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REVIEW

Recent Progress, Challenges and Prospects in Monitoring Plastic-Derived Xenoestrogens Using Molecularly Imprinted Sorbents

Priyanka Narula · Raghubir Singh · Varinder Kaur · Ashok Kumar Malik

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Abstract Indoor and outdoor exposure to plastic-derived xenoestrogens, such as phthalates and phenolic compounds, can adversely affect endocrine and reproductive systems in humans and wildlife. To accomplish the extraction of plastic-derived xenoestrogens from environmental samples, molecularly imprinted polymers (MIPs) have been proved to be selective, efficient, and reliable sorbents. Despite some problems associated with the use of MIPs as sorbents, these have been found to be of considerable interest due to their advantages of selectivity, easy synthetic procedures, and better stability over commercially available solid sorbents. Modifications in their synthetic strategies are continuously in progress and new approaches are being made through graphene oxide substrates, nanostructured platforms, nanoferrites, cryogels, and co-electropolymerization to design better sorbents. Apart from this, efforts to create molecularly imprinted solid phase microextraction (SPME) fibers have also been successful in improving the efficiency of the methodology. In future, the use of MIPs developed from advanced synthetic strategies, or as sorbents for more robust techniques like SPME and microextraction on packed sorbents, will add new horizons to explore the potential of MIPs in the field of plastic-derived xenoestrogens. This review presents various challenges, as well as progress and prospects associated with the extraction of plastic-derived phthalates and phenolic compounds using molecularly imprinted sorbents.

Keywords Microextraction on packed sorbents · Molecular imprinting · Molecularly imprinted polymers · Phenolic compounds · Phthalates · Plastic-derived xenoestrogens

Abbreviations

AA	Acrylic acid
AN	Acrylonitrile
AM	Acrylamide
BBP	Benzylbutylphthalate
BPA	Bisphenol A
BPE	Bisphenol E
BPF	Bisphenol F
BPM	Bisphenol M
DAIP	Diallyl-*m*-phthalate
DAP	Diamylphthalate
DBP	Dibutylphthalate
2,4-DCP	2,4-Dichlorophenol
DEHP	Diethylhexylphthalate
DEP	Diethylphthalate
DES	Diethylstilbestrol
DMP	Dimethylphthalate
DMT	Dimethylterephthalate
DNOP	Di-*n*-octylphthalate
DPP	Dipentylphthalate
DVB	Divinylbenzene
E2	Estradiol
ED	Electrochemical detection
EDMA	Ethylenedimethacrylate

P. Narula · V. Kaur (✉)
Department of Chemistry, Panjab University, Chandigarh 160014, India
e-mail: var_ka04@yahoo.co.in

R. Singh
Department of Chemistry, DAV College, Sector 10, Chandigarh 160010, India

A. K. Malik
Department of Chemistry, Punjabi University, Patiala 147 002, India

EGDMA	Ethyleneglycoldimethacrylate
E-MIP	Electromagnetic molecularly imprinted polymer
FBPA	4,4′-(Hexafluoroisopropylidene)-diphenol
GO	Graphene oxide
MAE	Microwave-assisted extraction
MAM	Methacrylamide
*m*BP	Monobutylphthalate
*m*EP	Monoethylphthalate
MEPS	Microextraction by packed sorbents
MG	Macroporous gels
MIM	Molecularly imprinted microsphere
MIP	Molecularly imprinted polymer
MISPE	Molecularly imprinted solid phase extraction
MAA	Methacrylic acid
*m*MP	Monomethylphthalate
NP	Nonylphenol
4-*n*-NP	Linear nonylphenol
NPEO1 and NPEO2	Ethoxylated derivatives of nonylphenol
ONP	*o*-Nitrophenol
PVA	*p*-Vinylbenzoic acid
*p*AAm/MIP	Polyacrylamide based MIP
SBSE	Stirbar sorptive extraction
SPE	Solid phase extraction
SPME	Solid phase microextraction
TBBPA	Tetrabromobisphenol A
TBP	*p*-*tert*-Butylphenol
TCBPA	Tetrachlorobisphenol A
TCP	2,4,5-Trichlorophenol
TRIM	Trimethylolpropanetrimethacrylate
4-VP	4-Vinylpyridine

Introduction

Plastic-derived xenoestrogens are non-steroidal endocrine disruptors, which are introduced into the environment due to the production and excessive consumption of polymeric substrates [1]. They are mainly comprised of phenolic compounds, especially bisphenolic compounds and phthalate esters. Phenolic compounds and phthalates are released from polymeric or plastic materials into the environment and are capable of passing into water, air, soil, food, and living organisms. Phenolic compounds are extensively used as antioxidants in the production of polymers to control the chain growth through a free radical mechanism, whereas phthalates are mainly employed as plasticizers, softeners, and diluents in the production of plastics, rubber, styrene, cellulose, food products, packages, toys, water pipes, etc. [2–8].

These exogenous compounds interfere with the endocrine system of living organisms responsible for the maintenance of homeostasis, reproduction, development, and behavior, and hence cause hazardous effects even at trace levels. They are known for causing onset of diseases such as male infertility, kidney and prostrate diseases, and malfunctioning of the immune system in males. They are also responsible for skeletal defects, soft tissue defects, and egg shell thinning and productivity defects in avian species. In addition, bisphenol A and other xenoestrogens are known to be highly carcinogenic [9].

Due to the large chemical diversity of xenoestrogens and their metabolites, fast, reliable, and tailor-made specific analytical protocols are required for their determination in environmental samples. Commercially available solid sorbents have proved to be useful for pre-treatment but they are not designed for the selective recognition of analytes. This leads to a partial co-extraction of interfering substances. Therefore, molecular recognition is needed in order to enhance the selectivity of the extraction. This particular advantage is offered by molecular imprinting, which is capable of selectively analyzing an analyte from multianalyte systems. Molecularly imprinted polymers (MIPs) have a predetermined selectivity for a particular molecule called the template molecule. It is easy to use and cost efficient which made this technique a breakthrough. The highly cross-linked structure of these sorbents consists of micro-cavities formed after the removal of the template molecule, and can be used to absorb or adsorb the target molecule. Molecular imprinting has been used to prepare sorbents in the form of powder, mesoporous silica particles, thin films, and solid phase microextraction (SPME) fibers.

For many endocrine disruptors, including xenoestrogens, techniques employing MIPs as extraction sorbents have been successful for routine analysis [10–15]. This review surveys the current state of new monitoring strategies and challenges involved in the application of molecularly imprinted materials for the determination of plastic-derived xenoestrogens. Current trends and future perspectives in the analysis of toxins originating from the high production of chemicals and their extensive use by consumers are of priority for scientists; therefore, new horizons to achieve better results are also outlined in this review.

Background

The most commonly used sorbents are MIPs, which demonstrate very good thermal and chemical stability, and therefore can be used in aggressive and harsh media. They are of high mechanical strength and can withstand heat and

pressure. They are cost effective and economical and are capable of repeated use for extraction purposes without affecting the results. Due to these advantages, MIPs have many useful applications in sensors and enantiomeric separations, as well as in bio-medical and analytical fields. The use of MIPs as sorbents is advantageous over conventional solid surfaces because they are highly selective as compared to commercially available sorbents, and allow the preconcentration of analytes in the presence of interfering moieties. Moreover, their compatibility for chromatographic separations allows their on-line use in packed columns. Above all, when packed in SPE cartridges, they allow processing of large volumes with minimum sample manipulation.

