

ASSESSMENT OF THE GREENNESS OF MOLECULARLY
IMPRINTED POLYMERS USED IN SAMPLE PREPARATION

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Highlights

- AGREEMIP tool is used for assessing the greenness of MIP synthesis procedures
- Scores obtained clearly show that there is an abuse of the use of green-related terms
- Guidelines for greening MIPs used in sample preparation are provided
- Reduction of the amounts of toxic solvents during MIP synthesis is one of the key aspects

Journal Pre-proof

ASSESSMENT OF THE GREENNESS OF MOLECULARLY IMPRINTED POLYMERS USED IN SAMPLE PREPARATION

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Abstract

It is now widely accepted that the incorporation of molecularly imprinted polymers (MIPs) into sample preparation techniques has enabled unprecedented selectivity performance of analytical methods for the determination of a wide range of analytes in biological, food and environmental samples. However, according to the Principles of Green Chemistry and the subsequent Principles of Green Sample Preparation, it is clear that MIPs are far from being considered green materials, both due to the common harmful reagents and the experimental conditions used for their synthesis. Accordingly, new greener routes for MIP synthesis have been proposed in recent years. However, although the titles of some of the published papers include terms such as 'green MIP' or 'sustainable MIP', such improved properties have only been assessed intuitively and it is therefore unclear whether such claimed green or sustainable MIPs are actually so. Therefore, in the present review, published papers using apparently green MIPs in sample preparation were evaluated using the recently developed metric tool AGREEMIP. Such a tool is based on the assessment of 12 criteria related to the greenness of the different reagents used, energy requirements and other aspects of MIP synthesis procedures. The final values of performed AGREEMIP assessment ranged from 0.28 to 0.80. The scores obtained after the

AGREEMIP assessment clearly show that, although slight improvements have been achieved in terms of greenness, there is an abuse of the use of green-related terms and further development is needed. In this context, some guidelines for greening MIPs are provided.

Keywords: Molecularly imprinted polymers; sample preparation; green metrics; AGREEMIP.

Glossary

μ -SPE: micro solid-phase extraction

AA: acrylic acid

APTES: (3-Aminopropyl)triethoxysilane

CE: capillary electrophoresis

DAD: diode array detector

DES: deep eutectic solvent

DMF: Dimethylformamide

EDGMA: ethylene glycol dimethacrylate

IL: ionic liquid

LPME: liquid-phase microextraction

MAA: methacrylic acid

MIP: molecularly imprinted polymer

SBSE: stir bar sorptive extraction

SPME: solid-phase microextraction

TEOS: tetraethyl orthosilicate

1. Introduction

In spite of the significant development in analytical instrumentation during last decades, sample pretreatment is still unavoidable, especially in trace analysis of different analytes in complex samples, which requires the trace enrichment and clean-up of target analytes from other matrix components in a reproducible manner. In this regard, several microextraction techniques have been developed, such as solid-phase microextraction (SPME), liquid-phase microextraction (LPME), stir-bar sorptive extraction (SBSE) and micro solid-phase extraction (μ -SPE), and all of them result appropriated for nowadays sample preparation requirements. In addition, a great variety of new sorbents (i.e. restricted access materials, carbon nanotubes, graphene, metal organic frameworks, coated magnetic nanoparticles, etc.) have been incorporated showing an excellent absorption capacity for target analytes from complex matrices [1,2]. Moreover, their “micro” nature makes them well-suited to cope with the Principles of Green Chemistry [3,4] and the Principles of Green Sample Preparation [5], since all of them allow decreasing the amount of sample and reagents. Thus, it leads to a reduction in the amount of hazardous wastes and, in general, they are suitable for the use of safer chemicals and procedures with lower energy requirements.

