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# Molecularly imprinted polymer based enantioselective sensing devices: A review

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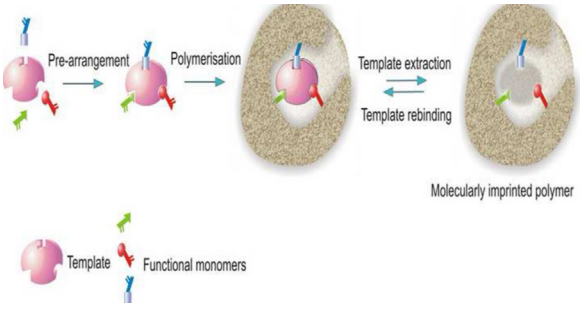
## HIGHLIGHTS

- Impact of chirality has significant ramifications in many fields of economic interest.
- MIP provides a unique opportunity for the creation of 3-dimensional cavities.
- MIP-based chiral recognition sets an exotic trend in development of chiral sensors.
- We present about rational design of chiral sensors as selective and sensitive devices.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Chiral recognition is the fundamental property of many biological molecules and is a quite important field in pharmaceutical analysis because of the pharmacologically different activities of enantiomers in living systems. Enantio-differentiating signal of the sensor requires specific interaction between the chiral compounds (one or a mixture of enantiomers) in question and the selector. This type of interaction is controlled normally by at least three binding centers, whose mutual arrangement and interacting characteristics with one of the enantiomers effectively control the selectivity of recognition. Molecular imprinting technology provides a unique opportunity for the creation of three-dimensional cavities with tailored recognition properties. Over the past decade, this field has expanded considerably across the variety of disciplines, leading to novel transduction approaches and many potential applications. The state-of-art of molecularly imprinted polymer-based chiral recognition might set an exotic trend toward the development of chiral sensors. The objective of this review is to provide comprehensive knowledge and information to all researchers who are interested in exploiting molecular imprinting technology toward the rational design of chiral sensors operating on different transduction principles, ranging from electrochemical to piezoelectric, being used for the detection of chiral compounds as they pose significant impact on the understanding of the origin of life and all processes that occur in living organisms.



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## 1. Introduction

Continuous assays of metabolic substances having the asymmetric carbons in their structures have significant impact on the understanding of the origin of life and all processes that occur in living organisms. Most of biochemical systems functioning in living organisms involve chiral interactions resulting from different stereochemistry of numerous biologically active compounds such as amino acids, sugars, peptides, proteins, and polysaccharides. The presence of chiral compounds in human biological fluids (serum, urine, and spinal fluids) as normal metabolites due to human metabolism or drug metabolism warrants an accurate methodology for monitoring level of these molecules in bio-fluids, since their higher or lower levels could be correlated as substantial indicative (marker) of functional abnormalities in human bodies.

A huge interest in chiral analysis emerges from the fact that the present pharmaceutical and chemical industries rely on the synthesis of enantiomeric components to the large extent. Although, these isomers do not possess any physical differences, they can have different influences on living organisms. As such it is most important to synthesize drug with particular ingredient of pure enantiomer. The fact, how the chiral purity is important for pharmaceutical industry, can be illustrated by the worldwide sale of chiral components as a racemate, which decreased from 35% in 1983 practically to zero in 2001. Thus, the prognosis of revenues from chiral technology now demonstrated over triple growth during past 10 years in the quest for pure chirals and predicted the involvement of 15 billions of dollars business [1].

Many examples, showing that enantiomers differ in bioactivity, rate of reaction or time of dissolution and each enantiomer manifests a different disease, can be found in the literature. So, it is very important to find analytical method that can discriminate between the D- and L-enantiomers. These methods should reveal reliable analytical information, fast analysis, and could be applicable for the continuous monitoring of enantiomers in biological fluids.

Separation and determination of enantiomers are currently being performed most commonly by chromatographic and electrochemical methods. However, the sampling process in enantioselective analysis may introduce a lot of uncertainties, especially when a separation method uses inadequate chiral selector [2]. Alternatively, the introduction of different types of enantioselective sensors and biosensors assure the reliability of the assay, as the enantiomers can be determined without prior separation, directly from the matrix, involving only dissolution and dilution steps [2–7].

Nature has attracted and inspired scientists for many years to develop chiral selectors with enhanced properties, akin to natural processes in nature. In this context, several kinds of chiral selectors viz., cyclodextrins (CDs), crown ethers, macro-cyclic antibodies, serum albumin, quinine/quinidine derivatives, and calf thymus DNA (ctDNA) have been fabricated. The paradigms of these 'intelligent' systems are of biological origin that could be exploited for chiral separations [8]. Although, biological receptors have specific molecular affinity and have widely been used in diagnostic bioassays and chemo/biosensors, they are often produced via complex protocols with a high cost and demand specific handling conditions because of poor stability. Moreover, the natural recognition elements for many analytes under investigation are often difficult to be procured [9–12]. One of the most burgeoning technologies of this century for the preparation of biomimetic materials is undoubtedly molecular imprinting. This is a most versatile technique to produce highly selective synthetic receptors and can, in principle, be applied to molecular structures (templates) spanning from small ions to large bio-macromolecules [10,12,13]. Simply put, the method involves the formation of molecular cavities in a synthetic polymer matrix that are complementary in terms of functional and structural characteristics to a template molecule/entity.

Now-a-days, the ability of molecularly imprinted polymers (MIPs) to selectively recognize and bind the template structure, in the presence of closely related chemical species, has made them of interest for use in quantitative discrimination of chiral molecules prevalent in real world samples. Furthermore, MIPs have obviously an edge over conventional chiral selectors in terms of the ease of preparation, scalability, low material cost, and flexibility. As a result, the molecular-imprinting approaches have extensively been exploited to produce target-specific chiral stationary phases (CSPs) for a broad range of chiral compounds [14,15] including amino acid derivatives [16], peptides [17], natural compounds, and a variety of drugs [14]. In general, MIP-based CSPs have excellent chiral recognition properties for the template (chiral) species and are endowed with the characteristics of high enantioselectivity, high substrate-specificity, and elution predictability. The added feature of these CSPs is their capability to discriminate, not only between enantiomers but also between structurally closely-related stereoisomers.

Although, in recent reviews [18–20], the diverse applications of MIPs for enantioselective recognition have been discussed emphasizing only capillary electrophoresis chromatography (CEC), high-performance liquid chromatography (HPLC), and other chromatographic techniques, a very limited account of enantioselective MIP-sensors were provided. We have also reported a monograph which presented a useful guide to researchers, exploiting MIP technology for potential applications in the development of nano-structured sensors as highly sensitive and selective medical devices [21], but this is not effective to provide much information about the enantioselective sensors. This review is meant to update MIP-researchers in the enantio-sensing field, highlighting important enantio-sensing methods hitherto contemplated for chiral discrimination and quantification, involving the specificity of MIP core shells featured in different shapes and textures.

## 2. Molecularly imprinted chiral polymers

Molecular imprinting is a process to generate specific cavities (binding sites) representing molecular signature of template (analyte) embossed in a polymeric matrix (Fig. 1) [11]. This process involves the use of a template molecule which attaches covalently, or interacts specifically via weak forces with monomeric functional groups, and thus promotes the formation of a unique cavity upon polymerization. Template removal is, consequently, accomplished by either chemical cleavage or simple extraction in a proper solvent. This liberates the corresponding functional groups located within polymer embedded cavities. The size, shape, and functional-group arrangement of these cavities are complementary to the template molecule, and hence can act as template-specific chiral binding sites [10].

Synthesis of MIPs by the covalent approach, developed by Wulff [22], refers to a molecular imprinting strategy where the template and monomer units are attached by covalent bonds to form a template-monomer complex after a chemical reaction, independent of polymer formation. Copolymerization of this template-monomer with high proportion of cross-linker, in porogenic solvent, results in a polymer which has template covalently bound within the polymer body. Removal of template and subsequent rebinding step will both involve chemical reactions and the rebound template will be indistinguishable from template immediately retrieved after polymerization.

Currently, non-covalent molecular imprinting, introduced by Mosbach [23], is the more widely applied technique to create the MIPs. It involves the typical forces of attraction between molecules such as hydrogen bonds, ion-pairs, dipole-dipole interactions, hydrophobic interactions, and van der Waals forces to generate adducts of template and functional monomers in solution. Compared to covalent bonding, these interactions are weaker and allow rapid and reversible binding, as needed for example in chromatographic separation and sensing applications. However, at the same time, because of the weaker interaction, usually large excess of functional monomers are required during the polymerization in order to have effective imprinting.

Among many applications, MIPs are natural choice for the preparation of solid phases with chiral cavities for selective adsorption [24,25]. The most viable applications of the derived CSPs are for HPLC analysis. Most of the CSPs are non target-specific, and thus the use of molecular imprinting technology extends discriminating abilities to the tailored solid phase for the desired enantiomeric separation. Many efforts have been made in establishing dedicated MIP formats for the specific chromatographic resolutions; for example, porous monoliths [26,27], spherical beads [28–34], silica-supported films [35,36] and many more [37–40]. Despite the major advances achieved in the preparation of chromatographically suitable polymer formats, enantioselective MIPs do not compete with established non-target-specific CSPs when challenged with real-world analytical and preparative HPLC separation problems. Under conventional isocratic mobile phase conditions, MIP-type CSPs suffer from poor chromatographic efficiency and peak tailing that is particularly severe for the more retained (imprinted) enantiomer. Even minor increase in the sample loading on MIP-based CSPs causes major loss in enantioselectivity; the complete loss of enantioselectivity may be observed with amounts of sample with which the commercial CSPs still operate under linear chromatographic conditions.