In past years, solid phase extraction (SPE) gained the interest of researchers as an extraction technique because it offers fast and reproducible results in addition to cleaner extracts. Moreover, it eliminates the need of emulsion formation, reduces the solvent consumption, and needs small sample sizes relative to its analogous techniques. It is used with MIPs and is referred to as MISPE. There are number of reports on SPE in the literature, and therefore it is not discussed here in detail [16–25].

Conventional Synthetic Strategies

MIPs can be prepared by mixing template molecules (imprint molecule, target molecule), functional monomers, cross-linking monomers, and a radical initiator in a proper solvent, most often an aprotic and nonpolar solvent. Subsequently, this pre-polymerization mixture is irradiated with UV light or subjected to heat in order to initiate polymerization. In molecular imprinting, the template molecule can be coordinated with the functional monomer through covalent or non-covalent bonding and then polymerized with a cross-linking agent. The removal of the template molecule generates three-dimensional cavities, which are complementary in both shape and chemical functionality arrangement with the template.

Synthetic strategies for MIPs involve different methods like bulk polymerization, suspension polymerization, and precipitation polymerization [16–22]. In bulk polymerization, polymers are formed and then ground and sieved to the desired particle size (25–50 μm). This method is less time consuming due to the easy procedure, but it shows limitations due to wastage of materials, as only 50 % of it is useable. Sometimes, it also shows low capacity and poor site accessibility for the template molecule because binding sites may be destroyed in the grinding process. Secondly, the particles have irregular dimensions and morphologies, which cause asymmetric peaks in chromatographic analysis when used in an HPLC column.

To achieve a spherical shape of the molecularly imprinted particles, suspension polymerization is used, which involves the use of water to make a suspension, and surfactant to disperse the particles in a suspension. MIPs prepared with suspension polymerization possess different-sized particles depending upon the conditions used for polymerization. Use of water and surfactant during the synthesis of polymer may result in the weakening of the monomer–template interaction and solubilization of the reactants. To overcome these problems, suspension polymerization using mineral oil came into existence. This involves the formation of droplets of pre-polymerization mixtures in the oil phase and eliminates the need for a stabilizer (or surfactant) used in classical methods. This method leads to the formation of monodispersed beads of MIPs. Molecularly imprinted microspheres are also obtained by multi-step swelling and polymerization. It utilizes polystyrene seed particles to give shape to the particles. Seed particles undergo swelling by microemulsion droplets and pre-polymerization, which is followed by photo-thermal polymerization to form mono-dispersed MIPs. Again, the use of water as continuous phase interferes with the template–monomer interactions.

Precipitation/dispersion polymerization is another alternative to form microspheres. In the precipitation polymerization method, poly-dispersed particles are obtained due to polymerization in the medium whereas dispersion polymerization involves swelling in the medium. The details of the method are discussed in the next section. Table 1 summarizes the methods and materials used for the synthesis of sorbents reported for the analysis of xenoestrogens.

Challenges in Conventional Synthetic Strategies

The major challenges associated with the classical strategies used for the synthesis of MIPs are discussed below.

Incomplete Removal of Template

Conventional synthetic methods of MIPs involve the use of the target molecule as a template, but template removal always remains a challenge. Therefore, different strategies have been tried by researchers for complete removal of the template. It has been found that reports on the analysis of BPA using conventional synthetic routes for developing MIPs have been covered in the reviews published on endocrine disruptors, so to avoid repetition, these methods are not discussed in detail in the present review [1, 10–15]. A best example is the separation of bisphenol-A (BPA) by imprinted polymers prepared with phenyl methacrylate and

Table 1 Comparison of various techniques, materials, and methods used for the analysis of xenoestrogens

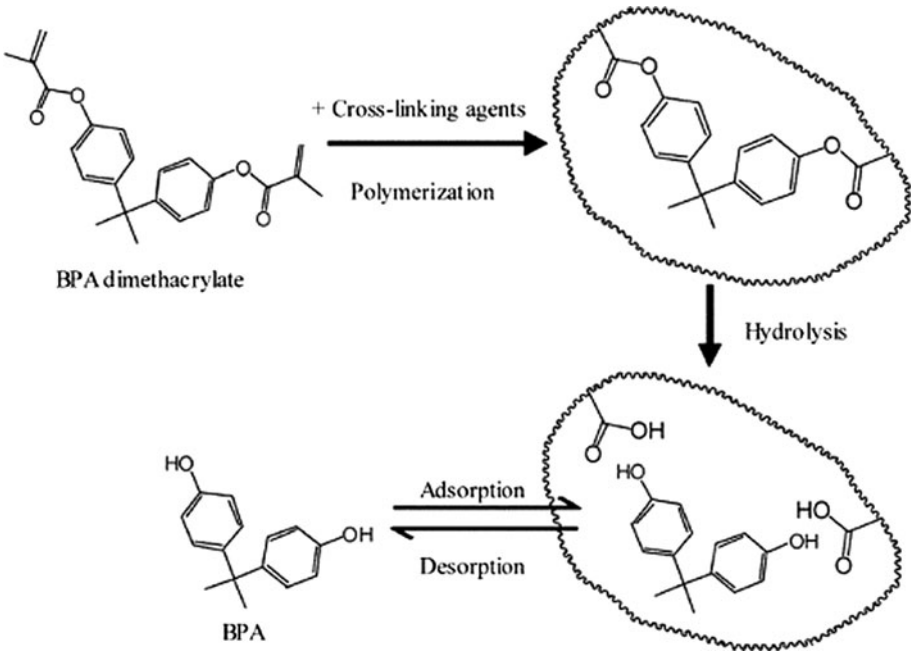
Strategy used for developing MI sorbent	Technique used	Analyte	Template	Monomer	Cross-linker	References
Bulk polymerization	MIP–SPE –SBSE– GC–SIM–MS	BPA	4,4′-(Hexafluoroisopropylidene)-diphenol	4-VP	TRIM[a]	[29]
Bulk polymerization	MISPE–HPLC	BPA, BPE, BPF, BPM, TCBPA, TBBPA, ONP, TCP	BPE	4-VP	EDMA	[31]
Precipitation polymerization	MISPE HPLC-FL	NP, 4-*n*-NP, NPEO1, NPEO2	4-*n*-NP	MAA or 4-VP	DVB-80	[33]
Bulk polymerization	MISPE–HPLC	mEP, mBP, mMP, DEP, DBP	mBP	MAA, 4-VP	EGDMA	[34]
Bulk polymerization		DEP, DBP, DPP, DEHP, DNOP, DMT, DAIP	DPP	Allyl-β-CD and MAA	AM	[35]
Bulk polymerization	MISPE GC–MS,	DMP, DEP, DBP, DAP, DNOP,	DBP	MAA, AA, MMA, AN, AM	EDMA	[36]
Water in oil suspension polymerization	MIP–SPE–GC–FID	DMP, DEP, DBP, DEHP	DEHP	MAM	MAM[b]	[37]
Macroporous gel MIP monoliths	pAAM/MBA cryogel−MISPE–RP–HPLC	BPA	4,4′-Dihydroxy-2,2-Diphenyl-1,1,1,3,3,3-trifluoropropane	4-VP	TRIM	[38]
Precipitation polymerization	MIM–MIN–HPLC	DEHP, BBP, DBP	DEHP	MAA	EGDMA, TRIM	[40]
Suspension polymeriztion	MISPE–GC–MS	DMP, DEP, DBP, DAP, DNOP	DBP	MMA	EDMA	[41]
Bulk polymerization		DMP	DMP		Styrene, DVB	[42]
Imprinted membranes	Imprinted membranes-HPLC-FL	Bisphenol A	Bisphenol A	DMA–BPA	DVB	[43]
MIP-SPME fiber	MIP–SPME–GC/MS	DMP, DEP, DBP, DAP, DNOP	DBP	MAA	EDMA	[53]
Precipitation polymerization	MEPS–LVI–GC–MS	BPA	17β-Estradiol	MMA, *p*-VBA	EGDMA	[57]

