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Authors Can Li, Zihua Zhang, Pingyong Liao, Fei Fan, Junchang Wang, Yue Xu, Xuejun Zhao and Wenbin Liu

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ORCID® iDs Can Li - <https://orcid.org/0009-0005-1738-2783>



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Functionalized Magnetic Covalent Organic Framework Composites for Enrichment of Synthetic Cannabinoids in Wastewater Coupled with UPLC-MS/MS Analysis

Can Li^{+[b]}, Zihua Zhang^{+[b]}, Pingyong Liao^[b], Fei Fan^[b], Junchang Wang^[b], Yue Xu^[b], Xuejun Zhao^{[a][b]*} and Wenbin Liu^{[a][b]*}

^[a] Shanghai Key Laboratory of Crime Scene Evidence, Shanghai Research Institute of Criminal Science and Technology, Shanghai 200072, China

^[b] Shanghai Yuansi Standard Science and Technology Co., Ltd., Shanghai 200072, China

^[+] These authors contributed equally to this work.

Abstract

Synthetic cannabinoids (SCs) represent the most rapidly proliferating class of new psychoactive substances, and their detection in urban wastewater is critical for drug situation monitoring. However, the low concentrations and complex matrix of wastewater pose significant challenges for sample pretreatment. Herein, three magnetic covalent organic framework composites (Fe₃O₄@COFs-1 to -3) with different functional groups were prepared *via* in situ growth of COF shells on Fe₃O₄ nanospheres. Systematic characterization revealed that Fe₃O₄@COFs-1 (chlorine-functionalized) exhibited the highest BET surface area (1194 m²/g), excellent crystallinity, superior thermal stability, and favorable hydrophilicity (water contact angle ~60°). Adsorption evaluation using nine SCs as targets and nine common drugs as controls demonstrated that Fe₃O₄@COFs-1 possessed the best comprehensive adsorption performance and selectivity. Under optimized conditions (methanol as binding solvent, pH=8, 40 min adsorption, 0.1% formic acid in acetonitrile as eluent, 30 min elution), the maximum adsorption capacity for 5F-CUMYL-PINACA reached 18.11 µg/mg, with an average of 16.45 µg/mg across nine SCs. The material retained over 65% adsorption efficiency after 5 reuse cycles. Coupled with ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS), the established method

showed good linearity (1–150 µg/L, $r^2 > 0.99$), low detection limit (0.5 µg/L), and satisfactory precision (RSD < 15.6%). This work provides an efficient and convenient approach for the enrichment and determination of SCs in urban wastewater.

Keywords: Synthetic cannabinoids; Magnetic covalent organic frameworks; Dispersive solid-phase extraction; UPLC-MS/MS; Wastewater-based epidemiology; Functional nanomaterials

1. Introduction

New psychoactive substances (NPS) have emerged as the "third generation" of drugs following traditional and synthetic drugs. As of early 2026, over 1,300 NPS have been identified globally, with synthetic cannabinoids (SCs) accounting for more than 31%—the largest and most rapidly evolving category.^[1-3] SCs are synthetic compounds that selectively activate cannabinoid type 1 and/or type 2 receptors, exhibiting significantly higher pharmacological potency and addictive potential than natural cannabis.^[4-8] Their structural diversity enables illicit manufacturers to evade regulatory control by continuously modifying chemical scaffolds.^[9,10] SCs are often disguised as e-cigarette liquids, herbal incense, or plant-based products, making them highly concealable and particularly harmful to adolescent populations.^[11,12]

Wastewater-based epidemiology (WBE) has become a core technology for international drug monitoring, offering population-wide coverage, real-time early warning, and privacy protection.^[13-21] By analyzing chemical biomarkers in municipal wastewater, WBE enables comprehensive and objective assessment of regional drug abuse trends.^[22-25] However, target analytes in wastewater are typically present at trace levels in a complex matrix, necessitating efficient sample pretreatment for enrichment and cleanup.

Covalent organic frameworks (COFs) are crystalline porous polymers constructed from organic building blocks linked by strong covalent bonds, featuring high surface areas, tunable pore structures, and excellent chemical stability.^[26-35] Integrating COFs with magnetic Fe₃O₄ nanoparticles yields core-shell

magnetic composites that combine the selective adsorption capability of COFs with rapid magnetic separation, offering unique advantages in sample pretreatment.^[36-39]

In this study, three functionalized magnetic COF composites ($\text{Fe}_3\text{O}_4@\text{COFs}$ -1 to -3) were designed and prepared by varying the dialdehyde monomer functional groups. The materials were systematically characterized, and their adsorption performance toward nine SCs was evaluated. After optimizing adsorption and elution conditions, a magnetic dispersive solid-phase extraction (MDSPE) method coupled with UPLC-MS/MS was established for the rapid and sensitive detection of SCs in wastewater.

