# Selective removal of contaminants of emerging concern (CECs) from urban water cycle via Molecularly Imprinted Polymers (MIPs): potential of upscaling and enabling reclaimed water reuse

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## Abstract

Contaminants of emerging concern (CECs) are one of the main barriers in the water cycle as they limit the water reuse due to their adverse effects on humans and the ecosystem. Natural and/or engineered ecosystems, such as conventional wastewater treatment processes, are not designed to remove CECs and contribute to the bioaccumulation in organisms considering high volumes of treated water discharges. The adoption of innovative solutions to upgrade urban water cycle facilities has gained relevance for the removal of these substances from final effluents. Molecularly imprinted polymers (MIPs) show promising selective removal toward a wide range of CECs. However, this solution is still limited to lab/bench scale and needs to be critically analyzed and assessed for possible scale-up in real environment. Therefore, in this review, an overview of the fate and occurrence of CECs in wastewater is initially reported together with the state-of-the-art in adsorption mechanisms to remove these compounds. In the central part of the paper, an evaluation of MIPs synthesis and their status in removing CECs from water matrix are presented. An upscaling pathway of MIPs column from lab- to pilot-scale is given to be applied for enhanced CECs removal and safe water reuse in irrigation/fertigation. Finally, possible integrations of MIP columns to real wastewater treatment facilities is discussed and advantages and disadvantages of the potential solutions are addressed to enhance their sustainability.

**Keywords**: adsorption; contaminants of emerging concern (CECs); molecularly imprinted polymer (MIP); tertiary wastewater treatment; upscaling; water reuse

## 1. Introduction

Agriculture practices, industrial discharges, and everyday activities play an important role in releasing pollutants via wastewater. These practices generate various organic contaminants which alter the water cycle causing a global concern linked to their eventual impact on wildlife and human health [1,2]. In recent years, many articles have appeared reporting the presence of new compounds, called "contaminants of emerging concern (CECs)", in wastewater and aquatic environments. The United States Environmental Protection Agency (US EPA) defines CECs as new chemicals which impact on the environment and human health is poorly understood [3]. These CECs, natural or synthetical, can be found in water and wastewater treatment plants (WWTPs) in low concentrations, in the order of µg or ng per liter, but with the risk of contaminating and accumulating in the environment [4]. The ecotoxicological effects, fate, and behavior of CECs are not well understood, as they are not presently included in an international regular monitoring program [5,6]. The NORMAN project, established in 2005, is one of the largest world's classified records of CECs occurring in the environment with over 1036 CECs together with their by-products and metabolites. These can be further categorized in 30 classes based on their origin and type such as pharmaceuticals, pesticides, plasticizers, hormones. All these compounds may generate high risks to human health due to their bioaccumulation in the fatty tissue, while biomagnification can give rise to undesirable long-term effects [3].

Most of these micropollutants are sent to conventional WWTPs where only a partial removal is obtained by stripping, adsorption and/or biological degradation. This is mostly due to the complex structure and chemical heterogeneity of the CECs as well as to the predicted no effect concentration since conventional treatment units/processes are not designed to remove CECs, while even at very low concentrations they are discharged in final effluents and accumulate in aquatic organisms and adversely affect growth and reproduction [7]. Conventional secondary processes (i.e. activated sludge and trickling filters) represent the most extensively used and studied processes in WWTPs. However, these processes are not designed to remove CECs resulting in their discharge to receiving surface waters [8]. Alternative treatment options must be considered for selective CECs removal such as advanced oxidation processes, nanofiltration and reverse osmosis membranes [1,9]. However, most of these methods require high investment and maintenance costs, complicated procedure for the wastewater treatment and sometimes cause secondary pollution due to the formation of oxidation by-products, which in some cases might be more toxic than the initial compound. Moreover, physicochemical treatments such as coagulation and flocculation processes are generally unable to remove endocrine disrupting compounds (EDCs), pharmaceuticals and personal care products (PPCPs). Conversely, adsorption processes do not add undesirable by-products and can be considered superior to other techniques in wastewater treatment in terms of simplicity of design and operation [10].

The demand for finding local solutions and using non-conventional water resources has been increasing, especially in water-scarce areas like the Mediterranean Region where the lack of good quality of irrigation water is already limiting the agriculture [11]. The greatest challenge in this scenario is represented by the adoption of low-cost wastewater treatment technologies in these areas and ensuring compliance with all health and safety standards regarding the reuse of treated wastewater effluents. At this point, non-conventional adsorption technology based on molecularly imprinted polymers (MIPs) represent a valid tool to remove selectively one or more specific target molecules in the wastewater and surface water cycle. MIPs, obtained through a radical polymerization synthesis, are characterized by highly selective sites or cavities with a specific affinity for a target molecule, since they are capable to imitate the complex mechanisms typically occurring between antibodies and biological receptors [12]. These polymers have high mechanical properties and can be used in a wide range of applications and with different types of matrices such as biological fluids or aqueous environmental solutions. The peculiar properties of MIPs, that will be discussed in Section 4, make them very interesting tools in different areas of application, including separation and purification methods [13,14], sensors and biosensors [15,16], catalysis [17], and drug delivery [18–20]. In the last decade, many studies reported  the synthesis and the application of MIP technology to the removal of a wide range of CECs such as diclofenac, ketoprofen and ibuprofen (non-steroidal anti-inflammatory drugs, NSAIDs), ciprofloxacin and sulfamethazine (antibiotics), triclosan and parabens (PCPs), bisphenol A (plasticizer) and atrazine (pesticide), from water and/or wastewater with high removal performances [21,22]. Up to date, MIP columns have been successfully implemented in the CECs removal from the water matrix, for pre-treatment analytical measurements but only at the lab-scale [23–25], whereas its implementation in WWTPs has yet to be considered. If MIPs features such as particles and pores size, possibility of regeneration for multiple times, high affinity and mechanical and chemical resistance are considered, it is evident that MIP columns have high potential to be integrated in urban water cycle facilities especially in small-scale decentralized WWTPs designed for water reuse. In most cases, effluent water from these innovative wastewater treatment configurations have such a high quality to comply with the minimum requirements for irrigation; but the presence of CECs may strict its potential for reuse. At this point, adsorption columns using MIPs as an advanced treatment may help to overcome this problem and thus to close the water loop in the water-scarce regions by enabling reclaimed water reuse.

In this review paper, a detailed overview of the most common CECs found in wastewater and the current status of their removal techniques from water matrix is initially provided. The adsorption mechanisms of MIPs for enhanced CECs removal from water/wastewater are further presented with their specific applications. Since the up-to-date applications of MIPs are limited to lab-scale, we provide the basic but crucial steps to follow while considering to upscale MIP adsorption columns to pilot scale. Furthermore, innovative ways to integrate MIP columns to real wastewater facilities are introduced with possible demonstrative-scale proposals to ensure the safe reuse of treated effluent for irrigation with respect to the minimum requirements for water reuse of the European Parliament and of the Council [26]. Benefits and drawbacks of the application of MIPs to remove CECs from wastewater are then discussed and possible solutions are presented to enhance the sustainability of MIPs in water reuse systems. The highlights of this paper can support decisions towards further development of MIPs in removing CECs from water environment.

## 2. Contaminants of emerging concern

CECs, also known as emerging compounds [27], are natural or synthetic chemicals together with their transformation products, frequently detected in water bodies, which are not commonly or only partially monitored in the environment. CECs may cause environmental damage and suspected harmful effects on the ecosystem and human health [3]. The steady release of CECs to the environment has been predicted to be occurring for a long time and through diverse sources [28] with concentrations ranging from μg to ng per liter. The list of compounds and chemicals in the CECs group are significantly large and ever-expanding with the introduction of new commercial chemicals, changes in use, and disposal of chemicals currently in widespread use and further identification of new molecules [29]. Since conventional WWTPs are not designed to remove this wide range of molecules, many of these remain in considerable concentration in the effluents, and subsequently in the surface waters [4]. As shown in **Fig. 1**, many CECs, such as atrazine (pesticides), diclofenac (NSAIDs), propanolol (β-blockers), ethynilestradiol (estrogens), and ciprofloxacin (antibiotics), are characterized by low removal rates in WWTPs and this fact underlines the importance of studying these compounds in depth. However, as highlighted by Ben et al. [30] , the type of treatment used in the plant can be favorable for one or more categories of CECs with respect to the others. Moreover, in some cases, by-products that are still harmful to the environment and human health can be formed in these processes as in oxidative treatments. In this section, four main categories of CECs are reviewed that received a particular interest for their frequent presence in water bodies.