[a] 2,2′-azo-bis-(2-methylpropionitrile)

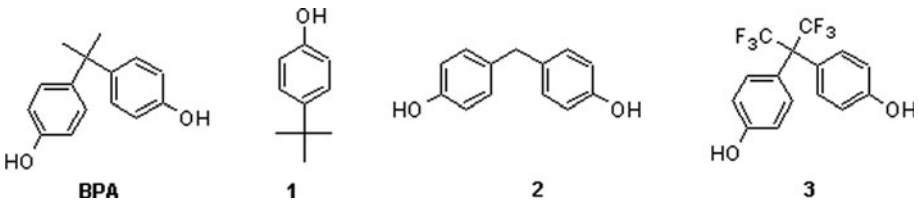
[b] Ammonium persulphate as initiator

BPA methacrylate as the template molecule [26]. In the synthetic route (Scheme 1), BPA dimethacrylate is bonded to the polymeric network through covalent bonding, which hydrolyses to form BPA and –COOH groups as active functional moieties capable of re-binding with the analyte. It is observed that the template molecule is retained in the polymer even after washing with different organic solvents, which bleed during the analysis procedures and interfere with the actual concentration of analytes. This is a major drawback as the analyte is present at ultra-low levels and the release of small amounts of the template from the sorbent may lead to erroneous results. In such cases, the use of a pseudo-template is the best alternative to cope with template bleeding. The pseudo-template is a molecule which resembles the target in structure and is separated analytically from the real target. Some of the pseudo-templates used for the analysis of BPA are shown below, and which resemble the structure of BPA (Scheme 2).

Bisphenol A has been successfully analyzed using *p-tert*-butylphenol (**1**) as pseudo-template. One of the methods describes the use of *p-tert*-butylphenol (TBP) as a pseudo-template through a two-step swelling and polymerization method. The synthesized polymer was packed in the pre-treatment column for the concentration of BPA followed by detection with ED or UV [27]. In addition, 4,4′-methylenebisphenol (**2**) was also used as a pseudo-



Scheme 1 Synthetic route for molecularly imprinted polymers using BPA dimethacrylate as template (reproduced with permission from Ref. [26])



Scheme 2 Dummy templates used for the determination of BPA; *1 p-tert* butylphenol *2* 4,4′-methylenebisphenol *3* 4,4′-(hexafluoroisopropylidene)-diphenol

template to develop MIPs by the swelling treatment of polystyrene seed polymer [28].

In another approach, 4,4′-(hexafluoroisopropylidene)-diphenol (FBPA) (**3**) was employed as a mimic template to determine bisphenol A, as their structures are very similar to each other. The presence of $–CF_3$ in a mimic template instead of $–CH_3$ of BPA makes its separation easy in HPLC [29].

Haginaka et al. [30] for the first time demonstrated the use of isotopic analogue of BPA called BPA-d^{16} as a dummy template in the preparation of MIPs. The target bisphenol analytes were then separated from the bled template by liquid chromatography–mass spectrometry (LC–MS) analysis. The MIPs synthesised in this way also have certain drawbacks, as the isotope templates are expensive and exposure to the environment may lead to secondary pollution. Therefore, the use of less toxic dummy templates is preferred in order to avoid the risk of isotopic template exposure. In a recent report, Bisphenol E was used as a template to detect a group of bisphenols because of its reduced endocrine disrupting capability, high selectivity, and high recovery [31].

Apart from choosing a suitable dummy template, extraction methods to remove complete templates have also been optimized. Garcinuno et al. reported microwave-assisted extraction (MAE) to accomplish the problem of the bleeding of the template from the polymer during elution of the sample. In this method, the temperature of the washing solvent and the MIP was maintained at 100 °C for about 20 min under standard MAE conditions. After extraction, the vessels were allowed to reach room temperature before being opened, and then their contents were transferred to a vacuum filtration system to remove the washing solvent. The process of extraction was repeated to remove the whole template from the polymer. The MIP obtained was utilized for the extraction of various analogues of diethylstilbestrol (DES) using on-column SPE [32].

Template removal also depends upon the type of interactions involved in functional monomers and templates. Sometimes, it is difficult to remove templates from MIPs prepared via covalent imprinting due to the strong binding forces. Therefore, non-covalent imprinting can be tried in the synthesis of MIPs, because it offers much more flexibility in terms of its functionalities on a template that can be targeted [33–36]. In non-covalent imprinting, the selection of a functional monomer depends upon the presence of acidic, basic, and neutral groups. It has been

shown that methacrylic acid is a monomer which interacts with the template through H-bonding, formal ion-pair formation, and sometimes weak dipole–dipole interactions. 4-Vinylpyridine is a basic monomer which possesses an electron-rich, π-electron ring system and is capable of interacting through electron-deficient aromatic rings, acid–base interactions, and H-bond formation. However, major implications for the design of non-covalently imprinted polymers arise due to the unstable and dynamically rearranged pre-polymerization complex of the template and the functional monomer. Monobutylphthalate is a metabolite of dibutylphthalate and shows interactions with the above-mentioned functional monomer through H-bonding due to the presence of a –COOH group. Therefore, MIPs prepared via non-covalent imprinting have been successfully utilized for the analysis of environmental samples [34].

Hydrophobic Interactions

A major problem arises in the ethyleneglycoldimethacrylate (EGDMA) backbone because, it is associated with the template molecule through hydrophobic interactions; therefore, interferences from other components of the matrix are observed. These interferences can be minimized by polar surface modification of the MIP, which can be achieved by two methods; the addition method and the dispersion method. In the former, the polar monomer is added at the time of polymerization, but in the latter, the polymer obtained after multistep swelling treatment is dispersed in the mixture of polar monomers to modify the surface of the polymer. Watabe et al. modified the surface of the polymer using both methods and utilized it for column-switching HPLC analysis. Surface modification achieved by the dispersion method is better as the polymer surface is modified externally as well as internally, but in the addition method, the external surface of the polymer is modified [28].

