting technology may be divided into covalent and non-covalent approaches [5,6]. Bulk polymerization is the most commonly used technique to prepare new types of LC column filling medium (stationary phase) because of the highly efficient process and low laboratory equipment costs. The LC columns filled with MIP stationary phases prepared by bulky polymerization techniques are mostly used in preparative separation of racemic mixtures (for example in organic chemistry to clean and separate the reaction products) and not in analytical chemistry – in the field of assess the optical purity of defined chemical compound. The main drawback that should be pointed out is that the synthetized polymer particles of a developed stationary phase often are characterized by irregular shapes, forms and dimensions [7–12]. To obtain more regular shapes and optimal dimensions of MIP particles containing the filling of HPLC columns it is recommended better to prepare new MIP material using for example silica-gel surface modification polymerization technique. The surface characteristic of MIP particles using the above mentioned polymerization technique is much more appropriate for the packing material of HPLC columns, but is characterized by lower efficiency than bulky polymerization [13,14].

The first report on the application of the MIPs for enantioseparation has taken place in 1978 [15]. In this published work, the template 4-nitrophenyl-α-D-mannopyranoside was covalently linked to a monomer to form 4-nitrophenyl-α-D-mannoside-2,3,4,6-di-o-(4-vinylphenylboronate), which was then co-polymerized with styrene and divinylbenzene. In other works, non-covalently molecular imprinting has been reported to be a more direct and flexible approach because of its use of a larger range of compounds including chiral molecules that can be imprinted [16,17]. The most extensively applied as the templates have been several compounds and its derivatives including L-Phenylalanine anilide, L-phenylalanine, (S)-naproxen, (2)-nicotine and other chiral drugs [17,18]. Methacrylic acid (MAA) has been usually used as the functional monomer. Normal formats of MIPs for enantioseparation mainly include monoliths, particles, and membranes. Other important milestones reported in the field of enantioseparation process using wide spectrum of MIP materials are outlined in Fig. 1 [19–26].

Molecularly imprinted chiral stationary phases (MICSP) have predetermined selectivity, since they are prepared by using one of the pure enantiomers as template, which is rarely obtainable with conventional CSP. For example, in the case when the enantioseparation is carried out in an HPLC column packed with a given (R)-enantiomer-imprinted stationary phase, the corresponding (S)-enantiomer will elute before the (R)-enantiomer, since the latter will be more retained [5,6]. In general, these systems allow the enantioresolution with selectivity factors (α) ranging from 1.5 to 5 or even greater. However, in many cases enantiomers are not completely separated due to the large peak broadening and tailing, especially of the more retained enantiomer. Obviously, this drawback becomes more problematic when a separation of more than two compounds is necessary. The observed peak broadening and tailing is probably connected with the heterogeneity of binding sites, in terms of both affinity and accessibility, and different association and dissociation kinetics [6].

Although many other competing technologies exist, MIP-mediated chiral recognition phenomena continue to attract interest from the scientific community. An ever-increasing body of data accumulated in numerous studies, however, has provided a basis for clearer understanding of true potential and inherent limitations of MIP materials in chiral recognition applications [5]. The interest of such methodologies applying MIP materials in the field of chiral separation techniques over the years 1991–2017 (obtained from Scopus Web Site data base) are illustrated in Fig. 1. Moreover, MIPs sorbents or filling mediums prepared for separation techniques are characterized by many advantages including easy preparation methodology, high physical and chemical stability (resistance to high temperatures, organic and inorganic solvents and pH conditions). In addition, this type of sorption/filling medium might be used repeatedly by applying an appropriate regenerative procedure. Taking into account the advantages previously mentioned, the MIP materials become suitable solutions as a stationary phases/mediums for the following separation

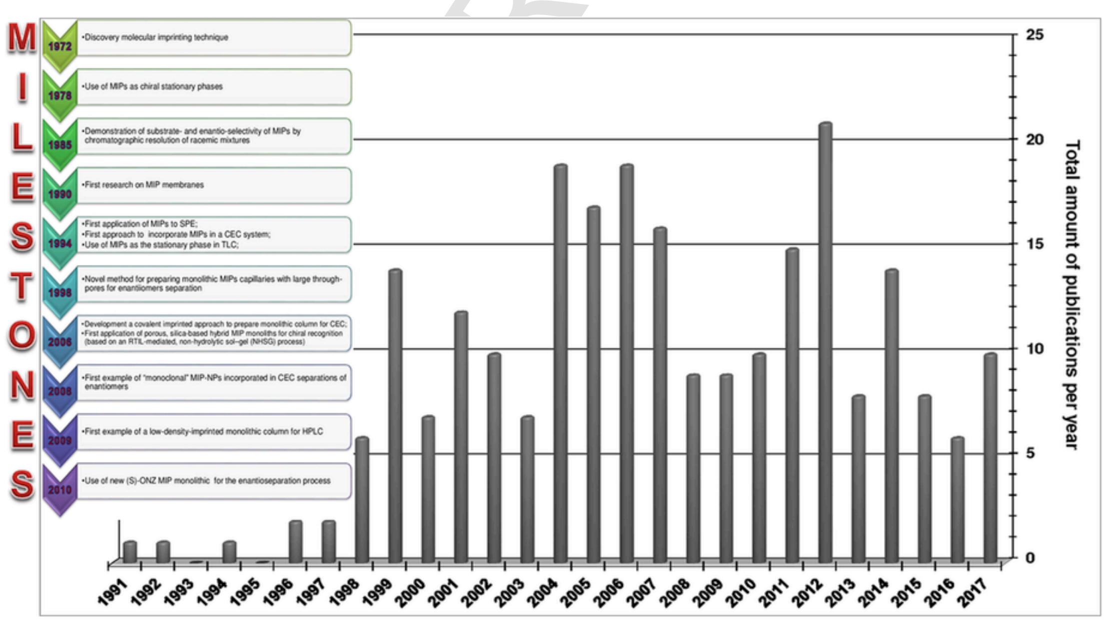

Fig. 1. The milestones of MIPs development and the general degree of MIPs applications in the field of stationary phases used in analytical separation techniques (Scopus Web Site data base).

techniques: chromatography (especially HPLC); CECs, electrochemical and biomimetic sensors; quartz crystal microbalance; solid phase extraction (SPE) and in the field of membrane separation [27].

