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# A historical perspective and the development of molecular imprinting polymer-a review

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**ABSTRACT**

Molecular imprinting is an emerging technology which enables us to synthesize the materials with highly specific receptor sites towards the target molecules. Molecularly imprinted polymers (MIPs) are a class of highly cross-linked polymer that can bind certain target compound with high specificity. Such techniques have been progressively employed in a wide scope of applications such as development of various analytical techniques such as solid-phase extraction (SPE), liquid chromatography, capillary electro chromatography, binding assays and biosensors, mostly in bio-analytical areas. The aim of this review paper is to give a fundamental description of the molecular imprinted polymer and to give the reader an insight into the main developments are discussed, Particular emphasis will be placed on their role as affinity materials in separation science. Discussing first general aspects in MIP history and preparation and then dealing with various application aspects.



**Capsule Summary:** A molecularly imprinted polymer is a polymer that has been processed using the molecular imprinting technique which leaves cavities in polymer matrix with affinity to a chosen "template" molecule. The process usually involves initiating the polymerization of monomers in the presence of a template molecule that is extracted afterwards, thus leaving complementary cavities behind. Present paper details historical perspective and the development of molecular imprinting of polymer were reviewed.

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## INTRODUCTION

Molecular imprinting is an emerging technology which enables us to synthesize the materials with highly specific receptor sites towards the target molecules. Molecularly imprinted polymers (MIPs) are a class of highly cross-linked polymer that can bind certain target compound with high specificity. The polymers are prepared in the presence of the target molecule itself as the template. The concept behind the formation of the selective binding sites is schematically shown in Figure 1 (da Silva et al., 2015; Deshmukh et al., 2015; Huynh and Kutner, 2015; Owens et al., 1999; Vasapollo et al., 2011; Wei et al., 2007).