Sorbents with a methacrylate or divinylbenzene backbone impart a hydrophobic character to the polymer, and therefore these materials are not suitable for determination in aqueous medium because of the non-specific interaction observed in the monomer and the template. On the other hand, materials obtained from poly(acrylamide) and poly(2-hydroxyethylmethacrylate) show reduced non-specific interaction in aqueous media. To avoid the non-specific interactions in aqueous media, Memon et al. [37] reported the development of MIPs using methacrylamide and *N,N'*-methylene-bis-acrylamide as monomer and cross-linker, respectively (Scheme 3). The method is simple and inexpensive and proved to be much better than various bulk and precipitation methods. The MIPs so formed were applied to determine the concentrations of di(2-ethylhexyl)phthalate (DEHP) at trace levels in the environment through the MISPE technique coupled to GC-FID.

Selection of Solvent

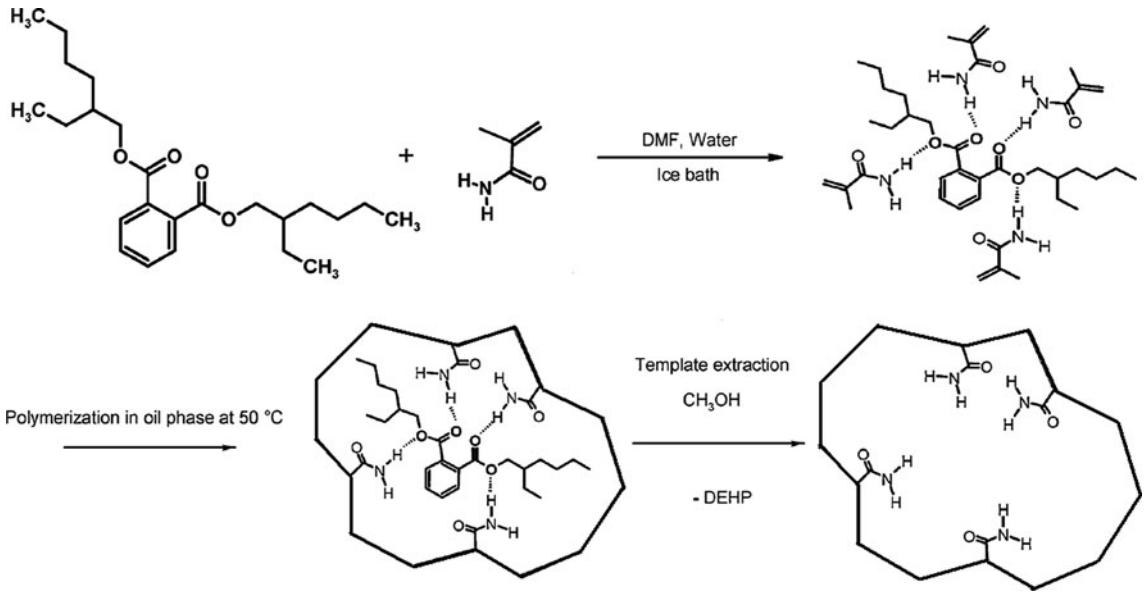
It is important to remove interference due to foreign moieties using a suitable solvent as they may lead to erroneous results. To wash the interferents from the analytical sample, acetonitrile (ACN) has been found to be a good washing solvent. ACN, being a polar but weak hydrogen bonding solvent, does not interfere with the specific template–MIP hydrogen bond interactions. On the other hand, methanol is a better elutant as it is a strong hydrogen bonding solvent and is able to break the specific interaction between the polymer and the template [29].

The effect of washing and elution solvents on both the removal of the template and the recovery of the target has also been suggested in the literature. It has been observed that organic solvents including DMSO, MeOH, ACN and MeOH/acetic acid (90:10, v/v) cause higher template bleeding than aqueous solvents. Among these solvents, MeOH/acetic acid mixture is the best eluent for removing the template as it shows the highest template bleeding due to strong hydrogen bonding, and ionic interactions between the template and binding sites on the MIP [31].

Apart from this, the nature of solvent also affects template–monomer interactions during the synthesis of the polymer. The template–monomer interactions are mainly governed by hydrogen bonding which is generally strong in nonpolar solvents. Owing to these interactions, the analyte is retained in the imprinted and non-imprinted polymer to a considerable extent. Therefore, to minimize such nonspecific interactions, it is better to use ACN and toluene in varying ratios. Higher concentrations of ACN cause complete disruption of nonspecific interactions, but the specific interactions are also simultaneously reduced [33].

Recovery of Target

The most important parameter, which decides the significance of the developed sorbent, is the recovery of the target from its surface. Turiel et al. observed during the MISPE analysis of nonylphenol and its derivatives that recovery of analytes depends upon the type of interactions involved in the monomer and the template, the size of the analyte, and the nature of the solvent used for extraction. In the reported work, different functional monomers were tried to develop the most selective MIP for the extraction of nonylphenols (NPs). It was observed that vinylpyridine-based MIPs were engaged in specific as well as non-specific interactions;



Scheme 3 A synthetic route for imprinting of DEHP in poly(methacrylamide-co–*N*,*N*-methylene-bis-acrylamide) (reproduced with permission from Ref. [37])

therefore, regeneration of polymers was difficult. Thus, it is better to use methacrylic acid as a monomer to synthesize MIP under optimum conditions [33].

Another factor on which the recovery of analytes depends is the size and chemical properties of the analyte, which has been proved in the analysis of ethoxylated derivatives of nonylphenol (NPEO2). The larger size and chemical properties of NPEO2 prevent its approach towards binding sites and reduce its recovery. Sometimes, target analytes such as NP and 4-NP compete with each other to reach binding sites. Therefore, a significant effect of size is observed in the rebinding mechanism in MIPs [33].

Cartridge Clogging

In some cases, analysis of endocrine disruptors in environmental samples encounters the problem of cartridge clogging due to high backpressure. Therefore, monoliths have been tried as alternative supports to traditional beaded sorbents. Monoliths are porous materials with low hydraulic resistance and fast separation of analytes with high efficiency. They are rigid, and consist of small as well as large pores. Cryogels are those monoliths or macroporous composite systems which consist of macroporous gel (MG) monoliths embedded with MIP particles and prepared at subzero temperatures. Porous monoliths have been used as chromatographic medium for the particulates containing fluids. One of the main features of the porous monoliths is the separation of analytes at high speed without losing column efficiency. The monoliths known as macroporous gels or cryogels typically have interconnected pores with a proper balance between the small and large pores, thus allowing liquid to flow without any resistance. These composites have been utilized for the detection of BPA at sub-ppm levels [38].

Various MG/MIP monolith systems comprised of polyacrylamide-MIP (pAAm/MIP), chitosan/MIP, and PVA/MIP were prepared by Noir et al. to analyze endocrine disruptors at low concentrations from water and waste water. Among these, pAAm-based monoliths were proved to be an appropriate stationary medium for chromatography of particulate-containing fluids. The surface area and pore volume showed a significant effect on the adsorption efficiency. The PVA/MIP was utilized for further testing, owing to its better drying and re-swelling properties, to achieve complete recovery of estradiol (E2) from waste water effluents [39].

