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Research Article

Synthesis and Characterization of Magnetic Molecularly Imprinted Polymers Targeting Capsaicin

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Abstract

A novel magnetic molecularly imprinted polymers (MMIPs) was developed for the adsorption of capsaicin, a key component of capsaicinoids widely used in food additives and topical pharmaceuticals. Excessive use of capsaicin can lead to respiratory, skin, and oral disorders, necessitating effective monitoring methods. This study aimed to synthesize MMIPs and magnetic molecularly non imprinted polymers (MNIPs) using 4-vinyl pyridine as the functional monomer and ethylene glycol dimethacrylate (EGDMA) as the crosslinker, combined with an initiator in a 1:4:20 molar ratio. Magnetite nanoparticles (Fe_3O_4) were incorporated to facilitate magnetic separation. Characterization via particle size analyzer (PSA), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) confirmed the successful synthesis of Fe_3O_4 nanoparticles, MNIPs, and MMIPs. PSA analysis for Fe_3O_4 nanoparticles showed an average size of 140.2 nm with a polydispersity index (PI) of 0.313, MMIPs showed an average particle size of 746.6 nm and a PI value of 0.397. FTIR spectra revealed characteristic absorption bands at 3429 cm^{-1} (O-H), 2958 cm^{-1} (C-H), 1732 cm^{-1} (C=O), 1155 cm^{-1} (C-O), and 580 cm^{-1}(Fe-O), indicating successful Fe_3O_4 modification. SEM-EDS analysis showed non-spherical morphology due to bulk polymerization. TEM image results showed Fe_3O_4 nanoparticles were successfully coated with a molecularly imprinted polymer (MIP). The developed MMIPs effectively have a robust synthesis method and thorough analysis, laying the groundwork for future applications.

Keywords: 4-vinyl pyridine, EGDMA, capsaicin, MMIPs, adsorption

1. INTRODUCTION

Capsaicinoids, a group of lipophilic alkaloids derived from vanillylamide and branched-chain C_9-C_{11} fatty acids, are the primary compounds responsible for the pungency of chili peppers [1,2]. Among these, capsaicin and dihydrocapsaicin dominate, constituting nearly 90% of the total capsaicinoid content. Capsaicin, in particular, finds applications beyond the food industry, where it is valued for its anti-inflammatory, antimicrobial, antimutagenic, anti-tumor, antioxidant, and analgesic properties [1,3–5]. It has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the topical treatment of neuropathic pain. However, excessive capsaicin exposure poses significant health risks, including gastrointestinal disturbances such as heartburn and diarrhea and more severe reactions like choking, disorientation, and inflammation, as demonstrated in animal studies where oral doses of 60–80 mg/kg caused severe intestinal inflammation in rats [6,7]. Capsaicin's toxicity is reflected in its acute oral LD50 of 47.2 mg/kg in rats, with a human estimate of 0.5–5.0 g/kg. Given these risks, monitoring capsaicin levels in humans is essential [8]. Moreover, its widespread use in the food and pharmaceutical industries raises environmental concerns due to potential wastewater contamination, necessitating careful monitoring of its presence. Effective and selective extraction methods are crucial for accurately analyzing capsaicin in complex matrices, ensuring safety in human consumption and environmental protection.

Several methods, such as spectrophotometry, gas chromatography (GC), high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-mass spectrometry (LC-MS), have been used for capsaicin analysis, offering high selectivity but often requiring complex and time-consuming preparations [8,9]. Adsorption techniques have emerged as a more efficient alternative, with molecularly imprinted polymers (MIPs) showing significant potential. Traditional methods, including aqueous two-phase systems, macroporous resins, and mesoporous silica, face limited selectivity and low adsorption capacity [1,10,11]. To address these issues, MIPs provide a promising solution, offering high specificity, improved adsorption capacity, and simpler preparation processes for capsaicin analysis.