The aim of this review is to provide a critical overview of the current role of MIP-type affinity materials in the multidisciplinary field of chiral recognition, with the focus on applications in enantioselective separation by chromatographic techniques. The coverage of this review is selective rather than exhaustive, and concentrates on innovative concepts rather than incremental improvements. We conclude that MIPs are very promising materials to be used as selective stationary phases in chromatography although further developments are necessary in order to fully exploit their potential.

2. MIPs: a selective sorption medium for enantioresolution by liquid chromatography

Enantiomers of bioactive compounds may exhibit different physiological effects on pharmacological activity, metabolism processes, and toxicity when being ingested by living organisms [28]. Thus, effective separation of chiral compounds (both analytical and preparative enantioseparations origin) is important and often required in fields including food and agrochemical industries, medical chemistry, drug development, enzyme engineering, catalyst technology and the material sciences. Chiral HPLC, possessing advantages of accuracy and generality, is still the most important technique for the analysis of enantiomeric optical purity and rapid achievement of enantiomerically pure materials, although it is relatively time-consuming and labour intensive [28]. HPLC has been the most extensively applied technique for chiral separation in last few decades.

In HPLC, indirect and direct resolution methods can be used for enantioseparation. In indirect mode, the two enantiomers interact and form stable diastereoisomers with strong bonds are formed before the chromatographic separation can take place in non-chiral stationary phase and require the use of high purity derivatizing reagents. Moreover, this mode is time consuming and purification steps may be required [29]. Thus, the direct method is mainly employed enantioresolution mode. Here the CSP is present into the column interacting continuously with the enantiomers to be separated. Diastereomeric complexes with the involvement of weak bonding are formed during the LC and then achieving their separation [30].

Many efficient CSP's exist although most of the chiral recognition elements incorporated into these CSPs are non-target-specific in nature, and the reliable prediction of the separability and order of elution of a given pair of enantiomers is still elusive [5]. In 1985, the application of MIP materials combined with the LC technique for the separation of amino acid derivatives was described [24]. Since then, MIPs have become increasingly popular as CSPs in HPLC. The MIPs are introduced to overcome some limitations of conventional CSPs, and offer the unique opportunity to tailor CSPs with predefined chiral recognition properties by using the enantiomers of interest as binding-site-forming templates. Moreover, due to the simplicity of operation chirality transfer from a templating enantiomer to the polymer network also eliminates the need for lengthy synthetic routes, sophisticated receptor designs, and elaborate immobilization procedures. In addition, MICSPs are characterized by excellent chiral recognition properties for the templating chiral species, which are manifested in high enantioselectivity, pronounced substrate-specificity, and predictable order of elution, with the enantiomers employed as templates being the more strongly retained species [5]. In consequence, technology of molecular imprinting has been extensively applied to manufacture of target-specific CSPs for a wide range of chiral compounds including a variety of drugs of abuse [23] and pharmaceuticals [3,31], naturally occurring compounds [32], amino acid derivatives [33] and many other specific chemical compounds determining by HPLC technique.

However, some difficulties and drawbacks of MICSPs in HPLC exist. The most important are difficulties associated with the engineering of suitable chromatographic formats as well as the inherently poor mass-transfer characteristics of imprinted polymers [34]. Since chromatographic columns for chiral recognition are mainly packed with particles derived from bulk polymers by the traditional grinding and sieving procedure, irregular particles with relatively broad size distributions exist resulting in packing's of irreproducible quality which manifests in poor column efficiency and high column back pressure. Moreover, although this method can be easily carried out in any laboratory, it is not appropriate for large-scale production. In addition, limited commercial application of MIP-CSPs was are apparent because of previously mentioned reasons. More specifically peak broadening and tailing have both thermodynamic and kinetic characteristics [35], which depends on the association constant and sample load with an increasing trend for high values. To improve chromatographic efficiency, the replacement of non-covalent imprinting with covalent and the use of several strategies for obtaining uniformly sized spherical microspheres is practised.

In the last few years, several polymerization strategies have been proposed in the literature including precipitation, suspension, and multi-step swelling and polymerization. Application of these polymerization techniques gives the possibility to prepare the spherical imprinted particles, with a narrow size distribution, and polymer monoliths which may be used as chromatographic stationary phases (Table 1). Much research effort has been invested in establishing dedicated MIP formats for chromatographic applications, for example porous monoliths, spherical beads, and silica-supported films. Normal formats of MIPs for enantioseparation in HPLC include monoliths, particles, and membranes. The application of these formats in HPLC are described generally and listed in Table 1.

2.1. MIPs particles used in liquid chromatography

As it was previously mentioned, MIPs particles characterized by appropriate morphological and physicochemical properties, might be prepared by application such methods as precipitation, suspension, and multi-step swelling polymerization, which were briefly described in Table 1. However, due to the fact that the preparation of MIPs particles by bulk polymerization is inefficient, and they present poor separation behaviour when are applied as CSPs, the surface imprinting technique (SIT) was introduced [47]. To manufacture surface molecular imprinted polymers (SMIPs), the MIP should be typically grafted on the supporting materials surface, such as silica gel, however, the recognition ability of this kind of SMIP was sensitive to the grafting conditions. Schematic representation of SMIP-CSP preparation is presented in Fig. 2. Silica gel particles surface-coated with chiral selectors as CSPs for chiral separation by HPLC was first time reported in 1986 [48]. This coating method has now been extensively applied for enantioseparations mainly due to its high separation efficiency and simple preparation process. Compared to the surface grafting method, the coating method process is simpler and the final surface is more homogeneous. In SMIPs, the recognition sites are more easily accessible with favourable binding kinetics. In SIT, less template molecules are applied in comparison to what is used in conventional imprinting techniques since the template is only used in the surface coating step [47]. This technique has been applied in the imprinted coating on numerous different types of nanomaterials including silica particles [49], nanowires [50], nanotubes [51] and magnetic

Table 1
Application of various types of MIP formats in HPLC systems.