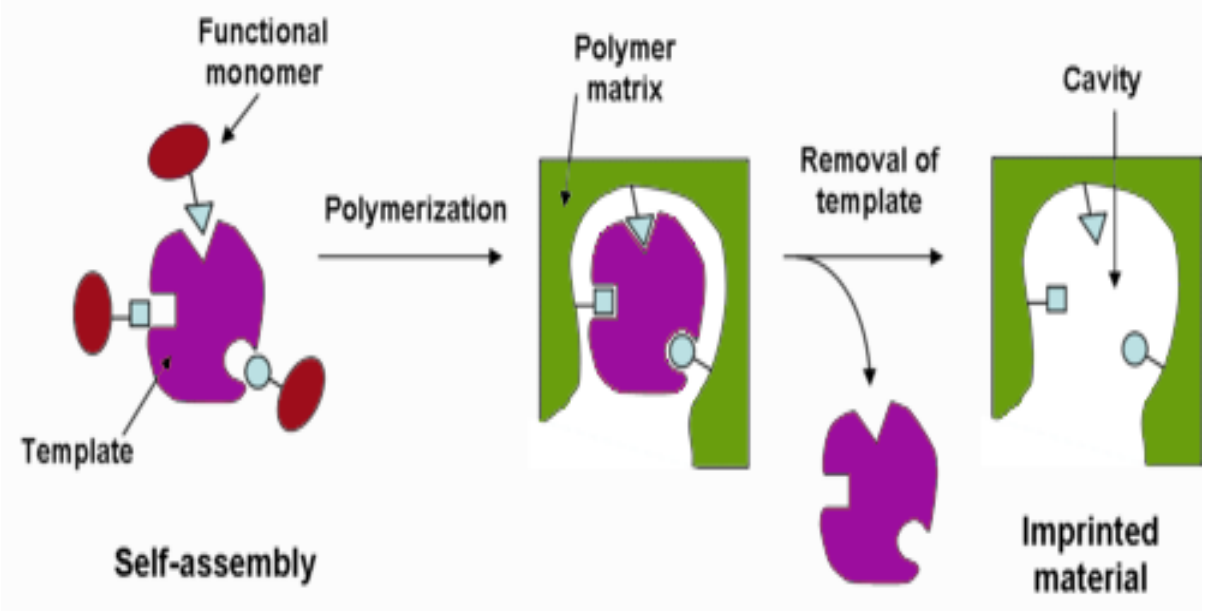


**Fig. 1:** Basic molecular imprinting concept

In brief, the template interacts with functional monomers before being cross-linked by cross-linker in polymerization process. The specific binding site complementary to the target analyte is generated upon the removal of the template from the solid polymers (Lok et al., 2009). There have been several review articles on general introduction of MIP (Owens et al., 1999; Vasapollo et al., 2011; Wei et al., 2007). Here we review the history of molecular imprinting, from the introduction of the technique in conjunction with silica matrices in 1931 until the beginning of the 1970s, when the techniques was first applied to organic polymers. A brief overview is given regarding the evolution of molecular imprinting in organic polymers. However, although interest in the technique is new, the concept itself has a long history. 1972 marked the start of molecular imprinting technology as we know it today, when the laboratories of Wulff and Klotz independently reported the preparation of organic polymer with predetermined ligand selectivities. Template molecules which were present during polymerization or derivatives therefore, were recognized by the resultant molecularly imprinted polymer (MIP). Wulff introduced a new approach that allowed the introduction of functional groups at defined positions in synthetic network polymers. This approach is often referred to as covalent molecular imprinting, to distinguish it from the noncovalent approach developed by Mosbach and his co-workers in the early 1980s. According to a recent comprehensive review (Vasapollo et al., 2011), the main advantages of MIPs are their high affinity and selectivity for the target molecule (template). MIPs have higher physical strength, robustness, resistance to elevated pressure and temperature and inertness against various chemicals (organic solvents, acids, bases, and metal ions) compared to biological media such as proteins and nucleic acids. Furthermore, their production costs are low and their lifetimes can be as long as several years at room temperature. MIP has excellent stability, ease of preparation and low cost for most of the target analysts make them attractive for numerous applications. Over 1450 references related to the use of MIPs in a large range of application areas have been recently collected (Alexander et al., 2006). Therefore, MIPs have been already successfully used as an alternative tool to these biological entities in several analytical fields such as separation of enantiomers in LC or CEC (Ansell, 2005; Zhao-Sheng Liu, 2007, binding assays (Ansell, 2004; Lavignac et al., 2004) and sensors (Avila et al., 2008; Holthoff and Bright, 2007). In recent years, the development of MIPs for solid-phase extraction (SPE) has been extensively reported (Blanco-Lopez et al., 3004; Caro et al., 2006; Fengxia et al., 2006; He et al., 2007; Pichon, 2007; Pichon et al., 2006; Tamayo et al., 2007) in the areas of environmental, food and pharmaceutical analysis including their use as selective sorbents for the extraction or for the clean-up of different classes of compounds from various complex matrices. SPE is the most advanced application area of the MIP (Alexander et al., 2006). Most of the developments in MIP production during the last decade have come in the form of new polymerization techniques in an attempt to control the arrangement of monomers and therefore the polymers structure.

**History- journey of MIP from 1931–2013**

In a paper published (Polyakov, 1931) by Polyakov reported the effects of presence of different solvents (benzene, toluene

and xylene) on the silica pore structure during drying a newly prepared silica. When $H_2SO_4$ was used as the polymerization initiator (acidifying agent), a positive correlation was found between surface areas, e.g. load capacities, and the molecular weight of the respective solvents. Later on, in Dickey reported the polymerization of sodium silicate in the presence of four different dyes (namely methyl, ethyl, n-propyl and n-butyl orange). The dyes were subsequently removed, and in rebinding experiments it was found that silica prepared in the presence of any of these "pattern molecules" would bind the pattern molecule in preference to the other three dyes. Shortly after this work had appeared, several research groups pursued the preparation of specific adsorbents using Dickey's method. Some commercial interest was also shown by the fact that Merck patented a nicotine filter, consisting of nicotine imprinted silica, able to absorb 10.7% more nicotine than non-imprinted silica (Erlenmeyer, 1965). The material was intended for use in cigarettes, cigars and pipes filters. Shortly after this work had appeared, molecular imprinting attracted wide interest from the scientific community as reflected in the 4000 original papers published in the field during for the period 1931–2009. The technology was then expanded by the effort of Mosbach and coworkers in 1980s (Andersson et al., 1984). The MIPs possess several advantages over the conventional immunosorbent (IS). They show high selectivity and affinity, high stability and the ease of preparation (Piletsky et al., 2006). The MIPs can be used repeatly without loss of activity with high mechanical strength and durable to harsh chemical media, heat and pressure compared to biological receptors (Lavignac et al., 2004). Chemical stability studies demonstrated that the polymers kept >95% of their affinity even after 24 h of exposure to autoclaving treatment, triethylamine, 10M HCl acid and 25% $NH_3$. Heat treatment revealed that the polymers are thermally resilient and able to retain their chemical affinity, as the MIP will not degrade up to temperatures of 150 $^oC$ (Svenson and Nicholls, 2001). They can be stored for years without loss of affinity for the target analyte. Researches in this technology have grown rapidly due to its potential application in various fields, ranging from chemical, pharmaceutical, engineering, material science and biotechnological industries. Now a day's researcher focusing on, molecularly imprinted core–shell nanoparticles (Zhao et al., 2013) are the wonderful materials with the superiority of good accessibility to the target species and low mass-transfer resistance. As reported in a recent review (Lucena, 2012), MIPs have widely been utilized as the kernel coating materials for SBSE technique. Also in recent paper (Prasad et al., 2013) author reports a combination of molecularly imprinted stir bar sorptive extraction and complementary molecularly imprinted polymer-sensor for the analysis of dopamine as a biomarker of several neurodegenerative diseases occurred at ultra-trace level.