## 3. MIP-based chiral sensing devices

Chiral sensor is a device that detects enantioselectively and evaluates the amount of enantiomer. Stefan et al. [3] reported electrochemical sensors which were emerged as very good alternative for structural analysis (IR, NMR, Raman, MS, X-ray diffraction, Neutron diffraction), with the aided advantages of high reliability in terms of precision, reproducibility, speed, and moreover, without requiring any prior separation of the substance that has to be determined. Generally, a chiral sensor is composed of an enantio-specific (chiral discriminating) recognition surface and a transducer part. To increase the specificity of recognition part, several modifications [41] with biomolecules [42], bio-mimetic imprint polymers [37,43,44], and bio-mimetic supra molecules [45,46] were attempted; and in all investigations so far, the necessity of 3-point interactions was assigned for the chiral discrimination [47]. Among the most promising materials for the modification of chiral sensors, MIPs are considered to be best because of their practical applications as synthetic recognition elements of high endurance, low cost, and easy preparation. The key to the chiral sensors is to establish a reliable link between the target binding event and transducer. Therefore, the major concern for the development of MIP-based chiral sensors is how to measure the analyte binding with MIP core shells. Typically, the MIP-based chiral sensors are fabricated by assembling MIP materials onto the surface of transducer, enabling the analyte binding to be transformed into a measurable signal. In general, the efficiency of sensors does not only depend on the selectivity and sensitivity of MIPs to target species, but also on the approaches of transducing signal output. The optimal transduction approach to a readable

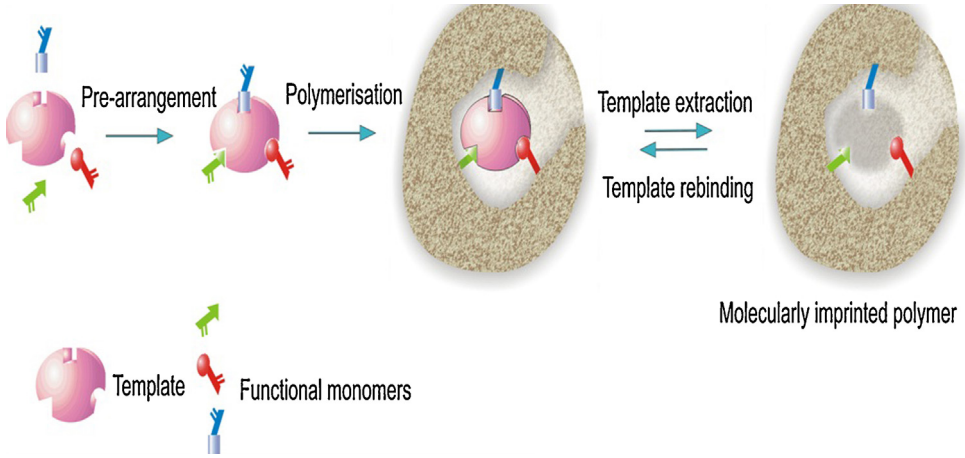


**Fig. 1.** Schematic representation of molecular imprinting process.

**Table 1**
MIP based electrochemical chiral sensors.

| S. No. | Polymer composition[a] | Polymerization | Sensitivity | Linear range | Remarks | Ref. |
|---|---|---|---|---|---|---|
| 1. | MAA (*M*)/EDMA (*C*)/L-PAA (*T*)/AIBN (*I*) | UV at 0 °C | – | – | The cross-linker:monomer: print molecule molar ratio was 20:4:1; two detection techniques, UV adsorption and potentiometric measurements were used for enantiomeric separation of L-PAA | [48] |
| 2. | Titanium tetrabutoxide-carboxylate complex/ methylferrocene carboxylic acid, 2-phenyl-butanoic acid, and 2-propanoic acid (*T*) | Sol–gel | 0.10 mM (*R*-methylferrocene carboxylic acid); 0.6 mM (*S*-methylferrocene carboxylic acid); 0.08 mM (*R*-2-phenylbutanoic acid); 0.50 mM (*S*-2-phenylbutanoic acid); 0.10 mM (*R*-2-propanoic acid); 0.45 mM (*S*-2-propanoic acid) | 0.05–6.25 mM (*R*-methylferrocene carboxylic acid); 0.125–6.25 mM (*S*-methylferrocene carboxylic acid); 0.0625–1.25 mM (*R*-2-phenylbutanoic acid); 0.25–2.5 mM (*S*-2-phenylbutanoic acid); 0.05–1.25 mM (*R*-2-propanoic acid); 0.3–1.25 mM (*S*-2-propanoic acid) | $TiO_2$ film thickness was found to be $85 \pm 10$ μm; $3.68 \times 10^{18}$ imprinted sites per gram were associated with the $TiO_2$ sensing interface | [49] |
| 3. | Pyrrole (*M*)/L-lactate (*T*)/ poly(vinylpyrrolidone) (steric stabilizer)/ peroxodisulfate (oxidizing agent) | Thermal at 30 °C followed by electrochemical over-oxidation at +1.5 V | – | – | Over-oxidized PPy colloid with a L-lactate template showed higher affinity for L-alanine than for D-alanine with an uptake ratio (L/D) of as high as $11 \pm 4$ under optimum conditions | [50] |
| 4. | 4-Vinylphenylboronic acid(M)/EDMA (C)/ phenyl α-D-mannopyranoside (*T*)/ AIBN (*I*) | UV light | – | – | Three different kinds of polymers were studied; batch measurements with unstirred samples were affected by strong solvent-polymer interactions | [51] |
| 5. | OTS (silylating agent)/*N*-CBZ-Asp (*T*) | – | – | $5.0 \times 10^{-6}$–$1.2 \times 10^{-2}$ M | Sensitivity of the sensor resulted from the transduction induced by the proton transfer; template imprinting was confirmed by X-ray photoelectron spectroscopy; the ratio of CBZ-Asp to OTS on the ITO surface during co-adsorption was 1:2.4; enantiomeric selectivity coefficient ranged between $4.0 \times 10^{-3}$ and $9.0 \times 10^{-3}$ | [52] |
| 6. | Pyrrole (*M*)/tyrosine (*T*) | Thermal at 90 °C followed by treatment in a potential window of −0.1 to 0.5 V at a sweep rate of 0.1 V $s^{-1}$ | 5 mM | 5–45 mM | The thickness of PPy film was ~60 μm (by SEM images); selectivity ratio (L/D) was increased from 9.4 to 25.8 by increasing the template concentration from 5 to 45 mM | [53] |
| 7. | MAA (*M*)/EDMA (*C*)/PAA (*T*)/AIBN (*I*) | Thermal at 60 °C for 12 h | – | 0.5–1 μM | Chiral discrimination was performed in organic solvents; the MIP grafted on electrode in non-polar solvent expresses chiral discrimination in non-polar solvents | [54] |
| 8. | *o*-PD and DA (*M*)/Glu (*T*) | Electro-polymerization in the potential window of −0.5 to 0.8 V at 20 mV $s^{-1}$ | 4.7 μM (L-Glu) and 5.9 μM (D-Glu) | 16.7–250 μM | The optimized molar ratio of OPA and DA was 3:2; CV measurements were performed in 0.1 mM KCl solution containing 10 mM $K_3Fe(CN)_6/K_4Fe(CN)_6$ at 50 mV $s^{-1}$; enantiometric selectivity coefficients for L-Glu and D-Glu was found to be 24 and 15, respectively | [55] |
| 9. | Pyrrole (*M*)/CSA (pseudo-*T*)/Phe (*T*) | Electro-polymerization at constant current of 0.3 mA for 30 min | – | 5–200 ppm | The adsorption of chiral Phe were performed by dipping the de-doped PPy nanowires coated Pt electrodes into a solution of phenylalanine at a constant voltage of 0.6 V for 5 min; the average diameter of | [57] |

**Table 1** (*Continued*)

| S. No. | Polymer composition[a] | Polymerization | Sensitivity | Linear range | Remarks | Ref. |
|---|---|---|---|---|---|---|
| | | | | | PPy nanowires was approximately 100 nm; PPy films have strong chiral recognition capacity even after 1 month | |
| 10. | Phenol and 3-hydroxyphenyl boronic acid (*M*)/D-glucose and D-mannose (*T*) | Electro-polymerization in the potential window of 0.0–0.35 V at 10 mV $s^{-1}$ | – | – | Electro-polymerization was performed at pH 10.3; the analysis of glucose was carried out by chronocoulometric measurements in the presence of redox-active (ferrocene-functionalized D-glucose); for glucose imprinted polymer association constant, total number of imprinted sites and density of imprinted sites were found to be $(170 \pm 30)\ M^{-1}$, $2.1 \times 10^{16}$ and $3.4 \times 10^{21}$ sites $cm^{-3}$, respectively, while for mannose association constant and density of imprinted sites were $(870 \pm 40)\ M^{-1}$, and $1.5 \times 10^{21}$ sites $cm^{-3}$, respectively | [58] |
| 11. | AM (*M*)/Boc-L-Trp (*T*)/EDMA (*C*)/AIBN (*I*) | Thermal at 30 °C in water bath | 20 μM (Boc-D-Trp) and 140 μM (Boc-L-Trp) | 74–4000 μM (Boc-D-Trp) and 400–4000 μM (Boc-L-Trp) | Optimal molar ratio of monomer to cross-linker was 1:5; MIP film thickness was measured to be around 2.5 μm; +1.2 V was used as the optimal detection potential for amperometric measurements | [59] |
| 12. | TEOS, PTMOS, and MTMOS (*M*)/His (*T*) | Electro-deposition in the potential window of −0.8 to +0.9 V at 50 mV $s^{-1}$ | $5.8 \times 10^{-9}$ mol $L^{-1}$ | 2.0 μmol $L^{-1}$–1.0 mmol $L^{-1}$ | The electrochemical measurements were conducted in 10.0 mL of 10.0 mmol $L^{-1}$ $K_3[Fe(CN)_6]$/$K_4[Fe(CN)_6]$ (1:1) phosphate buffer solution containing 1.0 mmol $L^{-1}$ L-His CV measurement was carried out in the range of −0.8 to +0.9 V with a scan rate of 50 mV $s^{-1}$; DPV was performed from −0.9 to +0.9 V; amperometric measurements were carried out at potential of +0.6 V | [61] |
| 13. | DAU (M)/EDMA (*C*)/Thyroxine (*T*)/chloroform (*I*)/TEA (reducing agent)/Cu II/bpy complex | AGET-ATRP at 60 °C | 0.0084 ng $mL^{-1}$ (D-thyroxine), 0.0087 ng $mL^{-1}$ (L-thyroxine) | 0.06–15.0 ng $mL^{-1}$ | MIP was modified on the surface of vinyl group functionalized silver wire; MIP was characterized by FT-IR and SEM studies; the optimized coating thickness of MIP film on silver wire realized was 33.4 μm; the sensing device could be used for as many as 160 consecutive extractions; the combination approach was validated in human blood serum and pharmaceutical samples | [62] |
| 14. | DAU (*M*)/EDMA (*C*)/Thyroxine (*T*)/chloroform (*I*)/TEA (reducing agent)/Cu II/bpy complex/carbon powder | AGET-ATRP at 60 °C | 0.0062 ng $mL^{-1}$ (D-thyroxine), 0.0060 ng $mL^{-1}$ (L-thyroxine) | 0.009–17.32 ng $mL^{-1}$ | All voltammetric measurements were performed at pH 6.0; DPASV runs were recorded in the potential range varying from −0.9 to −0.3 V after analyte accumulation for 150 s at −1.2 V at a scan rate of 10 mV $s^{-1}$; CV experiments were performed within the potential window of −1.1 to | [63] |