Type of polymerization technique	General description	Ref.
Imprinting in preformed beads	• The most direct way to achieve spherical imprinted beads. • Polymerization takes place inside the pores or by grafting of MIP films on the surface of preformed beads (e.g., silica, alkyl-silica, TRIM, resins). • Silica beads have been the most commonly employed due to the fact that they are commercially available in a wide range of sizes and porosities.	[36,37]
Precipitation polymerization	• One of the easiest and well-suited proposed methods to get MIP micro-spheres with the appropriate characteristics. • The preparation protocol involves the polymerization of the standard mixture (template, monomer, and cross-linker) in the presence of a much higher amount of porogen agent, than that typically applied in the bulk polymerization technique. • The growing polymer chains are unable to occupy the entire volume of the vessel, which results in a dispersion of micro-gel particles in the applied porogen agent. • The obtained particles are characterized by much more homogeneous binding sites distribution compared to particles prepared using general bulky polymerization technique.	[38,39]
Suspension polymerization	• A well-established polymerization technique for the preparation of polymer materials in beaded forms. • An organic-based medium (monomers in organic solvent) is mixed with an excess (4–10-fold) of water containing a selected type and the amount of suspension stabilizer (e.g., polyvinyl alcohol). • The two phases are vigorously mixed by stirring to form a suspension of organic droplets in the aqueous phase with the final bead size associated with the size of the droplets. • The application of this preparation protocol, often termed aqueous suspension polymerization, to make imprinted beads has been scarce since water is thought to disrupt the non-covalent interactions (e.g., hydrogen bond formation) between the template molecule and the monomers.	[40,41]

Table 1 (*Continued*)

Type of polymerization technique	General description	Ref.
Multi-step swelling and polymerization	• One of the most suitable procedure for the synthesis of monodisperse imprinted beads with a high yield, however a laborious procedure. • The seed particles (polystyrene latex, ~1 μm) are swollen employing a micro-emulsion of initiator and a low molecular weight activating solvent (e.g., dibutyl phthalate) in water – the sodium dodecyl sulphate is used as a stabilizer. • Once the emulsion droplets have been absorbed into the seed particles, this dispersion is added to a second dispersion containing monomers, cross-linker, porogen agent, and template dispersed in water using a polymeric stabilizer such as polyvinyl alcohol. • The mixture is stirred for several hours until the droplets are absorbed into the seed particles. • The dispersion is purged with an inert gas stream and polymerization is initiated. • The size of the imprinted beads might be controlled by changing the polymerization process conditions (e.g., volume ratios of the various dispersion phases).	[42,43]
Surface imprinting	• Novel surface imprinting solution, mainly based on synchronous graft-polymerizing and molecule imprinting process on inorganic particles and polymeric microspheres through the action of surface initiating systems. • Prepared solid materials are characterized by more accessible binding sites, faster mass transfer rate and more effective ability to recognize the characteristic molecules of defined chemical compounds. • The main advantages of this technique are as follows: (i) the imprinted wholes are more accessible to the template molecules; (ii) good comprehensive properties of the prepared imprinted materials; (iii) large specific surface area of the particles leading to excellent binding affinity and selectivity; (iv) fast binding rate and fast desorption rate of the surface imprinted materials.	[44]

Table 1 (*Continued*)

Type of polymerization technique	General description	Ref.
Reversible deactivation radical polymerization (RDRP)/controlled radical polymerization (CRP)	• This solution gives high possibility to obtain well-defined macromolecular architectures with controlled particles topologies, terminal functionalities, livingness, co-monomer arrangements (block, random or graft), molecular weights, and narrow molecular weight distributions. • RDRP techniques consist of the atom transfer radical polymerization (ATRP), from which many other related techniques are derived, such as supplemental activators and reducing agents (SARA), single electron transfer living radical polymerization (SET-LRP), activators generated by electron transfer (AGET), activators regenerated by electron transfer (ARGET), nitroxide-mediated polymerization (NMP), and reversible addition fragmentation chain transfer (RAFT) • Mentioned techniques are mainly based on the application of a mediating agent capable of reversibly deactivating active chains, such that the majority of living chains are maintained in dormant form.	[45,46]

nanoparticles [52]. The SIT is important for the formation of MIPs on the support particles surface. MIPs created by this technique present highly uniform shape and size, and therefore, more efficient particles can be prepared. As a results faster mass transfer, higher binding capacity, and easier adsorption and removal of templates than traditional MIP particles are obtained [3].

An example of the application of this method to enantio-separation was presented by Dong et al. [53]. In the work, SMIP-coated CSPs (SMIP-CSPs; poly-methacrylic acid as the matrix) were successfully prepared by coating an (R)-DABN (1,1-Binaphthalene-2,2-diamine) imprinted polymer on silica gel particles which showed an excellent resolution ability for the racemic DABN by HPLC. The prepared SMIP-CSP showed the highest separation factor (3.39) for the resolution of the DABN racemate, more than their previous work (2.14) using MIPs produced by bulky polymerization technique [54].

In SIT, the selection of functional monomers also has an extreme difference what is illustrated in a paper published in 2012 [55]. A L-Phe imprinted polymer based on monodisperse hybrid silica microspheres ($MH\text{-}SiO_2$) with $-CH{=}CH_2$ groups was synthesized by SIT, while the $MH\text{–}SiO_2$ was synthesized by a sol–gel process in aqueous media using tetraethylorthosilicate (TEOS) and 3-methylacryloxypropyl trimethoxysilane (MATES) as the precursors. Compared with the imprinted polymer prepared with β-cyclodextrin (β-CD) or MAA as functional monomer, the imprinted polymer prepared with both β-CD and MAA as binary functional monomers holds the highest adsorption capacity. Under the optimum chromatographic conditions, a complete baseline separation of phenylalanine racemates was observed using the column packed with the imprinted polymer prepared with both β-CD and MAA as binary functional monomers. The separation factor and resolution of the imprinted polymer towards phenylalanine racemates were calculated as 1.41 and 1.46, respectively, which is higher than that of other imprinted polymers [55].