**Synthesis of molecularly imprinted polymers**

Molecular imprinting has been demonstrated in silica and in synthetic organic polymers, but it is organic polymers that have found the most favour and indeed probably have the most to offer to the affinity separation area. The rest of this article will therefore deal exclusively with molecular imprinting in the latter medium. Most methods for preparation of MIPS include three steps: firstly, mixing and interacting the functional monomers with the imprinted molecules; secondly, copolymerizing the cross-linkers with the functional monomers; thirdly, removing the template from the imprinted polymers. Recently, new methods for preparation of MIPS have been proposed, involving normal suspension polymerization (Hosoya, K.; Yoehizako, 1996), suspension polymerization in perflurocarbon (Mayes et al., 1996), seed polymerization, graft polymerization, polymerization of reactive surfactants (Ye et al., 2001), precipitation polymerization (Ye et al., 1999), etc.

**1. Choice of the template**

The binding strength of the polymer as well as the fidelity in the recognition depends on the number and type of interaction sites, the template shape, and the monomer template rigidity (Sellergren, 1999). Templates offering multiple sites of interactions for the functional monomer are likely to yield binding sites of higher specificity and affinity for the template. A MIP is usually synthesized for a specific analytical use that implies the choice of a given template molecule. The criteria to consider when selecting a candidate molecule are its cost, its availability and, of course, its chemical functionalities defining its ability to strongly interact with monomers. A quantitative structure binding relationship was demonstrated by imprinting a number of structurally related basic *N-het*erocyclic by co-polymerization of methacrylic acid (MAA) and ethylene glycol dimethacrylat~(EDMA) (Shea et al., 1993; Vlatakis et al., 1993). High affinity and selectivity were reported when **9-**ethyladenine was used as the template (Spivak et al., 1997; Yu and Mosbach, 1997). Sellergren and Dauwe observed similar effects in their studies on imprinting a series of similar structurally triazine templates. A notable increase in affinity and selectivity was obtained with an increase in the basicity of the templates. Furthermore, MIPs prepared with a template that forms a two-point interaction with MAA, such as ametryn exhibited higher affinity and selectivity for the template than for a structurally similar compound such as prornetryn (Dauwe and Sellergren, 1996). The shape and size of the template in some cases may be sufficient to create steric complementarity for efficient discrimination between two molecules, i.e., the imprinting of amino acids with N-protecting groups. Selectivity of amide MIPs was ascribed to the hydrogen bonds formed between the sample molecule and amide groups at the recognition sites of the MIP and to the size and shape of the amino acid molecule (Yu and Mosbach, 1997). Templates that possess conformational rigidity that can fit in the cavity of the polymer with minimal change in conformation will increase the affinity and selectivity in the recognition (Avila et al., 2008).