However, regardless of the microextraction technique chosen, the extraction process is governed by the partitioning of target analytes between the sample and an acceptor phase (liquid or stationary phase). Unfortunately, such acceptor phases roughly cover the polarity scale and thus target analytes are co-extracted with other matrix compounds, which can negatively affect the determination of analytes by current chromatographic techniques. Accordingly, in most cases, the introduction of several washing steps using harmful solvents is necessary to remove interfering compounds, thus reducing the inherent advantages of microextraction techniques. As an alternative, the use of immunosorbents [6,7], aptamers [8] and molecularly imprinted polymers (MIPs) [9,10] have been proposed as excellent materials capable of successfully



performing selective extractions. However, MIPs have some advantages in terms of stability under different experimental conditions and ease of synthesis.

For MIP synthesis, following the non-covalent approach [11], a template molecule is dissolved in a proper solvent (porogen) able to maximize intermolecular interactions with selected functional monomers in presence of a large amount of a cross-linker. Then, polymerisation takes place thermally or by UV-radiation. Once the polymer is obtained, template molecule is removed by exhaustive washing leaving cavities, complementary in size, shape and functionality, within the polymer matrix and thus able to recognize the template molecule (and related compounds) in rebinding experiments. Originally, MIP particles were used as sorbent for solid-phase extraction (SPE) and later MIP synthesis was readily adapted for the preparation of suitable formats for SPME [12,13], SBSE [14–16] and other micro-extraction techniques [17–19] and thus they are considered ideal materials for selective sample preparation.

However, from a Green Chemistry perspective, most of the reagents used for MIP synthesis are toxic and a large amount of solid or liquid waste is produced, thus posing a threat to both humans and the environment. Accordingly, in order to make MIP synthesis greener, some guidelines were recently proposed in an intuitive manner [20–23] taking into account the different steps of MIP synthesis. Among these, it is important to highlight the 14 principles of green molecular imprinting technology, represented by the acronym GREENIFICATION (Figure 1), proposed by Arabi et al. [20], which include recommendations for the green synthesis of MIPs and have been further exploited by the same authors evaluating different MIPs, so-called greenificated MIPs, whose synthesis follows one or more of the 14 proposed principles [22]. In this regard, the replacement of the typical acrylic-based monomers (i.e., acrylic acid (AA) and methacrylic acid (MAA)) by greener monomers or the use of natural polymers (biopolymers), such as chitosan, cellulose or silk fibroin, to prepare non-toxic,



biodegradable, and biocompatible MIPs have been proposed [24–27]. In addition, the use of greener solvents such as ionic liquids (ILs) [28] or deep eutectic solvents (DESs) [29,30] has been successfully employed as porogen as an alternative to conventional solvents typically used in molecular imprinting (i.e., acetonitrile, toluene). It seems obvious that greener alternatives to the synthesis of MIPs are already available, and several papers have been published in recent years claiming green synthesis of MIPs for sample preparation. However, some questions remain: are such strategies green enough? What would be the greener approach? In this regard, the main aim of this review is to assess the different strategies proposed for the green MIP synthesis using the recently proposed AGREEMIP tool [31], in order to provide to the sample preparation field with an insight into which aspects of MIP synthesis still need to be improved in order to make it truly green.

2. AGREEMIP tool

As mentioned above, it is intuitively possible to design new green MIPs following the GREENIFICATION guidelines given in Figure 1, but such an approach does not allow to have a quantitative measure of the environmental impact of the different changes introduced for their synthesis. In this regard, AGREEMIP tool was recently proposed to assess and compare the greenness of MIP synthesis procedures [31]. AGREEMIP is able to produce an overall score on a scale of 0-1 by calculating the weighted average of individual scores for 12 evaluation criteria covering the different reaction mixture components, energy requirements and details of MIP synthesis procedures. The assessment can be performed using user-friendly open-source software, which can be freely downloaded from mostwiedzy.pl/agreemip. The result of the assessment is an easy-to-interpret pictogram showing the performance in each criterion, the weighting of the criteria and the overall performance in terms of greenness. The AGREEMIP tool, its development and detailed scoring are described elsewhere [31]. However, a summary of the 12 criteria considered is provided below for a comprehensive reading of this paper.