One of the most important parameter of MIP-based CSP on the silica-gel bead is the thickness of the film, due to the fact that it has an important impact on the separation results. The thickness and morphology of the film of MIP-based CSP are very difficult to control. However, an application of the “grafting from” approach in which the grafting reaction can proceed by polymerization from the surface can effectively control the thickness of grafted polymer. This was approached has been used and demonstrated, e.g. for the separation of the enantiomers of the citalopram [56]. For this purpose, the iniferter-mediated grafting approach to develop a surface-imprinted CSP was employed. Firstly, MIP chiral selectors were grafted to the surface of porous silica particles, after which a homogeneous material was formed. This material had a stronger interaction with the S-enantiomer of the drug. In this way, an optimal thickness was obtained which provided the best resolution of the analysed racemate.

Another method which allow the tuning of the morphology of the film of MIP-based CSP as well as complex framework, and functionality of a well-defined MIP, is reversible-deactivation radical polymerization (RDRP), especially addition fragmentation chain transfer polymerization (RAFT) [3]. The latest technique makes use of a chain transfer agent (CTA) in the form of a thiocarbonyl compound (or similar) to afford control over the molecular weight and polydispersity during a free-radical polymerization. RAFT has been proven to be able to reduce heterogeneity of resultant polymers. The RAFT would contribute much to the controllable development of MIP-based CSPs on the supporting materials to obtain excellent MIPs with high homogeneity and capacity [3]. Information on application of organic polymer-based particles MIPs in HPLC are provided in Table 2.

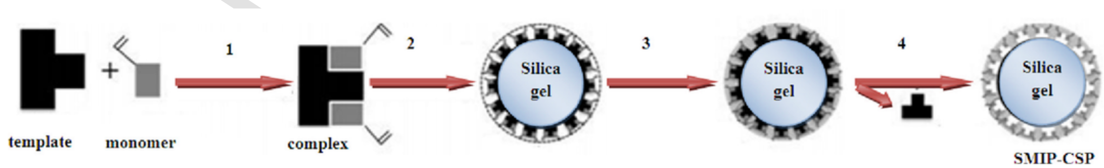

Fig. 2. Schematic representation of SMIP-CSP preparation: 1) pretreatment; 2) coating on silica gel; 3) surface polymerization; 4) removal of template.

Table 2
Information on the application of organic polymer-based monolith, particles and membranes MIPs in HPLC systems.

Format	Template	Functional monomer	Cross-linker	Solvent
Particle	L-phenylalanine	MAA/acryloyl-β-CD	EGDMA	ACN/water (17:3, v/v)
Particle	R-BNA	MAA	EGDMA	Not mentioned
Particle	S-citalopram	Itaconic acid	EDMA	ACN
Monilith	(*S*)-1,l′-Bi-2-naphthol	4-VP	EDMA	ACN/water
Monilith	L-phenylalanine anilide, D-phenylalanine anilide	Acrylic acid	EDMA	Cyclohexanol, 1-dodecano
Monilith	Ketoprofen	4-VP	EDMA	[BMIM][BF_4]/DMSO (4:1, v/v)
Monilith	R-mandelic acid	4-VP	EDMA	DMSO/DMF/[BMIM][BF_4]/Co^{2+}
Membrane	Ractopamine	MAA	EDMA	Dimethyl sulfoxide
Membrane	CBZ-L-tyrosine	MAA	TRIM	Chloroform
Membrane	Ractopamine	MAA	EGDMA	Dimethyl sulfoxide

ACN (acetonitrile); β-CD (β-cyclodexrin); [BMIM][BF4] (1-butyl-3-methylimidazolium-tetrafluoroborate); DMF (dimethylformamide); DMSO (dimethyl sulfoxide); EDMA (ethylene glycol dimethacrylate); EGDMA (ethylene glycol dimethacrylate); MAA (Methacrylic acid); 4-VP (4-vinylpyridine); TRIM (1,1,1-Tris(hydroxymethyl)propane Trimethacrylate).

2.2. MIP monolithic materials

Due to the advantages such as low cost, ease of preparation, good stability, high reproducibility, rapid mass transfer and versatile surface chemistry, monolithic materials have been widely used for various applications in LC. Among these materials MIPs are of high importance and have recently been applied extensively in HPLC for chiral separations. The preparation process of monolithic MIPs is more straightforward and convenient in comparison to particles. The combination of monolithic column and MIPs combines the high efficiency of chromatography as well as the high selectivity provided by MIPs. The *in situ* polymerization method employed in 1993 [58], was used to prepare molecularly imprinted monolithic polymer rods. In the procedure of MIP preparation, a template compound, a cross-linker, and a functional monomer were mixed in a stainless steel column and heated. Thus, the polymerization occurred in the column, greatly shortening the pre-preparation time. After polymerization, the template and porogenic solvents are removed by exhaustive washing with an acetic acid-methanol mixture. It need to be noted that a suitable porogenic solvent should meet three criteria [64]: (i) template molecules, initiator, monomer, and cross-linker must be soluble in the porogenic solvents; (ii) the porogen should be able to create large pores, which can modify the flow-through property of the resulting polymer; and (iii) the porogenic solvents should have low polarity. Low polarity can have weak interferences to the interaction between the imprint molecule and the monomer during polymerization, being important to obtain MIPs with high selectivity.

In situ technology integrates the advantages of monolithic column and molecularly imprinted technology, which is prepared by a very simple, one-step, free-radical polymerization process directly within a chromatographic column without the tedious procedures of grinding, sieving and column packing [25].

Two MIP monolithic matrices exist: organic polymer-based monoliths (the major MIP monolith matrices) and silica-based molecularly imprinted monolith (mainly used for chiral recognition by electrochromatographic techniques). The first type of MIP monolithic matrices has been extensively investigated since a lot of variety of monomers are available and stable in different pH environments. The most common monomers used to prepare this type of MIP includes MAA, 4-vinylpyridine (4-VP) and acrylamide (AA).