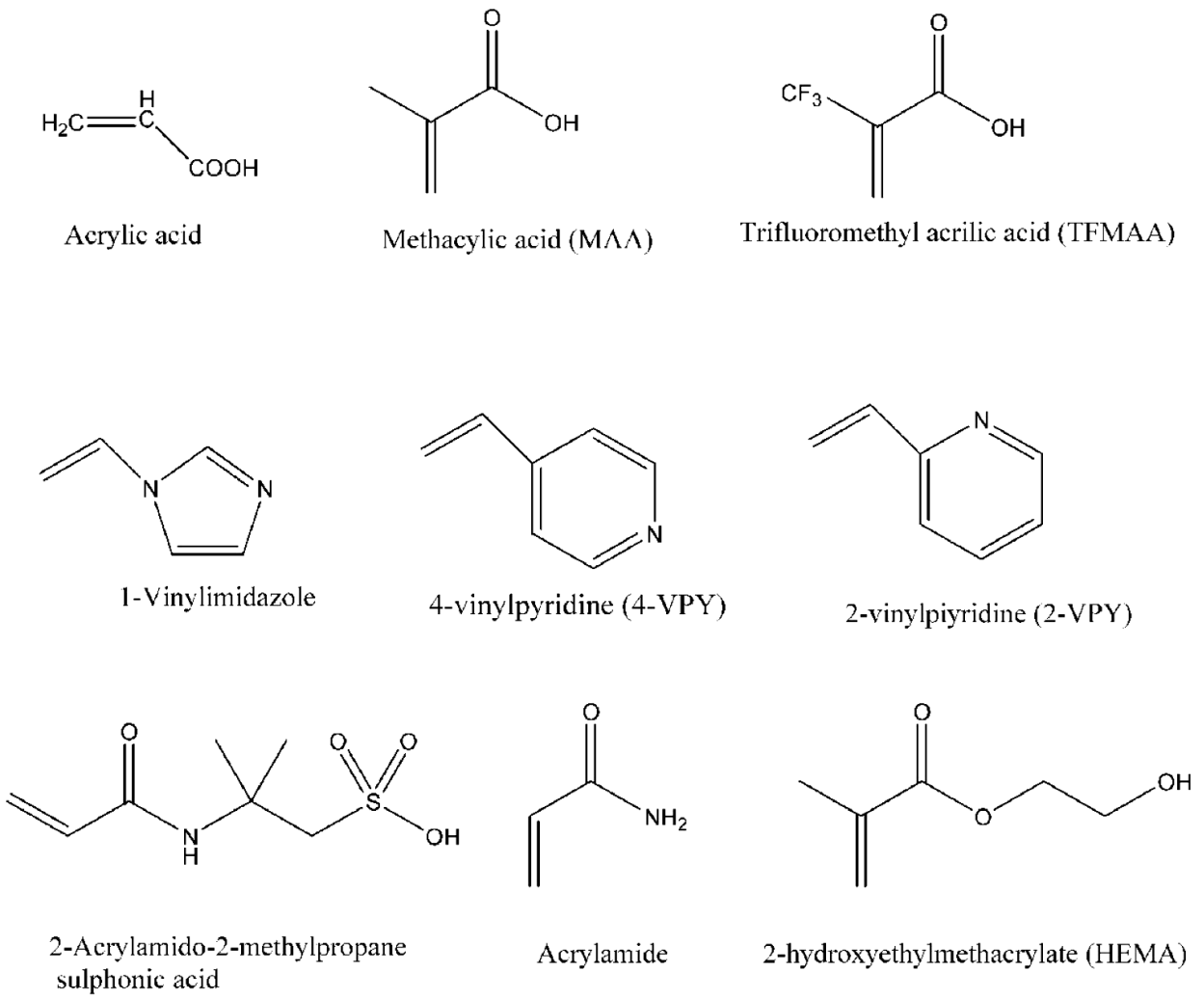


**Fig. 2:** Structure of the most common monomers used for molecular imprinting (Vasapollo et al., 2011)

In addition to the type of template, the ratio of the template to the functional monomer has been known to play a key role in the selectivity and sensitivity in the imprinted. Polymers when the possible interactions involved inside the matrix are taken into account. The optimum ratio has to be determined for each individual template. Investigations on the effect of stoichiometry have been reported in several imprinting studies. In 2008 Yi Ge et al. studied that successfully imprinting of large biomolecules such as proteins and cells (Yi Ge et al., 2008).