Non-uniform Distribution of Binding Sites

Although bulk polymerization has been the most common and simple method to prepare beaded MIPs, the particles obtained in such a way possess heterogeneous binding site distribution with poor site accessibility and low mass transfer kinetic properties for the target analyte, due to irregular particle shapes, which exhibit low separation efficiency for target molecules. Thus, the production of spherical MIPs has been achieved by suspension polymerization or emulsion polymerization. These strategies use highly polar organic solvents or water, which possibly decreases the non-covalent interactions between the

functional monomer and the template during the polymerization step. Therefore, precipitation polymerization has been used as a new strategy for producing monodisperse spheres, i.e. molecularly imprinted microspheres (MIMs). The polymeric spheres formed in this way are protected from aggregation during polymerization by their cross-linker and are completely surfactant-free. In this process, both template and monomer are dissolved in porogen and the mixture is placed in a refrigerator at 0 °C for 30 min. After adding a cross-linker and initiator, the mixture is sonicated in a water bath. The mixture is sparged with nitrogen to remove traces of oxygen and then placed in a thermostat bath at 60 °C for 24 h to obtain MIMs, which, prepared by this method, have been successfully utilized to determine di(2-ethylhexyl)phthalate, which is a common plasticizer and is used to improve the flexibility of polyvinylchloride [40].

Another process for preparing MIMs is the suspension polymerization process, which is utilized for the determination of di-butylphthalate (DBP) in aqueous media. In this method, a dispersing agent and surfactant were dissolved in porogen followed by the addition of a template molecule and a functional monomer. After stirring for some time, a cross-linking agent and initiator were added to the reaction media, and the obtained solution was purged with nitrogen. Polymerization was carried out at around 60 °C in a water bath for about 10 h to get uniform-sized MIMs. The obtained microspheres possessed higher affinity for binding phthalates like DMP, DEP, DAP and DNOP as compared to NIMs, due to their structural resemblance. The sizes of DMP, DEP, and DAP were similar to DBP, which allowed the entry of these molecules into the cavities of the MIMs, whereas the introduction of DNOP was restricted due to their large size. This makes the MIMs advantageous for the evaluation of group analytes [41].

Recently, a two-step strategy for membrane emulsification of monomers followed by their polymerization in droplets of emulsion has been reported. During the first step, emulsions of monomers are obtained by means of a membrane emulsification process. The second step is typical suspension polymerization. Polymer microbeads obtained from this method possess a regular shape and very narrow diameter distribution. Membrane emulsification is the useful method for the formation of monodispersed particles with improved affinity to separate species. The use of a two-step process results in highly efficient sorbents with enhanced capacity of analyte uptake. MIP microspheres prepared from styrene:DVB (4:6) in hexane for dimethylphthalate were checked for their sorption in the presence of diethylphthalate and dibutylphthalate, but they showed highest selectivity to dimethylphthalate and are recommended for use in sorption membrane filtration hybrid processes [42].

Progress in Synthetic Strategies

Molecularly Imprinted Membranes

It has been observed that BPA levels in serum increase significantly in patients who depend on dialysis therapy, and therefore molecularly imprinted membranes were developed to recognize BPA from human blood without altering the serum composition. BPA selective membranes were prepared using hybrid MIPs (Fig. 1). These membranes bind bisphenol derivatives effectively from mixed aqueous solutions of phenol and bisphenol analogs. Hybrid molecularly imprinted membranes successfully recognized and bound BPA selectively in serum containing BPA in sub-ppb levels [43].

Molecularly Imprinted Graphene Oxides

Recently, a new strategy was reported by Li et al. to prepare highly porous surfaces developed using a graphene oxide (GO) platform to improve the affinity for binding, the diffusion barrier and mass transfer. GO–MIP can be prepared in three steps (Scheme 4). It involves the preparation of GO flakes using Hummers method, which are grafted with a RAFT agent to form GO–RAFT followed by the formation of nano-film of MIPs on the surface of the GO using surface RAFT polymerization. GO-based MIPs have been found to be highly sensitive with efficient kinetic properties. It is advantageous to use GO because it has a large surface area due to its two-dimensional structure, which in turn offers efficient extraction of the template and very high rebinding capacity. It also helps in binding the molecules on the surface of the polymer due to a high surface-to-volume ratio, which improves the kinetics and accessibility to the target species. In addition, it eliminates the problem of noise, which is a common problem in conventionally prepared polymers. These features contribute to make an attractive combination of GO–MIP, which shows higher affinity and sensitivity to the target analyte, and a more homogeneous distribution of recognition sites [44].

Magnetic Molecularly Imprinted Polymers

Previously, polymerization in molecular imprinting was initiated by adding a free radical initiator, most commonly AIBN. However, side reactions during the polymerization process results in broad size distribution and poor capacity and accessibility of the target molecule due to the uncontrolled rate of chain propagation. Reversible addition fragmentation chain transfer has been found to be most promising for controlling the polymerization, and it leads to the formation of end-capped polymeric chains. In the analysis of various analytes using MIPs, the separation of

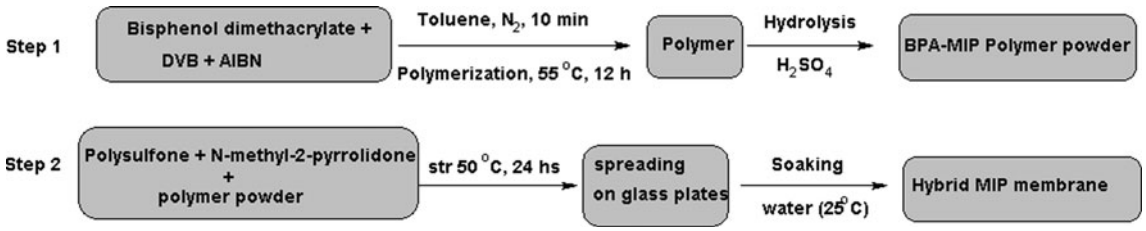
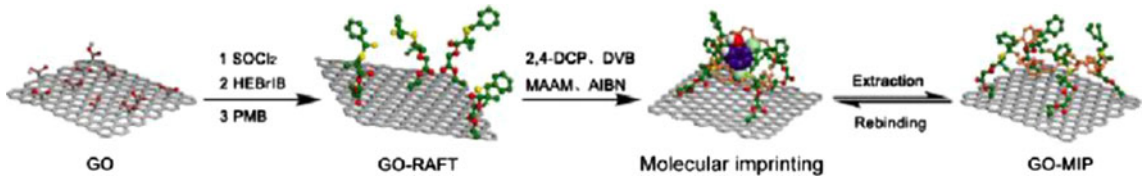
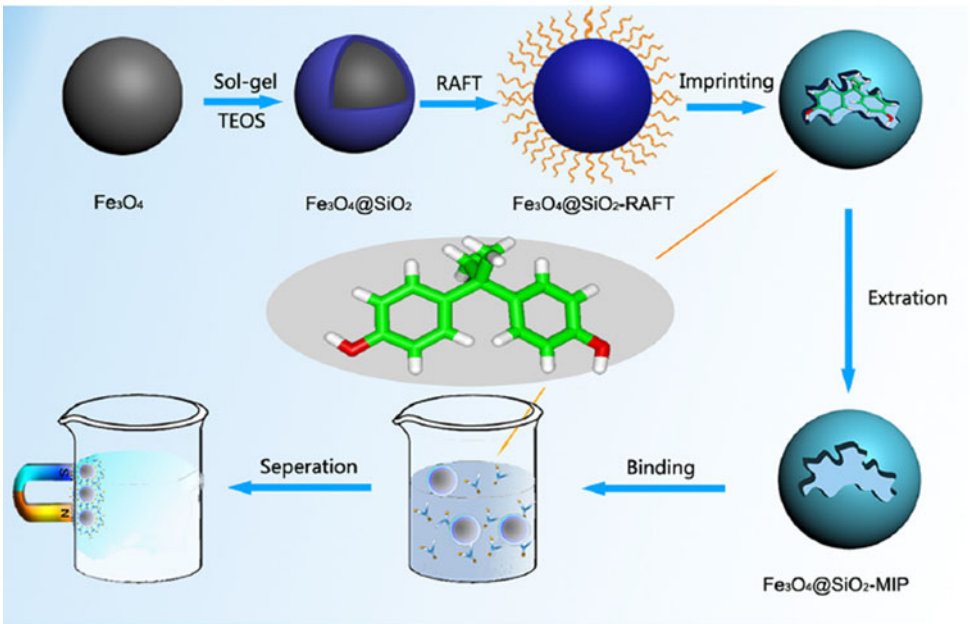