MIPs are known for their high selectivity and sensitivity in targeting specific compounds [12]. These polymers are synthesized through polymerization of monomers, cross-linkers, initiators, and templates. The template molecules interact with the polymer network via ionic, covalent, or hydrogen bonding interactions. After polymerization, the templates are removed, leaving behind hollow polymers capable of highly selective template recognition [7]. MIPs offer advantages such as good storage stability, excellent recovery and reproducibility, and broad applicability across various sample types [13]. They are effective for analyzing complex samples and are widely used in chemical analyses [12].

Recent studies have explored different methods for capsaicin adsorption, including the use of MIPs with 4vinylpyridine (4-VP) as a functional monomer and azobisisobutyronitrile (AIBN) as an initiator, achieving a maximum adsorption capacity of 30.76 mg/g [2]. Other research has demonstrated successful capsaicin adsorption using MIPs with methacrylic acid as the functional monomer and benzoyl peroxide (BPO) as the initiator[7]. Both studies utilized ethylene glycol dimethacrylate (EGDMA) as a cross-linking agent.

Although molecularly imprinted polymers (MIPs) are effective, traditional separation methods like filtration or centrifugation can be time-consuming and costly, reducing research efficiency [14]. MIPs can be modified with magnetic particles to overcome this, allowing separation via an external magnetic field [15]. Magnetic molecularly imprinted polymers (MMIPs) provide rapid binding and separation with uniform shapes, eliminating the need for grinding [14]. Liu et al. (2020) successfully synthesized MMIPs for capsaicin separation with a detection limit of 0.1388 µg/kg, though their use of multiple templates indicated a need for improved selectivity and sensitivity. Modifications with magnetic particles, as demonstrated by Uzuriaga-Sánchez et al. (2017) and Rizqi Utami et al. (2021), enhance separation efficiency, while Fe_3O_4 (magnetite) is favored for its superior magnetic properties, conductivity, and biocompatibility compared to other iron oxides [16]. This study advances selectivity by focusing exclusively on capsaicin and employs a simpler, more efficient MMIP synthesis process than Liu et al. (2020), making it a promising solution for capsaicin separation.

This study aims to synthesize Magnetic Molecularly Imprinted Polymers (MMIPs) using capsaicin as the template, 4-vinylpyridine (4-VP) as the functional monomer, ethylene glycol dimethacrylate (EGDMA) as the cross-linker, benzoyl peroxide (BPO) as the initiator, and ethanol as the porogen solvent. The synthesis employs bulk polymerization, where the template, functional monomer, and cross-linker are mixed and polymerized with BPO, resulting in a polymer network that encapsulates the template. Although this method may lead to heterogeneous particle sizes due to subsequent grinding and sieving, it remains famous for its simplicity [17,18]. 4-VP is selected for its strong covalent bonding capabilities with capsaicin, while hydrogen bonding further enhances interactions[7]. Wang et al. (2018) successfully synthesized MIPs using 4-VP as a monomer through bulk polymerization, demonstrating the effectiveness of 4-VP in the creation of MIPs. EGDMA improves the selectivity and effectiveness of the MMIPs, and BPO provides superior radical formation for a uniform polymer structure[7]. Ethanol acts as a porogen, facilitating components' dissolution and forming defined pores[19,20]. The synthesized MMIPs will be characterized using Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy-energy dispersive spectroscopy (SEM-EDS), transmission electron microscopy (TEM), and particle size analysis (PSA), providing insights into their structural and functional properties for selective capsaicin adsorption.

2. RESEARCH METHODS

2.1 Material and Instrumentations

The materials used were capsaicin (Merck, ≥98%), 4-Vinylpyridine (Aldrich, ≥95%), ethylene glycol dimethacrylate (Merck, ≥98%), benzoyl peroxide (Merck, 75%), polyvinylpyrolidone (Aldrich, Mw 55,000), $FeSO_4.7H_2O$ (Aldrich), $FeCl_3.6H_2O$ (Aldrich), NH_4OH, methanol (Aldrich, ≥99.8%), ethanol (Aldrich, ≥99.8%), and deionized water.