## 2. Types of monomer and cross-linker

The choice of monomer is very important in order to create highly specific cavities designed for the template molecule. Typical functional monomers (Figure 2) are carboxylic acids (acrylic acid, methacrylic acid, vinyl benzoic acid), sulphonic acids (2 acrylamido-2-methylpropane sulphonic acid), heteroaromatic bases (vinylpyridine, vinylimidazole). The extensive use of methacrylic acid (MAA) is due to its capability to act both as hydrogen bond and proton donor and as hydrogen bond acceptor. Moreover, more strong functional monomers were developed via metal coordination interactions to bind specific amino acid sequences (Hart et al., 2001).

New functional monomers, based on polymerizable amidines and ureas, have been developed for stoichiometrically imprinted polymeric receptor of B-lactam antibiotics, reducing non-specific adsorption (Urraca et al., 2006). The best monomers for synthesizing imprinted materials are selected considering strength and nature of template-monomer interactions .The cross-linker also plays a major role in synthesis of imprinted polymer. The cross-linker is important in controlling the morphology of the polymer matrix, serves to stabilize the imprinted binding sites and imparts mechanical stability to the polymer matrix in order to retain its molecular recognition capability (Sellergren, 1999). Different cross-linkers have been used.

Ethylene glycol dimethacrylate (EGDMA) and trimethylolpropane trimethacrylate (TRIM) are the most commonly employed. It has been found that the cross linker has less effect on the specific interactions between the template and functional monomers and more effect on the physical properties of the polymer reported by some author. TRIM as cross-linker gives polymers with more rigidity, structure order and effective binding sites than EGDMA. Mosbach, (1998) reported that, In the case of precipitation polymerization method, by optimizing the amount of cross-linker and reducing the concentration of the template, the polymer binding properties are improved and the level of non-specific interactions is decreased (Ye et al., 2000). In another study, Mosbach, (1998) also reported that, the type of cross-linker strongly influences the final size and yield of MIP nanoparticles (Yoshimatsu et al., 2007). In fact, when divinylbenzene was used as the cross-linker, polydisperse MIP particles were obtained in low yield, whereas, trimethylolpropane trimethacrylate (TRIM) led to uniform nanoparticles in high yield (90%).

**Application of MIP**

The different application areas, including separation sciences and purification, sensors and biosensors, catalysis and drug delivery are important application of MIPs because of its peculiar properties. It becomes an emerging technology with the potential for wide-ranging applications in food manufacturing, processing, analysis and quality control. It has been successfully applied in food microbiology, removal of undesirable components from food matrices, detection of hazardous residues or pollutants and sensors. Molecularly imprinted solid phase extraction (MISPE) is the most common application so far. Application of MIP in CEC is an area of increased attraction. Some author reported specific forms of MIPs such as monoliths particles and membranes etc. SPE is a very useful sample pretreatment/ enrichment method. The potential usefulness of MIP in drug delivery is very attractive, and there are some review articles on this topic (Alvarez-Lorenzo et al., 2004; Byrne et al., 2002; Cunliffe et al., 2005). Application of MIP as artificial enzymes or receptors for antibodies has also been reviewed in some articles. Application of MIP in sensors is a hot topic of a huge future commercial market. Among them, some author are focused on specified items such as electrochemical and optical sensors. In addition, there are some miscellaneous reviews of particular interests such as drug discovery with MIPs (Rathbone, 2005), MIPs incorporated with electrically conducting polymer (Pik et al., 2009), and template removal from the MIP matrix (Lorenzo et al., 2011).