**Table 1** (*Continued*)

| S. No. | Polymer composition[a] | Polymerization | Sensitivity | Linear range | Remarks | Ref. |
|---|---|---|---|---|---|---|
| | | | | | −0.2 V at various scan rates (10–200 mV $s^{-1}$) | |
| 15. | NPA (*M*)/EDMA (*C*)/Trp (*T*)/chloroform (*I*)/TEA (reducing agent)/Cu II/ bpy complex/carbon powder | AGET-ATRP at 60 °C for 6 h | 0.24 ng $mL^{-1}$ | 0.9–18.6 ng $mL^{-1}$ (lower) and 24.23–840.2 ng $mL^{-1}$ (higher) | MIP-carbon fiber of diameter 0.8 mm was used as electrode; all voltammetric measurements were performed at pH 2.0; DPASV runs were recorded in the potential range varying from +0.8 to +1.5 V after analyte accumulation for 75 s at −0.2 V at a scan rate of 10 mV $s^{-1}$; CV experiments were performed within the potential window of +0.5 to +1.7 V at various scan rates (10–200 mV $s^{-1}$); the diffusion coefficient (D) calculated from Anson plot was $9.23 \times 10^{-5}$ $cm^2$ $s^{-1}$; the heterogeneous rate constant value was $1.48 \times 10^{-2}$ cm $s^{-1}$ | [64] |
| 16. | NPA (*M*)/EDMA (*C*)/Trp (*T*)/chloroform (*I*)/TEA (reducing agent)/Cu II/ bpy complex | AGET-ATRP at 60 °C for 4 h | 0.0261 ng $mL^{-1}$ | 0.15–30.0 ng $mL^{-1}$ | The optimized thickness of MIP fiber was 1.0 mm; the device could be used for as many as 100 consecutive extractions; the combination approach was validated in human blood plasma, CSF, and pharmaceutical samples; the technique resulted in enrichment factor of about 40-fold and found 9 times more sensitive to that expected from the MIP-sensor | [65] |
| 17. | 2-Acryl amidoethyldihydrogen phosphate (*M*)/EDMA (*C*)/L-His (*T*)/$Cu^{+2}$/*N*,*N*′-diethyldithiocarbamate modified PGE (iniferter)/ MWCNTs | UV light for 5 h | 1.980 ng $mL^{-1}$ | 9.9–342.8 ng $mL^{-1}$ | Voltammetric measurements were performed at pH 8.0; DPASV runs were recorded in the potential range varying from −0.5 to +0.4 V after analyte accumulation for 90 s at a scan rate of 10 mV $s^{-1}$; CV experiments were performed within the potential window of −0.6 to +0.4 V at various scan rates (10–500 mV $s^{-1}$); the electron-transfer rate constant, surface coverage, and diffusion coefficient (D) calculated were $5.680 \times 10^{-2}$ $s^{-1}$, $1.679 \times 10^{-6}$ mol $cm^{-2}$, and $2.739 \times 10^{-4}$ $cm^2$ $s^{-1}$, respectively | [66] |
| 18. | Benzidine (*M*)/Met (*T*) | Electro-polymerization in the potential window of –1.0 to +1.0 V at 150 mV $s^{-1}$ | 2.4–3.0 ng $mL^{-1}$ | 11.7–206.3 ng $mL^{-1}$ | PGE was first modified with MWCNTs-COOH; the optimized thickness of polymer film was found to be 2.5 nm; the electron-transfer rate constant, surface coverage and diffusion coefficient (D) calculated were $7.7 \times 10^{-1}$ $s^{-1}$, $6.81 \times 10^{-8}$ mol $cm^{-2}$, and $1.00 \times 10^{-2}$ $cm^2$ $s^{-1}$, respectively; any single electrode could be used for about 90–100 consecutive runs, with quantitative recoveries, after regeneration by the method of template retrieval | [67] |
| 19. | Benzidine (*M*)/Met (*T*) | Electro-polymerization in the potential window of –1.0 to +1.0 V at 125 mV $s^{-1}$ | 0.0098 ng $mL^{-1}$ | 0.03–30.00 ng $mL^{-1}$ | Detection of Met was performed at pH 2; six types of combination approaches were compared; the | [68] |

**Table 1** (*Continued*)

| S. No. | Polymer composition[a] | Polymerization | Sensitivity | Linear range | Remarks | Ref. |
|---|---|---|---|---|---|---|
| | | | | | technique resulted in enrichment factor of about 25-fold and found 336-times more sensitive to that expected from the MIP-sensor; detection performed in human blood plasma and pharmaceutical samples | |
| 20. | Indole-3-acetic acid (*M*)/Asp (*T*) | Electro-polymerization in the potential window of −1.6 V to +1.6 V at 100 mV $s^{-1}$ followed by over-oxidation in the potential range of −1.6 to +2.0 V | 0.025 μM (D-Asp) and 0.016 μM (L-Asp) | 0.15–8.9 μM | Voltammetric measurements were performed at pH 3.1; DPASV runs were recorded in the potential range varying from −0.5 to +0.4 V after analyte accumulation for 120 s at a scan rate of 10 mV $s^{-1}$; CV experiments were performed within the potential window of −0.7 to +0.7 V at various scan rates (10–200 mV $s^{-1}$); any single electrode could be used for as many as 30 times with quantitative recoveries; the results of 10 successive runs showed a RSD of 0.9% | [69] |
| 21. | NAPD (*M*)/EDMA (*C*)/Asp (*T*)/MWCNTs-TNPs-CHPA complex (*I*)/TEA (reducing agent)/Cu II/bpy complex | AGET-ATRP at 60 °C for 4 h | 1.73–1.79 ng $mL^{-1}$ | 9.98–532.72 ng $mL^{-1}$ | "Surface-grafting from" approach was adopted for immobilization of MIP film on PGE surface; DPASV runs were recorded in the potential range varying from −0.2 to +0.6 V after analyte accumulation for 150 s at a scan rate of 10 mV $s^{-1}$; CV experiments were performed within the potential window of −0.2 to +0.8 V at various scan rates (10–100 mV $s^{-1}$) | [70] |
| 22. | NAPD (*M*)/EDMA(*C*)/Asp (*T*)/TNPs-CHPA complex (*I*)/TEA (reducing agent)/Cu II/Bpy complex | AGET-ATRP at 60 °C for 4 h | 0.031 ng $mL^{-1}$ | 0.10–10.00 ng $mL^{-1}$ | Silica fiber was used as solid support for immobilization of MIP film (31.1 nm thick); two types of MIP fibers were prepared by "grafting from" (method I) and "grafting to" (method II) approach; MIP fiber (method I) was found superior to MIP fiber (method II) in term of sensitivity; detection carried out in blood serum and CSF samples | [71] |
| 23. | 5-MTCA (*M*)/PGA (*T*)/$CuSO_4$ | Electro-polymerization in the potential window of −2.0 V to +2.0 V at 50 mV $s^{-1}$ | 0.77 ng $mL^{-1}$ | 2.8–170.0 ng $mL^{-1}$ | All CV runs were scanned under anodic stripping mode within the potential window −0.2 to +0.6 V at different scan rates (10–200 mV $s^{-1}$); DPASV runs were recorded from −0.2 to +0.4 V at 10 mV $s^{-1}$; the optimized CV cycles $n = 5$, scan rate 50 mV $s^{-1}$, and template-Cu(II)-monomer ratio 1:1:2, were adjudged as best parameters for obtaining the maximum current response | [72] |
| 24. | Aniline (*M*)/dinoseb (*T*)/R-CSA (chiral inducing agent) | Electro-polymerization in the potential window of −0.3 to 1.0 V followed by application of a constant potential of 0.5 V for 300 s (for *R*-selective sensor); −0.3 to 1.1 V followed by application of a constant potential of 0.6 V for 300 s (for *S*-selective sensor) at scan rate of 0.05 V $s^{-1}$ | $2.28 \times 10^{-6}$ M (*R*-dinoseb) and $1.89 \times 10^{-6}$ M (*S*-dinoseb) | $8 \times 10^{-6}$–$1.0 \times 10^{-4}$ M | The voltammetric sensors showed good repeatability and reproducibility (<10% RSD and <20% RSD) and were able to detect the target enantiomer from a racemic mixture | [73] |
| 25. | PCEMMA (*M*)/L-Phe (*T*)/TEAH | Electro-polymerization in the potential window of 0.0 to 2.0 V at 100 mV $s^{-1}$ | 1.37 μM | $2.5 \times 10^{-6}$–$2.5 \times 10^{-2}$ M | 20 CV cycles were optimized for electro-polymerization; no interference was observed | [74] |

**Table 1** (*Continued*)

| S. No. | Polymer composition[a] | Polymerization | Sensitivity | Linear range | Remarks | Ref. |
|---|---|---|---|---|---|---|
| | | | | | with the assay of L-phe in the presence of other D/L amino acids; X-ray photoelectron spectroscopy analysis was used to investigate the surface composition of MIP-film; selectivity coefficient was found to be $5.75 \times 10^{-4}$ | |
| 26. | β-CD-MWCNTs/PAN/CE/TEOS, ethoxyethanol, PTMOS, and MTMOS/L-Phe (*T*) | Electro-deposition in the potential window of −0.9 to +0.9 V at 50 mV $s^{-1}$ | $1.0 \times 10^{-9}$ mol $L^{-1}$ | $5.0 \times 10^{-7}$–$1.0 \times 10^{-4}$ mol $L^{-1}$ | DPV measurement were carried out in potential range of −0.2 to +1.0 V; amperometric measurements were performed at potential +0.4 V; all electrochemical detections were carried out at pH 7.0; detection performed in blood serum samples without any sample pretreatment | [75] |
| 27. | EDOT, HA, HPC, collagen/mandelic acid (*T*) | Electro-polymerization at constant current density of 0.2 mA $cm^{-2}$ for 600 s | | | Voltammetric measurements were performed in potential range of −0.2 to +1.2 V in 100 mM KCl; effect of pH on determination of mandelic acid was studied | [76] |
| 28. | *o*-PD (*M*)/L-Trp (*T*) | Electro-polymerization | $0.3 \times 10^{-8}$ mol $L^{-1}$ | $1 \times 10^{-8}$–$21 \times 10^{-8}$ mol $L^{-1}$ | Highly selective, specific, simple and inexpensive; detection performed in blood serum samples | [77] |

*Abbreviations:* EDMA, ethylene glycol dimethacrylate; Trp, tryptophan; AIBN, 2,2′-azobisisobutyronitrile; 4-VP, 4-vinyl pyridine; MAA, methacrylic acid; Dansyl-Phe, dansyl-phenylalanine; Asp, aspartic acid; AM, acrylamide; Glu, glutamic acid; His, histidine; Bpy, 2,2′-bipyridyl; PAA, phenylalanine anilide; EDOT, 3,4-ethylenedioxythiophene; HA, hyaluronic acid; HPC, hydroxypropyl cellulose; TEOS, tetraethylorthosilicate; PTMOS, phenyltrimethoxysilane; MTMOS, methyltrimethoxysilane; PCEMMA, poly[2-(N-carbazolyl) ethylmethacrylate-co-methacrylic acid]; Phe, phenylalanine; TEAH, tetraethylammonium hexafluorophosphate; CSA, camphorsulfonic acid; MTCA, 5-methyl-2-thiophene carboxylic acid; TEA, triethylamine; CHPA, 2-chloro-N-(4-hydroxy-phenyl)-acetamide; NAPD, N-acryloyl-pyrrolidine-2,5-dione; DAU, 1,3-diacryloyl urea; NPA, 4-nitrophenyl acrylate; AGET-ATRP, activator generated by electron transfer based atom transfer radical polymerization; PGE, pencil graphite electrode; Met, methionine; CD, cyclodextrine; CV, cyclic voltammetry; DPV, differential pulse voltammetry; *o*-PD, o-phenylenediamine; DA, dopamine; OTS, octadecyltrichlorosilane; CBZ-Asp, carbobenzoxy-aspartic acid.