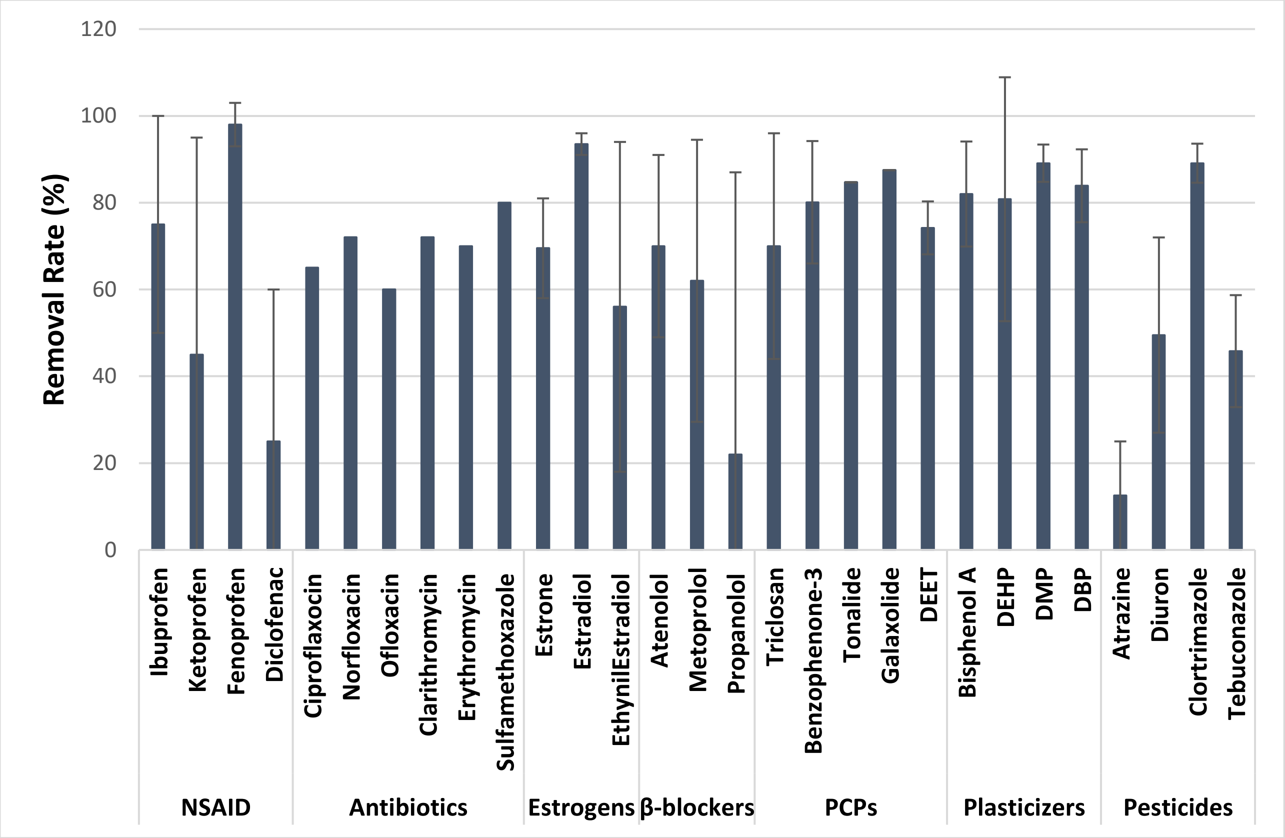

**Fig. 1.** CECs removal rate in percentage by WWTPs [4,30–33].

### 2.1. **Pharmaceuticals**

Pharmaceuticals represent one of the most critical environmental issues for industrialized countries, due to their widespread use in the treatment of diseases, injuries, or illnesses on humans and veterinary [34,35]. Pharmaceutically active compounds, contained in drugs and medicine, are complex molecules with different functionalities and physicochemical properties to have specific biological activities. Due to their huge number, these compounds are classified in several subclasses, but in this review, emphasis will be given to those categories which are most detected in urban water and wastewater [33].

Non-steroidal anti-inflammatory drugs (NSAID) are the most used compounds for pain relief; NSAID-type CECs are often detected in surface water and compounds like ketoprofen, ibuprofen, naproxen, paracetamol, diclofenac, and mefenamic acid are particularly resistant to conventional wastewater treatment methods which are not very effective in their removal [36]. Hormones and estrogens are considered an important emerging contaminant due to their directly disrupt effects on the endocrine systems and long-term persistence of living organisms [37]. Respect to other estrogens, 17α-ethinylestradiol is a common female oral contraceptive with endogenous activity [38,39], usually present in wastewater and particularly difficult to remove. Antibiotics are complex organic molecules used for the inhibition and elimination of pathogenic bacteria. The compounds most frequently identified in the environments are amoxicillin, ciprofloxacin, erythromycin, and penicillin [40].

### 2.2. Personal Care Products

PCPs is a common term used to indicate several products, which can be found and bought without a prescription in health, beauty and drug department stores. The most used CECs in PCPs are organic UV-filters, preservatives and fragrances. The substances in PCPs are generally conjugated to other drugs and pharmaceutical contaminants as in the case of antidandruff shampoo [41]. Among the most detected PCPs in surface water [42], parabens has to be considered; they are chemicals used as preservatives in cosmetics and pharmaceuticals [43]; also triclosan is another compound widely used as an antimicrobial in soaps, deodorants, skin creams, toothpaste, and plastics [44] and commonly detected in surface water [41,45]. Many of these pollutants can enter the organisms through direct ingestion or by absorption through the skin where they can bioaccumulate thanks to their lipophilic nature, are excreted through urine or simply removed by washing them off [46], and eventually end up in aquatic and/or soil environments.

### 2.3. Plasticizers

Plasticizers consist of clear colorless, oily liquids of low molecular weight generally used as additives to improve flexibility or distensibility to facilitate material handling in the processing and formulation of finished products [47,48]. Based on their chemical structure, plasticizers can be divided into diverse categories [49]; among them, phthalates received a lot of attention due to their wide use and release in water bodies. They are esters of phthalic acid containing a benzene ring with two functional ester groups such as in diethylhexyl phthalate (DEHP), diethyl phthalate (DEP), and dibutyl phthalate (DBP) [50]. Due to their relatively low molecular weight, phthalates can easily migrate and spread into the environment; moreover, because of their lipophilic nature, phthalates can pass through natural barriers such as skin, lung and gut tissue of humans with the consequences of bioaccumulation and biomagnification [51,52].

### 2.4. Pesticides

Pesticides constitute any mixture of substances that can prevent, destroy, repel, or mitigate a pest; in which fungicides, herbicides, bactericides, and insecticides are the main categories [53] that can be found as pesticides contamination through surface runoff from agricultural areas and wastewater in urban areas [54]. Based on the chemical structure it possible to recognize many sub-classes [55], such as organochlorines (including aldrin and DDT), organophosphates (diazinon and malathion), carbamates (carbaryl and propoxur), triazines (atrazine), and chloroacetamides (metolachlor and alachlor). Unfortunately, since pesticides are stable in the environment, as in the case of organochlorines which have a long environmental half-life, they bioaccumulate in the food chain, and the extensive use of these substances easily cause poisoning through various toxicity mechanisms. Their application in the liquid form contaminates the environment more than their application as a powder [56].

## 3. Adsorption mechanism of CECs

Advanced treatment technologies have been developed over time to reduce the adverse impacts of pollutants in the environment, such as adsorption, biological, and oxidation processes. Adsorption processes, capable of moving contaminants from one phase (liquid such as water) into another (as solid), have been widely used in the removal of CECs [29,57]. The adsorbing material is called the adsorbent or sorbent, while the substances being adsorbed are the adsorbates; their properties and the interactions occurring between them are quite specific and depend on their composition and chemical nature [58]. The adsorption mechanism involves intermolecular transfer of contaminants onto the solid surface of the sorbent upon physical or chemical interactions. In the physical adsorption process, different types of interactions such as electrostatic, hydrogen bonds, steric, π–π stacking, Van der Waals forces, and dipole induced dipole interactions are involved. Otherwise, during chemisorption processes, the pollutants are adsorbed through chemical covalent bonds established with the sorbent. Once adsorbed, contaminants are hardly removed from the sorbent which cannot be easily regenerated because of strong forces between them. Chemical adsorption commonly occurs between metallic ions and adsorbents that have several functional groups, whereas for organic contaminants, the main mechanism of interaction would be physical [59]. However, the two processes can occur alternatively but also simultaneously, depending on the type of technology used.

### 3.1. **Definitions and models**

In a solid-liquid system, adsorption results in the removal of contaminants from the solution and their accumulation on the solid surface until saturation of the adsorbates capacities; after a certain time of contact, a dynamic equilibrium between the analytes in solution and the analytes adsorbed on the solid phase is established [60]. The relationships between mass of adsorbate adsorbed per unit weight of adsorbent and liquid-phase equilibrium concentration of adsorbate are represented by adsorption isotherms. Several adsorption isotherms were developed and proposed to describe the specific interactions between them, such as Langmuir [61], Freundlich [62], Sips [63], Redlich-Petersen [64] and others. Among these, the most used models to describe adsorbents material in water and wastewater matrices are Langmuir and Freundlich; these isotherms are considered also for Molecularly Imprinted Polymers, even though the adsorption characteristics of these polymers are often estimated from the Scathcard equation [65]. In fact, the Scatchard plot analysis allows to have further information on the affinity of binding sites of MIPs toward each target molecules which can be selectively adsorbed (Eq. 1). The Langmuir adsorption model (Eq. 2) is the simplest one and can be applied when a single adsorbate is adsorbed by a series of energetically equivalent sites on the homogeneous surface of the solid, as in the case of chemisorption process. Otherwise, Freundlich isotherm (Eq. 3), is applicable to adsorption processes that occur on heterogenous surface [66]. The three isotherms model are reported below:

$$\frac{q_e}{C_e} = (q_m - q_e)K_d \quad (1)$$

$$q_e = \frac{q_m K_l C_e}{1 + K_l C_e} \quad (2)$$

$$q_e = K_f C_e^{1/n} \quad (3)$$

where $C_e$ (mg/L) is the concentration of the analyte at the equilibrium, $q_e$ and $q_m$ (mg/g) is the mass of adsorbate per unit mass of adsorbant material, at the equilibrium and at maximum adsorption, respectively; $K_l$ is the Langumir consant (mg/g), $K_f$ is the Freundlich costant (mg/g) and 1/n is the exponent of non-linearity; $K_d$ is the Scatchard constant. The main characteristics of the Langmuir isotherm can be expressed by a dimensionless constant called the separation factor ($R_L$), Eq. (4):

$$R_L = \frac{1}{1 + K_l C_0} \quad (4)$$

where $K$l is Langmuir constant (mg/g) and $C_O$ is initial concentration of adsorbate (mg/L). Depending on this value, the process is defined unfavorable (when $R_L > 1$), linear (when $R_L = 1$), favorable (when $0 < R_L < 1$), and irreversible (when $R_L = 0$).