2.1. Criterion 1: Removal of Polymerization Inhibitors.

Removal of polymerisation inhibitors from used reagents is recommended in polymer synthesis and such a procedure may generate solid or liquid waste. Accordingly, the best scenario (and thus a score of 1) is when no waste is generated, whereas a score of 0.5 or 0.2 is assigned when solid or liquid waste is generated, respectively, since the former is easier to handle.

2.2. Criteria 2-7: Functional Monomer, Template, Cross-Linking Agent, Porogen/Solvent and Other Reagents/Adjuvants/Carriers, Core/Particle Preparation, and Surface Modification.

The different components of a typical polymerisation mixture (template, functional monomer, cross-linker and porogen) and any other reagent used are treated in the same way, but independently assigned to a single criterion. Each criterion takes into account both the quantity of the compound and its associated risk. Penalty points are assigned as a function of the hazard statements associated with each compound, as proposed by Tobiszewski et al. [32]. In general, increasing the amount of reagent and/or increasing the severity of the hazards will result in a sharp decrease in the final score for each criterion.

2.3. Criterion 8: Polymerization Initiation.

Polymerisation can be initiated in a number of ways, the most common being the addition of an initiator to the polymerisation mixture, which thermally decomposes into free radicals capable of initiating the polymerisation reaction. Depending on the efficiency of the energy supplied to the system (conventional heating, sonication, microwaves, etc.), a score is assigned (the more efficient, the higher the score). Higher scores are also given if the polymerisation is initiated in a more sustainable way (i.e. UV radiation, electropolymerisation or self-polymerisation).

2.4. Criterion 9: The Size of the Polymer Particles.

Criterion 9 relates to the size of the polymer particles obtained and is therefore linked to how the polymer is disposed of after use and the risk to the operator of being exposed to polymer particles of different sizes. In this respect, the smaller the particle size, the higher the risk of exposure to the operator and therefore the lower the score. On the other hand, a score of 1 is assigned to what is considered to be the greener solution, i.e. carrying out *in-situ* polymerisation (i.e. preparing the imprinted fibres for SPME), as the entire polymerisation mixture is used and therefore no waste is generated.

2.5. Criteria 10 and 11: Template Removal

As mentioned above, in order to obtain selective binding sites within the polymer matrix, the template molecule must be removed after polymerisation. In general, template removal requires the use of large amounts of solvent and is energy consuming. Accordingly, the amount of solvent and the associated hazards are considered in Criterion 10 and scores are assigned in a similar manner as described above for Criteria 2-7. In addition, Criterion 11 relates to the removal technique. In this sense, the use of Soxhlet extraction, which requires long heating times using large amounts of organic solvents, represents the worst-case scenario and is therefore assigned a score of 0. On the other hand, the use of ultrasound or microwaves requires a shorter extraction time and consumes less energy and therefore receives a score of 1.

2.6. Criterion 12: Final Product Reusability.

Finally, Criterion 12 is not related to polymer synthesis but considers MIP reusability. For the single-use sorbent, the score equals 0, the application of MIP between 2- and 10-times scores 0.5, and the most favourable condition, thus scoring 1, is assigned to MIPs used more than 10 times.

Each of the proposed criteria has a different relative importance and therefore weights from 1 to 4 are applied and a higher weight means a greater importance when calculating the weighted average. The weight values for each criterion are listed in Table 1. Detailed information about the description of the pictogram (score, colours, circles and their size) was enclosed elsewhere [31].

3. Application of AGREEMIP for assessing the greenness of the synthesis of MIPs used in sample preparation.

AGREEMIP assessing tool was used to evaluate 30 different MIP preparation procedures defined in the literature as eco-friendly, sustainable, green solution or greener [26,30,33–60]. Table 2 shows the general information on the basic polymerisation mixture components and the final score provided by AGREEMIP assessment. Moreover, in mentioned Table 2, three of the most important criteria, which significantly impact on the green character of defined MIP preparation process, were also listed. Detailed reports with pictograms for each of the evaluated MIP synthesis procedures are included in Supplementary Information.