Fig. 1 Schematic for the synthesis of hybrid MIP membrane (reproduced with permission from Ref [43])



Scheme 4 Synthesizing graphene oxide-based MIP hybrids (reproduced with permission from Ref. [44])

Scheme 5 Synthesis route of surface-imprinted core–shell magnetic beads and their application for the removal of BPA with the help of an applied magnetic field (reproduced with permission from Ref. [45])



solid sorbents from the solution is also a very important step, and one way to make them separable is via synthesizing magnetic solids. They can be separated from the medium simply by applying an external magnetic field. Li et al. reported superparamagnetic core–shell beads with magnetic iron oxide covered with silica as the core and MIP as the shell have been reported using the suspension polymerization method. The magnetic beads were utilized to recognize bisphenol A from environmental samples.

Preparation of the surface-imprinted core–shell involves synthesis of Fe_3O_4 microspheres followed by the deposition of a thin layer of silica on the sphere surfaces (Scheme 5). Surface imprinting on the silica surface is achieved to make it molecularly imprinted. It is followed by the extraction of BPA and the generation of the recognition site, which leads to a surface-imprinted core–shell magnet with high affinity, selectivity, and easy separation behavior [45].

Molecularly Imprinted Biosensors

The first generation of MIP sensors was prepared by using imprinted polymers that were synthesized in the form of monoliths. The use of electropolymerization techniques for MIP synthesis is another possibility that permits the formation of ultra-thin polymer films on the surface of the electrode. The technique presents one of the most interesting methods for developing electrochemical sensors. The durability of MIPs make them useful as electrochemical sensor elements. Electrochemical sensors were first reported in the early 1990s when researchers from the

Klaus and Mosbauch group in Lund, Sweden, demonstrated the integration of a phenylalanine anilide-imprinted polymer into a field effect capacitance sensor and reported a significant reduction in the overall capacitance of the system on exposing the sensor to the template [46]. A microflow chemiluminiscence sensor has been developed for the indirect determination of dibutyl phthalate by hydrolyzing based on biological recognition materials. In the paper, a novel method for the determination of DBP using magnetic molecular imprinted polymer as the recognition element was developed [47].

Imprinting electropolymerization paved the way to improve the mass transfer, sensitivity, and accessibility of biosensors. It enabled the direct immobilization of the polymer matrix film onto the transducer's surface, allowing control over the film thickness. Advincula et al. employed anodic electropolymerization of both terthiophene and carbazole monomers to prepare electropolymerized MIPs (E-MIPs) for the detection of BPA. The effect of the copolymerization of 2-(2,5-di(thiophen-2-yl)thiophen-3-yl)ethanol and carbazole, 2-(9H-carbazol-9-yl)acetic acid was studied on the morphology of MIPs. Coelectropolymerization was achieved due to the intrinsic conductivity, stability, and processability of both the terthiophene and the carbazole monomers in both doped and neutral states. A novel protocol has been reported for sensing BPA by depositing E-MIP films based on copolymers of terthiophene and carbazole derivatives utilizing electrochemical impedance spectroscopy. An electropolymerized film forms a network film containing cavities for binding of BPA without the use of an added cross-linker [48].

Molecular Imprinting with Recent Techniques

Molecularly Imprinted Fibers for SPME

Solid phase microextraction (SPME) is a technique whereby an analyte is sorbed onto the surface of the coated silica fiber. This is followed by the desorption of the analytes into a suitable instrument such as GC or HPLC for the separation, with a suitable detector attached for quantification. Sorption of the analyte onto a suitably coated silica fiber or stationary phase is the most important stage. In spite of having numerous advantages, SPME has limited use because of the unavailability of fibers that are stable and durable in strong organic solvents. Moreover, commercially available fibers are not selective towards particular analytes; therefore, it is important to develop some polymeric fibers capable of extracting analytes selectively from multianalyte solutions [49–52].

In a recent report, SPME fiber was prepared from the molecularly imprinted polymer using dibutylphthalate as a template (DBP–MI–SPME). The MIP fiber was found to be homogeneous with good porosity (Fig. 2). DBP–MI–SPME fibers possessed special selectivity and affinity for five kinds of phthalates, namely, dimethylphthalate (DMP), diethylphthalate (DEP), dibutylphthalate (DBP), diamylphthalate (DAP), and di-*n*-octylphthalate (DNOP). Therefore, the sensitivities of phthalate determination could obviously be enhanced by the MIP-coated SPME–GC/MS method [53].

Molecularly Imprinted Polymers as Sorbents for MEPS

Microextraction on packed sorbents consists of a short LC column in a syringe in which the sample preparation takes place on the packed solid material. It is a new technique for sample preparation, which can be used on-line with LC or GC. It involves insertion of 1–2 mg of solid packing material either into the barrel of a syringe (100–250 μL) as a plug with polyethylene filters on both sides, or between the syringe barrel and the injection needle as a cartridge. MEPS was proved to be better compared with other techniques due to the following advantages [15, 54–56].

- It is better than commercial SPE because it is inserted directly into the syringe and a separate column is not required during operation.

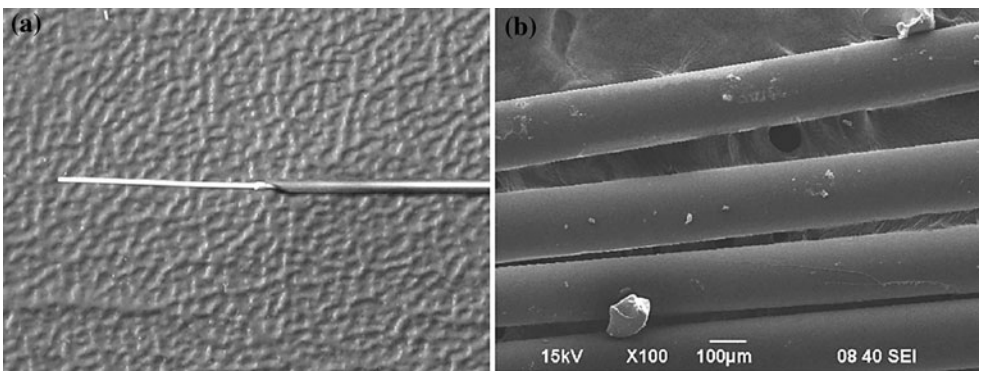


Fig. 2 **a** MI-SPME fiber. **b** Scanning electronic micrograph of MI-SPME fiber for dibutylphthalate (reproduced with permission from Ref. [53])

- The packed syringe may also be used several times (ca. 100 times) whereas conventional SPE cartridges are capable of single use only.
- It handles small (ca. 10 μL) as well as large (1,000 μL) sample volumes, and can be used for GC, LC, or CE applications.
- It reduces sample preparation time and organic solvent consumption as compared to LLE and SPE.
- It is less time consuming and can be used without major problems relative to SPME.
- It is more robust as compared to SPME, in which the sampling fiber is quite sensitive to the nature of the sample matrix.