A correct understanding and interpretation of the adsorption isotherms is fundamental for a correct interpretation of the relationship between the sorbent material and the adsorbates. The use of the adsorption models can provide a valuable tool to describe molecular recognition by MIPs. Such models may be critical in better understanding MIP behavior in complex systems where more than one adsorbate may simultaneously interact with the surface. In a recent study [67] , four isotherm models (Langmuir, Freundlich, Langmuir-Freundlich, and Brunauer Emmet and Teller (BET) were used to characterize the binding behavior of MIPs in the adsorption of five different phenolic compound: phenol (Ph), 2-methylphenol (2-MP), 3-methylphenol (3-MP), 2-chlorophenol (2-CP), and 4-teroctylphenol (4-OP). Even if MIPs tended to be nearly homogeneous and to have well defined binding sites, in this case the MIP has not only one type of binding site, but similar binding sites in terms of shape and active functionality which are involved when interacting with a given adsorbate. In fact, the Langmuir and Langmuir-Freundlich models gave the best fitting statistics for Ph, 2-MP, 3-MP, and 2-CP, whereas the recognition of the bigger and more hydrophobic 4-OP was explained only by the BET model, which implies the formation of multilayers adsorption sites; in this latter model the adsorption is based on the assumption that the energy of interactions between the adsorbing species and the surface is strongest in the first layer and decreases for subsequent layers deeper in the polymer matrix.

### 3.2. Removal of CECs

Many factors affect the adsorption process in a specific real case: surface area, nature and initial concentration of the analytes, temperature, pH solution, nature and amount of adsorbate. In order to remove CECs commonly found in wastewater, tertiary treatments must be implemented with sorbent material of different types. Removal efficiency and adsorption capacity of most common sorbents are summarized in **Table 1**.

Activated carbon (AC) is the most popular and widely used adsorbent in WWTPs. AC, prepared form various sources (e.g. coal, coconut shells, lignite, wood, etc.), is a charcoal physically and chemically treated to increase its adsorptive properties. The inorganic contents, after the pyrolysis process of the organic matter with oxidizing gases, are efficiently extracted from the carbonized material to produce powder (PAC) or granular particles (GAC) with high surface area [68,69]. AC has been considered as an effective adsorbent for treating persistent/non-biodegradable organic compounds such as CECs.

Biochar (BC) is a stable source of carbon obtained from biomass, by thermal or hydrothermal processes at high temperature with low or zero oxygen atmosphere, even if according to many authors it is difficult to distinguish BC from AC [70,71]. Similar to AC, BC can be further chemically activated through an acid or basic process which leads to the formation of new functionalities on the surface of the sorbent to enhance the interactions with the contaminants and to increase their adsorption [70,72].

Carbon nanotubes (CNTs) are carbon allotropes with a graphite-like structure which displays different adsorption characteristics depending on the degree of coil, the generation of the original sheet, diameter, internal geometry, physicochemical properties and the treatment process used for synthesis [73].

Clay minerals are well known natural materials with plastic properties, particles less than two micrometers composed mainly of hydrous-layer silicates of aluminum, though occasionally they may contain magnesium and iron. Because of their low cost, high porosity, and abundance in the environment, clays such as montmorillonite, mica, kaolinite, pyrophyllites (talc), bentonite, and diatomite are good candidates as adsorbents [10]. Numerous other sorbents have also been reported in the literature for removing CECs from water matrices including zeolites, metal oxide, graphene oxide, and polymeric resins [65,74,75]. In this regard, MIPs can be a valuable alternative sorbent thanks to their high selectivity to bind target molecule and their flexibility to couple with different materials to exploit synergic properties, as in the case of MIPs having a core shell of $TiO_2$ particles, obtained through a surface polymerization, used to remove and photocatalytically degrade the fungicide orto-phenylphenol [76].

**Table 1.** Removal efficiency and adsorption capacity of different sorbents.

| Matrix | Category | Adsorbent | Sorbent dose (mg/L) | Contaminant | Type of interaction | Isoterm models | Adsorption capacity (mg/g) | Removal (%) | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Hospital Wastewater | Active Carbon | PAC | 8, 23, 43 | Diclofenac | | | | 96, 98, 99 | [77] |
| | | | | Carbamazepine | | | | 98, 99, 100 | |
| | | | | Propanolol | | | | 91, 94, 94 | |
| | | | | Ciprofloxacin | | | | 10, 99, 99 | |
| | | | | Sulfemathoxazole | | | | 0, 34, 40 | |
| Acqueous Lab scale | | PAC | 10.04 | Ibuprofen | van der Waals, π-π stacking and hydrogen bonding | Based on the Langmuir and Freundlich model isotherms | 12.6 | 70 | [78] |
| | | | 19.20 | Ketoprofen | | | 24.7 | 88 | |
| | | | 19.78 | Naproxen | | | 39.5 | 90 | |
| | | | 19.28 | Diclofenac | | | 56.2 | 91 | |
| | | GAC | 1000 | Triclosan | | Langmuir isotherm | 41.5 – 18.5 | | |
| Acqueous Solution | Biochar | Acid rice husk | 5000 | Tetracycline | π-π stacking | Langmuir isotherm | 12 | | [79] |
| | | Alkali rice husk | 5000 | Tetracycline | | | 29 | | |
| Acqueous Solution | | N-biochar | 2000 | Diclofenac | π-π stacking | Langmuir isotherm | 231 | | [80] |
| | | | | Naproxen | | | 155 | | |
| | | | | Ibuprofen | | | 25.3 | | |
| | | O-biochar | 2000 | Diclofenac | | | 124 | | |
| | | | | Naproxen | | | 147 | | |
| | | | | Ibuprofen | | | 14.6 | | |
| Acqueous Solution | Carbon Nanotube | MWCNT (0$_2$=2,0%) | | Tetracycline | | Langmuir isotherm | 217.8 | | [81] |
| | | MWCNT (0$_2$=3,2%) | | | | | 269.25 | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | MWCNT ($0_2$=4,7%) | | | | | 217.56 | | |
| | | MWCNT ($0_2$=5,9%) | | | | | 210.43 | | |
| Acqueous Solution | | MWCNT ($0_2$=2,0%) | | Ciprofloxacin | | Langmuir isotherm | 150.9 | | [82] |
| | | MWCNT ($0_2$=3,2%) | | | | | 178.9 | | |
| | | MWCNT ($0_2$=4,7%) | | | | | 206 | | |
| | | MWCNT ($0_2$=5,9%) | | | | | 181.2 | | |
| Acqueous Solution | | SWCNT | 1000 | Ibuprofene | | | 231 | 100 | [83] |
| | | MWCNT | | | | | 81 | 100 | |
| | | O-MWCNT | | | | | 19 | 97 | |
| | | SWCNT | 1000 | Triclosan | | | 558 | | |
| | | MWCNT | | | | | 434 | | |
| | | O-MWCNT | | | | | 105 | | |
| Acqueous Solution | Clay Mineral | Bentonite | 30000 | Amoxicilline | elctrostatic | Langmuir and Freundlich | 20 | 88 | [84] |
| Acqueous Solution | | Montmorillonite | | Trimethoprim | elctrostatic | Langmuir and Freundlich | 60 | - | [85] |
| Acqueous Solution | | Kaolinite | | Ciprofloxacin | elctrostatic | | | 95 | [40] |
| Acqueous Solution | | Montmorillonite | 1800 | Sulfamidethoxine | elctrostatic | Freundelich | | 13 | [86] |
| | | | | Sulfemathoxazole | | | | 10 | |
| | | | | Tetracycline | | | | 99 | |
| | | | | Oxytetracycline | | | | 90 | |
| Acqueous Solution | Others | Zeolite | 20 | Ciprofloxacin | dipole dipole and π-π stacking | | | 51 | [74] |
| Acqueous Solution | | Fe/Mn | 1000 | Tetracycline | | | | 88 | [75] |
| Acqueous Solution | | Gaphene Oxide | 181 | Tetracycline | π-π stacking and cation-π bonding | Langmuir | 313 | | [87] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Acqueous Solution | MIP | Diclofenac | hydrogen bonding | 325 | 99 | [65] |
| | NIP | | | | 15 | |

## 4. **Molecularly imprinted polymers**

MIPs can be considered analogues of the natural antigen-antibody systems, constituted by synthetic receptors able to retain specific target molecules according to their chemical functionalization. MIPs potentially offer the specificity and selectivity of the biological receptors with the explicit advantages of durability with respect to environmental conditions and low cost.

