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# REVIEW ON THE APPLICATION OF DUMMY TEMPLATE MOLECULARLY IMPRINTED POLYMER ADSORBENT IN FOODS SAMPLES

## (Ulasan Mengenai Penggunaan Polimer Tercetak Molekul Templat Dami Sebagai Penjerap dalam Sampel Makanan)

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**Abstract**

A major concern was raised as several contaminants including pesticides, pharmaceuticals, and food additives that presence in foods and beverages and induce major effects in humans and food safety. Owing to significant matrix effects, current techniques for identifying harmful substances in food have significant disadvantages. New 'intelligent' adsorbents based on molecularly imprinted polymer (MIP) that exhibits high selectivity and affinity towards targeted contaminants have been developed. The adsorption/desorption kinetics are unfavorable, and mass transfer slows down due to poor site accessibility of the targeted molecules and the heterogeneous distribution of binding sites. Furthermore, the majority of the typical MIPs were made using a single template, whose recognition sites were only for one template molecule were unable to demonstrate high affinity and selectivity for multiple analogues due to the limited capacity and selectivity of typical MIPs. To overcome these shortcomings, dummy-template MIP (DMIP) was prepared by employing similar chemical structures with the targeted analytes as the templates to enhance the selectivity. This review discusses the selection of each component involved in molecular imprinting and its application in various extraction techniques. The related challenges are also described to provide insights for future research focusing on DMIPs for contaminants in food samples.

**Keywords**: dummy template, molecularly imprinted polymer, food additives, pesticides, veterinary drugs

**Abstrak**

Kewujudan bahan cemar seperti racun perosak, farmaseutikal, dan bahan penambah dalam makanan dan minuman telah menimbulkan kebimbangan yang tinggi, terhadap kesihatan manusia dan keselamatan makanan. Teknik penentuan bahan berbahaya dalam makanan mempamerkan kelemahan disebabkan oleh kesan matriks makanan. Penjerap "pintar" baharu yang terdiri daripada polimer tercetak molekul (MIP) berdasarkan templat dami telah dibangunkan. Teknik ini menunjukkan tahap kepilihan dan daya tarikan yang tinggi terhadap bahan cemar yang disasarkan. Kinetik penjerapan/nyahjerapan tidak memuaskan menjadikan proses pemindahan jisim menjadi perlahan. Ini kerana, pengedaran tapak pengikatan yang berbeza dan kebolehcapaian

tapak molekul yang disasarkan adalah lemah. Selain itu, kebanyakan MIP kebiasaannya menggunakan satu templat yang menyebabkan tapak pengecaman hanya sesuai untuk satu molekul templat dan tidak dapat menghasilkan daya tarikan dan selektiviti yang tinggi untuk berbilang analog disebabkan kapasiti dan kepilihan MIP biasa yang terhad. Maka, penyediaan MIP berdasarkan templat dami (DMIP) menggunakan struktur kimia yang serupa dengan sasaran analit sebagai templat untuk meningkatkan selektiviti adalah kaedah penting untuk mengatasi kelemahan ini. Ulasan ini membincangkan pemilihan setiap komponen yang terlibat dalam pencetakan molekul dipilih dan penggunaan dalam pelbagai kaedah pengekstrakan. Selain itu, ulasan ini juga membentangkan perspektif dalam menghadapi cabaran yang berkaitan DMIP untuk penyelidikan masa depan bagi bahan cemar dalam sampel makanan.

**Kata kunci:** templat dami, polimer tercetak molekul, bahan penambah makanan, racun perosak, ubat veterinar

## Introduction

Veterinary medicine, food additives and pesticide residues in food have drawn global attention because of their potential to cause health issues. However, it is extremely difficult to track and manage every food manufacturing and distribution chain since prolonged food scandals demonstrate that issues can still develop in spite of stringent food regulations [1]. The influence of several, complex matrix components makes it difficult to directly detect traces of analytes. The low levels of food contaminants in food of animal origins and the matrix effects need the adoption of an appropriate clean-up and pre-concentration technique prior to the quantitative analysis [2]. Thus, sample preparation becomes an essential step for complex sample matrices. The most popular technique for preparing samples for traces of analytes in food samples is solid-phase extraction (SPE), which uses a variety of sorbents, including as Oasis WCX, HLB, silica-based sorbents, and functionalized nanomaterials [3]. Since the majority of these materials lack specificity, undesirable compounds may co-extract with target analytes when working with complex foods. Therefore, molecularly imprinted polymers (MIPs), appeared in response to this demand.