After evaluating the greenness of the selected procedures for obtaining polymeric sorbents, it was noted that the average total value of AGREEMIP assessment was 0.49 ± 0.13 . Referring only to the average value itself for all 30 evaluated procedures defined in the literature as eco-friendly, sustainable, novel or greener solutions, it can be concluded that, in a general way, all “green” procedures are characterized by a moderate (0.4 to 0.6) degree of greenness. The lowest total value of AGREEMIP assessment (0.28) was obtained for procedure reported in [43], and the corresponding pictogram is shown in Figure 2a, in which the preparation process of magnetic MIPs dedicated for sample preparation and analysis of ractopamine is described. The impact of such low total value of AGREEMIP assessment was mainly caused by the application of organic solvents and reagents such as acetonitrile (as a porogen), acrylic acid (as a functional monomer) and ethylene glycol dimethacrylate (EDGMA) as a cross-linker.

Application of acrylic acid and EDGMA forces a preliminary step to purify them from polymerization inhibitors. Moreover, during the preparation of the mentioned type of magnetic MIPs, it was necessary to previously consume reagents and solvents for the synthesis of the carrier itself (Fe_3O_4) as well as the subsequent modification of its surface. A mixture of methanol:acetic acid (9:1) was used several times to elute the template. In addition, the paper lacks information on the possibility of multiple use of the developed polymeric material. Consequently, according to the accepted principle, it should have been assumed that it is used only once. The discussed example illuminates an important problem, which is the whole process of preparing the appropriate polymeric material, and not only its use, as a final product in the analytical procedure. It should be noted, that authors previously used appropriate computer modelling to select the right conditions for the synthesis. Additionally, at the stage of final determinations they used a green analytical technique such as capillary electrophoresis (CE) equipped with diode array detector (DAD).

Also, relatively low AGREEMIP assessment values (below total value of 0.35) were obtained for procedures described in references [42,44,53,56,60]. The low score in these analytical procedures is mainly influenced by the use of toxic and user- and environmentally hazardous solvents as porogenic agents (e.g., chloroform or dimethylformamide), as well as the use of significant amounts of organic solvents such as methanol:acetic acid mixtures to remove the template molecule from the polymer structure. A very interesting example is the procedure described by Chen et al. [53], with a final score of 0.34 (see obtained pictogram in Figure 2b), in which the final product is to be magnetic MIPs with ionic liquid (IL) for the extraction of carbaryl in food. The authors used the IL (1-butyl-3-methylimidazolium hexafluorophosphate ($\text{BMIM}^+\text{PF}_6^-$)) as an auxiliary solvent which was added to the polymerization mixture together with classical functional monomer (methacrylic acid). Of course, as in any such case, it was necessary to consume an appropriate amount of reagents and solvents in advance to obtain the



magnetic carrier and modify its surface before depositing the polymer sorbent. Moreover, the aforementioned IL was only an additive, and the main porogen in this procedure was still acetonitrile. Unfortunately, also in this case, information on the multiple use of the sorbent was not included in the paper, so it was necessary to assume its single use.

The highest score after AGREEMIP assessment (0.80) was obtained for the synthesis procedure described in [38], and its pictogram is shown in Figure 2c, where a novel green approach in the field of functionalized monomer for molecularly imprinted-enoxaparin polymer is described. New type of MIP was prepared *via* microwave synthesizer workstation. Enoxaparin was introduced as a template, itaconic acid was used as the functional monomer (previously selected using *in silico* studies), N,N'-methylenebisacrylamide was applied as a cross-linking agent and finally water was used as a porogen. Moreover, the high value of the conducted green analysis of the preparation of the MIP-type sorbent is also affected by the use of water to wash out the template molecules and the use of ultrasounds for this purpose. Probably the total value of AGREEMIP assessment will be much higher due to the fact that in the mentioned paper there is a lack of information about the reusability of developed novel green MIP. For this reason, for the AGREEMIP assessment it was assumed that described MIP was a single use material.