[a] *M* for monomer; C for cross-linker; *T* for template; *I* for initiator.

**Table 2**
MIP based optical chiral sensors.

| S. No. | Polymer composition[a] | Polymerization | Sensitivity | Linear range | Remarks | Ref. |
|---|---|---|---|---|---|---|
| 1. | (2-*N*-Dansyl) ethyl 3,3-dimethylacrylate (*M*)/EDMA (*C*)/L-Trp (T)/AIBN (*I*) | Thermal at 45 °C using oil bath for 48 h | – | 0.0–10.0 mM | Spectrofluorometer was used for fluorescent studies; *p*-nitrobenzaldehyde was used as quencher; dansyl moiety attached to functional monomer worked as fluorescent tag; the prepared MIPs need improvement in its sensitivity and selectivity | [78] |
| 2. | *N,N′*-Diethyl-4-vinylbenzamidine (*M*)/EDMA (*C*)/2,3-di-*o*-benzoyltartraric acid (*T*)/AIBN (*I*) | UV light for 6 h | – | – | Monomer film was adsorbed on glass plate modified with trichlorosilylpropylmethacrylate; separation factors for (*S, S*)-imprinted, (*R, R*)-imprinted, and reference polymer were found to be 1.19, 1.23, and 0.98, respectively | [79] |
| 3. | MAA (*M*)/EDMA (*C*)/L-3,4-dihydroxyphenyalanine (*T*)/AIBN (*I*) | UV light for 2 h | – | – | Highly ordered 3D macroporous hydrogel MIP films (2 μm thick) with highly selective and specific chiral molecular recognition properties; binding behavior of target is affected by the pH; maximum red shift (28 nm) of the emission peak was observed at 0.01 mM concentration of target | [80] |
| 4. | 4-VP and MAA (*M*)/EDMA (*C*)/dansyl-Phe (*T*)/AIBN (*I*) | Thermal at 50 °C using water bath for overnight | 0.025 μmol $L^{-1}$ (dansyl-L-Phe) and 0.075 μmol $L^{-1}$ (dansyl-D-Phe) | 0.075 to 250 μmol $L^{-1}$ | Uniform MIP microspheres of 0.7 μm diameter readily obtained using precipitation polymerization and characterized by SEM images; The MIP microspheres were fixed in micro-titer plates using poly(vinyl alcohol) as glue; the imprinted polymer showed the highest selectivity to the print molecule itself than other dansyl-amino acids; RSD for 11 parallel measurements of dansyl-L-Phe (0.78 μmol $L^{-1}$) was 8% | [81] |
| 5. | 6-Styrylcoumarin-4-carboxylic acid or 6-vinylcoumarin-4-carboxylic acid (*M*)/MMA or MAA (co-*M*)/EDMA (*C*)/(−)-ephedrine (*T*)/AIBN (*I*) | Thermal at 60 °C for 17 h followed by additional 2 h at 80 °C | – | – | The molar amount of fluorescent monomers used was fixed at 1:40 of the cross-linker for all polymers; ten different types of polymers were prepared and compared | [82] |

**Table 2** (*Continued*)

| S. No. | Polymer composition[a] | Polymerization | Sensitivity | Linear range | Remarks | Ref. |
|---|---|---|---|---|---|---|
| 6. | Aniline (*M*)/L-Asp (*T*)/APS | Chemical oxidation in ice-water bath for overnight | – | – | The pH value of pre-polymer solution was 3.8; the spectrofluorometric determination of L-Asp was performed at pH 1.0; the L-Asp imprinted PAn has high selectivity for L-Asp over D-Asp (enrichment amount of L-Asp and D-Asp were 81.2 and 60.1 μg, respectively and enrichment ratio of L-Asp to D-Asp was about 1.4) | [84] |
| 7. | Titanium tetra-*n*-butoxide/propranolol, 1,1′-bi-naphthol, and 2-(4-isobutylphenyl)-propionic acid (*T*) | Sol–gel polymerization | – | – | The (*R*)-propranolol-imprinted $TiO_2$ film showed an enantioselectivity of 1.26, while the enantioselectivity of the (*S*)-propranolol-imprinted $TiO_2$ film showed a value of 1.18; after the subtraction of nonspecific binding to the non-imprinted film, enantioselectivity of the imprinted films could be re-estimated as follows: 4.46 for (*R*)-propranolol and 2.38 for (*S*)-propranolol | [85] |
| 8. | AM (M)/EDMA (C)/L-Trp (T)/AIBN (I)/ modified graphene | Thermal at 65 °C | $2.11 \times 10^{-8}$ M | $2.10 \times 10^{-7}$ to $7.09 \times 10^{-4}$ M | Graphene was used to improve the adsorption capacity of MIP film while $Fe_3O_4$ nanoparticles for separation and immobilization; MIP particles size were found in the range of 100 to 200 μm; MIP films were characterized using FT-IR, XRD, UV, and SEM analyses; sensor could be used more than 100 times before the adsorption began to decrease | [86] |
| 9. | AM and MAA (*M*)/BIS (*C*)/PGA (*T*)/APS (*I*)/ TMEDA (accelerant) | UV at 5 °C | 4 μM | 0.01–0.20 mM | AMD was used to increase the swelling capacity of the MIPP; experiments performed at pH 4; MIPP had much better specificity to imprinted L-PGA than the other amino acids studied; the sensor was validated in MSG samples | [87] |

*Abbreviations:* EDMA, ethylene glycol dimethacrylate; Trp, tryptophan; AIBN, 2,2′-azobisisobutyronitrile; 4-VP, 4-vinyl pyridine; MAA, methacrylic acid; Dansyl-Phe, dansyl-phenylalanine; MMA, methylmethacrylate; Asp, aspartic acid; APS, ammonium persulfate; AM, acrylamide; BIS, *N*,*N*′-methylene bisacrylamide; PGA, pyroglutamic acid; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine.

[a] *M* for monomer; *C* for cross-linker; *T* for template; *I* for initiator.

**Table 3**
MIP based piezoelectric chiral sensors.

| S. No. | Polymer composition[a] | Polymerization | Sensitivity | Linear range | Remarks | Ref. |
|---|---|---|---|---|---|---|
| 1. | 4-Vpy and MAA (*M*)/ EDMA (*C*)/dansyl-L-Phe (*T*)/AIBN (*I*) | UV light for 12 h | 5 μg $mL^{-1}$ | 5–500 μg $mL^{-1}$ | Vinyl groups were introduced on the gold crystal before MIP polymerization on the surface, by immersing into ethanolic solution of thioctic acid-modified GMA and thioctic acid dodecane ester; the enantiomeric selectivity coefficient of the sensor is 6.7 | [43] |
| 2. | MAA (*M*)/TRIM (*C*)/ *S*-propranolol (*T*)/ AIBN (*I*) | UV light for 10 min | 50 μmol $dm^{-3}$ | – | MIP film was developed on the QCM crystal by the method of drop coating; the MIP film thickness was about 2 μm; enantiomeric selectivity coefficient of the sensor was found to be 5 | [88] |
| 3. | Pyrrole (*M*)/Glu (*T*) | Electro-polymerization at constant current density of 0.05–0.1 mA $cm^{-2}$ for 2 h followed by electrochemical over-oxidation in the range of −0.3 to +1.0 V (or +1.4 V) at rate of 40 mV $s^{-1}$ | – | – | Polymer film was characterized by FT-IR, ESR spectroscopy, and STM studies; the film thicknesses for the OPPy (L-Glu) and OPPy (D-Glu) films were found to be ~300 nm and ~650 nm, respectively, under the identical polymer conditions; the total frequency change for the L-cavity film was ~4 times as large as that for the D-cavity film; the maximum uptake for Glu was obtained at pH 1.7 and became almost negligible at pH 2.2 or higher | [89] |
| 4. | MAA (*M*)/TRIM (*C*)/ L-menthol (*T*)/AIBN (*I*) | UV light for 30 min | 200 ppb | 0–1.0 ppm | Crystals were coated with polymer using the sandwich coating method; apparent association constant (*K*) for affinity of the MIP toward L-menthol was found to be 4.5 ± 0.5 μM; no polymer and surface characterization was reported; enantiomeric selectivity coefficient of the MIP used in this work was 3.6 | [90] |
| 5. | MAA (*M*)/TRIM (*C*)/ L-serine (*T*)/AIBN (*I*) | UV light for 30 min | 2 ppb | – | The affinity of the MIP towards L-serine was evaluated by calculating apparent association constant (*K*) which was 35.45 μM | [92] |