### 4.1. Polymerization synthesis

MIPs synthesis is based on the formation of a complex between a target molecule (template) and a monomer, in which one or more functional groups able to interact between them are involved. In the presence of a large excess of a cross-linker, the initiator (in sub-stoichiometric amounts) promotes the formation of radicals and consequently the propagation of the radical polymerization. As the three-dimensional polymer network increases, the polymer loses the solvation by solvent and precipitates in solid form on the bottom of the reaction vessel [88]. After the polymerization process, the template is removed from the polymer through a washing procedure, which varies according to the interactions established between the monomer and the template, leaving specific recognition sites complementary in shape, size, and chemical functionality. Therefore, the resulting polymer selectively recognizes and binds only molecules based on chemical properties similar to the template molecule. Intermolecular interactions, between the target molecule and the functional groups present in the polymer matrix, guide the phenomena of molecular recognition. Similarly, Non-Imprinted Polymers (NIPs) are synthesized in the same way without using the target molecule during the pre-polymerization step and are used as a control to evaluate the efficacy of the polymerization obtained. The occurrence of intramolecular interactions between the monomer and the template before the polymerization process represents a preliminary essential condition for obtaining specific binding sites for the target molecule. We illustrated two main routes (**Fig. 2**) followed for the polymerization which depends on the nature of the pre-polymerization interactions between template and monomer [89]. MIPs can be formed by non-covalent intermolecular interactions, such as hydrogen bonding, ion coupling or dipole interactions, between the target molecule and the monomer, even if nonspecific binding sites can derive from an incorrect stoichiometric relationship between the template molecule and the monomers, thus leading to a reduction in the selectivity and in the efficiency of the synthesized polymer [90].

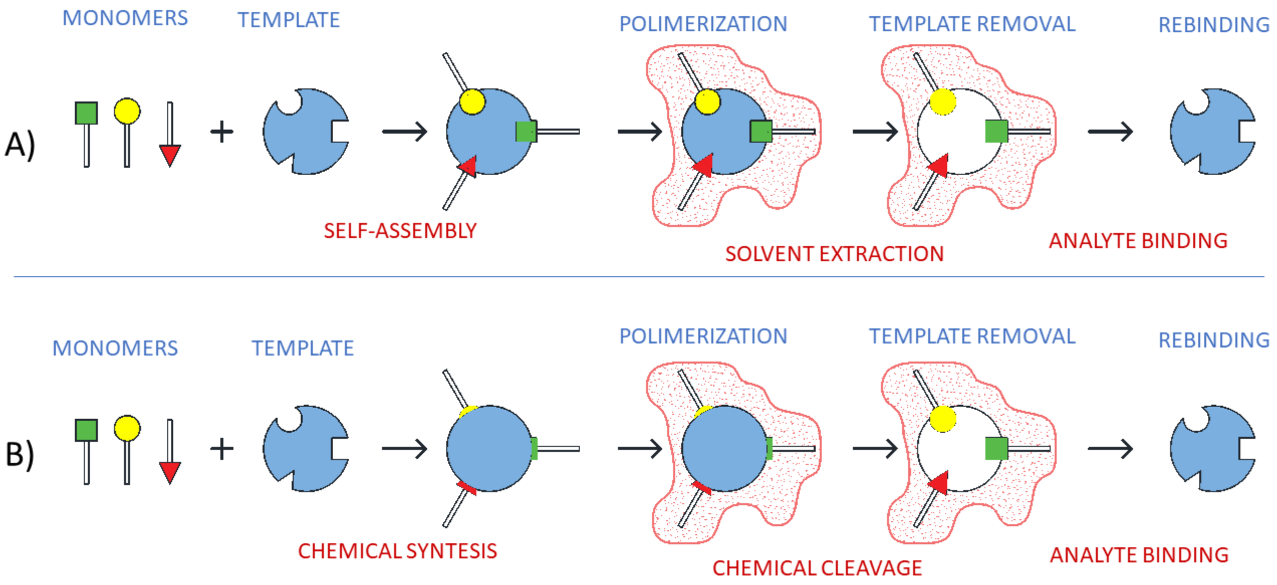

**Fig. 2.** Polymerization steps of MIPs through **a)** non-covalent **b)** covalent (adapted from [89]).

In the other case, covalent bonds with a defined 1:1 stoichiometry between monomer and template molecules are formed in the pre-polymerization phase. At the end of polymerization, the main issue is represented by the cleavage of the bond and the removal of the template molecules. Therefore, covalently imprinted MIPs must have reversible bonds that can be easily broken, without perturbing their geometry and chemistry which make them appropriate also in real matrices [91].

### 4.2. Type of synthesis

The main challenge of MIPs technology consists in the synthesis of a suitable polymer for a particular application field, without the disadvantages caused by temperature, pH, interferes and other parameters present in the solution of real matrices. In these last few years, many articles have appeared in the literature about different types of synthesis. Among these, bulk polymerization is the most common and simplest procedure with the reaction carried out in a small amount of solvent to have the precipitation of the polymer as a monolith, which is subsequently crushed and sieved [92].

However, this procedure has a low reproducibility, with partial destruction of the selective binding sites during the crushing and the additional risk of losing the most volatile fraction of the polymer or obtaining unwanted particle sizes [93]. A development of the previous method is represented by the precipitation polymerization which requires the use of larger volumes of porogenic solvents [94]. Once the critical mass is reached, the polymer is no longer solubilized and precipitates as spherical particles. In this way, the size and the porosity of the spherical particles are easily controlled by choosing the appropriate reaction mixture [95], but with the possibility that the monomer and the template could be irreversibly solubilized causing a partial loss of the reagents and hence a decrease of the polymerization yield [96]. Another option is represented by the emulsion polymerization in which two immiscible solvents are used in the presence of a stabilizing surfactant to obtain small droplets (micelles) inside which the polymerization reaction takes place [97]. A similar procedure, even though more complex, is represented by the Pickering emulsion polymerization [98], where solid particles are used to stabilize the small droplets formed in the mixture of two immiscible liquids, thus eliminating or reducing the dependence on surfactant emulsifiers and making the procedures cheaper. At the end of the polymerization, solid particles must be removed by an additional washing with an appropriate solvent, as in the case of hydrofluoric acid to leach silica nanoparticles [99]. Finally, the most innovative type of synthesis can be represented by the surface polymerization which involves the formation of a thin layer of the polymeric material, with its high molecular affinity, on the surface of different types of substrate. In this way, it is possible to exploit also the properties of the physical support; for example carbonanotubes (CNTs) can be used to increase the contact surface [100], $Fe_3O_4$ to create magnetic microparticles easy to separate [101], $TiO_2$ to combine photocatalytic processes [76] and $SiO_2$ to enhance a rapid mass transfer and faster binding kinetics [102,103]. Benefits and drawbacks for each type of polymerization useful to MIPs synthesis are summarized in **Table 2**.

**Table 2.** Benefits and drawbacks of different types of polymerization used to synthesize MIPs.

| Type of synthesis | Benefits | Drawbacks |
|---|---|---|
| Bulk polymerization | • Simplicity of method makes it possible to perform in any laboratory<br>• Do not require particular skills or sophisticated instrumentation | • Tedious procedures of grinding and sieving<br>• Wastage of useful polymer fraction, irregularly sized particles |
| Precipitation polymerization | • Nanoparticles size with easy separation.<br>• High surface area | • Low yield of synthesis<br>• Partial loss of the template during the synthesis<br>• High solvent consumption |
| Emulsion polymerization | • Allows to predetermine the polymer particle size<br>• Formation of spherical particles | • Complicated processes and use of stabilizers and surfactants can contaminate the MIPs<br>• Stabilizers and surfactants are difficult to remove from the resulting MIPs and may generally interfere with the imprinting procedure |
| Surface polymerization | • Spherical particles, highly reproducible results<br>• Applicable to most imprinting systems, particle size can be adjusted<br>• Features of particles joined to the selectivity of the final polymer | • Complicated procedures and reaction conditions<br>• Substrates can be synthesized too<br>• Bigger particles size |