Instrumentations used in this research are particle size analyzer Horiba SZ-100 (PSA), Fourier-transform infrared spectroscopy (FT-IR) Prestige-21 (Shimadzu, Japan), Scanning electron microscope SU3500 (SEM), and transmission electron microscope HT7700 (TEM).

2.2 Synthesis of Fe_3O_4 Nanoparticles

Fe_3O_4 nanoparticles were synthesized by the coprecipitation method. The synthesis of Fe_3O_4 nanoparticles aims to control their morphology and surface properties to optimize them for MMIP synthesis.

The synthesis process involved dissolving ferrous sulfate heptahydrate ($FeSO_4.7H_2O$) and ferric chloride hexahydrate ($FeCl_3.6H_2O$) at a molar ratio of 2:1 in 100 mL of deionized water. The solution was stirred at room temperature using a magnetic stirrer hotplate until a mixture was homogeneous. After 15 minutes of stirring, ammonium hydroxide (NH_4OH) was added dropwise to the mixture until the pH reached 11, resulting in a black precipitate indicative of Fe_3O_4. The precipitated Fe_3O_4 nanoparticles were then isolated from the solution using an external magnetic field. Subsequently, the Fe_3O_4 nanoparticles were dried in an oven at 60 °C.

2.3 Synthesis of Magnetic Molecularly Imprinted Polymers (MMIPs)

Magnetic molecularly imprinted polymers (MMIPs) were synthesized using capsaicin as the template molecule, 4-vinylpyridine (4-VP) as the monomer, ethylene glycol dimethacrylate (EDGMA) as the crosslinking agent, and benzoyl peroxide (BPO) as the initiator. 0.1 mmol capsaicin and 0.4 mmol 4-VP were dissolved in 10 mL of ethanol and stirred with a magnetic stirrer to create a pre-polymerization solution. Subsequently, two mmol of EDGMA, 100 mg of Fe_3O_4, and 50 mg of polyvinylpyrrolidone (PVP) were added to this solution. The mixture was sonicated for 15 minutes to ensure complete dissolution and mixing of all components. Then, 25 mg of BPO was added to the solution and purged with nitrogen gas for 5 minutes to remove dissolved oxygen. Polymerization was performed in an oil bath at 70-75 °C for 2 hours. The resulting MMIPs precipitate was separated from the solution using an external magnetic field and dried in an oven at 60 °C.

2.4 Material Characterizations

The size of Fe_3O_4 nanoparticles and MMIPs were determined using the particle size analyzer Horiba SZ-100 (PSA). The functional groups were identified by FT-IR Prestige-21 (Shimadzu, Japan) with a KBr pellet-type sample over the wavenumber range 4000-450 cm^{-1}. The Scanning electron microscope SU3500 (SEM) and transmission electron microscope HT7700 (TEM) were used to observe the morphology of materials.

3. RESULTS AND DISCUSSION

The synthesis of molecularly imprinted polymers (MIPs) involved the polymerization of MNIPs and MMIPs with and without capsaicin as a molding molecule, utilizing 4-vinylpyridine (4-VP) as a functional monomer and ethylene glycol dimethacrylate (EGDMA) as a crosslinking agent. Magnetic Non-Imprinted Polymers (MNIPs) are synthesized similarly to Magnetic Molecularly Imprinted Polymers (MMIPs), but without incorporating the template molecule, in this case, capsaicin. MNIPs serve as a crucial control in adsorption studies to demonstrate the specific recognition ability of MMIPs. The key structural distinction between MNIPs and MMIPs lies in the absence of a specific binding site in MNIPs for capsaicin, which allows for a comparative analysis to assess the selective binding performance of MMIPs. This structural difference highlights the role of template incorporation in conferring selective recognition capabilities to MMIPs. 4-VP was selected for its pyridine ring, which enables non-covalent interactions, such as hydrogen bonding, with the template molecule, facilitating easier extraction than covalent interactions[21,22]. EGDMA is noted for its hydrophilic properties, which enhance the MIP's recognition ability and adsorption of polar analytes. Free radicals, initiated by benzoyl peroxide (BPO) at 60°C, drive the polymerization process, with ethanol as a porogen solvent crucial for pore formation by dissolving components during polymerization. The mole ratio capsaicin: 4-VP: EGDMA (1:4:20) was optimized to create functional sites with high analyte affinity, while the appropriate amount of crosslinker ensures polymer stability and performance[23]. The compound used for extracting the template molecule is methanol. Methanol was chosen due to its biocompatibility, polarity, and ability to dissolve template molecules, enabling the removal of the template from the polymer and forming the desired mold. An illustration of the polymerization process is shown in **Figure 1**.