**Table 3** (*Continued*)

| S. No. | Polymer composition[a] | Polymerization | Sensitivity | Linear range | Remarks | Ref. |
|---|---|---|---|---|---|---|
| 6. | AM (*M*)/BIS (*C*)/L-His (*T*)/$K_2S_2O_8$ (*I*) | Electro-polymerization in the potential window of −0.4 to −1.4 V at 50 mV $s^{-1}$ | – | – | Optimized molar ratio of monomer and cross-linker was 25:1; electro-polymerization was performed using cyclic voltammetry (20 cycles for L-His and 30 cycles for D-His); thicknesses for MIP films were found to be 140 nm (D-His) and 135 nm (L-His) | [93] |
| 7. | MAA (*M*)/TRIM (*C*)/*S*-propranolol (*T*)/ABAH immobilized on carboxyl terminated monolayer of alkanethiol (*I*) | UV light at 4 °C for 2 h | – | 0.19–0.38 mM | Surface bound MIP film was prepared; no surface characterization was reported; sensor generated a response of up to 50 Hz for 0.19 mM concentration | [94] |
| 8. | AM (*M*)/TRIM (*C*)/Trp (*T*)/AIBN (*I*) | UV light | 8.8 μM | $8.8 \times 10^{-3}$–4.5 mM | Gold crystal was modified with thioctic acid-functionalized GMA and thioctic acid dodecane ester; 4 different kinds of MIPs were prepared and their performances toward enantioselective detection of Trp were portrayed in tabular form; surface characterization was performed by AFM | [95] |
| 9. | Pyrrole (*M*)/L-Asp (*T*) | Electro-polymerization at constant current density of 0.01 mA $cm^{-2}$ followed by over-oxidation at potential 1.2 V ($i$ = 0.025 mA $cm^{-2}$) | – | – | The thickness of MIP film was about 80 nm; electro-polymerization of pyrrole was performed in three different aqueous electrolyte composition: (A) in weakly acidic medium (pH 6), (B) in alkaline medium (pH 11), (C) in presence of polyelectrolyte [sodium poly (styrenesulphonate)] (pH 6) | [96] |
| 10. | Pyrrole (*M*)/L-Trp (*T*) | Electro-polymerization at constant potential 0.8 V followed by over-oxidation at potential 1.0 V for 10 min | – | – | Electro-polymerization was carried out at pH 6.5; PPy particles were about 1 to 2 μm in size (estimated from SEM); at enrichment time 25 min and pH 5.0, the highest peak current ratio of L-Trp to D-Trp was obtained | [97] |
| 11. | Aniline and aminophenol (*M*)/L-Glu (*T*)/ammonium persulphate | Pre-polymer polymer mixture was kept overnight in ice bath to obtain copolymer and a potential of −0.8 was applied for de-doping of template anions | – | – | A potential of +0.6 V was applied for rebinding of Glu and −0.6 V to eject Glu enantiomers; experiment performed at pH 3.8; rebinding ratio of L-Glu to D-Glu was 2.43 which attributed to the high selectivity of the imprinted polymer for L-Glu over D-Glu | [98] |
| 12. | MAA (M)/EDMA (*C*)/D-(+) methamphetamine (*T*)/AIBN (*I*) | Bulk polymerization | 11.9 pg $mL^{-1}$ | $10^{-5}$–$10^{-1}$ μg $mL^{-1}$ | Detection performed in urine samples from drug free individuals in the range of $10^{-3}$ to $10^{-2}$ μg $mL^{-1}$ with recoveries between 95.3 and 110.9%; MIP mixed with cyanoacrylate ester and THF in 6:2:1 ratio was spin coated on gold crystal; sensor responded within short response time (10–100 s) and showed good repeatability (RSD = 0.03–3.09%; $n$ = 3), good reproducibility (RSD = 3.55%; $n$ = 5), and good reversibility (RSD = 0.36%; $n$ = 3) | [99] |
| 14. | GAMA (*M*)/EDMA (*C*)/MA (*T*)/AIBN (i)/Bpy/$CuCl_2$/triethylamine (reducing agent) in case of glyco-MIP-A; GAMA (*M*)/EDMA (*C*)/MA (i)/benzyl *N*,*N*-diethyl dithiocarbamate (iniferter) in case of glyco-MIP-B | Activator generated electron transfer-atom transfer radical polymerization at 37 °C for 10 h (glyco-MIP-A); photo-polymerization for 4 h (glyco-MIP-B) | 0.18–0.21 ng $mL^{-1}$ | 20–210 ng $mL^{-1}$ | Two type of MIPs (glyco-MIP-A and glyco-MIP-B) were prepared; glyco-MIP-B modified QCM sensors were validated in real samples for analysis of MA; surface characterizations were performed (SEM and AFM); any single sensor could be used for as many as 45 times with quantitative recoveries indicating reusability of the proposed sensor | [101] |

*Abbreviations:* EDMA, ethylene glycol dimethacrylate; Trp, tryptophan; AIBN, 2,2′-azobisisobutyronitrile; 4-VP, 4-vinyl pyridine; MAA, methacrylic acid; Dansyl-Phe, dansyl-phenylalanine; Asp, aspartic acid; AM, acrylamide; BIS, N,N′-methylene bisacrylamide; GMA, glycidyl methacrylate; TRIM, trimethylolpropane trimethacrylate; Glu, glutamic acid; His, histidine; ABAH, 2,2′-azobis(2-amidinopropane) hydrochloride; GAMA, 4-gluconamidophenyl methacrylate; MA, malic acid; Bpy, 2,2′-bipyridyl.

[a] *M* for monomer; *C* for cross-linker; *T* for template; *I* for initiator.

signal output can be expected to maximize the selectivity and sensitivity of sensors. Different strategies have been utilized for immobilizing MIPs on the transducer surface such as *in-situ* polymerization, the production of thin films of MIP by surface coating, entrapment of MIP particles into gels or membranes, and production of MIP-based composites. In terms of signal transduction, various methods of measurement can be used, including electrochemical [48–77], optical [78–87], and mass sensitive methods [88–103]. With this insight into different types of sensing, we endeavored to summarize the recent advances on MIP-based electrochemical, optical, and mass sensitive chiral sensors (Tables 1–3).

### 3.1. Electrochemical chiral sensor

In contrast with the increasing number of MIP reports on chiral separations, it is surprising that the design of chiral electrochemical sensors based on molecular imprinting technology is rather scarce. During last few years, a remarkable progress in MIP-based chiral electrochemical sensing has been achieved by the use of voltammetric/potentiometric measurements.

A flow-through column electrode, based on the use of polymers imprinted against L-phenylalanine anilide (L-PAA), for enantiomeric resolution, UV absorption and potentiometric measurements, was developed [48]. The electrodes were placed at the end frits of the glass column in which the MIP was packed. The results showed that the potentiometric signals were exponentially proportional to the concentration; and the chromatograms were distorted (flattened) and resolution appeared worse.

Lahav et. al., [49] have reported the imprint of chiro-specific and chiro-selective molecular recognition sites in $TiO_2$ thin-films associated with a ion-selective field-effect transistor (ISFET) for a group of enantiomers; methylferrocene carboxylic acid, 2-phenyl-butanoic acid, and 2-propanoic acid. The respective sensors were prepared by coating $Al_2O_3$ gate interfaces of the ISFETs with ethanol or toluene solutions of titanium tetrabutoxide and the corresponding 2-phenylalkanoic acid enantiomers, followed by mild thermal curing. Characterization was carried out by the combination of impedance measurement and radio-active labeling experiments. The obtained results showed that the highly effective response of the sensor was not only selective between the pair of enantiomers, but also specific for the chosen analyte even in the presence of similar analogues.

Over-oxidized polypyrrole (OPPy) colloids, imprinted with L-lactate, were prepared to evaluate the performance of the proposed over-oxidation pseudo-template technique [50]. They selected alanine (Ala), which is structurally different from the template (lactate) only in one side chain, as a target for enantioselective recapture into the OPPy colloids.

Meanwhile, chiral recognition of the enantiomers phenyl-α-L- and phenyl-α-D-mannopyranoside in an MIP (D-enantiomer enacted as template) by isothermal batch and titration calorimetry in acetonitrile was investigated [51]. Authors found that direct calorimetric determination of the proportion of two points binding of the D- and L- forms in the imprinted polymer was not successful due to complexity of the rebinding process. Furthermore, it could also be shown that batch measurements, with unstirred samples, were affected by strong solvent-polymer interactions, such as swelling.

MIPs were also employed in the construction of chiral potentiometric sensors. An interesting class of potentiometric sensors was developed utilizing surface imprinting approach coupled with a nano-scale transducer, indium tin oxide (ITO) (effective surface area $1 \times 4\,cm^2$) modified with an octadecylsiloxane monolayer, in the presence of *N*-carbobenzoxy-aspartic acid (*N*-CBZ-Asp) as template [52]. Authors reported that sensor gave the expected higher potential output to L-isomer than D-isomer. The lower value of potentiometric selectivity coefficient for *N*-CBZ-L-Asp with respect to *N*-CBZ-D-Asp, in the phosphate buffer, indicated that the sensor was much more selective for the L-isomer over the D-isomer.

An electrochemical sensor was fabricated by imprinting D- and L-tyrosine (Tyr) on polypyrrole (PPy) film at the surface of Ni electrode [53]. The enantioselectivity of the imprinted film was ascertained by coulometry applying positive potential to induce adsorption of the target analyte. Authors reported that coating of PPy film on Ni electrode was difficult by the method of electropolymerization at potential below −0.5 V, so they used thermal polymerization as the method of choice in this study. Furthermore, the L-tyrosine imprinted PPy film exhibited good selectivity for its own template and showed only a minimal affinity for the tyrosine derivatives, dopamine, nor-epinephrine and epinephrine.

L- (or D-) PAA imprinted poly(ethylene glycol dimethacrylate-*co*-methacrylic acid) film was grafted at an ITO electrode surface (effective surface area 1.0 $cm^2$) to evaluate the effect of L- (or D-) PAA on the current of ferrocene probe in several organic solvents by the method of cyclic voltammetry (CV) [54]. The results indicated that the gate effect of MIP was instrumental to discriminate the template and its analogues exclusively in terms of their stereo-chemical structures, even all the differences in their chemical or physical properties were omitted. Furthermore, the chiral MIP sensor was limited only to non-polar solvents, which are major advantage over biosensors that cannot work in non-polar solvents.

Glutamic acid (Glu) is the main excitatory neurotransmitter in the brain, and an increase of extracellular Glu is believed to be partially responsible for brain damage resulting from the central nervous and mental disorders. The designed MIP of *o*-phenylenediamine (*o*-PD) and dopamine (DA) was successfully used as recognition element to a capacitive sensor for the enantioselective analysis of Glu on the gold electrode surface involving its modification via one step electrochemical copolymerization [55]. The sensor was evaluated with potentiostatic frequency scan, CV, and capacitance measurements. These sensors with acceptable sensitivity, stability, good reproducibility, and repeatability were also the first MIP capacitive sensor for both Glu enantiomers.

PPy is one of the most widely investigated conducting polymers due to its high conductivity and environmental friendly properties. The PPy membrane, with dummy template molecules of L-phenyl lactic acid, was polymerized electrochemically on to the surface of a carbon paste electrode by CV for the recognition of enantiomorphs of D- and L-Tyr [56]. Under the optimum conditions, the stripping peak current ratio of L-Tyr to D-Tyr was found to be 2.18.

PPy nano-wires possessed higher efficient surface area and thus, resulted in higher sensitivity and faster response time than that of bulky thin film. Huang et. al., [57] have successfully fabricated PPy nanowires (average diameter of ca. ∼100 nm) via electrochemical polymerization, in which the chiral camphorsulfonic acid (CSA) molecules acted both as the dopant and pseudo-template. Herein, the enantioselective interactions were established by electrochemical impedance spectra (EIS) and circular dichroism. The EIS results indicated that de-doped D-MIP-PPy and L-MIP-PPy nano-wires have distinctive capabilities for recognizing D- and L-phenylalanine (Phe), respectively.

A new kind of electro-generated MIP based on the electropolymerized poly(phenol/phenol-boronic acid) for the stereoselective and enantio-selective recognition of monosaccharides (D-glucose and D-mannose) was introduced [58]. The selective analysis of these monosaccharides was based on the competitive electrochemical assay that employed ferrocene-modified-monosaccharides as redox probes. The AFM images of MIP, on Au support, depicted a non-homogeneous polymer that yields “bumps” with surface coverage of ca. 45% and heights of up to ca. 150 nm, and the average thickness of the film was evaluated to be 36 nm.