### 4.3. Solvents, monomers and water compatibility

MIPs represent useful tools which can be exploited for different kind of applications through the control of the polymerization reaction conditions. Among them, the solvent reaction is one of the most important parameters in MIPs synthesis. First of all, it has to solubilize the reagents to favor the polymerization process but without forming strong intermolecular interactions with the monomer and target molecules which could interfere in the pre-polymerization process [104]; for this reason, aprotic solvents (acetonitrile, toluene) are generally used. Moreover, the chosen solvents should be porogenic to favor the formation of larger pores, thus enhancing the contact surface of the obtained polymer. At the same time, the solvent should have chemical properties similar to the matrices in which the polymer will be used, to guarantee a coherent microenvironment that facilitates the retention of the target molecule [105]. The choice of the solvent is also determined from the fact that MIPs have to be used in water matrices but, because of their hydrophobic nature, they have problems of water compatibility. The use of water mixtures with porogenic solvents during the polymerization [106], of more hydrophilic monomer such as 2-hydroxyethyl methacrylate (HEMA) [107], or the coating of surface nanoparticles with a broad range of functionalities to enhance its hydrophilicity [101] can be useful remedies to this problem. In addition to the factors affecting the solubility of the monomers and templates in the chosen solvent, also the selectivity of the monomers towards the CECs has to be taken into account. For example, methacrylic acid [95] and 2-vinyl pyridine [65] were used in similar synthesis, through precipitation polymerization, for the selective removal of diclofenac but, due to the different chemical interactions between the monomers and the diclofenac, the two obtained polymers exhibited different adsorption efficiencies, around 65 mg/g and 350 mg/g, respectively. Another example is given by Huang et al. [108], who described the synthesis of two different MIPs for the selective extraction of quercetin, through bulk polymerization using two monomers, 4-vinylpirydine (MIP-4VP) and acrylamide (MIP-AM). In this study, two SPE cartridges were filled with the two polymers and sequentially used to increase the selective removal of quercetin from a mixture with other analogue compounds. The adsorption behavior of the two polymers was also investigated and was found that MIP-4VP had a higher adsorption capacity than MIP-AM, 0.4 mg/g and 0.3 mg/g, respectively. With this method it is possible to take advantage not only from the different adsorption ability but also from the adsorption mechanisms of the two MIPs and a different extraction order may influence the binding affinity for quercetin. Considering the above, it is evident that this technology is rather complex but at the same time it has the advantage of being versatile and flexible and by choosing the appropriate reaction conditions it is possible to enhance the affinity and the selective removal for a specific molecule.

### 4.4. Enhanced removal of CECs via MIPs

The possibility to design micro and nanoparticles with predetermined features has favored the use of MIPs in many applications for the control and removal of CECs. For example, MIPs are widely used in detection and analysis of CECs, as well as sensing [15], sample pretreatment [109], and chromatographic fields [110]. In particular, in the analytical field, these polymers have seen a significant step forward in the samples' pretreatment, which is enriched and eluted in a new solution, avoiding the effects of the real matrix [111]. In this way, MIPs opportunely synthesized can be filled in SPE cartridges (Solid Phase Extraction), called MISPE [112], which can selectively retain specific molecules and subsequently release them after a washing with a different solution for the analysis. In the literature, several examples of MIPs application as adsorbent for CECs in a wide variety of matrices are reported which show that CECs are selectively adsorbed by these MISPE cartridges due to the different binding affinity as reported in **Table 3**. Generally, MIPs' performances are measured in terms of adsorption capacity and selectivity toward a particular target molecule. For the adsorption efficiency, batch tests are usually carried out by using different concentrations of the target molecule with MIPs as well as with NIPs to find the imprinting factor (IF) value, the main indicator of the selectivity properties of the polymer obtained in the synthesis [109]. The selectivity of a polymer toward a particular CEC is usually determined in batch tests performed in the presence of other CECs, as in the case of a polymer for diclofenac removal which was assayed also together with indomethacin and ibuprofen, and was found to have a removal rate of 100% for diclofenac, 57% and 0% for the other two drugs, respectively [93]. In another work by Cantarella and co-workers [92], MIP adsorption specificity toward diclofenac was compared with those toward other compounds as acetylsalicylic acid, trimethoprim and methyl orange and, despite similar physicochemical properties between all the compounds, MIP was able to adsorb 90 % of diclofenac and only less than 20% of the other compounds.

Although in MIPs syntheses one specific template molecule is generally used, the sites created in the polymer pores may have a cross affinity also for others compounds with physicochemical properties similar to those of the template. This is a crucial point for many polymers which are produced for the selective binding of a specific molecule but which are able to adsorb in the same binding site also other compounds with a similar chemical structure. In the study of Geng et al. [21], a proparazine-MIP was synthesized by a surface molecular imprinting technique on nano-$TiO_2$ particles and was found to efficiently adsorb proparazine with an imprinting factor of 16.04. Moreover, this polymer was also able to adsorb simazine and atrazine even if with a lower affinity. In a similar way, Vicario et al. [25] reported a surface polymerization on silica particles to obtain a MIP for the recognition of parabens (PCPs) in swimming pool water. Amount of 25 mg of MIP used with a time contact of 15 minutes, it was able to adsorb benzyl paraben with a removal percentage of 85% and, at the same time, also metylparaben and propylparaben with 65% removal in both cases. These results are consistent with the fact that methyl and propyl parabens have similar substituents and hence similar affinity for MIPs particles, while the benzyl groups have higher affinity for MIPs' binding sites.

MIPs use for the removal of CECs from real matrices may have some problems and difficult operating conditions. In fact, wastewater is one of the most complicated matrices which can be subjected to MIPs due to the presence of many interferences (i.e. solid particles, high ions concentrations) depending on the prior treatment configuration. MIPs particles may exhibit multiple sorption mechanisms, especially in complex real matrices, due to the coexistence of hydrophobic and hydrophilic structures within the polymer. The hydrophilicity of the binding sites in the core of the particles provides the selective interactions with the target molecule, meanwhile the outer layer can interact with other compounds via hydrophobic interactions and this could induce problems of surface contamination and cause a decrease in the selectivity of the polymer [112]. The need to detect and quantify CECs in wastewater matrices led to the development of new MISPE cartridges with high selectivity for specific class of molecules, rather than for a sole compound. In fact, as said above, similar compounds can access to the same binding sites, even if with different affinities. As reported in the study of Prieto et al. [113], a precipitation polymerization, starting from methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA) as the monomer and crosslinker, and using ciprofloxacin as the template molecule, was carried out to obtain MIPs able to remove selectivity ciprofloxacin, norfloxacin and ofloxacin. In other synthesis, fenoprofen [114] and ketoprofen [115] were used as the template molecules in bulk polymerizations to obtain MIPs sorbent for SPE able to retain also ibuprofen, in addition to the other two anti-inflammatory drugs. The prepared MISPE could be reused several times through regeneration with an appropriate washing solution.

One of the most important parameters to consider when dealing with aqueous matrices is the pH of the solution, since it substantially modifies the sorbent’s adsorption capacity. In fact, pH modifies all the ionizable functional groups present on the adsorbent as well as on the structure of the molecules dissolved in the solution. In this way, the chemical interactions between MIPs and the various CECs may be strengthened or weakened by a change in the pH and hence also the affinity of the binding sites toward the target molecule. For example, in the work of Samah et al. [93], MIPs, produced by bulk polymerization with diclofenac as the target molecule, have a decreased removal efficiency at pH above 3. However, it is not possible to establish a predicted trend for MIPs adsorption capacity toward target molecules with increasing or decreasing pH, as it depends on the most favorable chemical environment in which they are involved. Indeed, Bakhtiar et al. [116] found a decrease in MIPs adsorption capacity of 20% toward 2-phenilphenol when the pH was different from 7. Again, Dai and Cortalezzi [117] reported an increase in the adsorption capacity of a MIPs sensor toward 2,4 di-nitrotoluene as the pH value increased. Other parameters may influence MIPs’ adsorption efficiency, even if to a lesser extent than pH, as the ionic strength and the organic matter present in the wastewater.  The ionic strength affects has a similar effect to that of pH, in fact it may increase or decrease the adsorption affinity in the binding sites according to the chemical species and to the interactions involved. On the other hand, organic matter acts as interferes on the hydrophilic surface of the polymers reducing their affinity for a target molecule with a decrease in the adsorption efficiency; this type of behavior are reported in several papers where the MIPs are tested with different concentration of humic acid in batch test, where are evaluated their adsorption capacities [117,118].

In addition to the efficiency and selectivity illustrated above, another fundamental point to take in consideration when using MIPS is the possibility of regenerating the absorbent material and reusing it several times, attractive not only to save the material but also in terms of production sustainability. In fact, MIPs can effectively be recycled and used again without losing their performance. In the regeneration step, the molecules adsorbed on the polymer matrix are dissolved and removed by a solvent mixture, able to specifically solubilize the target molecules and to favor their elution. Generally, adsorption and regeneration are performed several times on the same polymer and the adsorption capacities during the cycles are evaluated. As shown by Vicario et al. [25], MISPE cartridges can be reused at least five times with a proper washing step using a solvent mixture of ethanol and acetic acid for the selective extractions of parabens; otherwise a mixture of acetonitrile and acetic acid was used to elute three different NSAIDs, as in the study of Madikizela et al. [24]. In another case, MIPs exhibited an excellent adsorption affinity for five different acidic pharmaceutical compounds used as template molecules, without loss of performance for fifteen regeneration cycles, by the use of methanol and acetic acid with a 9:1 ratio [118].