To minimize the template consumption as well as to improve the kinetic properties, another method was developed to prepare the MIP on the glass microspheres in the column [65]. The column was pre-packed with glass microspheres. Next, the pre-polymerization mixture was injected into the interstitial volume of the column. The polymerization took place *in situ* and the column could be directly used for HPLC after the template had been removed. The MIPs obtained exhibited higher efficiency, better kinetic properties, and low back pressure of the column.

To improve the separation efficiency, more effective imprinted sites are needed. It is often the case that the number of effective imprinted sites mostly depends on the ratio of monomers. In fact, the permeability is bad for traditional volatile organic solvents with high monomer content [3] and here room-temperature ionic liquids (RTIL) are used to overcome these drawbacks. Due to properties including low vapour pressure, excellent solvation qualities, and good chemical and thermal stability, RTILs are of high importance nowadays in separation science. In addition, RTIL may be classed as green solvents, which have temperate effects on the environment. Taking into account advantages of RTILs, these compounds present immense potential as replacements for traditional solvents in the MIP preparation process. For example, a MIP monolith with good permeability was successfully achieved using a strategy involving a high content of monomers in a dimethyl sulfoxide-dimethylformamide ([BMIM][BF_4])-based green solvent [59]. The imprinted monolith was prepared with ketoprofen or naproxen as a template, 4-VP as the functional monomer, and ethylene glycol dimethacrylate (EGDMA) as a crosslinking monomer. Column efficiency and permeability of the MIP monolith can be tuned by a mixture of [BMIM][BF_4]/DMSO. The approach allowed the creation of an imprinting system in a short polymerization time (<1.5 h) and higher imprinting factor (IF – 8.64) than the MIP prepared in a traditional volatile solvent. In another study, a new CSP based on MIP was prepared in RTIL by use of the metal pivot concept. Imprinted monoliths were synthesized by use of a mixture of R-mandelic acid (template molecule), 4-VP, EGDMA, and several metal ions as pivot between the template and functional monomer. A ternary mixture [BMIM][BF_4] containing metal ions was used as the porogenic system. Separation of the enantiomers of racemic mandelic acid was successfully achieved on the MIP thus obtained, with resolution of 1.87, whereas no enantiomer separation was observed on the imprinted monolithic column in the absence of metal ions. The results reveal that use of metal ions as a pivot, in combination with ionic liquid, is an effective method for preparation of a highly efficient MIP stationary phase for chiral separation. Information on the application of organic polymer-based monolith MIPs in HPLC are listed in Table 2.

2.3. Molecularly imprinted polymer-based membranes

For preparative applications, membranes can be used as the separation matrices, with the benefit that a continuous process can be designed, as compared to the batch wise operation of chromatography. MIP-based membranes were presented as feasible in HPLC for chiral separation in 1990s [62]. In the beginning, membranes were prepared either as free-standing thin films [66] or thin polymer films on the surface of solid supports [67] following standard imprinting recipes. Others have employed a phase-inversion precipitation technique starting from linear polymer precursors [62]. Imprinted polymer membranes can be also prepared by casting an imprinted polymer in the pores of a porous solid support, such as a polypropylene membrane. This solution was applied for enantioseparation of CBZ-tyrosine [62]. However, new developments of MIP-based membranes have appeared during recent years [3].

It is reported that both permselectivity and flux are important properties for membrane separation and it can be challenging to improve the flux of a MIP membrane without deterioration of permselectivity. Therefore, efforts have been made to maintain the quality of these two parameters. For example, in 2012, a molecularly imprinted nanofibre membranes (MINFMs) were synthetized and compared with traditional molecularly imprinted membranes (MIPMs) [61]. It was shown that the fluxes through the MINFMs gave one to two orders of magnitude higher than those of standard normal MIPMs without depression of permselectivity.

Additionally, other approaches to modify the properties of MIPMs exist. For example, an appropriate selection of substrate of MIPMs was presented to be a very important parameter [63]. For example, the synthesis of ractopamine MIPs nanotube membranes on anodic alumina oxide (AAO) nanopore surface by atom transfer radical polymerization (ATRP) was described, in which MAA was selected as functional monomer. AAO has a highly-ordered hexagonal nanopore array as well as adjustable pore diameter, thickness and shape, so the resultant polymers usually have uniform shape and size. Compared with the traditional methods, the method combined of imprinted layer-coated nanostructures with surface enrichment of the targets can significantly improve the binding capacity and kinetics of imprinted materials by increasing the number of binding sites at the material's surface [63]. Moreover, AAO-MIPs have a small dimension with a high specific surface area. The emergence of AAO as a nanoreactor for molecular imprinting can eliminate the limitations of traditional imprinting, such as incomplete removal of the template, small binding capacity, slow mass transfer, and irregularity in the shape of materials. Information on application of organic polymer-based membranes MIPs in HPLC are provided in Table 2.

2.4. MIPs template in capillary electrophoresis

Capillary electrophoresis (CE) is one of the techniques used for separating enantiomers. This technique is characterized by high efficiency, low consumption of solvents and selectors, simple instrumentation, as well as short analysis time when applied in practical problem solving in various industries including; chemical, pharmaceutical, biomedical, food and environmental. In general, the separation of enantiomers is obtained by adding the chiral selectors to the running buffer [68]. Various types of chiral selectors, including CDs and their derivatives, different classes of antibiotics, polysaccharides, proteins, crown ethers, chiral metal complexes, surfactants, chiral ion binding reagents have been successfully used to separate enantiomers [69]. At present, CDs and their derivatives (anionic and cationic CDs), remain the most commonly used chiral selectors in CE. Beyond chromatographic and electrokinetic techniques, hybrid technique such as CEC can be used to obtain pure enantiomers [70]. Application of MIP for analytical scale separation in CE and CEC are becoming more popular than in LC nowadays due to the intrinsic character of high separation efficiency and minimized requirement of the amount of MIP template in CE and CEC [71].