Qu et al. [59] have introduced *in-situ* molecular imprinting on micro-channel wall using acrylamide as a functional monomer and ethylene glycol dimethacrylate (EGDMA) as a cross-linker. The polymer was modified on a homemade carbon fiber micro-disk electrode for the separation and amperometric detection of butoxycarbonyl-tryptophan (Boc-Trp) enantiomers (used as templates during MIP development). The resulting MIP-coated micro-channel of micro-fluidic device (MIP-MCMD) achieved baseline enantioseparation of Boc-Trp within 75 s due to the large surface area and enough recognition sites on the wall of micro-channel. The designed MIP-MCMD showed fast separation, low reagent and sample consumption, and provided a facile platform for

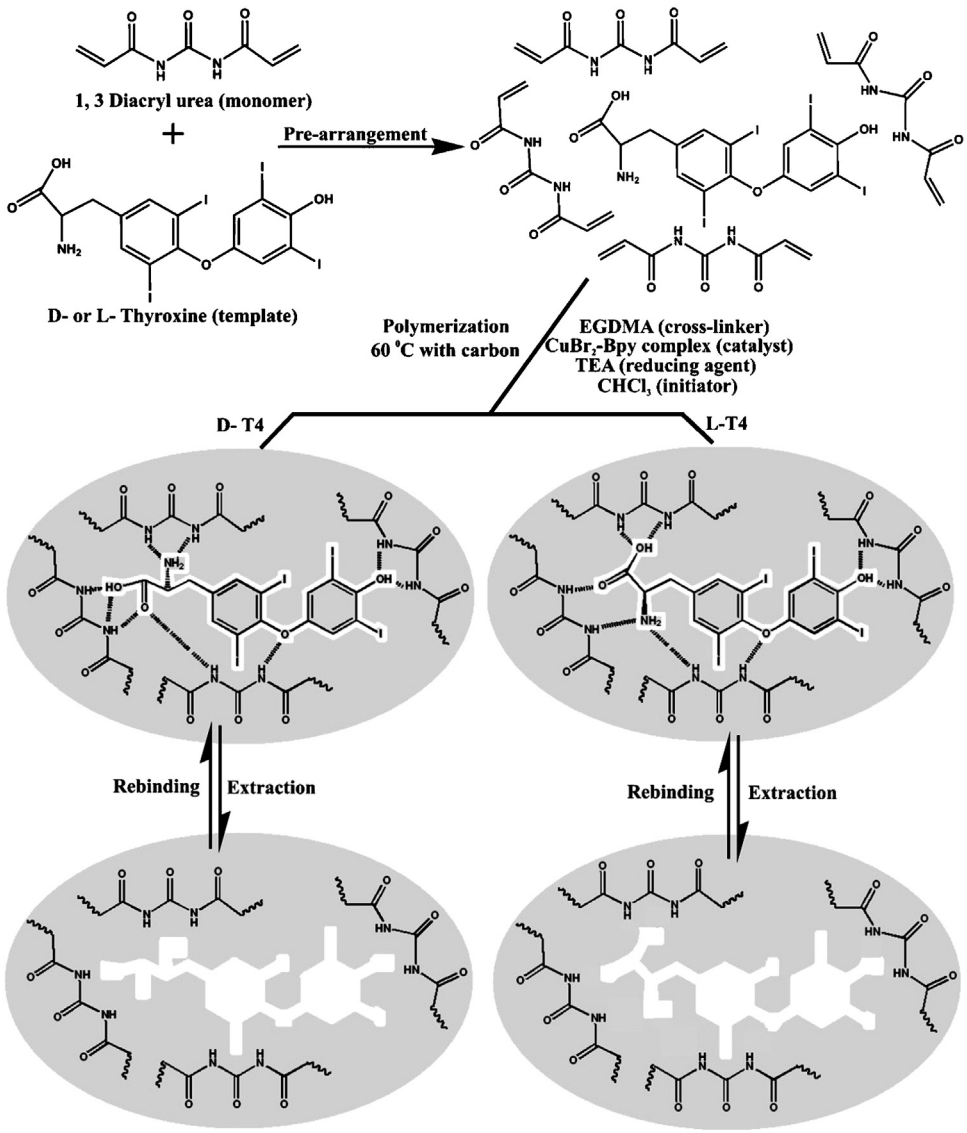


**Fig. 2.** Suggested enantioselective binding mechanism of D- and L-thyroxine in their respective MIP cavities [60].

high-throughput screening of enantiomer candidates and donor-receptor interaction research.

Meanwhile, an amplified self-assembled modified electrode for L-serine recognition, with molecular imprinted monolayer on electrodeposited porous gold film was developed [60]. The stable and instantaneous response to L-serine was achieved within 5 min.

The possibility of imprinting molecular recognition sites in monolayer system has successfully been explored but the effectiveness and utility of such systems were rather limited. Alternatively, the imprinting in layer-by-layer (LbL) assembled polymeric films for sensor fabrication was found to be very promising. A novel sensitive and selective imprinted electrochemical sensor (using ITO electrode) for the direct detection of L-histidine (His) by the combination of molecularly imprinted film and multi-walled carbon nanotubes (MWCNTs) was constructed, following LbL approach [61]. The proposed imprinted sensor was successfully employed for the detection of L-His in human blood serum using electrochemical methods involving CV, differential pulse voltammetry (DPV), and amperometric *i–t* curve.

Recently, Prasad and his group have developed various interesting electrochemical enantioselective sensors [62–72]. Thyroxine is a known disease biomarker that warrants a highly sensitive and selective technique to measure ultra-trace level, with enantio-differentiation of its optical isomers (D- and L-), in real samples. In this context, two seminal articles for enantioselective sensing of thyroxine with the help of differential pulse anodic stripping voltammetric (DPASV) technique [62,63] were reported. In the first report [62], the hyphenation between molecularly imprinted micro-solid phase extraction (MIMSPE) and a complementary MIP-sensor was proposed for enantioseparation, preconcentration, and analysis of D- and L-thyroxine. The proposed hyphenation approach was able to achieve the stringent limit of clinical detection of thyroid-related diseases, without any problems of non-specific false-positive contribution and cross-reactivity. The combination of two techniques (MIMSPE–MIP-sensor) helped biomarking primitive diagnosis of related diseases manifested at ultra-trace level in human biological fluids, which was rather impossible with the exclusive use of either of the techniques. This was due to the dual pre-concentrations incurred both at extraction and detection levels. In the second article [63], an improved, simple, and easy method was developed for the generation of stable molecularly imprinted sites in the polymeric

nano-film (192 nm thick). This utilized self-assembled monolayer (SAM) and subsequent layer-by-layer coatings via thermal cross-linking directly onto the surface of silver electrode (Fig. 2) [63]. Modified electrode was found to be practical for enantio-differentiation with highly sensitive determination of D- and L-thyroxine in biological and pharmaceutical samples allowing quantitative (100%) recoveries.

MIP-fiber sensor and the corresponding combination tool (MIMSPE–MIP-sensor) were devised for the enantioselective separation and quantification of D- and L-tryptophan (Trp) [64,65]. Both techniques enabled trace analysis of L-Trp in biological fluids, thus could be used for clinical diagnosis of stress-related diseases caused by acute tryptophan depletion.

A complex imprinted polymer (CIP)-based pencil graphite electrode (PGE) sensor for enantioselective trace level sensing of L-His was fabricated adopting "grafting from" approach [66]. This was feasible by an initial grafting of an iniferter onto a solid substrate (ormosil-modified PGE) to grow a polymer film of controlled thickness through photo initiated free-radical polymerization (Fig. 3). The proposed sensor could be considered suitable for the practical applications in biomarking histedinemia, a disease associated with L-His metabolic disorders, in clinical settings.

L-methionine (Met) is an essential amino acid found in proteins, foods, and pharmaceuticals. Any small deficiency from control level might manifest AIDS and HIV infection, toxemia, muscle paralysis, and depression. Its supplementation is necessary during the treatment of AIDS associated mylopathey as well as cancer. Contrarily, Met-depletion could be necessary in some cases to inhibit the tumor growth in preclinical model. Prasad et. al., reported two papers, for enantioselective detection of met isomers, based on electro-polymerized molecular imprinting approach [67,68]. For this, the surface initiated electro-polymerization of benzidine monomer was performed with simultaneous imprinting of template (D- and L-Met), first on carboxylated-MWCNTs anchored PGE [67] and second on pencil graphite fiber [68]. The modified PGE responded maximum differential pulse cathodic stripping voltammetry (DPCSV) response at optimized operating conditions in the wide range of L-Met concentrations [67]. On the other hand, the modified pencil graphite fiber was found suitable for MIMSPE experiment. A highly sensitive enantioselective analysis of D- and L-met with excellent analytical figures of merit could be achieved only on combination of both techniques (MIMSPE–MIP-sensor) [68]. The aforesaid methods were also validated for the enantioselective recognition of met isomers (D- and L-) quantitatively, in complicated matrices of real samples, without any cross-reactivity and false-positives.

Molecularly imprinted polymeric nano-materials (thickness 2.03 nm) for aspartic acid (Asp) enantiomers were electrochemically

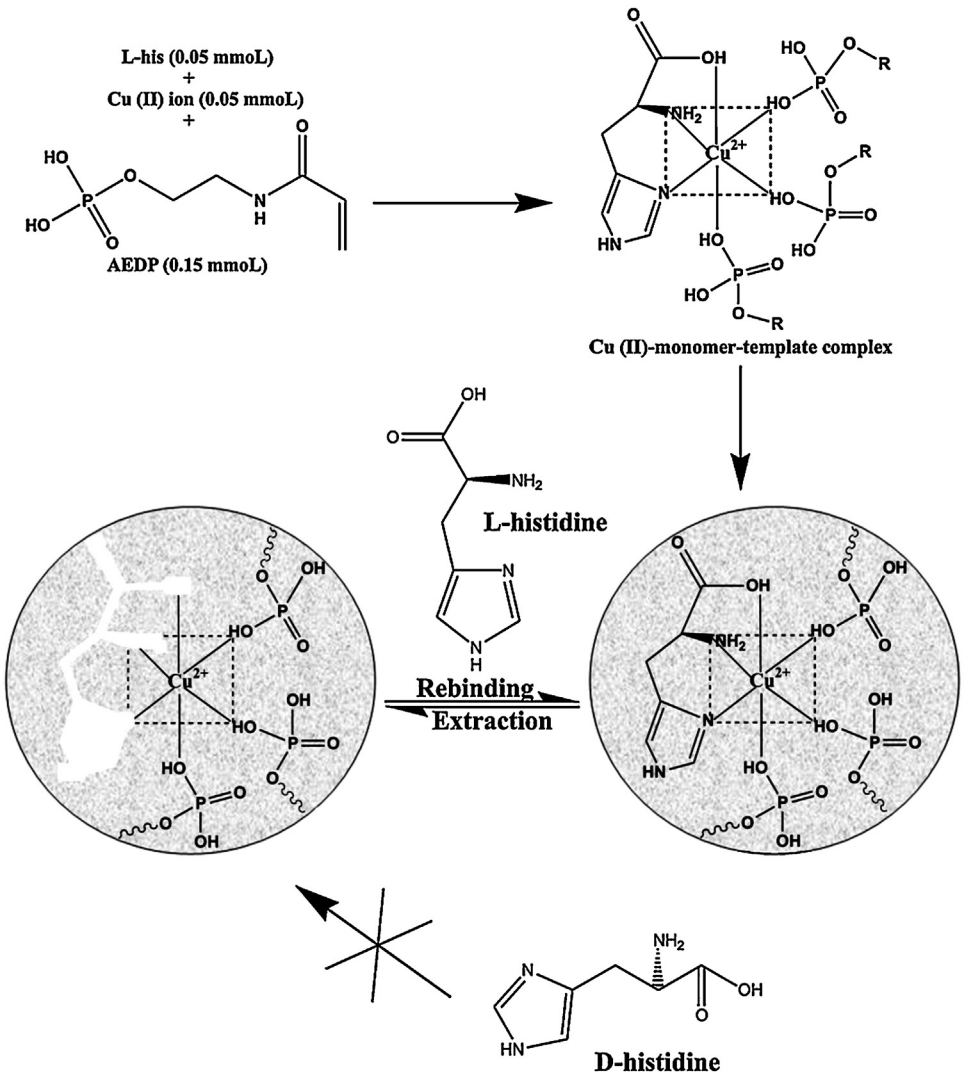


**Fig. 3.** Schematic illustration of enantioselective metal-mediated imprinting and rebinding of L-histidine [63]. AEDP: 2-acryl amidoethyl dihydrogen phosphate.