More recently, many articles have appeared in the literature describing a new MIPs' type of synthesis, called Multi-Template, in which several target molecules are used as templates. In this way, it is possible to extract, separate, and detect simultaneously different classes of chemical species, thus increasing MIPs utility and expanding their potential application. In particular, multi-template MIPs are highly desirable for a sustainable development of the processes. An example for NSAIDs multi-template MIPs was reported by Madikizela and Chimuka [24], who used a mixture of naproxen (NAP), ibuprofen (IBU) and diclofenac (DCF) in a 1:1:1 molar stoichiometry: an efficient adsorption was achieved only after 10 minutes, with also good values of IF as 1.25 (NAP), 1.42 (IBU) and 2.01 (DCF) while  the recovery rates were 38% for NAP, 69% for IBU and 87% for DCF. Another study reported by Dai et al. [118], described a multi-template MIP synthesized by precipitation polymerization for the selective removal of five acidic pharmaceuticals from wastewater. The adsorption of the five compounds was rapid and the binding equilibrium was achieved within 30 min. A decrease in the removal efficiency of five acidic pharmaceuticals by MIP was found in the pH range of 8–10, while with increasing ionic strength from 0 to 30 mmol/L the removal rate increased. For the treatment of large volumes of real matrices and, in particular, of wastewater significant amounts of polymers are needed. It follows that the implementation from the lab scale to the pilot scale is a crucial step which has to consider not only the adsorption capacities of the polymers but also practical and economic issues. In the study of Cantarella et al. [92], a bulk polymerization using methacrylic acid as the monomer was described for an efficient removal of diclofenac from wastewater. Despite the lower adsorption capacity and the reuse cycles seen in previous studies [65,95], 5 mg of MIP were able to remove in 10 minutes ~90% of diclofenac with an initial concentration of 32 mg/L from an aqueous solution, with an adsorption capacity of ~33mg/g. If compared with other type of synthesis, such as emulsion or surface polymerization, synthetic pathway represents a valuable strategy to obtain MIP materials being less time and solvent consuming. The adsorption performances for the selective removal of diclofenac from water suggested that MIPs might be successfully applied for water treatment even on a large-scale application.

**Table 3.** Experimental conditions in CECs recovery/removal from water matrices using MIPs.

| Matrix | CECs (Category) | Polymerization reaction condition | Washing method | MIPs evaluation | SPE condition | Regeneration (n) | Concentration of analyte (µg/L) | Ref. |
|---|---|---|---|---|---|---|---|---|
| Water and Soil samples | (Pesticides)<br>Propazine<br>Simazine<br>Atrazine | Surface Polymerization<br>Support: APTS-$TiO_2$;<br>Reagents: Propazine/MAA/EGDMA; AIBN;<br>Solvent: Toluene 50ml;<br>Conditions: 1°step 50°C, 6h; 2°step 60°C, 12h | Soxhlet extraction: (12h) MeOH:Hac (7:1)<br>Washing: MeOH.<br>Dried: under vacuum 80°C | Time contact: 8h;<br>Film thickness: 25-37µm<br>Adsorption Capacity: 6.8 mg/g<br>Imprinting Factor: 16.04 | Sorbent: 200 mg<br>Conditioning: MeOH (5 ml), $H_20$ (5ml);<br>Sample: 20ml<br>Washing: 2ml ACN:$H_20$ (1:4).<br>Elution: 2ml MeOH; | - | Linear Adsorption range: 0-11 mg/L.<br>Recovery %: 91.6–103.3 | [21] |
| Aqueous samples | (Preservants, PCPs)<br>Methylparaben<br>Propylparaben<br>Benzylparaben | Surface Polymerization<br>Support: Silica Particles;<br>Reagents: Benzylparaben/MAA/EGDMA; Benzoyl Peroxide;<br>Solvent: Toluene;<br>Conditions: 60°C, 4h | Repeated Washing: MeOH:HAc (9:1) for 8 times<br>Centrifugation: 5000rpm 15min<br>Final Washing: MeOH | Time Contact: 15min<br>Imprinitig Factor: 1.77; | Sorbent: 25mg<br>Sample: 10ml (flow rate 1 ml/min);<br>Washing: 2ml $H_20$ Ultrapure;<br>Elution: 0.5ml EtOH/HAc (8:2);<br>Cycles: 5 (times) | - | Range: 0.01 to 2.5mg/L;<br>Recovery %: 0.59 (MP), 11.0 (PP), 85.5 (BP); | [25] |
| Lake Water | (Antibiotics)<br>Sulfadiazine (SDZ)<br>Sulfathiazole (STZ)<br>Sulfamerazine (SMT)<br>Sulfamethazine (SMM)<br>Sulfamethoxazol (SMX) Sulfadoxine (SDX) | Multi-Templates Surface Polymerization<br>Support: VTTS-MGO@mSiO2; Reagents: Templates/MAA/EGDMA; AIBN;<br>Solvent: Toluene 50ml;<br>Conditions: 1°step 50°C, 12h; 2°step 50°C, 2h | Repeated Washing: MeOH:HAc (9:1)<br>Final Washing: MeOH and dried o.n.; | Time Contact: 15min<br>Imprinitig Factor: 2.47 (SDZ); 2.64 (STZ); 2.32 (SMT); 2.47 (SMM) 2.68 (SMX); 2.40 (SDX); | Sorbent: 20mg<br>Sample stirring: 50ml for 10min;<br>Elution: 2ml MeOH in 6min;<br>Cycles: 5 (times) | - | Conc.: 0.82 (SDZ), 1.11 (STZ), 0.59 (SMT), 1.01 (SMM), 0.87 (SMX), 1.12 (SDX); | [23] |
| Tap Water | (Plasticizers)<br>Dibutyl phthalate (DBP), Butyl benzyl phthalate (BBP) diethyl phthalate (DEP)<br>Dimethyl phthalate (DMP) | Precipitation Polymerization<br>Reagents: DBP/MAA/EGDMA (1:4:20); AIBN;<br>Solvent: ACN (20ml);<br>Conditions: Temp (60°C) | Repeated Washing: MeOH:HAc (9:1)<br>Final Washing: MeOH and dried 4h at 50°C.; | Time Contact: 45min<br>Adsorption Capacity: 22mg/g; | Sorbent: 200mg<br>Conditioning: MeOH (15ml), $H_20$ (15ml);<br>Sample: 15ml<br>Washing: 1ml ACN:MeOH(1:1).<br>Elution: 2ml MeOH; | - | Recovery %: 96 BBP, 94 DEP, 96 DBP, 94 DMP;<br>Conc.: 0.82 (SDZ), 1.11 (STZ), 0.59 (SMT), 1.01 (SMM), 0.87 (SMX), 1.12 (SDX); | [119] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| River Water | (Plasticizer)<br>Diethyl hexyl phthalates | Emulsion Polymerization<br>Reagents: DEHP/methacrylamide /N,N_-methylene-bis-acrylamide (2.56/14.1/5.188);<br>Solvents: DMF and H2O (2:8) 10ml and Oil mineral 20ml; Conditions: Temp. (50°C); Time (6h) | Soxhlet: (12h) MeOH<br>Washing: Acetone<br>Dried: Air flow | Surface Area:<br>Time Contact: 5min;<br>Adsorption Capacity: 49.83mg/g;<br>Imprinitig Factor: 12.86; | Sorbent: 5 mg (25-38µm)<br>Conditioning: $H_2O$ (5ml)<br>Sample: 5.0 ml<br>Elution: $CH_2Cl_2$ (1ml) | Sorbent: 20 mg<br>Sonication: $CH_2Cl_2$ (20ml)<br>Time: 30 min<br>Cycles: 6 (times) | Concentration range:<br>0.035 to 3.0 | [120] |
| Wastewater | (Antibiotics)<br>Ciprofloxacin<br>Norfloxacin<br>Ofloxacin | Precipitation Polymerization<br>Reagents: Ciprofloxacin/MAA/EGDMA (0.11/0.88/2.2);<br>AIBN; Solvent: MeOH (12 ml);<br>Conditions: Temp (60°C) | Ultrasound bath: (12h) MeOH<br>Vacuum Filtered: (8h) MeOH:HAC (1:1) and acetone | - | Sorbent: 100 mg (25-38µm)<br>Conditioning: MeOH /Hac (10ml) 1:1; MeOH (10ml) and $H_2O$ (10ml)<br>Sample: 1.6ml<br>Washing: MeOH (ml), H2O (1ml)<br>Elution: MeOH:Hac (1:1, v/v) | - | Influent:<br>0.697, 1.121, 0.925;<br>Effluent:<br>2.433, 0.741, 0.567; | [113] |
| Wastewater | (NSADs)<br>Fenoprofen | Bulk Polymerization<br>Reagents: Fenoprofen/2-VP/EGDMA; CAN;<br>Solvent: DMF and DMSO<br>Conditions: $Co^{2+}$ as Pivot | Soxhlet extraction: MeOH/HAc (9:1)<br>Washing: MeOH | Surface Area: 1607$m^2$/g<br>Adsorption Capacity: 38.8 mg/g;<br>Imprinitig Factor: 1.86; | Sorbent: 50mg (25-50µm)<br>Conditioning: 3 ml MeOH, 5 ml $H_2O$ (pH 5);<br>Sample: 50-200 ml<br>Washing: TEA/$H_20$<br>Elution: MeOH/EtOH/ACN (1-5ml) | Sorbent: 10mg<br>Elution: TEA/Water<br>Cycles: 5 (times)<br>Water spiked: 50mg/L | Influent: 0.08-0.068<br>Effluent: 0.47-0.040 | [114] |
| Wastewater | (NSADs)<br>Ketoprofen | Bulk Polymerization<br>Reagents: Fenoprofen/2-VP/EGDMA; CAN;<br>Solvent: ACN/Toluene (1:9) Conditions: 1°step 60°C, 16h; 2°step 80°C, 24h | Repeated Eluition: ACN:HAc (9:1)<br>Final Washing: ACN | Surface Area: 207$m^2$/g<br>Time Contact: 45min<br>Adsorption Capacity: 8.24mg/g | Sorbent: 14mg (25-50m)<br>Conditioning: 1ml MeOH, 1ml $H_2O$;<br>Sample: 50ml (pH 5 flow rate 1ml/min), dried 10min;<br>Washing: 1ml TEA/$H_20$ (5%)<br>Elution: 1ml MeOH | Sorbent: 10mg<br>Elution: 3ml Water and 3ml MeOH;<br>Water spiked: 5µg/L | Influent: 22.5-34mg/L;<br>Effluent: 1.14-5.33mg/L | [115] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Wastewater | (NSADs)<br>Naproxen<br>Ibuprofen<br>Diclofenac | Multi-Template Bulk Polymerization<br>Reagents: Multi-Templates/MAA/EGDMA; CAN;<br>Solvent: Toluene (50 + 25ml);<br>Conditions:<br>1°step 70°C, 8h;<br>2°step 70°C, 16h | Repeated Eluition:<br>ACN:HAc (9:1)<br>Final Washing:<br>ACN | Surface Area:<br>Time Contact: 10min;<br>Adsorption Capacity:<br>4.47 (NAP), 3.60 (IBU), 5.45 mg/g (DCF);<br>Imprinitig Factor:<br>1.25 (NAP), 1.42 (IBU), 2.01 (DCF); | Sorbent: 50mg (25-50μm)<br>Sample stirring: 10ml for 10min (pH 2.5);<br>Vacuum Filtration: 2ml MeOH:$H_20$ (1:9).<br>Elution: 2ml ACN:HAc (8:2); | Sorbent: 50mg<br>Elution: 2ml ACN:HAc (8:2);<br>Cycles: 5 (times) | Influent wastewater spiked with 50μg/L per Templates;<br>Recovery % 38 (NAP), 69 (IBU), 87 (DCF); | [24] |