3.1 Particle Size Analyzer (PSA) Characterization

The PSA diagram showing the particle size distribution of Fe_3O_4 nanoparticles and MMIPs is presented in **Figure 2**. Characterization results from Particle Size Analyzer (PSA) for Fe_3O_4 nanoparticles showed an average size of 140.2 nm with a polydispersity index (PI) of 0.313. This relatively low PI value indicates a narrow size distribution, suggesting a uniform synthesis of magnetite nanoparticles. Commercial Fe_3O_4 nanoparticles are typically found in the size range of 20 to 300 nanometers. This wide range allows for various applications, particularly in biomedicine and environmental remediation [16]. This indicates that the synthesized Fe_3O_4 nanoparticles fall within the standard size range for Fe_3O_4. Furthermore, Magnetic Molecularly Imprinted Polymers (MMIPs) synthesized with capsaicin as a template molecule showed an average particle size of 746.6 nm and a PI value of 0.397. The larger particle size of MMIPs compared to magnetite nanoparticles can be attributed to the polymer matrix surrounding the magnetic core, which is designed by selectively binding the capsaicin molecules. The polydispersity index (PI) measures the extent of molecular weight distribution. A higher PI indicates a larger range of molecular weights. The PI of a polymer is determined by dividing the average molecular weight by the sum of the average molecular weights [24–26].