synthesized onto MWCNTs immobilized PGE surface, based on doping/de-doping characteristics of the conducting polymer; poly (indole-3-acetic acid) [69]. Herein, the template (Asp) was a dopant which could easily be ejected from the polymer backbone after over-oxidation. Enantio-selective analysis of L-Asp was also validated as a disease biomarker in blood serum. Very recently, MIP-matrix nano-composite modified PGE sensor [70] and corresponding hyphenated device (MIMSPE–MIP-sensor) were reported [71]. The hyphenated device consisted of MIP grafted on $TiO_2$ modified silica fiber for the micro-extraction and the same MIP was utilized for MWCNTs/$TiO_2$ modified PGE sensor development. The hyphenated device can be recommended for the clinical assay of Asp at stringent limits in cerebro spinal fluid (CSF) samples of the patients suffering with neurological disorders, without any cross-reactivity and matrix effect.

A new class of PGE duly modified with molecularly imprinted metallo-polymer for enantio-selective sensing of D-/L-pyroglutamic acid (PGA), in aqueous and real samples (urine, CSF, and blood plasma), has been developed via electro-polymerization of copper (II)–5-methyl-thiophene–2-carboxylic acid complex [72]. The detection of isomers with this sensor was feasible by DPASV method, without any cross-reactivity and false-positives. This signified as a highly sensitive probe for the primitive diagnosis of several associated diseases (metabolic acidosis, 5-oxoprolinuria, etc.).

Electrochemical methods for the specific recognition of the enantiomers of the pesticides dinoseb were developed separately in the solution of *R*-camphorsulphonic acid (*R*-CSA) (contained aniline) at different electro-polymerizing conditions [73]. Authors reported that the *R*-specific sensor was able to preferably rebind the *R*-dinoseb in a medium where both enantiomers were present. On the other hand, the *S*-specific sensor preferably binds the specific *S*-dinoseb. However, it behaved non-specifically for very higher concentrations of *R*-enantiomer.

It is highly desirable to develop ideal electrochemical chiral sensors exhibiting high specificity, sensitivity, quick response as well as easy to regenerate in analyte detection. A hybrid MIP (prepared by hybridizing insulated poly(methyl acrylic acid) with conducting polycarbazole through covalent bond) chiral sensor for L-Phe was developed [74]. In this work an open circuit potential–time technique was exploited to reveal enantio-selective characteristics with the preferential response of L-Phe over D-Phe.

As a sensing material, the main drawback in using MIP is that it provides limited surface area, resulting in a very weak electronic signal. A very simple fabrication method, to resolve this problem, was developed by combining β-cyclodextrin (β-CD)–MWCNTs composite material with imprinted sol–gel film at the surface of polyaniline modified carbon electrodes for sensitive and selective determination of L-Phe [75]. The electrochemical behavior of the sensor toward L-Phe was investigated by CV, DPV, and amperometric *i*–*t* curve. Interconnected β-CD–MWCNTs composites film and the polyaniline layer possessed superior conductivity, high stability, and excellent electro-catalytic ability, thus provided possibilities of clinical application in physiological fluids.

Chiral conducting polymers by electro-polymerizing poly(3,4-ethylenedioxythiophene) (PEDOT) in the presence of chiral anions such as hyaluronic acid (HA) and anionic collagen or a chiral nematic phase (hydroxypropyl cellulose, HPC) were synthesized [76]. These polymers exhibited an excellent recognition between (*R*)-(−)- and (*S*)-(+)-mandelic acid using CV and square wave voltammetry. Authors reported that the comparison of the square wave voltammograms showed a significantly high current observed with (*R*)-(−)-mandelic acid for PEDOT-HPC/$ClO_4$ ($45.3 \pm 2$ μA) compared to the PEDOT/collagen ($17.5 \pm 1$ μA) and PEDOT/HA ($18.4 \pm 1$ μA) chiral sensors.

A new imprinted element, prepared by the electro-polymerization of *o*-PD on the gold electrode, for the electrochemical detection of L-Trp in human serum was proposed [77]. The enantioselective analysis of L-Trp was made by DPV measurements.

### 3.2. Optical chiral sensors

Development of fluorescent sensors for organic molecules is of practical importance in chemical, biological, and pharmaceutical sciences. Taking the template L-Trp as an example, a new way of making imprinted polymeric fluorescent sensors using functional monomer duly modified with a fluorescent probe was described [78]. In this work, the effect of D-Trp on the fluorescence intensity was about 70% of that for L-enantiomer. Furthermore, the effect of L-Phe and L-Ala on the fluorescence intensity change was much smaller than that of L-Trp.

The feasibility of using benzamidine-based MIPs as sensing materials in the aqueous phase for chiral sensors was demonstrated [79]. Using reflectometric interference spectroscopy method, the interactions between di-*o*-benzoyltartaric acid-imprinted thin polymer layers (<100 nm thick) and both enantiomeric structures of the template were detected. It was found that all derived MIP-sensors showed response time in the span of 30 min, consuming regeneration time only 45 min. The combination of the detected selectivity and the high stability of imprinted polymers led to a new promising material for chiral chemosensors.

Colloidal crystals have been widely used as templates to create porous films with highly ordered 3D inverse opal structures. The periodic variety of the refractive index of these porous films gives rise to interesting optical properties. Particularly, if the films are made from hydrogel polymers, they may swell or contract in aqueous solution upon environmental changes, which leads to spectral shifts in the Bragg diffraction wavelength. Thus, they can be used as self-reporting sensors to measure various environmental changes, such as pH and temperature. In this respect, colloidal silica crystals were adopted as template to prepare highly ordered 3D macro-porous MIP hydrogel films that displayed high selectivity and specific chiral molecular recognition properties [80]. These films generated a readable optical signal directly (self-reporting) upon selectively binding a target analyte, without the need for labeling. The underlying concept was not only a potential alternative to create optical diffraction-based chemical or biological sensors, but could also be used successfully in drug separation, clinical assays, and catalysis.

A fast, simple, and selective chemiluminescence (CL) assay coupled with MIP microspheres of uniform shape (prepared using precipitation polymerization method), was developed for chiral recognition of fluorescence-labeled dansyl-L-Phe and dansyl-D-Phe [81]. MIP microspheres were fixed in microtiter plates (96 wells) using poly(vinyl alcohol) as glue and after washing, the bound fraction was quantified based on peroxyoxalate chemiluminescence analysis (PO-CL). In the presence of dansyl-Phe, bis (2,4,6-trichlorophenyl) oxalate (TCPO) reacted with hydrogen peroxide to emit chemiluminescence. The signal was detected and quantified with a highly sensitive cooled charge-coupled device (CCD). The limitation of TCPO–$H_2O_2$-CL analysis is that suitable fluorescent species are scarce. To overcome this limitation authors used dansyl-amino acids as signaling element in this work.

Two new polymerizable coumarins (6-styrylcoumarin-4-carboxylic acid and 6-vinylcoumarin-4-carboxylic acid) were synthesized for the development of MIP-based fluorescent chiral sensor using (−)-ephedrine as template [82]. It was observed that the MIPs prepared taking a 1:1 ratio of template: fluorescent functional monomer in the absence of any co-monomer demonstrated best recognition characteristics

and exhibited a decrease in fluorescence intensity response to template binding. However, the selectivity of (−)-ephedrine was poor in the recemate mixture. Furthermore, at higher concentration of ephedrine, no chiral selectivity was seen with MIPs due to the saturation of binding sites.

The increasing requirements for enantiomerically pure compounds demand appropriate materials as well as efficient strategies for analytical and preparative separations of enantiomers. Many new chiral separations based on the use of chiral mesoporous materials have appeared in the field of chiral technology. Nearly all aspects of this technology, including synthesis, separation, and analysis can be benefited substantially from the use of chiral porous materials. Chiral-mesoporous-polypyrrole nanoparticles (CMPPy) with spherical shape and high surface area (sizes ca. 3.5–3.7 nm in diameter) were synthesized by templating chiral block copolymers of poly(ethylene oxide), and chiral blocks of L-/D-Glu or L-/D-Phe and characterized by FT-IR, SEM, TEM, HRTEM and SAXRD techniques [83]. The chiral resolution of the copolymer-extracted CMPPy nanoparticles and chiral separation kinetics, using a racemic mixture of valine, were probed by circular dichroism and optical polarimetry.

Kong et al. [84] have created affinity sites for L-Asp in polyaniline (PAn) texture and utilized for enantioselective recognition of L- and D-Asp using fluorescence spectrometry. The PAn prepared was with positive charge on its backbone, and L-Asp anions in the solution are expected to compensate this, resulted in formation of PAn doped with L-$Asp^{-}$ (PAn/L-$Asp^{-}$). Meanwhile, imprinting of (*R*)- and (*S*)-enantiomers of propranolol, 1,1′-bi-naphthol, and 2-(4-isobutylphenyl)-propionic acid in $TiO_2$ nano-thin films, modified on quartz plates by spin coating, were examined for chiral discrimination of propranolol enantiomers [85]. The assessment of template incorporation, template removal, and re-binding were conducted through UV–vis measurements and specific selectivity (almost 100% for (*R*)-propranolol and 95% for (*S*)-propranolol) was achieved.

Graphene has attracted considerable attention in recent years for its two-dimensional structure and extraordinary properties. This unique nanostructure holds a great promise for potential applications in nanomaterials and nanotechnology. A novel flow injection chemiluminescence (CL) system of $KMnO_4$—$SnCl_2$—CHOH, based on graphene oxide–magnetite-MIP (GM-MIP), was developed for the determination of L-Trp in drug samples [86]. Authors investigated seven different polymers to study the adsorption capacity of L-Trp and found that GM-MIP (adsorption capacity = $11.9 \times 10^{-5}$ mol $g^{-1}$) was more appropriate to use in CL sensor, with the recoveries of added L-Trp in drug samples in the range of 96.8–102.0%.