Taking into account the information listed in Table 2, it might be noticed that several of analysed MIP preparation procedures were characterized by strong/high (between 0.6 and 0.8) degree of greenness. This mainly applies to the evaluated procedures described in [45], [46] and [52] reaching scores of 0.64, 0.70 and 0.69 (pictograms shown in Figure 2d-f), respectively. Arabi et al. [45] describes a green approach and hazardous waste elimination solution in the field of hydrophilic molecularly imprinted nanospheres for the extraction of rhodamine B. As a carrier for the imprinted polymers, the carbon sphere (obtained by the carbonization of glucose in aqueous media) was introduced. The polymerization process was performed under



room temperature and the elution of template molecules from the polymer structure was performed using 5% acetic acid solution. Unfortunately, in the paper there was a lack of information about the reusability of the developed green MIP, which impact on the final score of AGREEMIP assessment. As for the another paper published by the same group [46], in which the preparation process of water-compatible molecularly imprinted nanoparticles for the extraction of hydrochlorothiazide from human urine is described, the most important impact on the final score (0.70) was associated with the amount of reagents and solvent used in core particles preparation and their surface modification. The polymerization process was performed also under room temperature, due to this fact there was no additional power consumption for heating the polymerization mixture. The template molecules were removed from the polymer structure by deionized water/ammonium hydroxide (9:1 v/v) solution by using several times sonication. Finally, in a case of paper published by Elfadil et al. [52], the authors described a new and simple method for the extraction and determination of erythrosine B in food samples. At the sample preparation process, the polydopamine-based MIP coating magnetic nanoparticles was synthesized without the necessity of using a polymerization initiator (self-polymerization process). The template molecules removing from the polymer structure was performed using 0.1M NaOH. The most sensitive point of this procedure was the consumption of a significant amount of reagents and solvents to obtain the magnetic carrier and modify its surface.

Finally, it is important to point out that the lack of information on the reusability of new MIPs is rather common to all the evaluated papers in this review. Such lack of information makes it necessary to assume that obtained MIPs, after one sorption-desorption cycle, have to be disposed and thus final score is negatively affected. However, such penalty does not likely correspond with the real stability and reusability of MIPs. It is well-known that MIPs are stable and reusable as a consequence of the great chemical stability of the main polymer backbone of



(meth)acrylic MIPs consisting exclusively of carbon atoms. In this sense, MIP stability and reusability are in line with green chemistry principles, since the polymer can be used repeatedly and thus the amount of solid wastes is reduced. However, in parallel, MIPs discharged in the environment should be avoided since their great stability prevents them to be easily degraded. At the best of our knowledge, studies on the (bio)degradability of MIPs are very scarce. For instance, Paruli et al. [61] studied radical-mediated thiol-yne chemistry as a new MIP synthesis route, which allows the incorporation of ester-based polythiols into the polymer network, rendering MIPs hydrolysable under basic and acidic conditions, potentially facilitating their degradability in the environment. Recently, bio-based MIPs were synthesized using a vegetable oil-derived cross-linker, epoxidized soybean acrylate (ESOA) [62]. ESOA-based MIPs showed sensitivity to a fungal lipase, and thus such MIPs could be degraded by the enzyme. These two examples demonstrate that the obtainment of both reusable and degradable MIPs is already possible and further studies in this area are expected in the near future.