CE is an effective method of analysis for a wide range of applications because it is fast and requires a small amount of solvents and reagents [72]. CE has proved to be a powerful technique for separation of chiral compounds. Since it has the advantages of high resolution of such compounds one of the most successful areas of application of CE is chiral amino acid analysis. To obtain a high resolution of the target enantiomers, the choice of separation mode is one of the most important issues in the CE analysis of both amino acid and other compound enantiomers. Separation modes in CE involve the addition of appropriate CSs into a background solution (BGS). The most commonly used modes are: (i) cyclodextrin-modified capillary zone electrophoresis (CD-CZE); (ii) CD electrokinetic chromatography (CDEKC); (iii) micellar EKC (MEKC); (iv) CD modified MEKC (CD-MEKC); (v) chiral ligand-exchange CE (CLE-CE); (vi) affinity CE (ACE) and (vii) non-aqueous CE (NACE) [73].

One of the key separation modes for CE enantiomers analysis is CD-CZE in which "neutral" CDs are added to the BGS as CSs. The migration of ionic compounds in the CDs zone results in a chiral separation. In CE-CZE natural α-, β-and γ-CDs and derivatized CDs which include hydroxypropyl-α-CD (HP-α-CD), HP-β-CD, methyl-β-CD (Me-β-CD) and dimethyl-β-CD (DM-β-CD) can be used [74]. Besides labelled amino acids [75] CD-CZE enantioseparation of alkyl and aryl monoesters of *N*-blocked aminophosphonic acids [76], structurally complex basic drugs [77], deprenyl and its major metabolites [78], cyclic antidepressants [79] have also been applied.

In the CDEKC separation mode "charged" CDs are added to BGSs as the CS in contrast to CD-CZE mode. The charged CDs functions act as a pseudo-stationary phase for the enantio-separation. When the ionic CDs interacts with a racemic mixture, analytes transfer from the surrounding water phase due to the electrophoretic migration of the charged CDs [87]. For CDEKC anionic [80] and cationic CDs [81] are produced, however, the dominant CDs group, due to its resolution powers and their commercial availability, are highly sulphated CDs (HS-CDs) [82]. Various types of CDs are highly effective for separation of racemic amino acids and their derivatives using the CDEKC [83,84]. Recently progressed analytical approaches employing CDEKC in the area of enantioselective analysis of drugs metabolites, and biomarkers in biological samples have been described [85].

MEKC which can separate both neutral and charged analytes by the capillary electrophoretic technique, was developed in 1982 and the first paper was published in 1984 [86]. MEKC is also another important mode of CE which is also widely used for the enantio-separation. In this solution the chromatographic principle is based on the distribution equilibrium between immiscible phases and distinct from the ACE binding stoichiometry between analytes and chiral micelles which is not required and also more complex relationship with the concentration of the chiral selector compared to the complexing components [87]. A fully automatized MEKC-MS method was developed for the chiral analysis of D- and L-amino acids [88]. As one of many possibilities of using the MECK model, the enantio-separation of four stereoisomers of palonosetron hydrochloride (PALO) [89] might be carried out.

Coupling MEKC using achiral and/or chiral surfactants with chiral recognition ability of CDs (CD-MEKC mode) uses a micellar solution containing CDs as a BGS. Since the MEKC mode gives good resolution of compounds closely related to each other based on small differences in partition coefficients with respect to the micelle, it is suitable for separation of many types of enantiomers in samples which are often characterized by complex matrix composition [73]. In fact, many applications of CD-MEKC to real sample analyses have been reported. The content of catechins and methylxanthines in green tea has been determined by a CD-MEKC method with the addition of hydroxypropyl-β-cyclodextrin [90]. A CD-MEKC method with HP-γ-CD as chiral selector for the enantiomeric separation of econazole have also been reported [91]. There are reports where CD-MEKC method has been developed for the simultaneous separation of a group of parent phthalates [92] or separating conjugated linoleic acid (CLA) isomers [93]. In all cases the CD-MEKC method was simpler, safer and more economical, than HPLC and GC methods.

CLE-CE technique was used for the first time in 1985 for the enantioseparation of D,L-amino acid and because of low cost, high convenience and controllable enantiomer migration order it is of growing interest. The widely-used chiral ligands in CLE-CE mode are L-AAs, D-AAs, L-AAs derivatives and some chiral organic acids [94].

NACE was first introduced in 1984 however, the first publications on the separation of enantiomers with the NACE mode were available in 1996 [95]. NACE has been proved to be a powerful tool to achieve the enantioseparation of, nine structurally similar chiral anticholinergic drugs [96] and for the chiral separation of some β-blockers and β-agonists using di-n-amyl L-tartrate–boric acid complex as the chiral selector [97]. Isomers of amino acids are separated by both NACE and ACE mechanisms [73].

A number of publications on biological, food and pharmaceutical applications of the CE chiral separation have appeared. It has been shown that CE is an appropriate technique for the quantitative determination of many enantiomers even in complex sample matrices [73].

3. MIPs: a sorption medium for enantioresolution by capillary electrochromatography technique

CEC is a hybrid separation technique that combines elements and advantages of LC and electrophoresis [98]. The stationary phase used in CEC have been greatly developed due to the various requirements of microscopic separation. Due to the low cost and favourable molecular recognition capability and stability of MIPs, they have also found use in chromatography [99]. The combination of the MIP technique with capillary CEC takes advantage of the selectivity of MIPs and utilises the high CEC efficiency [98]. The approach was first applied in 1994 [26], since then, this has been a commonly used technique in separation sciences [98] and highly selective stationary phases within chiral separations [100]. The development of MIP-charged capillary columns suitable for CEC applications, was more difficult than for HPLC, essentially, it is required to develop dedicated MIP formats. In the literature several protocols allowing the synthesis of MIPs using the appropriate characteristics in CEC have been proposed [5]. First attempts were performed by packing MIP particles inside the capillary [6]. In Table 3 currently used examples of different approaches to MIP-type capillary formats were generally described.