Molecular imprinting can be defined as a technique that create the artificial template-shaped of recognition sites which specifically pair the forms, sizes, and function-groups of the specific molecules in polymer matrix [4]. Since MIP selectively separates and concentrates target molecules from complicated samples, it is considered as an excellent technique because of its special recognition sites that are cross-linked on the surface of the substrate [5]. The MIP also has a high potential to be an effective, simple, stable, reusable, and template-specific option for the determination of various analytes present in food and beverages samples which outperform other analytical procedures since it can achieve enhanced trace targets molecules from complex matrix; hence, making it suitable to quantify targets with low limit of detection (LODs) while maintaining the target molecules and their structural analogues for higher specific and sensitivity of detection compounds [4,5]. The MIPs were mostly synthesized in bulk polymerization. In most cases, covalent or non-covalent interactions between the functional monomer and the target molecule occurred during polymerization while a cross-linking agent was present. Following the template removal, the polymer will be left with specific, recognizable three-dimensional (3D) voids which exhibit selective recognition for the specific target molecules [6]. Owing to the aforementioned molecular memory, the complementary cavities will likely rebind to the template with high selectivity and high affinity. They are additionally able to use the MIP technique to differentiate between the target molecule and other molecules in the matrix. In comparison to other identification systems, MIPs have contributed many adaptations in fields including extraction and separation, drug delivery, chemical sensors and artificial antibodies due to their high stability, reusability, low cost and simple preparation [1,7]. Selectivity in the polymerization of target analytes is a highly distinctive characteristic of MIPs in comparison with other materials. Their distinct characteristic renders them an innovative substitute for catalysts and adsorbents. A "molecular imprinting effect" can be observed in spherical particles, bulk monomers and surface imprinting when corresponding 3D cavities and the appropriate functional group are present. The identification of advanced developments in molecular

imprinting process for trace analysis in contaminated food samples are discussed in this review. Based on the recently published papers, researchers are keen on using molecularly imprinted polymers as sensitive analysis tools in food samples. In spite of this, there are some drawbacks when using the traditional methods for preparation of MIPs. For instance, the bulk polymerization process requires the polymer to be crushed to the appropriate size, which lowers the yield of the polymer and may destroy the affinity sites. Consequently, partial template removal, restricted binding capability, and poor mass transfer result from the laborious process of removing the original templates that are inside the bulk materials (template leakage) [8].

Dummy template molecular imprinted polymer (DMIP) is a branch of MIP developed to create a multitude of recognition sites types in a single MIP synthesis [9]. DMIP has piqued interest due to its ability to be used for multiple analytes in a single sample, making it more cost-effective in a short span of analysis time. Some recent findings that demonstrated excellent analyte recognition abilities when using DMIP include fluoroquinolone antibiotics [10–12], organophosphorus [9,13], patulin [14], phenothiazine [15] and sulfonamide [16] in food samples. While contrasted to traditional single template MIPs, DMIP can potentially be used to generate a multitude of recognition sites that could each selectively recognise a group of analytes at the same time. As a result, it may be possible to reduce the quantity of experiments, chemical usage, waste production, cost, and time required for analysis. However, MIPs' susceptibility to template molecule leakage could lead to faulty quantitative measurement of trace analytes and the generation of waste that could be hazardous. In order to overcome such challenges, the target molecule has been replaced with a synthetic dummy template that is similar in size, conformation, and functional groups with the targeted analytes [17]. For an instance, Zhao et al. have developed the DMIP based on magnetic–$NH_2$@GO@MIP as adsorbent in magnetic solid phase extraction (MSPE) of pyrethroids in fruit juices. In this case, the DMIP was prepared by means of the less hazardous than pyrethroid dummy surface molecular imprinting process, which involves employing 3-phenoxybenzoic acid as the dummy template, ethylene glycol dimethacrylate (EGDMA) as the cross-linker and acrylamide as the functional monomer [17]. The developed DMIP provided specific recognition sites with excellent adsorption capacity. On the other hand, imine-linked molecularly imprinted covalent organic frameworks were successfully synthesised to extract cyanopyrethroids, with fenvalerate used as the dummy template. The synthesized DMIP has low detection limits, excellent chemical stability, high selectivity and adsorption capacity [18]. MIPs have been widely accepted and used in a range of research disciplines, including the analysis of food samples, due to their outstanding modification capabilities, low cost, and ease of preparation. Combining DMIP with other state-of-the-art technologies, like nanotechnology and electrochemical technology, allows for adherence to a wider range of target molecular recognition requirements. With this integration, the controllability and application attributes of molecularly imprinted materials can be improved. The enhancement of food safety and improvement of life quality has been extensively acknowledged as a result of the success made by DMIPs in many domains.

Upon conducting a comprehensive literature review, it was found that, in contrast to traditional MIP techniques (single template), a relatively limited number of publications had been published for DMIP for the determination of pesticides, food additives, toxins and veterinary drugs from food and beverages samples. Consequently, this review covered the development of DMIP adsorbents, encompassing the technique of molecular imprinting, the different chemicals ought to establish DMIPs, including solvents, templates, and monomers, as well as an overview of the applications of DMIP that have been reported in the literatures. In light of many analytes found in foods originating from animals, this review aims to objectively review DMIPs, their benefits and drawbacks including challenges, and their potential applications in food analysis.

## Synthesis of DMIP

Since MIPs have the capability to pre-treat and pre-concentrate the target molecules in complicated samples with high selectivity, cheap and strong durability, they are a highly popular choice among researchers.

Considering this, MIPs have been used in food sample preparation due to their exceptional qualities in the areas of clean-up, extraction, quantification, recovery and removal.

Well-known chemical processes including copolymerization by crosslinking, grafting or coupling—which use crosslinkers, functional monomers and template molecules—are the most widely used techniques to synthesize MIPs. The spatial arrangement in which the template configuration and conformation persist as cavities may be determined by the polymerization process of functional monomers and cross-linkers. The removal of the template to rebind the analyte can leave partial or complete sterile and chemical cavities (imprints) in the polymer network. [6].