Molecularly imprinted photonic polymer (MIPP) is a new type of sensor, developed by combination of photonic crystal templating method and molecular imprinting technique. The MIPP film consists of a three-dimensional, highly-ordered and interconnected macro-porous array. The unique photonic lattice characteristics of MIPP can provide a readable optical signal upon rebinding target analytes due to the change in the diffraction peak associated with the physicochemical changes of the hydrogel network. In particular, the recognition events of imprinted cavities will give rise to obvious color changes to the film that is typically easily visible to the naked eye, when the periodic lattice of photonic crystal is located in the visible spectral region. A colorimetric imprinted photonic polymer sensor was developed for the chiral recognition of PGA in monosodium glutamate samples via infiltrating polystyrene photonic crystal template with precursor and PGA molecules, followed by thermal polymerization [87]. The chiral recognition events could directly be visualized with contrast color changes; and readable optical signals through the diffraction peak shifts.

### 3.3. Piezoelectric chiral sensors

In principle, measurement of mass could be the most suitable method for the detection of any analyte since mass is the universal property of matter. Piezoelectric devices such as quartz crystal microbalance (QCM) can provide an extremely sensitive measurement to the mass of the analyte binding at the surface of piezoelectric materials, accompanying a decrease in the oscillation frequency of a piezoelectric crystal.

Haupt et. al., [88] have designed an enantioselsective acoustic sensor based on MIP for chiral β-blocking drug, *S*-propranolol, and QCM, as a transducer. The sensor was able to discriminate between the *R*- and *S*-propranolol enantiomers in acidified acetonitrile solutions.

Electro-polymerized OPPy system has been proved to be superior to other molecularly imprinted techniques, offering an excellent chiral selectivity. For instance, an OPPy film for the enantioselective detection of L- and D-Glu was reported using electrochemical-QCM (EQCM) and fluorometric technique [89]. It was found that L-Glu was recaptured ∼30-fold faster into the film than D-Glu, affording a great deal of enantio-differentiation. The OPPy (L-Glu) film has significantly high selectivity for L-Glu not only over D-Glu but also over some other amino acids.

For the first time, enantioselctivity within an MIP utilizing a single monomer-functional moiety interaction was reported [90]. A thin permeable MIP film was created on the surface of a gold coated QCM electrode for detection of L-menthol. The sensor exhibited no change in resonating frequency upon addition of 2 ppm of all terpenes (limonene, menthone, citronellol, citronellal, and D-menthol). This technique could be employed to determine the concentration of terpenes in atmosphere.

Cao et. al., [43] have presented a suitable mean of preparing highly selective and sensitive QCM sensors *via* self-assembly and molecularly imprinting techniques for chiral discrimination of L- and D-dansyl-Phe. These systems in sensor technology provided an opportunity for the development of other acoustic wave sensors exhibiting both selectivity and stability.

A continuous MIP rod for L-Phe derivatives as template using MAA as functional monomer and EGDMA as cross-linking agent was prepared [91]. The enantiomers D- and L-Phe were successfully resolved on a QCM sensor with the selectivity factor and resolution 1.87 and 1.09, respectively. The sensing system exhibited good sensitivity, selectivity, and ideal separation of target enantiomers.

A piezoelectric sensor, coated with a non-covalently imprinted recognition element, was presented for enantioselective detection of L-serine [92]. The enantioselectivity of the MIP coating was also investigated for L-serine and D-serine resulting in an enantiomeric selectivity coefficient of 4.8.

Electro-polymerization has been regarded as a promising procedure for the preparation of imprinted membranes in respect that the polymeric membranes can easily be grown and adhered to the electrode surface, and the thickness of the membrane can be controlled by the circulating charge. A stereo-specific L-His/D-His-imprinted membrane was constructed by electro-polymerizing acrylamide onto a gold-coated quartz crystal electrode and characterized using AC impedance spectroscopy and piezoelectric techniques [93].

Ultra-thin MIP film (below 50 nm thick) was modified directly on a gold-coated QCM resonator in well-controlled and reproducible manner using surface initiated radical polymerization approach [94]. The sensor displayed certain chiral selectivity toward the original template, (*S*)-propranolol, at a concentration higher than 0.38 mM in aqueous solution. Furthermore, different branches of MIP-coated sensors exhibited good reproducibility and long-term stability.

A highly selective and sensitive QCM sensor for Trp enantiomers was fabricated [95]. The sensor with cross-linker/monomer (molar ratio) value of 2.21 exhibited the optimum sensitivity and enantio-selectivity for L-Trp with enantiomeric selectivity coefficient 6.4. The signal obtained with the sensor after binding of template L-Trp to the imprinted membrane was about four-fold to three-fold larger than that obtained with the D-Trp enantiomer.

An EQCM sensor was developed involving electro-synthesis of L-Asp imprinted PPy film [96]. The synthesis of PPy/L-Asp film was strongly influenced by electrolyte composition and pH value. Authors reported that the electro-deposition in weakly acidic media (pH 6) led to synthesis of film that did not exhibit enantioselectivity for L-Asp, while electro-polymerization in alkaline media (pH 11) resulted in smooth and homogeneous films that followed the over-oxidation/de-doping and exhibited good enantioselectivity at pH 1.6. Moreover, they reported that PPy/L-Asp films, synthesized by electro-polymerization in the presence of polyelectrolyte, uptake L-Asp only, in the case of potential-induced uptake/release of target molecule.

OPPy film exhibited improved selectivity, which was attributed to the removal of positive charges from the PPy backbone because of the introduction of oxygen functionality, such as carbonyl groups. The electro-synthesis of molecularly imprinted OPPy films with cavities complementary to L-Trp was reported for the enantioselectivity detection of L-Trp and D-Trp using EQCM technique [97]. During electro-polymerization of pyrrole, L-Trp anions were compensated by the positive charge of the PPy backbone and resulted into the formation of PPy film doped with Trp. Under optimized conditions, L-Trp was inserted about 2-times higher into the imprinted polymer film than D-Trp. The same group also utilized the reversible redox property of poly(aniline-*co*-*m*-aminophenol), synthesized by copolymerization of aniline and *m*-aminophenol, to create an electrode column as the conducting stationary phase for Glu enantiomers [98]. The prepared MIP column exhibited high selectivity for L-Glu over D-Glu, which was confirmed by EQCM and fluorescence spectrometry.

A piezoelectric quartz crystal sensor based on MIP coated gold electrode of an AT-cut quartz crystal was developed for enantioselective and quantitative analysis of *d*-(+) methamphetamine (MA) [99]. The sensor exhibited great selectivity for *d*-(+) MA except when the sensor was used to measure the enantiomer *l*-(−) MA and a homolog (phentermine).

Recently, an innovation to thin-film molecular imprinting was presented for the sensitive detection and effective discrimination of chiral compounds using a portable QCM transduction technique [100]. The facile approach involved: (i) colloidal sphere layering of latex particles onto the surface via a Langmuir–Blodgett-like technique followed by, (ii) template molecular imprinting using electro-deposition of a single functional and cross-linking monomer.

More recently, a QCM sensor, having enantio-selective ability to analyze malic acid enantiomers with high sensitivity, was fabricated using a biomimetic ultra-thin film of MIP (termed as glyco-MIP, synthesized using sugar moiety) [101]. The glyco-imprinted polymer sensor demonstrated exclusive specificity for L-malic acid, concomitantly present with D-malic acid and respective analogs. The rational design of malic acid/glyco-monomer complex, with composition 1:2, was predicted on the basis of theoretical modeling. The proposed sensor demonstrated a fast, reliable, enantio-selective and quantitative response to malic acid isomers, in real samples.

Riskin et al. [102] have fabricated surface plasmon resonance (SPR) sensor on Au surface for amino acids (for example, L-Glu, L-Asp, L-His, and L-Phe) by creating imprinted sites in the electro-polymerized gold nanoparticles (AuNPs) composites functionalized with thioaniline and cystein. Meanwhile, they also developed a SPR sensor for the synthesis of molecularly imprinted AuNPs composites on electrodes by electrochemical means for chiro-selective recognition of mono- or disaccharides [103]. The method was based on the formation of a boronate complex between the respective saccharide and the boronic acid ligands associated with the AuNPs. For this, they first functionalized Au nanoparticles ($4.5 \pm 0.5$ nm) with 4-mercaptoaniline, mercaptoethane sulphonic acid, and mercaptophenyl boronic acid, followed by electro-polymerization on the surface of 4-aminothiophenol modified gold electrode along with mixture containing selected saccharide (glucose in present case) and bis-aniline (as cross-linker). Electro-polymerization was performed in the potential window of −0.25 to 0.7 V followed by over-oxidation at 0.7 V for 2 h. From the result obtained, authors estimated the association constants of D-glucose and L-glucose and concluded that chiro-selective imprinted recognition sites may be generated in the electro-polymerized Au nanoparticle composites.

## 4. Conclusion

In summary, the impact of chirality on almost any chemical and biological process is well recognized and has significant ramifications in many fields of economic interest. The increasing requirements for enantiomerically pure compounds demand appropriate materials as well as efficient strategies for analytical and preparative separations of enantiomers. At the same time, this aim is very important for future technology because most important chiral substances are bio-related molecules and their sensing contributes to biology, biotechnology, and pharmacy. In this context, the research works described in this review have clearly shown that MIP-based enantioselective sensing devices could be used successfully in detection and discrimination of chiral compounds prevalent at trace levels in real samples. However, in most cases enantioselectivity obtained by chiral sensors are still not sufficient for practical applications in routine analysis to compete with reported separation methods and commercial exploitation of molecular imprinting is still in its infancy. Furthermore, MIPs cannot yet provide a total replacement for biological molecules in terms of capacity, selectivity and homogeneity of binding affinity. However, their potential for use in separation and sensing applications is clear, considering their low cost and robustness. The development of MIPs and sensing systems need to be solved before commercial applications start. The main challenges include: (1) the enhancement of specific molecular affinity and reduction of non-specific adsorption by the design of MIP; (2) the development of a general synthesis protocol for MIPs with uniform shape and size; (3) the development of multi-sensors with multiplexing capabilities and high integration through the use of nano-fabrication. The future efforts to address these concerns by multidisciplinary approaches will progressively extend the real applications of MIPs in chiral sensors as well as many other fields.

MIP nanomaterials with different forms such as nanoparticles, core–shell/hollow nanoparticles, nano-wires, nano-tubes, and nano-films have been synthesized in a controlled way by the employments of nanotechnologies and surface chemistry. The imprinting of molecular recognition sites at nanostructures has greatly improved the removal of templates and the binding capacities and kinetics of molecular recognition, compared with the traditional imprinted bulky materials. Nano-sized MIP materials with high surface-to-volume ratio are characterized by their capability of binding target molecules with similar affinity and selectivity to those of antibody, whereas they offer a higher physical/chemical stability and better engineering possibility than biological receptors. In particular, MIP nanomaterials as molecular recognition elements have exhibited remarkable

advantages for the applications in biomimetic chemo/biosensors which are least employed in the fabrication of chiral sensors.

Advances in MIP chemistry can be expected in the near future and should facilitate the direct production of MIPs in the form of nanoparticles on a continuous basis. This will then provide the missing impetus for investment in MIPs, leading to a new generation of superior, commercially available affinity materials in the field of enantio-sensing.

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