Examples of applications of MIPs as a sorption medium in CEC chiral separation techniques are currently one of the most attractive topics in chromatography. For example, a number of short OT-MIP columns for chiral separation of various pharmaceuticals (especially NSAIDs) and other compounds was presented where excellent efficiencies in chiral separation of template enantiomers as well as non-chiral separation of nonpolar and polar test solutes was obtained [110]. In other studies, monolithic MIP for chiral separation of nateglinide and its L-enantiomer, using an *in situ* method was designed and prepared. Experiments have shown that chiral detection was dependent on stereochemical structures and arrangement of functional groups in the MIP cavities. The thermodynamics of the enantioseparation indicated an enthalpy-controlled process [111]. Selectivity of (S)-naproxen MIP monoliths, which was prepared by an *in situ* thermal-initiated polymerization, was also examined. The study results showed that good chiral recognition was not only dependent on the MIP monoliths, but also on the CEC parameters such as amount of organic solvent, pH range of buffer solution, salt concentration, column temperature and addition of for example surfactants [112]. Use of MIPs for CEC enantiomer separation of propranolol using a partial filling technique was also reported. This method allows altering of the amount of MIP used for a certain separation which, in turn, is beneficial for fast optimization [112]. MIP stationary phases synthesized by an *in situ* photo-initiated polymerization reaction for rapid separation of propranolol were studied as well [113].

MIPs as a sorption medium in CEC represent a novel method and a promising tool for the demanding or special analytical separation tasks, such as chiral separation. The MIP–CEC system might be employed in miniaturised analysis systems in general. Promising potential of MIP–CEC has been increasingly evident since more and more CEC-based MIPs stationary phases have been successfully prepared and increasingly used in fields such as drug or food analysis [113].

4. MIPs: a selective solid materials in capillary liquid chromatography

Capillary LC and CEC are well known as powerful analytical techniques based on the differential distribution of analytes between the mobile and stationary phases leading to their general migration patterns. The use of *in situ* modified capillaries in both HPLC or high performance capillary electrophoresis (HPCE) instruments offers many mechanical and optical advantages [114]. In tubular, especially porous layer open tubular (PLOT), formats faster regeneration and higher linear velocity can be achieved in comparison to packed bed capillaries. There are many types of stationary phases that can be used in the nano-analytical separations in capillaries. MIPs have a number of advantages (high resolution and reproducible retention, fast analysis time and very conservative use of reagents) when applied as CSP materials. The development of enantioselective MIPs have great interest in the context of being used for capillary LC as well as CEC mode in monolith or PLOT [115]. One example is when MIP-coated capillaries have been evaluated in separations of the ketoprofen racemate [115] or racemic amlodipine and naproxen [116].

5. Summary and future challenges

From the analytical chemistry point of view (assessing the purity of obtained chemical compounds) it is necessary to successfully improve and developed new types of sorption materials which might be considered and applied as a stationary phases in advanced analytical separation techniques. Suitably developed and well characterized material employed as a stationary phase allows for effective separation and optimal identification of chemical compounds in enantio-separation processes, especially in a case of biological, medical, environmental and pharmaceutical samples. The possibility of "creative design" of stationary phase for a specific chemical compound using molecularly imprinted techniques gives an opportunity to increase the selectivity and sensitivity of applied analytical methodology.

Nevertheless, it should be highlighted that such polymeric materials employed as stationary phases in different types of separation techniques, must be characterized with appropriate particle size (mesh), particles diameter and geometry, high porosity and specific surface area. Due to this fact, the whole process of preparation and characterization of new types of polymer material as a stationary phase in separation techniques requires appropriate knowledge, skills,

Table 3
Adaptation of molecular imprinting technology to capillary electrochromatography systems [5,6].

	Name and description of protocol to prepare specific MIP columns for CEC technique		Target analytes	Applied reagents	Advantages	Ref.
Packed capillaries	Capillaries packed with particulate MIPs	• Conventional bulk polymerization; grinding and sieving; placing the MIP particles (<10 μm) in selected fused silica capillaries leaving one part of the capillary free of packing in order to allow in-column detection. • Stabilization of the particle packings within the capillaries accomplished by entrapment in supporting material surfaces.	D,L-aromatic amino acids; Tricyclic antidepressant drugs (TCAs)	Functional monomer – MAA; Crosslinker – EDMA; Initiator – AIBN	Higher resolution than that obtained by HPLC using the same particles	[101]
	Capillaries packed with silica-grafted MIP films	• Modification with an azo-initiator of silica particles characterized by a well-defined particle size (10 μm diameter), shape and pore system (1000 Å), that might be subsequently employed to graft MIPs. • Fused silica capillaries were packed over a length corresponding to 8 cm, using a pneumatic amplification pump.	D,L-aromatic amino acids;	Functional monomer – MAA; Crosslinker – EDMA; Initiator – ACPA; Solvent/porogen – DCM or toluene	Comparable enantioselectivity with that shown in LC. Exhibited improved performance in terms of plate number, selectivity, analysis time, inter/intra-day and intercapillary reproducibility.	[102,103]
	In situ dispersion (precipitation) polymerization	• Methacrylate-based imprinted polymers for pentamidine were achieved inside the capillary in the form of agglomerates (approx. 10 μm) of globular particles with sizes ranging from 2 to 4 μm.	Pentamidine (PAM)	Functional monomer – MAA	Electrolyte could be pumped hydrodynamically through the capillaries, causing rapid phase changes and micro-chromatographic possibilities with high plate numbers.	[26]

Table 3 (*Continued*)

Name and description of protocol to prepare specific MIP columns for CEC technique		Target analytes	Applied reagents	Advantages	Ref.
Acrylamide entrapped MIP capillary columns	• Entrapped MIP capillary columns were developed using an acrylamide gel as the entrapping medium. • MIP particles were suspended in a mixture of acrylamide and bisacrylamide. • Prepared suspension mixture was transferred into the capillary and then subsequently heated at 40°C to form the appropriate network gel.	D,L-aromatic amino acids;	Functional monomer – MAA; Crosslinker – EDMA; Initiator – ACPA; Solvent/porogen – chloroform	Polymer is rigid and stable enough to be employed in CEC	[104]
Silica-based entrapped MIP capillary columns	• MIP particles were placed into the capillary applying so-called "temporally" generated frit • The capillary was flushed with a mixture of potassium silicate and deionized water and heated from 40 to 160°C for several days to form appropriate silica-based network; • The frit might be easily removed from the capillary by cutting the corresponding end.	D,L-dansylphenylalanine	Functional monomer – MAA or Styrene; Crosslinker – EDMA; Initiator – AIBN	Significant increase in separation efficiency.	[105]