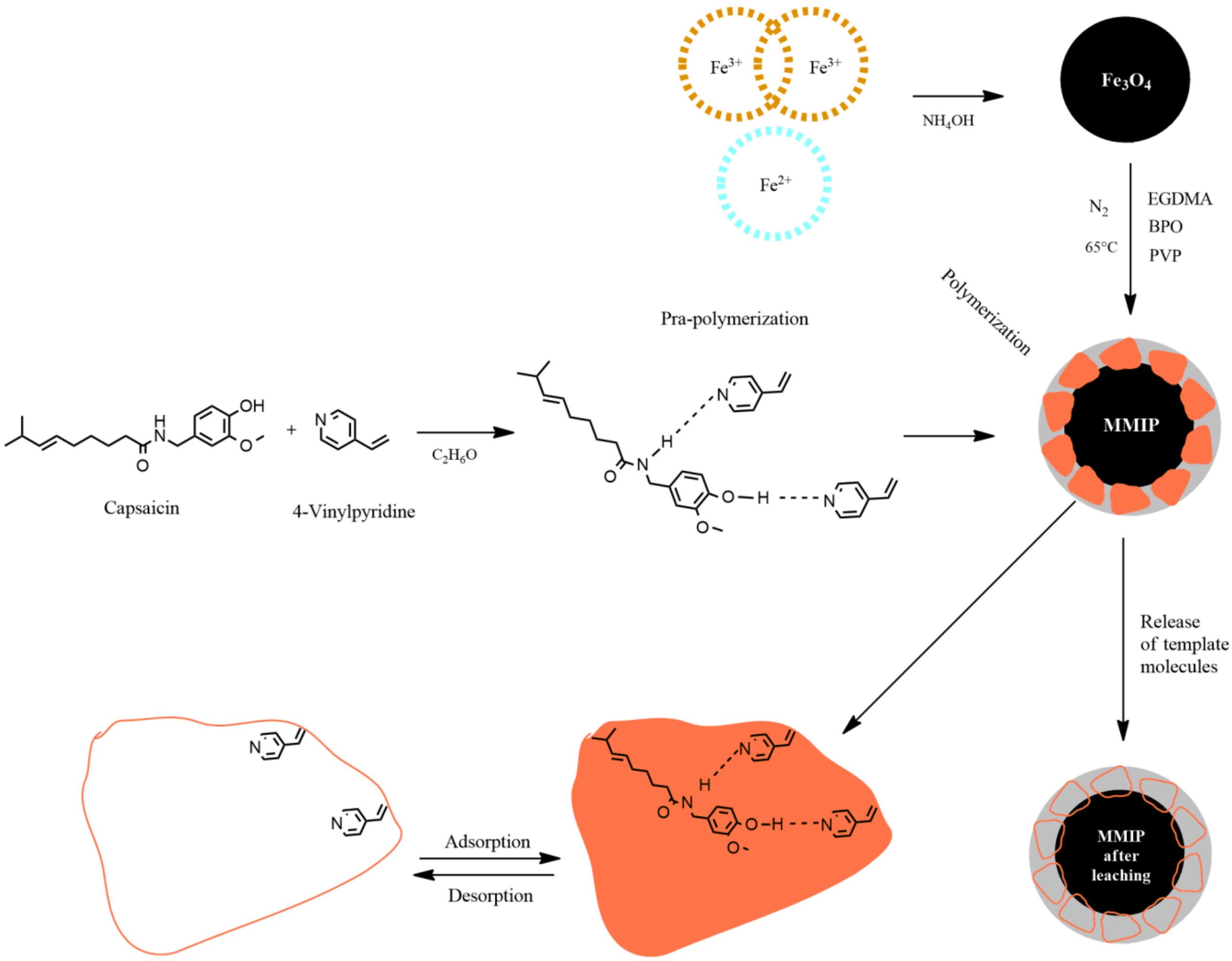

Figure 1. Illustration of synthesis MMIPs

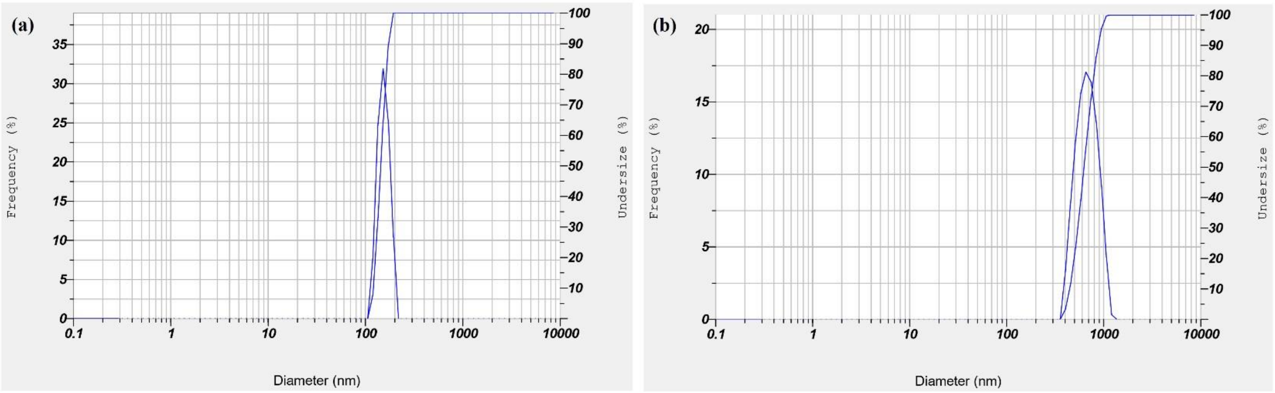

Figure 2. Particle size distribution (a) Fe_3O_4 nanoparticles and (b) MMIPs

3.2 Fourier Transform Infrared (FTIR) Characterization

FTIR analysis was performed to identify functional groups in Fe_3O_4 nanoparticles, MNIPs, and MMIPs, with the resulting spectra shown in **Figure 3**. The spectra reveal an absorption peak at 3429 cm^{-1}, corresponding to the vibration of the -OH group on the surface of Fe_3O_4. Additionally, a peak at 580 cm^{-1} corresponds to the FeO vibration in Fe_3O_4, confirming the successful synthesis of these nanoparticles. For MNIPs and MMIPs, the FTIR results show an absorption peak at 2958 cm^{-1}, indicating the vibrations of the C-H group. Furthermore, the peaks at 1732 cm^{-1} and 1155 cm^{-1} represent the vibrations of the C=O and C-O groups from EGDMA, respectively. The peaks at 1732 cm^{-1} and 1450 cm^{-1} are attributed to the vibrations of the C=C and

C=N groups from 4-VP. In addition, there was a decrease in intensity at the 1288 cm^{-1} peak of MMIPs after leaching, indicating that the C-N functional group on capsaicin was stretched. The peak observed at 3429 cm^{-1} not only shows the vibration of the -OH group in Fe_3O_4 but also corresponds to the N-H vibrations from the functional