Typically, the MIPs synthesis are inseparable from functional monomers and template molecules, regardless of which synthesis method is chosen. The four steps of the preparation process, which can be categorized in four steps: (1) the development of composites (such as graphene oxide, silica, carbon materials, metal organic framework) with an ideal surface area and pore structure to serve as a imprinting substrate; (2) the generation of monomer-template molecule complexes via non-covalent, covalent or semi-covalent reaction between functional monomers and template molecules; (3) providing a rigid polymer around the monomer-template molecule complexes; (4) utilising an appropriate method to remove the polymer's template molecules, leaving behind specified recognition sites that complement the template molecules in terms of their chemical function, structure, and shape [7]. In this instance, during polymerization, stable template-monomer complexes have to develop chemically and thermally, and the template molecules possess inert functional groups. It is significant to keep in mind that in traditional MIP synthesis, the target molecule is usually utilised as a template molecule. The selection of functional monomers is another significant choice in polymerization, since these molecules must interact strongly with the template molecule during the pre-polymerization stage. In the non-covalent approach, these interactions are usually defined by hydrogen bond acceptor and donator [19].

In recent years, several novel methods were developed to resolve the problem related to template leakage in the typical MIP synthesis. An advance development of MIP was introduced in order to overcome those shortcomings, namely dummy-template MIP (DMIP) that capable to enhance the selectivity towards targeted analyte. The DMIP has increasingly fascinated more interests and achieved great advances as it allows more than one analyte that belongs to the same group to be extracted using the same DMIP adsorbent [20]. DMIP demonstrated greater affinity and selectivity for the two templates in comparison to the use of single-template MIPs or non-imprinted polymers [11]. DMIP are generated in a similar manner as MIP, using specific cross linker and functional monomers, however with the incorporation of one or two dummy templates (not the same compound to the target analytes) to enhance the selectivity of the target molecules. Table 1 summarises the various composition and preparation methods of DMIPs as reported in the literatures.

DMIP has the ability to selectively rebind templates and analogues based on the artificially tailored "recognition" effect [21]. It is crucial to employ the right compounds with a specific binding affinity in preparing the ideal DMIP with excellent adsorption performance and high selectivity to meet with different application requirements. Molecular imprinting in DMIPs requires the interaction of functional monomer with the template and the formation of suitable cavities. Increased stability and high binding capacities resulted from stronger interaction between the functional monomer and the template, which enhance the selectivity and recognition capabilities of cavities [22]. After the template molecules are removed, functional monomers are attached around them via the cross-linker and maintained the hard structure of the DMIP. The cross-linker has three functions in the DMIP; (i) to regulate morphology of the synthesise polymer; (ii) to provide the polymer mechanical stability; and (iii) to ensure the stability and shape of the cavities. Solvents in molecular imprinting are typically referred to as porogens (to generate porosity). Porogens also serve as dispersion agents during the DMIP preparation process. The appropriate selection of solvent can lead to the more macroporous polymer structure and increasing its

contact surface. In actuality, the porogen may penetrate the polymer structure during the polymerization process and are then removed during the treatment stage [23]. Acetonitrile (ACN), dimethyl sulfoxide (DMSO), chloroform, N,N-dimethylformamide (DMF) and toluene are examples of porogens that are frequently utilised [24,25]. The use green co-porogen such as choline chloride and glycerol deep eutectic solvent (DES) facilitated the formation of template. This may due to the fact that DES has a high viscosity, the templates can disperse steadily, which aids in the formation of imprinting cavities [13].

Other important components of DMIP synthesis includes cross-linkers and initiator. Cross-linkers serve as rigidifying agents, fixing the functional monomers around the template while retaining the geometry of the cavities and the exact location of the functional groups in the polymer even after the template is removed. The cross-linker is essential since it regulates the polymer's rigidity and flexibility [26]. EGDMA is the most commonly used crosslinker as it may provide adequate rigidity during the imprinting process [10,12,27].

However, initiators are necessary for the chemical polymerization process to occur. The most widely utilised reactions are those that are based on free radicals, in which the polymerization process begins with the breaking of the azo or peroxide bonds of the initiator as a result of high enough thermal or UV photonic activation energy. Because of their electrophilic qualities, the free radical forms produced by this method target the vinyl groups of the crosslinker or the functional monomer. The most common initiator of free radical polymerization is azoisobutyl nitrile (AIBN) [26].

To develop DMIP with high selectivity towards the target analytes and minimum template leakage, the selection of dummy template is very critical. However, the susceptibility of MIP to template molecule leakage could lead to inaccurate quantification of trace analytes and the generation of waste that could be hazardous. In order to overcome these challenges, the target molecule (as template) has been replaced by a dummy template that is identical in size, shape, and functional groups. For instance in a study by Sun et al. [10], a number of unique DMIPs have been developed as highly selective sorbents for fluoroquinolones (fleroxacin, enrofloxacin, norfloxacin, ofloxacin, ciprofloxacin, pefloxacin, gatifloxacin and lomefloxacin) utilising the non-poisonous chemical, daidzein as dummy template from fish samples. When employed for the selective extraction of eight fluoroquinolones, the DMIP synthesized using porogen (dimethylsulfoxide−acetonitrile (1:1.8, v/v)) exhibited the most significant imprinting factors (IF) for fluoroquinolones, ranging from 13.4–84.0.