2. Results and Discussion

2.1 Characterization of $\text{Fe}_3\text{O}_4@\text{COFs}$ Composites

Morphology (TEM). Fe_3O_4 nanospheres exhibited uniform spherical morphology with smooth surfaces and diameters of 100–150 nm. All three $\text{Fe}_3\text{O}_4@\text{COFs}$ composites displayed clear core-shell structures, with Fe_3O_4 cores encapsulated by uniform COF shells. High-magnification images revealed ordered mesoporous channels within the COF shells, confirming the porous crystalline structure (See Supplementary Fig. 1 and Fig. 2 for details).

Chemical structure (FTIR). Pure Fe_3O_4 showed a characteristic Fe-O stretching band at 580 cm^{-1} . All composites retained this peak while exhibiting new COF characteristic absorptions: O-H/N-H stretching ($\sim 3400\text{ cm}^{-1}$), C=N imine bond stretching ($\sim 1650\text{ cm}^{-1}$), aromatic C=C skeleton vibrations ($1600\text{--}1450\text{ cm}^{-1}$), and C-O/C-N stretching ($1300\text{--}1000\text{ cm}^{-1}$). The C=N peak at 1650 cm^{-1} confirmed successful Schiff-base polymerization and COF growth on Fe_3O_4 surfaces. Gradual intensity increases from $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 to -3 corresponded to increasing COF loading (Fig. 1a).

Thermal stability (TGA). Pure Fe_3O_4 showed <5% weight loss below $200\text{ }^\circ\text{C}$ (surface water) and retained about 87% mass at $900\text{ }^\circ\text{C}$. All composites exhibited three-stage decomposition: residual solvent removal (< $200\text{ }^\circ\text{C}$), weak bond decomposition ($200\text{--}400\text{ }^\circ\text{C}$), and main chain pyrolysis ($400\text{--}800\text{ }^\circ\text{C}$). $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 demonstrated the highest thermal stability with the highest decomposition onset

temperature and slowest weight loss, retaining about 53% residual mass. (See Supplementary Fig. 3 for details).

Framework order (Raman). All composites showed D bands ($\sim 1350\text{ cm}^{-1}$, disorder) and G bands ($\sim 1580\text{ cm}^{-1}$, ordered conjugation). $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 exhibited the lowest I_D/I_G ratio with multiple clear fingerprint peaks ($1000\text{--}1300\text{ cm}^{-1}$), indicating the highest conjugation degree, structural order, and lowest defect content—consistent with its superior TGA performance (See Supplementary Fig. 4 for details).

Crystal structure (XRD). Pure Fe_3O_4 displayed characteristic diffraction peaks at $2\theta = 30.1^\circ, 35.5^\circ, 43.1^\circ, 53.4^\circ, 57.0^\circ$, and 62.7° , corresponding to the (220), (311), (400), (422), (511), and (440) planes of the inverse spinel structure. All composites retained these peaks, confirming that COF coating did not disrupt the Fe_3O_4 crystal structure. In the low-angle region ($2\theta < 10^\circ$), $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 and -2 showed sharp COF diffraction peaks, indicating excellent long-range order and high crystallinity, whereas $\text{Fe}_3\text{O}_4@\text{COFs}$ -3 exhibited only broad background signals (Fig. 1b).

Porosity (BET). N_2 adsorption-desorption isotherms and pore size distribution of three composite materials were analyzed. Three $\text{Fe}_3\text{O}_4@\text{COFs}$ exhibited type IV isotherms with micro-mesoporous hierarchical structures. $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 showed the highest BET surface area ($1194\text{ m}^2/\text{g}$) with a sharp micropore peak at 2.5 nm and uniform mesopore distribution, indicating highly crystalline COFs with maximized micropore volume. $\text{Fe}_3\text{O}_4@\text{COFs}$ -2 ($1176\text{ m}^2/\text{g}$) showed similar micropore features but slightly higher mesopore content. $\text{Fe}_3\text{O}_4@\text{COFs}$ -3 ($1022\text{ m}^2/\text{g}$) exhibited weakened micropore peaks and increased mesopore proportion. (Fig. 1c and 1d).