groups in capsaicin, which overlap with the -OH group. Based on **Figure 3**, the MMIPs spectrum shows a sharper absorption peak at 3429 cm^{-1} compared to the absorption peak in the MNIPs spectrum. This suggests a distinct difference between the NIPs and MIPs that have formed. Additionally, the MNIPs and MMIPs exhibit similar locations and appearances of the major bands, suggesting that the template leakage is negligible [27]. These findings confirm the successful synthesis of MMIPs.

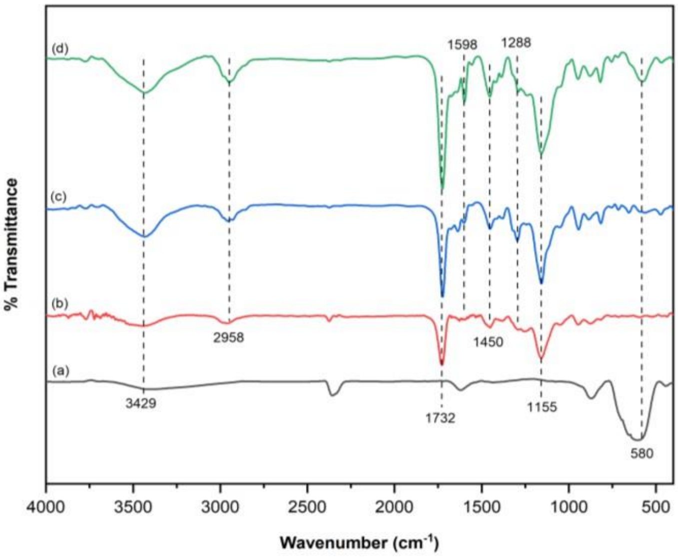

Figure 3. FTIR Spectra of (a) Fe_3O_4 nanoparticles, (b) MNIPs, (c) MMIPs, and (d) MMIPs after leaching

3.3 Scanning Electron Microscope-Energy Dispersive Spectroscopy (SEM-EDS) Characterization

The morphology of Fe_3O_4 nanoparticles, MNIPs, MMIPs before leaching, and MMIPs after leaching was observed using SEM, as shown in **Figure 4**. **Figure 4(a)** reveals that Fe_3O_4 nanoparticles appear to be agglomerated, suggesting that nanoparticles interact with each other due to their magnetic properties. **Figures 4**(b), (c), and (d) demonstrate that MNIPs and MMIPs before and after leaching also to be agglomerated, indicating the successful coating of Fe_3O_4 nanoparticles within the polymer matrix. Furthermore, these particles are non-spherical and non-uniform, attributed to the bulk polymerization method used for synthesis.