On the other hand, a dummy surface imprinted polymer employing 3-phenoxybenzoic acid has been developed recently for the extraction pyrethroids from fruit juices using magnetic solid phase extraction (MSPE) . The DMIP was synthesized using acrylamide as the functional monomer and EGDMA as the cross-linker. 3-phenoxybenzoic acid is a less harmful template than pyrethroids was used as dummy template. The material has strong adsorption capacity and specific recognition sites. In another research, cyanopyrethroids were efficiently extracted using fenvalerate as the dummy template from imine-linked molecularly imprinted covalent organic frameworks. The synthesised materials showed excellent selectivity, significant adsorption capability, low detection limits and improved chemical stability [18].

Table 1. Summary of various composition and preparation methods of DMIPs as reported in the literatures.

| Analytes | Template | Monomers | Cross linker | Porogen | Initiator | Ref. |
|---|---|---|---|---|---|---|
| Fleroxacin, ofloxacin, norfloxacin, pefloxacin, ciprofloxacin, lomefloxacin, enrofloxacin and gatifloxacin | Daidzein | 4-VP | EGDMA | Dimethylsulfoxide– acetonitrile (1:1.8, v/v) | AIBN | [10] |
| MCPA, 4-chlorophenoxy acetic acid, 2,4-D and 2,4-dichlorophenoxy propionic acid | Phenoxyacetic acid | 4-VP | EGDMA | N,N-dimethylformamide | AIBN | [24] |
| Fenpropathrin, lambda-cyhalothrin, cyfluthrin, fenvalerate and deltamethrin | 3-phenoxybenzoic acid | Acrylamide | EDGMA | Acetonitrile | AIBN | [17] |
| *N*-nitrosodibutylamune, *N*-nitrosodinpropylamine, *N*-nitrosodiphenylamine, *N*-nitrosopiperidine, *N*-nitrosomorpholine | Benzhydrol, 5-nonanol and *N*-formylpyrrolidine | MAA | EDGMA | Acetonitrile-$H_2O$ (3:1, v/v) | AIBN | [25] |
| Carbofuran, carbaryl, methiocarb, azinphos-ethyl, azinphos-methyl, parathion-ethyl, parathion-methyl, diazinon, fenitrothion, chlorpyrifos and profenofos | Tyrosine and tryptophan | - | EDGMA | Ethanol:water (80:20, v/v) | Potassium peroxodisulfate | [27] |
| Fluoroquinolones and sulfonamides | Pipemidic acid (PA) and sulfabenzamide (SB) | MA | DGDMA | Chloroform | AIBN | [12] |
| Azinphos-methyl, azinphos-ethyl, parathion-methyl, parathion-ethyl, | Caffeine-$H_3PO_4$ *and* *N*-(diethoxyphosphinothioyl)- | Caffeic acid and glutamic acid | EDGMA | 50.0 mL of 70% ethanol and 1.0 mL of DES (choline | Ammonium peroxodisulfate | [13] |

| Analytes | Template | Monomers | Cross linker | Porogen | Initiator | Ref. |
|---|---|---|---|---|---|---|
| fenitrothion, profenofos and chlorpyrifos | L-phenylalanine | | | chloride:glycerol) | | |
| Patulin | 6-hydroxynicotinic acid | MAA | Trimethylolpropane trimethacrylate | Methanol | AIBN | [14] |
| Estrone, 17β-estradiol, estriol, ethinylestradiol, dienestrol, diethylstilbestrol and hexestrol | Genistein | MAA | EDGMA | Toluene | AIBN | [28] |
| Enrofloxacin and ciprofloxacin | Gatifloxacin | 1-vinylimidazole | EDGMA | Acetonitrile: 1-octanol (1:1 v/v) | - | [29] |
| Cloprostenol | Bimatoprost | 2- vinyl pyridine | EDGMA | Ethanol | AIBN | [30] |

The use of single dummy template was restricted to the selectivity of single group analyte. To address this drawback, two (dual) dummy template with combined molecular structure that are almost similar with both groups of the targeted analytes. With a dual dummy template MIP (DDMIP), it is possible to establish multiple forms of recognition sites that can distinguish a particular group of targets selectively. As a result, it may be possible to reduce the number of trials, chemical usage, waste production, expenditure, and time required for analysis. For instance, a dual dummy templates MIP (DDMIP) were used for simultaneous extraction of eight fluoroquinolones and eight sulfonamides by Song et al., [12]. Pipemidic acid and sulfabenzamide are selected as dual dummy templates for both drug classes in samples of chicken and pork. The SPE column containing DMIP adsorbent can be reused for about 80 times. The column exhibits high recoveries (92 – 99%) and high absorption capacities (34.9–74.2 μg) to these pharmaceuticals, indicating that template leaking was at minimum rate when compared to a single dummy template. The recoveries from the spiked blank samples ranged from 86.1 to 109.4%, and the limits of detection for the two classes of pharmaceuticals in meat were in the range of 1.0–3.4 ng/g [12]. Both methods that were described, DDMIP showed higher selectivity towards the targeted analytes with excellent recoveries. Furthermore, the utilisation of pipemidic acid and sulfabenzamide dummy templates facilitates simultaneous extraction of multiple analyte groups through various recognition site types that can concurrently selectively distinguish a group of targets.