### 4.5. Upscaling MIP columns: from lab- to pilot-scale

Given their specific selectivity for one or more class of compounds, MIPs are excellent candidates to be implemented in tertiary treatment for the targeted CECs removal. The potential applicability of MIPs on a large scale was highlighted by Cantarella and colleagues [92] based on the extreme selectivity of the adsorption process and the reusability of the material by easy and efficient adsorption/regeneration cycles. Whereas the upscaling behavior of GAC adsorption columns for removing CECs has been tested [121], to the best of our knowledge, no pilot or demonstrative-scale of MIP columns in water and/or wastewater treatment has been done so far and related studies have been limited to lab-scale up to date. Therefore, we provide a basic necessary pathway to follow while upscaling MIPs particles in adsorption columns in real environment. In **Fig. 3**, the scale up route is divided into four main phases. The synthesis and vast production of polymers needs a further scaled-up step to control reaction yields and MIPs property, which must be reproducible and constant. One of the most crucial point is the removal of the template molecule by using large amount of organic solvents (see **Table 3**) per unit mass of polymer produced. Therefore, it is fundamental to find a proper side process to recover these solvents to minimize the environmental impact and to limit the production cost for the overall process sustainability. About this aspect, different methods can be applied to recover solvents: distillation is the most common and well-established technique used to separate solvents from aqueous or other organic mixtures. Due to the high boiling point of many CECs used as templates, the waste solvent can be distillated by heating and recondensation to leave CECs in a small fraction and to recover the recycled solvent. Alternatively, adsorption processes can be used to remove contaminants from the solvent but these procedures are not so feasible with organic matrices mainly constituted by methanol and high concentration of CECs as those obtained from template removal with other adsorbent materials. Finally, membrane processes can be a valuable solution compared to the others due to their inherent simplicity and energy efficiency, avoiding undesirable phase change, as in case of distillation. In the study of Cseri et al. [122], the three processes are compared for the methanol recovery in terms of carbon footprint. The distillation process has a linear production of $CO_2$ higher than the adsorption one up to 70% of solvent recovery due to the high energy consumption, above 70% the adsorption process requires excessive amounts of adsorbent because of the highly concentrated solution. Membrane filtrations can be considered the greenest process but, it may be affected by high implementation and maintenance costs which have considered in the entire MIPs process life cycle assessment. The MIPs' characterization can be done through instrumental analysis and experimental laboratory test. In the first case, chemical information obtained through FTIR and NMR analysis may not give a certain presence or absence of a specific organic compound in a polymer, as well as the orientation in space of the essential functional groups in the pre-polymerization phase. Conversely, Scanning Electron Microscopy (SEM), Dynamic Light Scattering (DLS) and Thermogravimetric Analysis (TGA), provide data on physical properties of the MIPs synthesized, such as surface area and size of pores and particles [111]. In the second step, lab-scale experimental batch tests are conducted to determine the adsorption affinity to different CECs through isotherms analysis and kinetic studies [95]. Successively, continuous flow tests in column are further conducted to verify the best configuration to implement in pilot-scale and to determine the MIPs' properties, when the flow passes through the column. Similarly of GAC or other sorbents material [57,123,124], empty bed contact time (EBCT) is a fundamental parameter to replicate the laboratory conditions on a pilot scale, which represents the time it takes for the flow to pass through the column at given reactor volume and flow rate. Once the optimal conditions are set, the experimental data collected in lab scale must be confirmed through installation of the column, commissioning and long-term validation.

Finally, MIPs adsorption behavior must be verified through the monitoring of CECs concentration in the effluent and evaluate the MIPs regeneration necessity and frequency. Due to the different CECs concentration in the influent and also due the diverse effluent requirements for the discharging or the safe reuse, is not easy to establish a common regeneration procedure. Given the maximum adsorption capacity and designed the best process condition, it is possible to estimate the treatable volume and predict when the break and breakthrough of the column could happen. However, a straight and continuous monitoring of the effluent is necessary to detect the CECs concentration removed by the treatment. The economic aspects of the technology must be considered, and clearly the MIPs are more expensive than GAC sorbents concerning the synthesis, while the MIPs are easily regenerated maintaining their removal performance.

An interesting study by Razali et al. [125], compared seven different adsorption materials for the treatment of wastewater contaminated by N-methyl-2-pyrrolidone (NMP) and N,N-dimethylformamide (DMF). Most of the tested adsorbents showed good performances, in particular MIP, functionalized with phenylboronic acid, showed superior performance being able to adsorb 677 and 502 mmol DMF and NMP per kg adsorbent, respectively. Most of the compared adsorbent were regenerated up to 10 times without any loss of performance.

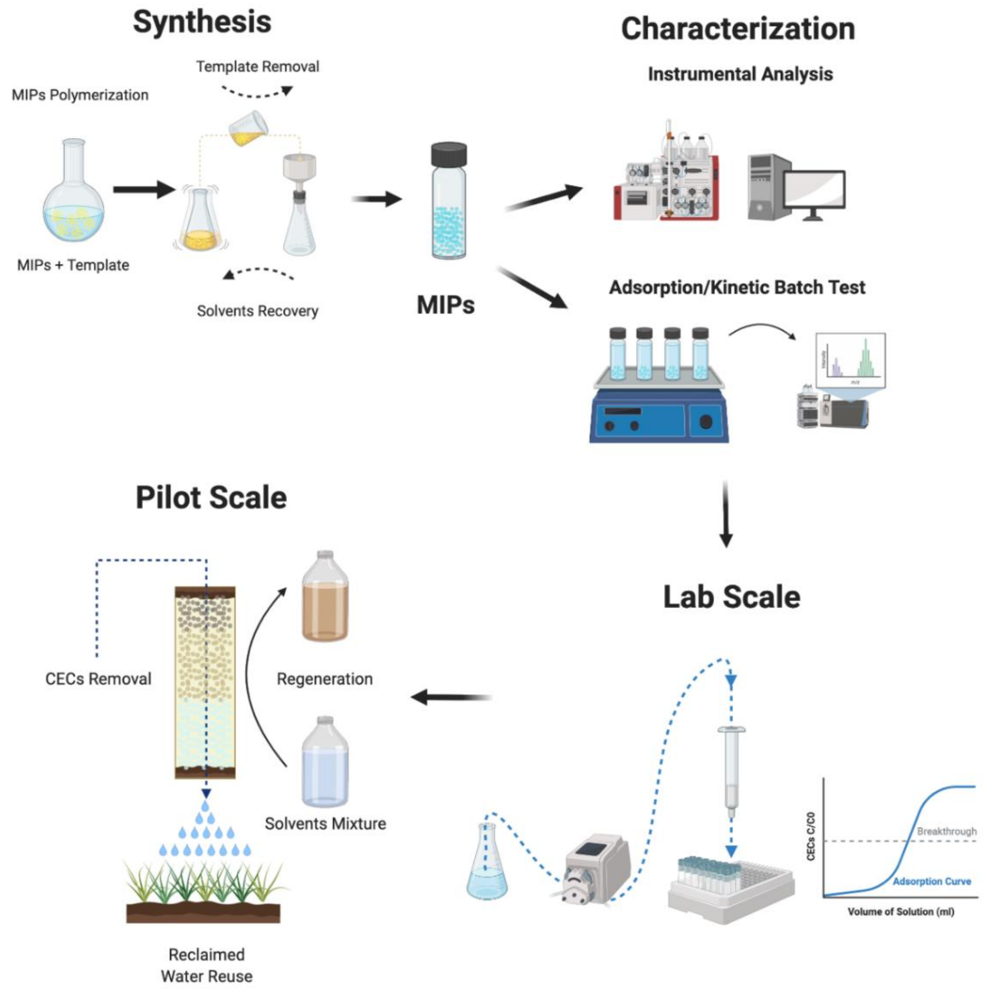

**Fig. 3.** A possible upscaling pathway for MIPs application to wastewater treatment for enhanced CECs removal and safe water reuse in irrigation/fertigation.