**1. Separation**

MIPs were frequently used as Chiral Stationary Phases (MIP-CSPs) in High Performance Liquid Chromatography (HPLC) to obtain enantiomeric resolutions of racemic solutions of different compounds, such as amino acid derivatives and drugs. In 1985, the first studies were made by Mosbach group that realized an MIP sorbent used as stationary phase in LC, to separate amino acid derivatives (Sellergren et al., 1985). Sellergren and co-workers prepared an acrylic polymer by non-covalent imprinting procedure for selective enantioseparation of D or L-Phenylalanine ethyl esters to evaluate the enantio and substrate-selectivity for some amino acid derivates (Szabelski et al., 2002). Solid Phase Extraction (SPE) is important area of application of MIPs in analytical chemistry. MIP for Solid-phase extraction (MISPE) has been applied both in on-line and off-line procedures. Molecular imprints were prepared using L-phenylalanine anilide as the print molecule and methacrylic acid as the functional monomer. Methacrylic acid interacts ionically with the primary amine of the print molecule and via hydrogen bonding with the amide function. In the HPLC mode such polymers were shown to exhibit efficient enantiomeric resolution of a racemic mixture of the original print molecule (Daniel et al., 1989). Researchers focused on the imprinting of amino acid derivatives was to attempt to make imprints of adducts of these compounds with pyridoxal to create sites which could recognize both the amino acid moiety and the pyridoxal moiety of the Schiffs base. It is reported that first imprinting carried out of a coenzyme-substrate analogue, N-pyridoxyl-L-phenylalaninanilide (l), allowing both enantiomeric separation and facilitation of a model reaction involving pyridoxal (Andersson and Mosbach, 1989). In chromatographic applications, in early days optical resolution is achieved using as the stationary phase either a chiral material or chiral selectors coupled to a non-chiral support material. Now a day's molecular imprinting, has gained increasing interest for the preparation of chiral stationary phases. There are lots of work was performed on the chiral separation (Mayes and Mosbach, 1997; Mosbach et al., 1998; Wulff, 1995). By use of molecular imprinting, chirality may be introduced into polymer matrices starting from, in most cases, chiral building blocks. This chirality is thus a consequence of the asymmetry carried by the template. Molecularly imprinted materials have been employed as chiral matrices in different separation techniques (Armstrong et al., 1998; Fischer et al., 1991; Kriz et al., 1994; Schweitz et al., 1997). A characteristic of imprinted chiral stationary phases for chromatography is the predetermined elution order of the enantiomers, which depends only on the enantiomers used as the template molecule. For instance, if the D-enantiomers is used as the template, it will be retained more by the polymer than the L-enantiomers, and *vice versa.* The discrimination of enantiomers is often very efficient with molecularly imprinted materials yielding highly efficient chiral separations (Matsui et al., 1996; Ramstrom et al., 1994). Up to midst, the stationary phase most commonly used in thin-layer chromatography (TLC) has been silica particles. Much research has been directed toward the variation of the stationary phase in order to achieve selective interactions with the analyte. For instance, silica particles have been modified by introducing amino-, cyano-, or diol-bonded

groups, thus changing the ~e1ectivity.l~O ne interesting approach would be to make use of the predetermined molecular recognition properties of MIPs. We therefore decided to investigate the use of MIPS as the stationary phase in TLC. This was expected to offer a quick and powerful analysis/separation technique which could be performed using simple and inexpensive equipment results successfully demonstrate the feasibility of the manufacture of thin-layer chromatography plates coated with molecularly imprinted polymers. TLC plates with specificity for a desired molecule (or enantiomers thereof) can be made for fast and simple analyses. In particular the predetermined chiral selectivity of the prepared TLC plates may be applicable in the pharmaceutical industry. The manufacture of optically pure drugs is of great importance in order to avoid possible side effects. The asymmetric synthesis of such drugs, or their large-scale enantiomeric separation on chiral stationary phases or molecularly imprinted polymers, could readily be followed by using molecularly imprinted thin-layer chromatography plates (Kriz et al., 1994). Scientists successfully prepared molecularly imprinted polymers (MIPS) for 4-nitrophenol by a thermal polymerization method using 4-vinylpyridine (4-VP) and ethylene glycol dimethacrylate (EDMA) as functional monomer and cross-linker, respectively. The obtained materials were evaluated with respect to their selective recognition properties for 4-nitro phenol by HPLC using organic and aqueous eluents. Furthermore, the specific binding sites that have been mated during the polymerization process were analyzed via radio ligand binding assays. The successful imprinting against 4-nitrophenol provides a new opportunity for advanced separation materials used in environmental analysis (Janotta et al., 2001). Authors attempted to fabricate a highly selective and sensitive bulk acoustic wave (BAW) sensor based on molecularly imprinted microspheres (MIM). Dipyridamole, 2, 2', 2'', 2'''-(4-8-dipiperidinopyrimido [*5,4-d*] pyrimidine-2, 6-diyldinihilo tetra ethanol, was used as template. The MIPS were characterized by using "EM and the Scatchard analysis. Influencing factors such as ethanol, pH value and the weight ratio of polyvinyl chloride (PVC) to MIM were investigated. The sensors, which were modified by WC, were also successfully applied to the determination of Dipyridamole in water and urine, and the results were satisfactory (Zhang et al., 2003). Report that long open tubular molecular imprinted polymer capillary columns with excellent separation efficiencies in chiral and non-chiral separation by capillary electro-chromatography. Authors reported that Molecularly Imprinted Chromatography is one of the most traditional applications of molecularly imprinted polymers especially for Liquid Chromatography (LC) with MIPs usually synthesized by bulk polymerization, ground and sieved mechanically and subsequently packed in a chromatographic column (Haginaka, 2008). 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. There have been a few reports in the literature dealing with molecularly imprinted membranes that exhibit selective binding or transport of a target analyte (Hedborg et al., 1993; Mathew-Krotz and Shea, 1996; Kobayashi et al., 1995; Piletsky et al., 1995). Some of them were designed for application as the recognition element in sensors (Hedborg et al., 1993; Piletsky et al., 1995). Membranes were prepared either as free-standing thin films or thin polymer films on the surface of solid supports following standard imprinting recipes. Others have employed a phase-inversion precipitation technique starting from linear polymer precursors (Kobayashi et al., 1995). In a paper author reports a different approach towards the development of molecularly imprinted polymer membranes for the resolution of racemates. To obtain mechanically stable membranes for preparative application, the imprinted polymer was synthesized in the pores of polypropylene membranes. The amino acid derivative CBZ-tyrosine was chosen as the target molecule, and a standard polymer recipe for non-covalent imprinting was used (Dzgoev and Haupt, 1999). Lei Ye et al., reported preparation of extremely stable and specific adsorbents for the product *Z*-L-Asp-L-Phe-OMe (*Z*-aspartame) using the emerging technique of molecular imprinting. This new methodology may find use in various synthetic applications such as high pressure and temperature stability, allowing MIPs to withstand sterilization conditions