4. Conclusions and future remarks

In this work, AGREEMIP tool has been used for assessing the greenness of 30 synthesis procedures of MIPs employed in sample preparation. Selected procedures, mainly published during last 5 years, were those defined in the literature as eco-friendly, sustainable, green solution or greener. After evaluation, it was noted that the average total value of AGREEMIP assessment was 0.49, with most of them reaching scores in the 0.4-0.6 range. In this sense, it seems clear that synthesis procedures are characterized by a moderate degree of greenness and thus, in general, there is an abuse of using sustainability-related terms to define them. Even in some cases, obtained AGREEMIP scores for some synthesis procedures were lower than 0.3, and obviously they cannot be considered as green approaches.



Accordingly, to avoid confusion, it would be desirable to omit terms such as 'green' or 'sustainable' when defining current MIP synthesis processes, as just changing a single step to a more sustainable solution does not mean that the whole synthesis process becomes green. In this sense, AGREEMIP tool appears as a simple way of evaluating the greenness of MIP synthesis procedures and its use is highly recommended. By carrying out a proper greenness assessment, it will be easier to identify weaknesses in the synthesis process and thus which steps need to be improved. In this regard, by carefully observing the 30 papers evaluated in this work, it seems clear that the use of large amounts of toxic solvents as porogens and/or as washing solutions for template removal appears to be one of the key aspects in need of improvement. In addition, the amount of solid waste generated should be reduced by avoiding single-use materials and/or by using the entire polymerization mixture in *in situ* polymerization approaches towards the obtainment of miniaturized MIP formats (i.e. imprinted monoliths as fibers for SPME).

It should also be emphasized the fact that, for the preparation and appropriate modification of the polymer material carrier, significant amounts of solvents and reagents are consumed. These activities should also be taken into account when assessing the green nature of the newly obtained MIP. Unfortunately, this fact is very often overlooked and considered as an element that does not belong to the classical MIP preparation procedure. Therefore, also at this stage of development of a new type of selective molecularly imprinted sorbents, it is necessary to try to find more pro-environmental solutions in the form of less toxic and harmful solvents and reagents. Finally, last but not least, publishing information on the development of a new type of MIPs must include data on whether the material is single-used or reusable. The lack of such information makes it necessary to assume the disposability of the developed material every time.



CRedit authorship contribution statement

Mariusz Marć: Writing – original draft, review & editing, Investigation, Data curation. Antonio Martín-Esteban: Writing – original draft, review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data supporting this article have been included as Supplementary Information.

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Figure legends

Figure 1. The fourteen principles of green molecular imprinting expressed as the mnemonic device “GREENIFICATION”. Reproduced from ref. [20] with permission from John Wiley & Sons.

G	Generate minimal waste, appropriate waste treatment, recovery of waste to produce useful products
R	Renewable innocuous reagents
E	Expanding solvent-less/solvent-free imprinting approaches
E	Eliminate template through use of green solvents or development of solvent-free methods
N	No post-imprinting to avoid the consumption of auxiliary substances
I	Implement polymerization at mild conditions
F	Faster imprinting time
I	Improved degradability of MIPs at environmental conditions after use
C	Controlling polymerization without energy waste
A	Aqueous media as worthy porogen and solvent
T	Templating once, repeated use
I	Increase operator safety
O	Optimization via computational modeling, NIPs replacing MIPs
N	Note to design self-cleaning MIPs

Figure 2. Pictograms obtained using AGREEMIP assessment of synthesis procedures for the obtainment of: (a) conventional magnetic MIP [43]; (b) magnetic MIP with ionic liquid as co-solvent [53]; (c) truly green MIP using sustainable monomers and water as porogen [38]; (d) hydrophilic MIP [45]; (e) water-compatible core-shell MIP [46]; (f) polydopamine-based MIP [52].