## 5. Integration of MIP columns to urban water cycle facilities

The application of conventional adsorption columns to remove CECs from water has been successfully tested using GAC at pilot-scale [126] and even at full-scale [127]. However, MIPs are more advantageous for treatment of trace contaminants because they can be specifically designed to remove one or a group of target compounds. This is an advantage over nonspecific conventional adsorption technologies such as AC, which may be consumed removing large amounts of non-trace contaminants from the water [7]. As already discussed in previous sections, the degradation/removal of CECs is more likely to be applied using coupled treatment systems which can bridge the deficiencies in a single technology for the removal of these complex contaminants present in the water environment [29]. Various configurations can be developed to integrate MIP columns in urban water cycle facilities for enhanced removal of CECs. One possible configuration for municipal wastewater treatment is proposed in **Fig. 4**, that is currently being developed under the PRIMA/H2020 Project “FIT4REUSE” (fit4reuse.org), to produce a treated effluent that is suitable for reuse in irrigation according to required standards. A MIP column can be easily coupled after the up-flow anaerobic sludge blanket (UASB) and anaerobic membrane bioreactor (AnMBR). The UASB + AnMBR has been an innovative solution for municipal wastewater treatment especially in small-scale decentralized facilities where several advantages such as less energy cost, less fouling, and higher operating organic loading rate (OLR) can be achieved [128]. After a pre-treatment unit followed by a high-rate anaerobic treatment via UASB, AnMBR functions as post-treatment (polishing step) and even guarantees disinfection thanks to microfiltration [129]. The permeate of the AnMBR has often high quality and falls into Class A according to the European Regulation on minimum requirements for water reuse of the European Parliament and of the Council [26] since it is free from suspended solids and pathogens, while its nutrient-rich matrix allows a potential reuse in fertigation [130]. At this point, CECs can be the limiting factor for water reuse and the integration of MIP columns can be a promising solution based on the results obtained from lab-scale studies. The permeate can be introduced to MIP column as an advanced treatment step to enhance the removal of target CECs. The critical point here is that operating parameters of MIP columns is completely different than that of in other high-rate reactors. For instance, hydraulic retention time (HRT) is typically maintained in the range of 6-18h in UASB [131] and 4-16h AnMBR [132]; whereas, HRT/contact time is usually much lower in a MIP column (3-6min) [13,133]. The reactor volume required for MIPs is therefore very limited compared to others due to much lower contact time needed. In addition to operating conditions, the target CECs can vary with respect to local conditions. For instance, pesticides can be the dominant CECs in rural areas. Accordingly, the needs and characteristics of the pilot area must be clearly defined before the design and implementation of such treatment configuration. An additional disinfection unit (i.e. UV) can be also coupled at the end of the UASB + AnMBR + MIP configuration for a possible post-contamination in the MIP column.

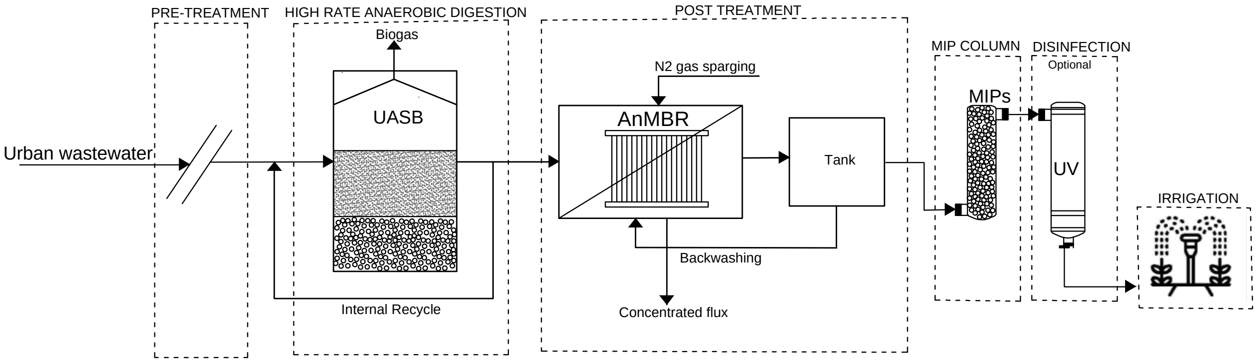

**Fig. 4.** A possible configuration for integrating MIP columns to urban water cycle facilities for enhanced CECs removal and enabling safe water reuse in irrigation/fertigation. This configuration is currently being developed under the PRIMA/H2020 Project “FIT4REUSE” (fit4reuse.org).

Although MIP columns offer promising applications for advanced wastewater treatment to remove CECs, they have certain limitations for up-scaling regarding cost and applicability. These limitations must be addressed with engineering solutions and at least partially eliminated in order to develop a sustainable urban water cycle framework as discussed in the next section.

## 6. Sustainability of MIPs in water reuse systems

Next generation wastewater treatment processes must be the best economically, environmentally and socially, so their selection and implementation can be adequate. When developing processes for solving a certain environmental issue, one must be aware that the use of resources and energy by these processes will result in additional environmental burdens [134]. Adsorption columns using MIPs can be a promising technology with elevated removal efficiencies of CECs and without the transformation of products (by-products). However, such adsorption-based processes do not provide a permanent solution since the target pollutants only change phase, so the treatment of the sorbent is also necessary after application. In addition, although having relatively lower cost of preparation compared to membrane technologies, the vast production of MIPs can be quite expensive and difficult which makes their fabrication quite challenging. At this point, NIPs can be favored [7]. Meanwhile, regeneration and subsequent reuse of MIPs/NIPs following their use for water and wastewater treatment can reduce the overall costs of treatment. A life cycle assessment (LCA) and life cycle cost analysis (LCC) should be applied to help with decision making and to provide a detailed overview of the environmental sustainability of these technologies, which is currently lacking in the literature.

A possible solution to ease the reproduction of MIPs at demonstrative and/or full-scale can be partially filling the adsorption columns with other materials in addition to NIPs/MIPs. Conventional adsorbents such as PAC or GAC can be used as co-adsorbent; whereas a competitive adsorption and selectivity may occur in the column for the target compounds. Then, MIPs can be saved by using inert materials (such as sand, glass beads, ceramic balls) in the adsorption column, and the efficiency of the adsorption process needs a further optimization of the mixing ratio of the materials.

Another point is that since the occurrence of CECs in wastewater is highly variable, a continuous operation of any single unit for the removal of CECs may not be necessary in a treatment configuration. Eventually, the adaptation of contamination sensors can be reasonable since recent developments in sensor technology promise faster screening approaches coupled with effective determination of target contaminants [135]. These systems can be integrated with early warning systems for CECs [136], and thus enable to operate if only the target compound is above a certain threshold concentration. When the concentration of a target CEC is high, these early warning sensor systems can activate the circulation of effluent through the MIP column. Nevertheless, the choice of the most appropriate technology or combination of different technologies vary based on the quality requirements and potential application of the reclaimed water. Considering that most of the total water demand is represented by irrigation (50% to 90%), there is no doubt that these innovative measures can help to address the water scarcity problem in the regions like Mediterranean that face severe water stress in the near future due to climate change.

## 7. Final remarks and conclusions

With this review paper, we highlight the potential of MIPs to be integrated to urban water cycle facilities to ensure water safety in case the CECs create barriers in practice. Several advantages such as no generation of oxidation or degradation byproducts and high regeneration potential make them promising candidates for future water applications. Up to date, MIPs have been used to recover and/or remove CECs from aqueous solution only at the lab-scale. Thus far, no studies have considered up-scaled application of MIPs in real operative environment. The high selectivity and strong affinity of MIPs to target compounds can replace conventional GAC/PAC based adsorption columns in wastewater treatment. However, the optimization of synthesis steps is crucial to establish vast production of MIPs in a high performance of CECs removal process. In any case when a MIP column is designed to be upscaled and integrated to a wastewater treatment scheme, their sustainability must be ensured. At this point, implementing LCA and LCC of MIPs in a relevant environment is highly recommended, which is currently lacking in the literature since these systems are highly innovative and further research is required.

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