In a recent approach, it has been used with large volume injection-in-port-derivatization–gas chromatography–mass spectrometry (LVI-derivatization–GC–MS) to determine endocrine disrupting compounds such as alkylphenols, bisphenol A, and natural and synthetic hormones in river and waste water samples. MIPs prepared by this method were found to be highly selective for the substances with estradiol-related structures. Analytes like bisphenol A, DES, and alkylphenols are not extracted efficiently by the prepared MIPs due to large differences in structure compared with the steroids. In addition, steroids, namely 19-Norethisterone or Equilin, were less selective, since the two differ in configurations from estradiols. The concentration of the target analytes found in treated waste water samples was higher than in river water, confirming waste water as a pollution source of EDCs. Hence, the successful use of the MEPS technique and its high recoverability and repeatability makes it suitable for μL detection of the analytes with reduced time and labor effort [57].

Analytical Applications

Sorbents synthesized with different strategies have been used to develop analytical methods for the evaluation of plastic-derived endocrine disruptors. The results of validation parameters of all the developed methods are summarized in Table 2. These clearly indicate that the method developed by Canale et al. [29] is highly sensitive and is able to detect BPA at ppb levels (10 ppb). It shows template bleeding due to the incomplete removal of the template in the extraction process, which may be attributed to the involvement of covalent interaction between the template and the monomer. MIMs are also found to possess good sensitivity as compared to classically synthesized MIPs. Utilization of MIMs is found to be more advantageous as they are suitable for group analysis [41].

The synthesized sorbents have also been utilized to evaluate various plastic-derived analytes from the environmental samples, such as river water, drinking water, waste water, sediments, and plant extracts under optimized conditions. All the sorbents were found to be selective with high binding capacities for the target analyte. Some of the chromatograms showing clear separation of analytes in the environmental samples are given in Fig. 3.

Furthermore, metabolites and degradation products of phthalates and phenolic compounds are as equally toxic as their parental compounds, so it is absolutely essential to determine their presence in environmental samples. As one example, long chain nonylphenol ethoxylated derivatives and their degradation products like 4-*n*-nonylphenol, nonylphenol isomeric mixtures, and short-chain nonylphenol ethoxylated derivatives contaminate sludge, which is a useful organic material for agricultural purposes.

It can be observed that laboratory-made MIP–SPE cartridges are better in selectivity of targets as compared to commercially available cartridges due to specific binding sites for interaction. One method utilizes MIP cartridges prepared in the laboratory for the analysis of spiked bottled water. The results obtained from both the developed cartridges and commercially available cartridges were equivalent for higher concentrations, but analyte recovery was less for the developed cartridges when lower concentrations were spiked. Therefore, the method is applicable to the samples having analyte concentration above 0.1 μg mL^{-1} [34]. Another method has been found to be valuable as compared to commercially available C_{18} cartridges because high recoveries of phthalates were obtained when milk samples were tested using a developed MIP. The polymer was derived from methacrylic acid and allyl-β-cyclodextrin as a monomer to selectively recognize dipentylphthalate in the mixture of phthalates. Adsorption of the template on the polymer was better than the MIPs utilized in conventional methods [35, 36]. In addition, the use of poly-acrylamide-co–*N*,*N*′-methylen-bis-acrylamide cryogels with imprinted particles prevents the clogging of the cartridges and is suitable for complex matrices. Therefore, it has been found useful for evaluating bisphenol A from diluted river water and wine samples [38].

Detailed analytical data for the evaluation of targets using GO–MIP and electropolymerized sorbents is not available, but as far as the selectivity of targets is concerned, these MIPs are highly selective and GO–MIPs can be further used as building blocks for nanoelectromechanical devices [44]. In addition, molecularly imprinted membranes may be applicable for the removal of BPA from blood medium, and may be suitable for artificial heart–lung or hemodialysis therapy [43]. Apart from this, surface-imprinted core–shell magnetic beads have also been utilized for the analysis of BPA in spiked drinking water samples. The selectivity, high affinity, and easy separation of the sorbent from the sample make them efficient sorbents for the analysis of environmental samples [45].

Table 2 Validation parameters for developed methods

Analyte	MIP–SPE -SBSE- GC-SIM-MS	Linear range (μg $L^{-1)}$ (regression constant)	LOD (μg mL^{-1}) [LOQ (μg mL^{-1})]	Precision (% RSD)	Accuracy (% recovery)	Real sample analyzed	References
BPA	MISPE–HPLC	(0.9969)	10 pgL^{-1} [1,000 ng L^{-1}]	4.6–10.1	90.2–99.8	River water	[29]
BPA, BPE, BPF, BPM, TCBPA, TBBPA, ONP, TCP	MISPE HPLC-FL	0.02–2.0 (0.998)	2.5–5.0 ng L^{-1}	15	63.0–94.0	River water	[31]
NP, 4-*n*-NP, NPEO1, NPEO2	MISPE–HPLC	NR	1.6–4.74 mg kg^{-1}	2–14, 6–8	60.0–104, 65.0–110	Sediment and sludge	[33]
mBP		0.05–10 (0.9995)	0.0165 μg mL^{-1}	7.8–11.1	61.9–82.8	Bottled water	[34]
DEP, DBP, DPP, DEHP, DNOP, DMT, DAIP	MISPE GC–MS	(0.9990–0.9997)	NR	NR	62.7–93.7	Cow milk	[35]
DMP, DEP, DBP, DAP, DNOP	MIP–SPE–GC-FID	(0.9871–0.9941)	0.013–0.022 μg mL^{-1} [0.040–0.056 μg mL^{-1}]	1.20–6.83	85.6–100	Soybean milk	[36]
DMP, DEP, DBP, DEHP	pAAM/MBA cryogel–MISPE–RP–HPLC	0.035–3.0 (0.9998)	0.011 μg mL^{-1} [0.035 μgmL^{-1}]	0.0168–4.799	95.0–99.3	River water	[37]
BPA	MIM–MIN–HPLC	NR	10 ng L^{-1}	NR	75.0–125	River water	[38]
DMP, DEP, DBP, DAP, DNOP	MISPE–GC–MS	0.05–10 (0.9941–0.9991)	0.00549–0.0216 μg L^{-1}	2.9–7.3	85.2–104.5	River water	[41]
DMP, DEP, DBP, DAP, DNOP	MIP–SPME–GC/MS	0.01–10 (0.9898–0.9993)	2.17–20.84 ng L^{-1} [0.02–0.34 μg L^{-1}]	1.50–5.31	94.5–105.3	Reservoir water	[53]
BPA	MEPS–LVI–GC–MS	NR	1.3–2.2 ng L^{-1}	4–22	81.0–103	Treated waste water and river water	[57]