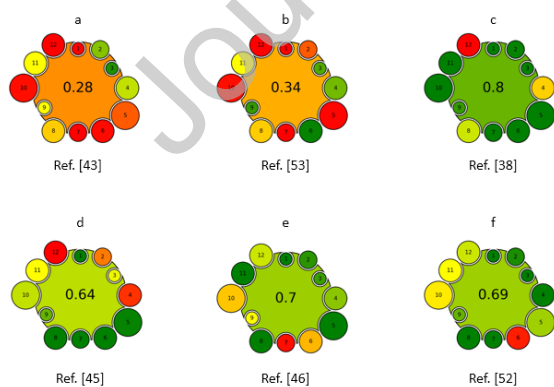


Table 1. Weights for the MIP synthesis analysis*

Criterion No.	Criterion description	Weight
1	Removal of polymerization inhibitors	1
2	Functional monomer	2
3	Template	1
4	Cross-linking agent	3
5	Porogen/solvent	4
6	Other reagents, adjuvants, or carriers	3
7	Core/particles preparation and surface modification	2
8	Polymerization initiation	3
9	Size of polymer particles	1
10	Template elution solvent	4
11	Template elution technique	3
12	Final product reusability	3

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Table 2. Summary of AGREEMIP analysis performed for selected MIP preparation procedures identified as more environmentally friendly or more economical solution.

Functional monomer(s)	Template(s)	Cross-linker	Solvent	3 of the most challenging factors in MIP preparation protocol	Final Agree MIP score	Ref
chitosan	valsartan; losartan	Lack of data or not used as a classical reagent	acetic acid	6. Other reagents, adjuvants, or carriers 7. Core/particles preparation and surface	0.48	[26]

				modification 10. Template elution solvent		
MAA	propazine	EGDMA	formic acid : L-menthol	1. Removal of polymerization inhibitors 10. Template elution solvent	0.61	[30]
3-amino-1,2,4-triazole	azinphos-methyl; parathion methyl	EGDMA	water	7. Core/particles preparation and surface modification 10. Template elution solvent 12. Final product reusability ^a	0.46	[33]
MAA	amiodarone	EGDMA	acetonitrile	5. Porogen/solvent 7. Core/particles preparation and surface modification 10. Template elution solvent	0.48	[34]
4-vinylpyridine	paclitaxel	EGDMA	acetonitrile	6. Other reagents, adjuvants, or carriers 7. Core/particles preparation and surface modification 10. Template elution solvent	0.45	[35]
caffeic acid;	azinphos-ethyl; parathion-ethyl	EGDMA	90% aqueous ethanol;	7. Core/partic	0.40	[36]

choline chloride; formic acid			polyethylene glycol	les preparation and surface modification 10. Template elution solvent 11. Template elution technique		
acrylamide; acrylic acid; N-isopropylacrylamide	S-metolachlor	N,N'-methylenebis(acrylamide)	water	2. Functional monomer 11. Template elution technique 12. Final product reusability ^a	0.51	[37]
itaconic acid	enoxaparin	N,N'-methylenebisacrylamide	water	12. Final product reusability ^a	0.80	[38]
short amylose	λ -cyhalothrin	tetrafluoroterephthalonitrile	N, N'-dimethylformamide	8. Polymerization initiation 10. Template elution solvent 11. Template elution technique	0.38	[39]
caffeic acid; glutamic acid	T1 caffeine-H ₃ PO ₄ ; T2 N-(diethoxyphosphinothioyl)-L-phenylalanine	EGDMA	choline chloride; glycerol; 70% ethanol	10. Template elution solvent	0.52	[40]
L-tyrosine; L-tryptophan	T1N-(diethoxyphosphinothioyl)-L-tyrosine; T2 phenyl carbamate	EGDMA	ethanol:water	7. Core/particles preparation and surface modification 10. Template elution solvent	0.49	[41]
caffeic acid; choline chloride; formic acid; beta-cyclodextrin	rifampicin	EGDMA	methanol	5. Porogen/solvent 7. Core/particles	0.34	[42]