Traditional methods of producing MIPs requires a large amount of hazardous organic solvents time and energy. In order to overcome these challenges, new MIPs have been developed based on green chemistry principles. Recently, an innovative biobased magnetic dual-DMIP with caffeine-$H_3PO_4$ with N-(diethoxyphosphinothioyl-l-phenylalanine) as dummy template was developed for the highly selective enrichment of organophosphorus pesticides (OPPs). The substance demonstrated rapid adsorption in approximately 20 s, as well as strong adsorption capacities and imprinting factors [13]. In another study, a novel magnetic dual-DMIP-derived from mangosteen peel waste was developed as adsorbent for MSPE for the determination of pesticides (OPPs and carbamate (CMP)) in fruit and vegetable

samples using tryptophan and tyrosine as dummy template [27]. This work employed a sustainable method to develop the DMIP using: (1) dual-dummy-template technology; (2) a green porogenic solvent (ethanol:water); (3) amino acids as biocompatible functional monomers and (4) a biobased magnetic substrate. The work showed low limit of quantification (LOQ) and acceptable accuracy for the simultaneous extraction of OPPs and CMP under optimum conditions.

By applying an imprinted layer on the surface of carriers through coating or grafting, surface MIP can be produced. In order to address the drawbacks of the classic MIPs' poor affinity and prolonged mass transfer, the imprinted binding sites are consequently found on the surface of the support materials. Currently, a few materials, such as nanotubes, magnetic nanoparticles and graphene have been used as solid supports for surface MIP. By using a surface molecular imprinting approach, magnetic multiwalled carbon nanotubes DMIP (mag-MWCNTs-DMIPs) has been developed as MSPE adsorbent of phenoxy carboxylic acid herbicides in cereals. The recoveries for the analytes in various cereals under the ideal MSPE conditions varied from 86.7 to 95.2%, with intra- and inter-day precision less than 8.5% and 10.6%, respectively. On the other hand, magnetic amine-graphene oxide ($Fe_3O_4$-$NH_2$@GO) was used as the carrier for DMIP [17]. The $Fe_3O_4$-$NH_2$@GO@MIPs exhibited superior adsorption properties and selectivity for five pyrethroid pesticides in fruit juices samples, as confirmed by adsorption and selectivity studies conducted on both $Fe_3O_4$-$NH_2$@GO@NIPs and $Fe_3O_4$-$NH_2$@GO@MIPs. Based on recent work in our lab, we have successfully incorporated magnetic graphene oxide (MGO) as the carrier for dual-DMIP (DDMIP) as MSPE adsorbent for selected fluoroquinolones. The schematic diagram of the DDMIP-MGO synthesis and MSPE analysis is depicted in Figure 1. In this study, pipemidic acid and nalidixic acid was selected as the dual dummy templates. As compared to the NIP-MGO, the adsorption performances of DDMIP-MGO towards fluoroquinolones showed higher selectivity and recovery.

**Application of dummy template molecularly imprinted polymer in foods of animal origin**

This section focuses on wide range of analytes including pesticides and veterinary drugs that have been identified and quantified using DMIPs in several extraction techniques. Their advantages and advantages were described based on their performances in term on recoveries and LOD in food of animal origins.

Table 2 summarises the applications of the DMIPs in various food matrices using several extraction techniques. As represented in the Table 2, all of these approaches detected low detection limits in food samples with high recoveries with the use of DMIP in their research.

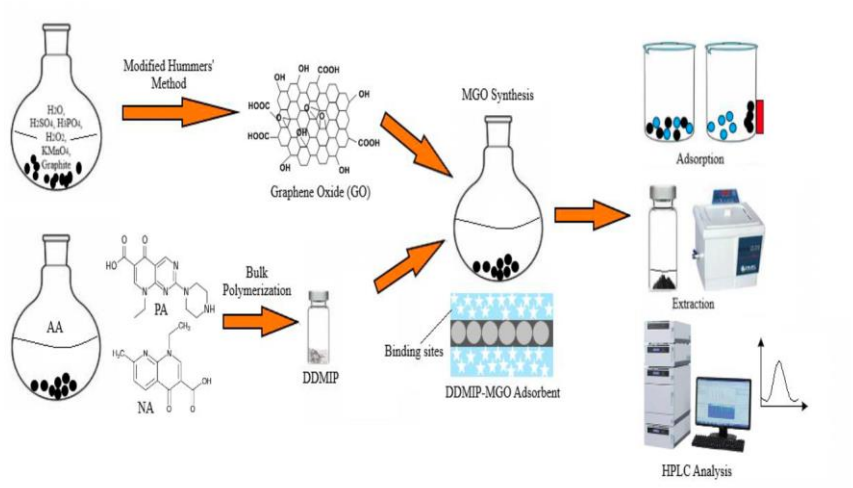


Figure 1. Schematic diagram for synthesis of DDMIP-MGO adsorbent and its analysis

**Food Additives and Toxins**

A vast range of food additives have been created over time to meet the needs of industrial food processing. Throughout its journey from industrial kitchens or production facilities to storage facilities, retail stores, and ultimately customers, processed food is kept safe and wholesome with the use of additives. Additives for food can be made chemically or derived from plants, minerals, or animals. When used excessively, several types of food additives may be hazardous to the well-being of humans [31].