Table 3 (*Continued*)

	Name and description of protocol to prepare specific MIP columns for CEC technique		Target analytes	Applied reagents	Advantages	Ref.
MIP monoliths	*In-situ* generation of superporous monoliths	• The fused silica capillaries were chemically modified – derivatized with [(methacryloxy)propyl] trimethoxisilane, which gives a possibility to covalent bonding of the methacrylic-based polymer to the capillary surface. • Chemically modified capillaries were indicted with MAA–TRIM–(R)-propranolol mixtures in toluene, a polar porogenic agent favouring the creation of MAA–template complexes. • Appropriate prepared capillaries were exposed at subambient temperatures to a UV-source to initiate photochemical polymerization reaction.	B-adrenergic antagonists (β-blockers) propranolol and metoprolol	Functional monomer – MAA; Crosslinker – TRIM; Initiator – AIBN; Solvent/porogen – toluene	Superporous structure of the polymers material allows to rapid solvent and electrolyte exchange, and easy regeneration of the capillaries by hydrodynamic pumping.	[106]
Capillary coatings	Open tubular (OT) capillaries, coated with a thin MIP film	• Fused silica capillaries were treated with methacryloxypropyltrimethoxysilane to assure “primer”vinyl groups for a surface-centered polymerization reaction; • Methacrylate-grafted capillaries were then loaded with pre-polymerization mixtures of different composition, and subjected to thermally induced polymerization process.	S(+)- and R(−)-2-phenylpropionic acid	Crosslinker – EGDM or DVB	Lack of significant back pressure (facilitating column regeneration and mobile phase exchange). Reduction of the risks of bubble formation and capillary clogging phenomena.	[107]

Table 3 (*Continued*)

Name and description of protocol to prepare specific MIP columns for CEC technique	Target analytes	Applied reagents	Advantages	Ref.
• Capillary walls were modified with 3-(trimethoxylsilyl)propylmethacrylate to ensure the anchoring points for the attachment of the polymer material. • After the polymerization process, to remove the residual solvents and to respectively shrink the polymer material into thin film layer, appropriate vacuum pressure was employed to the capillary.	D- and L-dansyl phenylalanines	Functional monomer – MAA or 2-VP; Crosslinker – EDMA or TRIM; Solvent/porogen agent – toluene	Higher degree of selectivity when used as stationary phases for chromatographic separations.	[108]
• Photolabile initiator was immobilized on the capillary walls just before placing the previously prepared polymerization mixture; • Polymerization was photo-induced and took place in the vicinity of the capillary surface. • Obtained MIP films were characterized by the thickness varying from 0.15 to 2 μm.	Enantiomers of propranolol	Functional monomer – MAA; Crosslinker – TRIM; Initiator – ACPA	Method designed for MIP coating preparation directly at any type of the surface, including in chip-based platforms.	[109]

time, and adequate laboratory facilities. The improperly prepared polymer material might lead not only to poor analysis results, but also cause damage (permanent or temporary) to expensive analytical equipment (e.g. applied detectors, such as mass spectrometers).

One of the main challenge in the field of application process of MIP stationary phases in advanced separation analytical techniques to assess the optical purity of chiral compounds, described in detailed in scientific literature, is to develop a MIP stationary phase that will be characterized by sufficient homogeneity and high density of the binding sites, having excellent chiral recognition properties and high mass transfer kinetics. Moreover, when preparing the new type of MIP stationary phase it is vital to select reaction conditions/method in such way to ensure high uniform of size and shape of synthetized MIP particles. In the case of developing a new preparation process, the most popular practice is the bulky polymerization technique. However, the solution for this problem, mentioned in many research papers, is to applied other polymerization techniques which helps to ensure the optimal shape and size of obtained MIP material particles, such as *in situ* multi-step swelling, suspension polymerization, or the surface molecular imprinting technique (using so-called microspheres) on a specific materials like silica gel, nanofibers or magnetic particles. Application of microspheres is one of the most optimal solution in a case of stationary phases in the field of enantio-separation process, due to the optimal size and shape of particles, which increase the efficiency of the separation and identification of chiral chemical compounds. However, using mentioned microsphere based polymerization techniques in many cases requires large amounts of reagents and solvents to prepare the optimal MIP stationary phase [1,5,7,117].

Furthermore, it is important for the preparation process of almost every MIP materials to select an optimal template molecule. In some cases it is difficult and expensive to source the chemical compounds. Moreover, the template monomer which will be the most suitable to develop new stationary phase is not soluble in any porogen solution and it is hard to perform the polymerization reaction. The solution for this problem might be the application of structural analogues of template molecules (dummy template imprinted polymers). However, the main drawback is the possibility to achieve an inadequate degree of selectivity of a developed sorption material to the specific chiral compound. The important challenge is to develop stationary phases in advanced separation techniques which might be applied successfully in large-scale enantio-separation processes and in every day chemical analysis, i.e. pharmaceutical or biotechnological origins within on-line systems. One of the main future trends in analytical chemistry origin concerning the rapid separation of chiral chemical compounds might be the newly developed enantioselective electrochemical sensors (*in-situ* rapid analysis). To designed and developed a desired electrochemical sensor it is important to cover the electrode's surface with a functionalized thin film layer which will be capable to “recognize” only one enantiomer. Such small-scale analytical devices might be impregnated with a thin film of a specific MIP material as a stationary phase, which greatly simplifies the qualitative and quantitative analysis factors of a selected enantiomer in biomedical, biochemical, pharmaceutical and environmental samples [118].

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