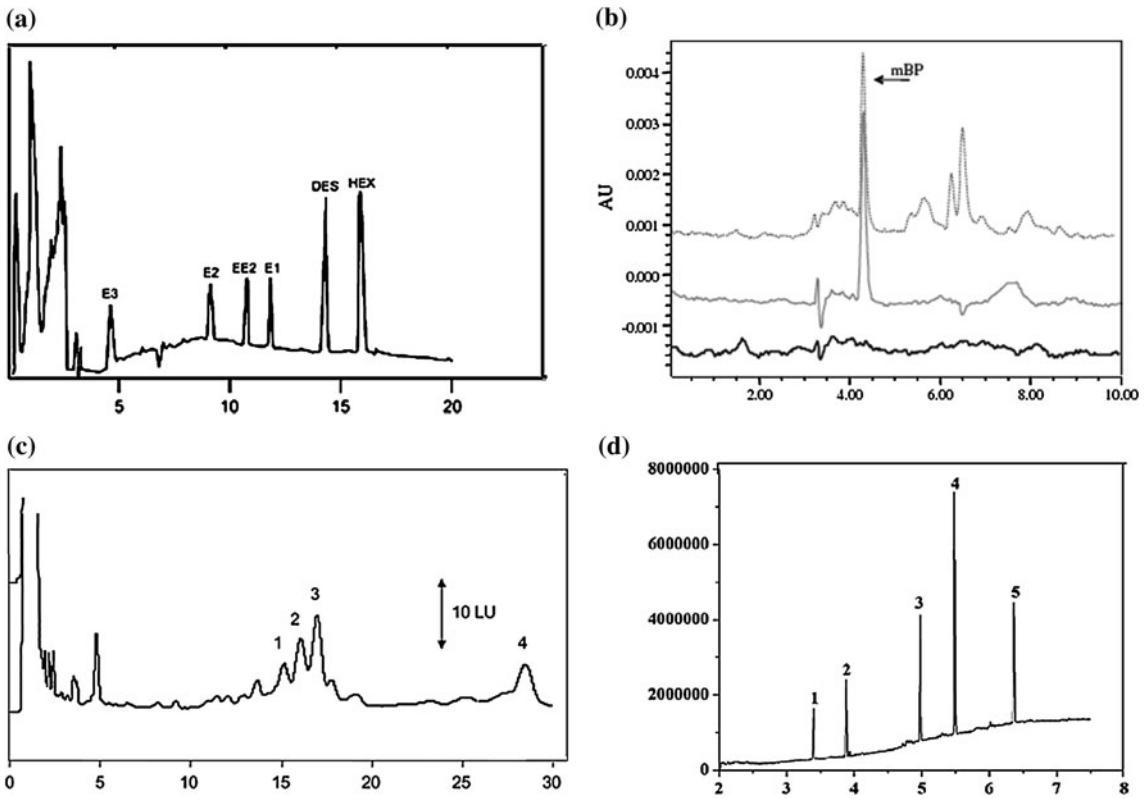


Fig. 3 Analysis of various environmental samples for plastic-derived endocrine disruptors; **a** river water; **b** sludge; **c** bottled water; **d** soybean milk (reproduced with permission from Ref. [31–34, 36])

Combinations of suitable techniques with MIPs give additional advantages to the method. It has been seen in the past that the use of column switching auto-pre-treatment using MIPs was successful in achieving better results. Basically, the column-switching concentration consists of a pre-treatment column attached to a HPLC column via a six-port flow change-over valve. It is an automatic pre-treatment technique and eliminates the need for manual pre-treatment of the sample using classical methods like evaporation or for transference between glassware, which may contaminate the samples [27]. Similarly, the multi-stir bar sorptive extraction (SBSE) single desorption procedure using MIPs involves the introduction of the analyte solution into a glass vial coated with the polymeric material followed by stirring of the solution using a magnetic bar for about 30–120 min. This results in the sorption of the analytes onto the polymer surface, which are then desorbed in a suitable solvent for analysis. The results obtained were found to be successful as compared to conventional stir bar sorptive extraction coupled to gas chromatography mass spectrometry (SBSE–GC–MS), due to the selectivity, simplicity, and repeated use of the MISPE cartridge. The results showed that the imprinted polymer retains FBPA more than does the target molecule BPA, while Bisphenol C, which only differs in having a methyl group in the ortho position to phenolic hydroxyls, is poorly recognized [29]. Among the recent techniques, MIP–SPME and MIP–MEPS combinations are proving highly sensitive due to detection limits at sub-ppb levels, and have also been found to be suitable for group analysis.

Future Perspectives

The enhanced possibilities for the analysis of plastic-derived xenoestrogens and their transformation products have brought new, unregulated compounds under scrutiny, which had not previously been considered. So the choice of the described compound classes in this review can be extended much further, and it is expected that transformation products and metabolites of the parent compounds will be emphasized in future research.

However, most monitoring methods suffer from bleeding and problems associated with the monomer–template interaction. Their use for the analysis of xenoestrogens present in waste water is also limited due to blockage of the cartridges. Therefore, their use has been restricted to a few preselected compounds, and very often is insufficient to assess the quality of water, since analytes that might be a

threat to the environment and human health are present at ppb or ppt levels.

Monolithic silica has recently found much efficient in the field of rapid separation, since it allows the use of elevated flow rates without the generation of excessive backpressure. In addition, sorbed analytes remain as sharp bands within the column, undergoing less band broadening than seen with many traditional particle-packed columns. These characteristics make short monolithic phases very suitable for rapid sample extraction at high loading flow rates, while maintaining high extraction efficiencies and sharp adsorbed analyte bands, as required for on-line elution onto analytical separation columns.

The development of high surface area molecularly imprinted polymers is still needed to achieve the confidence of potential users. To accomplish this aim, graphene oxide is a good platform for developing MIPs and can achieve better analytical data quality and technical characteristics. In addition, the development of nanospheres has also explored the potential of MIPs in this field.

Furthermore, the possibility of using molecularly imprinted polymers capable of direct use in aqueous samples will produce more applications with respect to speciation from synthetic samples prepared in organic solvents. Nevertheless, a proper extraction technique is required for the successful application of tailor-made sorbents. So far, MI-SPE is the most widely used technique for analytical determination of xenoestrogens in environmental samples. The technique is advantageous due to its automation, sensitivity, selectivity, accuracy, reliability, high throughput, and minimal sample manipulation. There is thus a growing interest in new techniques which are capable of detection at sub-micro levels. For this purpose, development and optimization of SPE and SPME extraction parameters will add new horizons to the research in the field of xenoestrogens. SPME and MEPS, which allow the efficient determination of the analytes and facilitate the elucidation of micropollutants in environmental samples, are the more powerful techniques. So far, however, the applicability of MI-SPME and MI-MEPS in the field of xenoestrogens has been limited. Nevertheless, these techniques have already been efficiently applied to pesticides, metal ions, drugs, and explosives, which are present at sub-micro levels. Using on-line SPME and MEPS with molecularly imprinted sorbents to improve the sensitivity of the method has been explored for the determination of phthalates.

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