A method was developed to extract and simultaneously extract trace amounts of maltol, ethyl maltol, vanillin and ethyl vanillin, from beverage samples using a combination of high-performance liquid chromatography (HPLC) and MSPE [32]. 3-hydroxy-2,6-bis(hydroxymethyl)-4-pyrone was employed as a dummy template for the new superparamagnetic DMIP ($Fe_3O_4$@MDMIP) using a sol-gel process. The $Fe_3O_4$@MDMIP adsorbent showed a maximum adsorption capacity ($Q_{max}$) of 609.99 mg/g, demonstrating good homogeneity and monodispersity with ranging from 2.07 to 2.71 indicating high selectivity. Under optimum conditions, $Fe_3O_4$@MDMIP demonstrated satisfactory accuracy (2.68–6.91% RSD), good linearity (2.07–463 ng/mL) and high recovery (91.2–107.1%). The enrichment factors were between 432 and 484, while the limits of detection varied from 44 to 201 ng/L. The results demonstrated excellent potential in routine analysis of food additives in food samples.

Another work used the precipitation polymerization approach to synthesise the DMIP, employing MAA as the functional monomer and benzhydrol, N-formylpyrrolidine and 5-nonanol as dummy template compounds [25]. In this study, due to the complexity of the N-nitrosamines compounds, 3 dummy templates were used to suit the their chemical structures which consequently affecting the amount of solvents needed for template removal. On the contrary, due to the spherical particles with loose and porous surfaces, the synthesised DMIP demonstrated excellent high adsorption efficiency, adsorption capacity and specific recognition ability towards N-nitrosamines. The developed method demonstrated excellent linearity ($R^2 \geq 0.9985$) under ideal circumstances, and its detection and quantification limits fell within the ranges of 0.03–0.65 ng/g and 0.1–1.95 ng/g, respectively.

With three spiking concentrations (5, 10 and 20 ng/g), satisfactory recoveries (61.0–105.2%) were also obtained with relative standard deviations ranging from 1.20 to 9.76%. The synthesized DMIP concluded that the binding sites in DMIPs were heterogenous based on Scatchard analysis. In addition, the calculated values for $K_d$ were 0.209 µg/mL and the $Q_{max}$ for the high-affinity binding sites was 8.111 mg/g. These findings showed that the N-nitrosamine approach had excellent selectivity, outstanding repeatability, and high sensitivity. As a result, it was an excellent method to enrich and detect N-nitrosamine in challenging food matrices.

A fascinating works have been carried out by He et al., to synthesis DMIP with 1-(2-pyridinylazo)-2-naohthalenol as a dummy template by coating the wells of a regular microplate for use as a chemiluminescence sensor [33]. HPLC-UV was employed to confirm the results of the optimized sensor of the seven Sudan dyes present in egg yolk. In term of selectivity, the DMIP exhibited high IFs (4.1–7.1) for the seven dyes and extremely low IFs (0.1–0.7) for the remaining four competitors (chlorpromazine, tetracycline, sarafloxacin, and amoxicillin). The sensor demonstrated excellent sensitivity (1.0–5.0 pg/mL), a rapid assay procedure (10 min), and a good recovery percentage of 70.5 –92.2%. It is also possible to reuse the sensor five times. Thus, this sensor may prove to be a valuable instrument in detecting Sudan dye leftovers in eggs.

By using 2-oxindole (2-oxin) and 6-hydroxynicotinic acid (6-HNA) as dummy template molecules, AIBN as an initiator, trimethylolpropane trimethacrylate (TRIM) as a crosslinker, methanol as a porogen solvent and MAA as a functional monomer, precipitation polymerization was utilized to effectively prepare DMIP with particular adsorption for patulin. The findings exhibited the high specific adsorption and selectivity of the SPE technique towards patulin, with mean recoveries ranging from 81.3 to 106.3% and %RSD less

than 4.5%. Compared to the quick, simple, affordable, efficient, robust, and secure "QuEChERS" method, the new method demonstrated increased patulin recovery and improved purification for genuine samples [14].