This method, which involves organic solvents and subsequent grinding and sieving processes, results in heterogeneous shapes, varying particle sizes, and diverse active sites. Despite these variations, the bulk polymerization method remains widely used due to its simplicity [17,18,24,28].

EDS analysis was conducted to determine the atomic composition of the polymer. The results for Fe_3O_4 nanoparticles, MNIPs, and MMIPs before and after leaching are presented in **Table 1**. **Table 1** indicates a reduction in the percentage of O and Fe atoms, likely due to the uneven distribution of Fe_3O_4 nanoparticles within the polymer and the low resistance of magnetite to the solvent used. Nevertheless, the presence of these elements, even in small amounts, imparts significant magnetic properties to the synthesized polymer. Additionally, the difference in the percentage of N atoms between MMIPs before and after leaching confirms the success of the leaching process, as it signifies the release of most capsaicin molecules from the polymer, resulting in the formation of capsaicin molecular molds in the MMIPs. The N atom percentage indicates capsaicin presence within the polymer, attributed to the amide groups in its structure[29].

3.4 Transmission Electron Microscope (TEM) Characterization

The internal morphology of Fe_3O_4 nanoparticles, MNIPs, and MMIPs before and after leaching was determined using TEM characterization. The resulting TEM image, as shown in **Figure 5(a)**, reveals that Fe_3O_4 nanoparticles tend to agglomerate due to their magnetic properties and Van der Waals forces. Moreover, **Figures 5**(b), (c), and (d) demonstrate that Fe_3O_4 nanoparticles are either encapsulated within or coated by the MIP, indicating successful synthesis of MNIPs and MMIPs before and after leaching. This finding aligns with prior research by Wang, Yuan, Zhu, Jin, and Xing (2018), which also confirmed that agglomerated Fe_3O_4 nanoparticles were effectively coated by the developed MIP, with the imprinting layer also successfully formed.

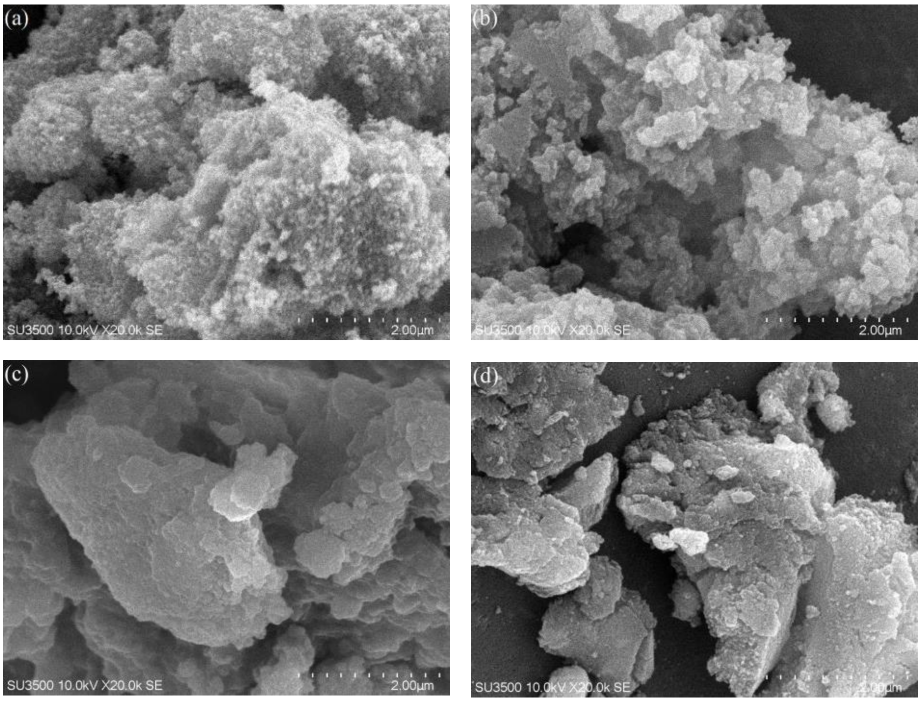

Figure 4. SEM images of (a) Fe_3O_4 nanoparticles, (b) MNIPs, (c) MMIPs before leaching, and (d) MMIPs after leaching