## 2. Sensors

MIPs exhibit exceptional chemical and thermal stability. These desirable properties have led to tremendous interest in the use of MIPs as recognition elements in chemical sensors and biosensors (Haupt and Mosbach, 2000). The general approach involves attaching the MIP onto the surface of a transducer that sensors binding events between the MIP and the target analyte and sends quantifiable signal to the user. In this paper, we attempted to fabricate a highly selective and sensitive BAW sensor based on molecular imprinted microspheres (MIM) . Dipyridamole, 2, 2', Z', z"-(4-8-dipiperidinopyrimido [5, 4-*d* 3 pyrimidine-2, 6-diyldinihilo tetra ethanol, was used as template. The MIPS were characterized by using TEM and the Scatchard analysis. Influencing factors such as ethanol, pH value and the weight ratio of polyvinyl chloride (PVC) to MIM were investigated. The sensors, which were modified by PVC, were also successfully applied to the determination of Dipyridamole in water and urine, and the results were satisfactory (Zhang et al., 2003).

## 3. Drug discovery

Recent developments in the field of biomaterials are based on molecular design of polymers with improved surface and bulk properties. Novel techniques of surface modification by addition of tethered chains can lead to materials with the ability to recognize biological and pharmaceutical compounds. Authors examined that Acrylic-based hydrogels are well-suited for mucoadhesion due to their flexibility and

nonabrasive characteristics which reduce damage-causing attrition to the tissues in contact. However, the adhesive and drug delivery capabilities of these devices can continue to be improved as presently known bioadhesive materials are modified and more bioadhesive materials are discovered. Tethering of long PEG chains on PAA hydrogels and their copolymers can be achieved by grafting reactions involving thionyl chloride, followed by PEG grafting. Also reported that various forms of adhesive hydrogels based on poly(acrylic acid) research. In our recent work, we have shown that (PAA) or poly (methacrylic acid) (PMAA) exhibit an unusual property of inhibition of the degradation of various peptides and proteins (including insulin) by proteolytic enzymes (Bures et al., 2001).

## CONCLUSIONS

The preparation methods of MIP include embedding method, affinity imprinting, freeze drying and surface imprinted method. Research direction for MIP in future includes understanding the mechanism of molecular imprinting and identification from molecular level, exploring new synthetic method, realizing the transfer of mol. Imprinting technique from organic phase to water phase, from non-polar solvent environmental and extending its application field.

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