Table 2. The applications of the DMIPs in various food matrices using several extraction techniques

| Analytes | Extraction | Detection | LOD | Recoveries (%) | Samples | Ref. |
|---|---|---|---|---|---|---|
| Cloprostenol | SPE | HPLC-UV | 30.5 ng/mL | 93.0 | Milk | [30] |
| Phenoxy carboxylic acid herbicides | MSPE | UPLC-MS/MS | 0.33 – 1.50 ng/g | 86.7 - 95.2 | Cereals | [24] |
| Pyrethroids pesticides | MSPE | GC-ECD | 0.007 – 0.015 µg/L | 72.1–106.8 | Fruit juices | [17] |
| Food additives | MSPE | HPLC-UV | 44 – 201 ng/L | 91.2–107.1 | Drinks | [32] |
| *N*-nitrosamines | SPE | HPLC-MS/MS | 0.03 – 0.65 ng/g | 61.0–105.2 | Meat products | [25] |
| Organophosphorus and carbamate pesticides | MSPE | HPLC-PDA | 0.05 – 1.49 µg/L | 80.0- 110.0 | Vegetable and fruit samples | [27] |
| Fluroquinolones and sulfonamides | SPE | UPLC-PDA | 1.0 – 3.4 ng/g | 92.0 – 99.0 | Pork and chicken | [12] |
| Organophosphorus pesticides | MSPE | HPLC-PDA | 0.015 – 0.030 µg/L | 80.0–117.0 | Vegetables, fruits and grains | [9] |
| Enrofloxacin and ciprofloxacin | MiMs | UHPLC | 0.3 and 0.7 µg/L | 84.5 - 97.0 | Egg | [29] |
| Sudan dyes | Microplate chemiluminescent sensor | HPLC-DAD | 1.0 – 5.0 pg/mL | 70.5 – 92.2 | Egg yolks | [33] |
| Estrogen | SPE | HPLC-MS/MS | 0.10 – 0.35 µg/L | 88.9 - 102.3 | Milk | [28] |
| Patulin | SPE | LC-MS/MS | 0.05–0.2 ng/g | 81.3 - 106.3% | Apple, apple juice, hawthorn, hawthorn juice, mixed juice, wines, and tomato | [14] |

**Pesticides**

Pesticides are used globally to boost product yields and income and can facilitate the control of insect pests. However, the majority of these pesticide residues have lengthy persistence, low biodegradability, and high chemical stability, all of which significantly jeopardise

the safety of animals and the environment. Therefore, it is crucial for establishing effective methods to identify the present of pesticides in food of animal origins both qualitatively and quantitatively, in addition to enforcing more stringent restricted criteria.

Yuan et al., has developed mag-MWCNTs-DMIPs as adsorbent in MSPE using phenoxyacetic acid as dummy template towards phenoxy carboxylic acid herbicides [24]. The distribution coefficient ($K_d$), selectivity coefficient (α) and relative selectivity coefficient (β) were used to evaluate the selectivity of mag-MWCNTs-DMIPs. Mag-MWCNTs-DMIPs displayed better adsorption capacity for target analytes than mag-MWCNTs-NIPs, but both DMIP have the similar adsorption capacity for the interferential compounds. This is mainly attributed to the presence of phenoxy carboxylic acid imprinted sites with matching functional groups and recognition cavities with appropriate size in mag-MWCNTs-DMIPs. Furthermore, the $K_d$ values of the four phenoxy carboxylic acid compounds were significantly higher than those of structural analogues and β values were larger than 1, indicating that mag-MWCNTs-DMIPs have specific recognition for the analyzed phenoxy carboxylic acid herbicides. Using MSPE UPLC-MS/MS detection, the synthesised mag-MWCNTs-DMIPs demonstrate a fast adsorption rate, satisfying adsorption capacity, and high selectivity. Under ideal MSPE conditions, the mean spiking recoveries for analytes in different cereals ranged from 86.7 to 95.2%.

Zhao et al. employed 3-phenoxybenzoic acid (3-PBA), a common structural unit of five different pyrethroid types, as a dummy template to overcome the issue of template leakage. The developed $Fe_3O_4$-$NH_2$@GO-MIPs-GC-electron capture detection (GC-ECD) achieved satisfactory recoveries with %RSD less than 10.8% for the quantification of pyrethroids in fruit juice [17]. By incorporating other supporting carrier including $Fe_3O_4$-$NH_2$ and GO, the adsorption capacity increased and the feasibility of the synthesised adsorbent also increased. By comparing the $Fe_3O_4$-$NH_2$@GO-MIP and $Fe_3O_4$-$NH_2$@GO-NIP, $Fe_3O_4$-$NH_2$@GO-NIP lower adsorption amounts because of the nonspecific recognition sites. In this study, the imprinting factor (IF) was measured with the IF of 3-PBA and other five pyrethroids were in the range of 1.96 - 2.65.

Magnetic adsorbent based on mangosteen peel DMIP fabricated using tyrosine and tryptophan template molecules was developed [27]. In under 30 seconds, high adsorption capacities ranging from 150.11 to 509.09 mg/g and IF approaching 2.2 were attained. The material was applied for extraction of OPPs and CMPs prior to HPLC analysis. Low limits of quantitation and detection were achieved under ideal circumstances, with ranges of 0.18–5.00 μg/L and 0.05–1.49 μg/L, respectively. Fruit and vegetable samples can be analysed effectively using the established methodology, resulting in satisfactory recoveries of 80–110%. The method showed potential as an analytical methodology for the sensitive enrichment of pesticide residues in vegetable and fruit samples.

An ecologically friendly magnetic DMIP (MDMIP) was developed by using a "one-pot" green synthesis that used mixed-valence iron hydroxide as the magnetic material, a deep eutectic solvent as the co-porogen, and caffeic and glutamic acids as binary monomers [13]. Excellent enrichment factors (940–1310 times), low detection limits (0.003–0.015 μg/L), and linearity ranging from 0.05–500 μg/L were demonstrated by the developed method. The OPPs in vegetable, fruit and grain samples were successfully determined yielding high recoveries (80–119%). This method offered a great deal of promise for assessing OPP residues in challenging matrices.