Table 1. Data of element analysis of Fe_3O_4 nanoparticles, MNIPs, MMIPs before leaching, and MMIPs after leaching

Sample	Element content (%)			
	C	O	Fe	N
Fe_3O_4 nanoparticles	0.00	58.80	41.20	0.00
MNIPs	77.47	20.78	1.55	0.15
MMIPs before leaching	72.57	19.71	5.08	2.64
MMIPs after leaching	75.36	19	3.97	1.67

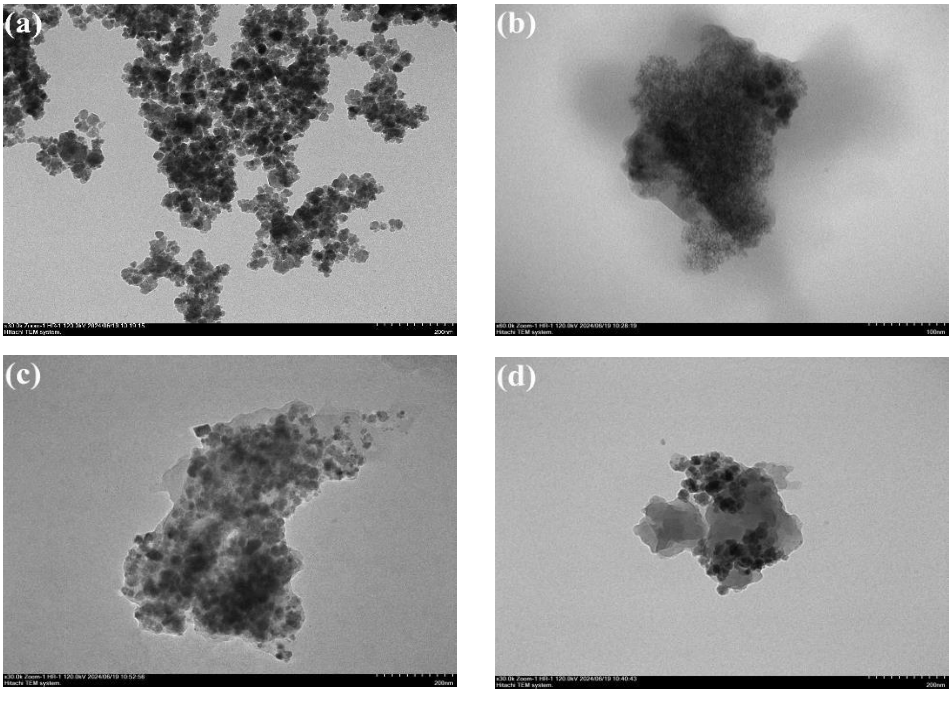

Figure 5. TEM images of (a) Fe_3O_4 nanoparticles, (b) MNIPs, (c) MMIPs before leaching, and (d) MMIPs after leaching

4. CONCLUSIONS

Magnetic Molecularly Imprinted Polymers (MMIPs) using capsaicin as the template were synthesized through bulk polymerization. Characterization techniques such as PSA, FTIR, SEM-EDS, and TEM confirmed the structural and functional integrity of the MMIPs. This research provides a robust synthesis method and thorough analysis, laying the groundwork for future applications. Further studies should focus on optimizing the selectivity and sensitivity of MMIPs by exploring alternative functional monomers and cross-linkers to enhance performance for a broader range of analytes.

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