				preparation and surface modification 10. Template elution solvent		
acrylic acid	ractopamine	EGDMA	acetonitrile	6. Other reagents, adjuvants, or carriers 7. Core/particles preparation and surface modification 10. Template elution solvent	0.28	[43]
MAA	malathion	EGDMA	chloroforme	5. Porogen/solvent 10. Template elution solvent 12. Final product reusability ^a	0.33	[44]
APTES	rhodamine B	TEOS	acetic acid	4. Cross-linking agent 12. Final product reusability ^a	0.64	[45]
APTES	hydrochlorothiazide	TEOS	water	7. Core/particles preparation and surface modification	0.70	[46]
MAA	norfloxacin; enrofloxacin	EGDMA	acetonitrile: methanol	5. Porogen/solvent 10. Template elution solvent 12. Final product reusability ^a	0.47	[47]
methacryloyl chloride	imidacloprid	EGDMA	Lack of data or not used as a classical reagent	6. Other reagents, adjuvants, or carriers	0.38	[48]

				7. Core/particles preparation and surface modification 10. Template elution solvent		
2-hydroxyethyl methacrylate	levofloxacin; 1,6-hexa-3,3'-bis-1-vinylimidazolium bromine ([BVIM]Br)	N,N'-methylenebisacrylamide	water	4. Cross-linking agent 10. Template elution solvent 11. Template elution technique	0.52	[49]
1-allyl-3-vinylimidazole bromide; 2-hydroxyethyl methacrylate	bisphenol A	N,N-methylenebis(acrylamide)	water	4. Cross-linking agent 10. Template elution solvent 11. Template elution technique	0.56	[50]
phloroglucinol	phenylephrine hydrochloride	hexamethylenetetramine	DES and water	8. Polymerization initiation	0.61	[51]
dopamine hydrochloride	erythrosine B	Lack of data or not used as a classical reagent	tris-(hydroxymethyl)-aminomethane	6. Other reagents, adjuvants, or carriers	0.69	[52]
MAA; ionic liquid (BMIM ⁺ PF ₆ ⁻)	carbaryl	EGDMA	acetonitrile	5. Porogen/solvent 7. Core/particles preparation and surface modification 10. Template elution solvent	0.34	[53]
p-vinyl benzoic acid	venlafaxine	EGDMA	dimethyl sulfoxide	10. Template elution solvent	0.61	[54]

				12. Final product reusability ^a		
1,4-butanediyl-3,3-bis'-1-vinyl imidazolium chloride; 2-acrylamide-2-methylpropanesulfonic acid	tylosin	N,N'-methylenebisacrylamide	water	10. Template elution solvent	0.63	[5 5]
chitosan; MAA	icariin	epichlorohydrin	2% acetic acid	4. Cross-linking agent 6. Other reagents, adjuvants, or carriers 10. Template elution solvent	0.32	[5 6]
MAA; N-Isopropyl acrylamide	sulfamethazine	EGDMA	acetonitrile	1. Removal of polymerization inhibitors 4. Cross-linking agent 6. Other reagents, adjuvants, or carriers	0.36	[5 7]
dopamine	norfloxacin	dopamine	ethanol	6. Other reagents, adjuvants, or carriers 7. Core/particles preparation and surface modification	0.54	[5 8]
APTES; phenyl trimethoxysilane	bisphenol A; 4-cumylphenol	TEOS	ethanol	7. Core/particles preparation and surface modification 10. Template elution solvent 11. Template elution technique	0.55	[5 9]

choline chloride; MAA	vanillin	EGDMA	DMF	5. Porogen/solvent 6. Other reagents, adjuvants, or carriers 7. Core/particles preparation and surface modification	0.33	[60]
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^aFinal product reusability – this point was highlighted due to the fact that in the paper there was a lack of information about the reusability of MIP. Therefore, the value for the worst-case scenario was adopted (single use of MIP)

Abbreviations: APTES - (3-Aminopropyl)triethoxysilane; DES – deep eutectic solvent (choline chloride and 1,4-butanediol); DMF – Dimethylformamide; EDGMA - ethylene glycol dimethylacrylate; MAA - methacrylic acid; TEOS - tetraethyl orthosilicate

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Graphical Abstract



Declaration of interests

- The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
- The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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