**Veterinary Drugs**

Veterinarian drug residues in the environment and food have drawn more attention recently since these substances have the potential to bioaccumulate in the food chain and jeopardise human and wild animal health. Overconsumption of residual veterinary drug can lead to allergic reactions, gastrointestinal problems, and bacteria resistant to antibiotics [34]. In a study by Shahzad et al., the selective extraction of cloprostenol from milk sample was developed using bimatoprost as dummy template [30]. Within 20 minutes of MIPs interaction, the kinetic evaluations demonstrated a

significant retention capacity. The polymer yield percentage varied between 53.5 and 92.3%. When determining the analytes from milk samples, the analysis using HPLC-UV revealed limits of quantification and detection of 30.5 and 86.7 ng/mL, respectively. For every milk sample that was spiked with cloprostenol, the recovery was greater than 91.54%. In addition, the studies demonstrated that MIPs exhibited specificity in cloprostenol adsorption when contrasted with other structural analogues.

Exogenous estrogens, such as diethylstilbestrol (DES), ethinylestradiol (EE2), dienestrol (DS) and hexestrol (HEX), among others, have been extensively employed in veterinary medicine to treat illnesses resulting in low levels of estrogen in the body or to enhance the growth of livestock. A technique was developed that employs genistein (GEN) as a dummy template molecule in Pickering emulsion polymerization to specifically identify seven estrogens in milk samples using DMIP-SPE prior HPLC-MS/MS [28]. With a correlation coefficient ($R^2$) of greater than 0.999, the method showed good linearity from 2 to 500 µg/L. For both intra-day and inter-day studies, the estrogens were recovered at three spiking levels (10, 100, and 250 µg/L), with a range of 88.9 to 102.3%. The limit of detection ranging between 0.10 and 0.35 µg/L. The selectivity of the synthesised DMIP towards the selected estrogens showed higher IF (range between 4.8-6.5) as compared the analytes with different analogues. The synthesised DMIP microspheres with the Pickering emulsion procedure generated a highly water-compatible adsorbent with a hollow, porous core structure and regular, uniformly sized pores. Thus, it has been demonstrated that the suggested approach is effective and trustworthy for routinely monitoring trace estrogen levels in complicated matrices like milk samples.

Another notable study was conducted by Yuan et al. using nylon-66 (NY-66) membranes as the subtracts, DMIP membranes (MIMs) were developed based on an eco-friendly "sandwich" method that required minimal organic reagent consumption under mild conditions [29]. The synthesized MIMs provided an exceptional sensitivity and accessible recognition sites. Based on the results obtained, since MIMs have larger surface areas and specific recognition sites for targeting analytes, their $K_d$ values were higher. This suggests that MIMs have a good binding capacity and were utilised for the extraction and recognition of enrofloxacin and ciprofloxacin from egg samples. The "sandwich" technology's synthesis pathway offered a number of benefits, including easy operation, time savings, minimal chemical pollution, and required mild conditions for the synthesis process.

**Conclusion and Future Perspectives**

As reviewed in this article, the ability to distinguish specific analytes in challenging media is demonstrated by the selective affinity obtained by imprinted cavities for multiple types of targets. DMIPs have advanced remarkably in previous years. Here, we addressed in detail the numerous applications of DMIPs as well as their preparation techniques. The DMIPs have been widely used in sample preparation, sensing and enrichment/elimination as they can economically identify and eliminate many targets selectively. DMIP allows more than one analyte that belongs to the same group to be extracted using the same DMIP besides reducing template leakage. This review also breaks down on several components that have to be emphasized while synthesizing DMIP including template selection, functional monomer properties, cross-linker choice and lastly porogen solvent selection and how each component affect the formation and performance of DMIP. The DMIP's performance also been discussed by measure of different metrics, among which are selectivity, stability and reusability, sensitivity as well as recovery.

There has been a noticeable growth in research as well as the implementation of discoveries, even if the DMIP potential is still rather unexplored. Nonetheless, there are still certain areas that could be investigated and improved in the future. The impact of remixing multiple targets and the heterogeneity imprinting sites within the polymer framework, which cause the DMIP selectivity to be lower than that of single template MIPs, should be given consideration. In this case, stepwise preparation method during polymerization process can be used to increase their selectivity. In order to address template leakage issue in DMIP especially in identifying multiple

trace analytes, it can be achieved by using a system enhanced by nanoMIPs, fragment imprinting, dummy templates imprinting, or physical assistance in removing templates. Green and effective polymerization techniques are always required. Sophisticated polymerization technique in a gentle environment is welcome to replace harsh synthetic conditions. Degradable and biocompatible raw materials can be used in an economical and ecologically responsible manner. The polymerisation system may be designed and the recognition mechanism of DMIPs can be analysed using computer and quantum chemistry simulation technologies, which will help in the reasonable and scientific preparation of DMIPs. Green synthesis of DMIPs and their low cost, together with intelligent application, present prospects.

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