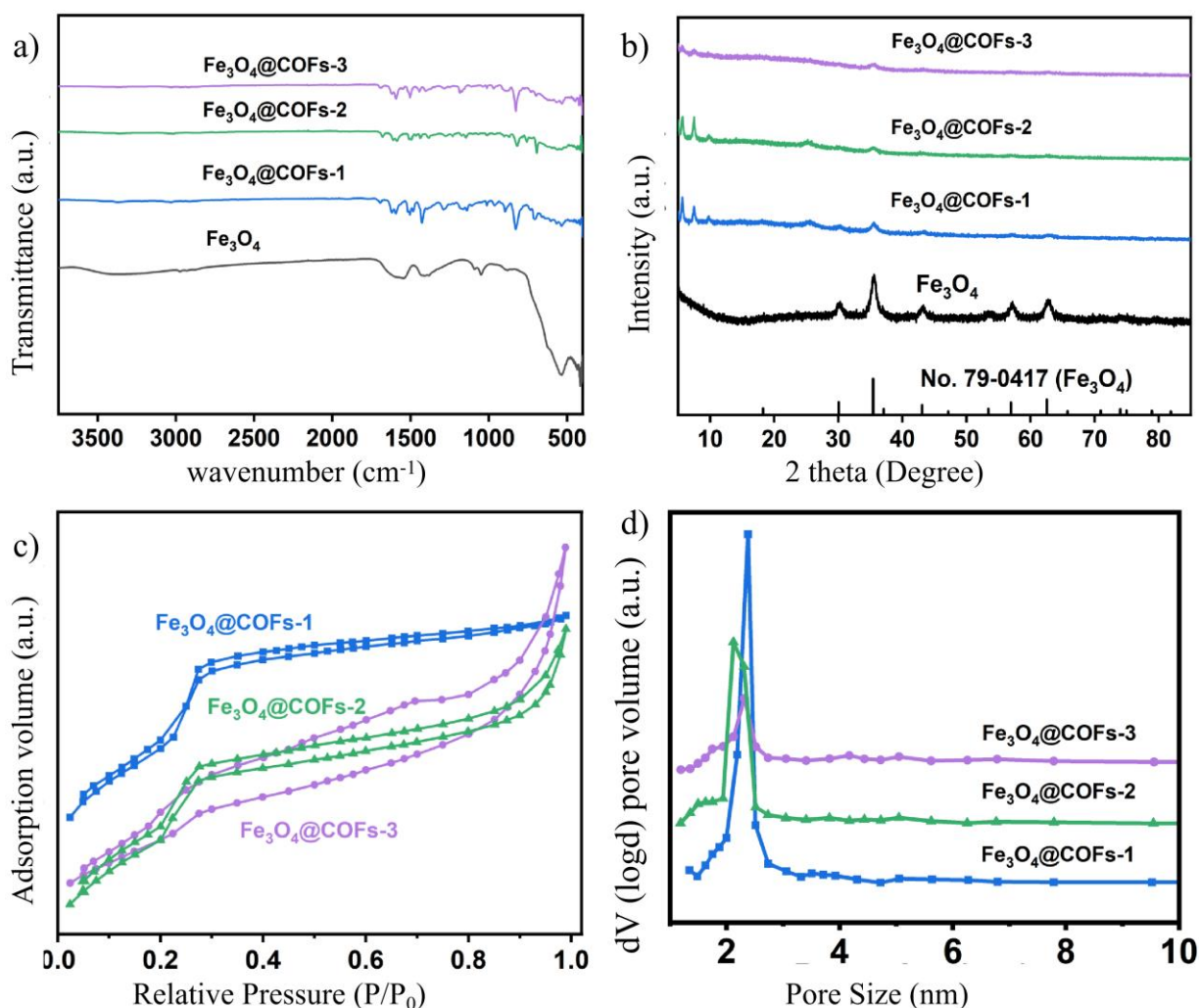


Figure 1. a) FTIR spectra of Fe_3O_4 and $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 to -3; b) XRD patterns of Fe_3O_4 and $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 to -3; c) N_2 adsorption-desorption isotherms of $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 to -3; d) Pore size distributions of $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 to -3.

Surface wettability. $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 showed the lowest water contact angle ($\sim 60^\circ$), indicating hydrophilic behavior attributed to the strong electron-withdrawing effect of chlorine atoms enhancing surface polarity, combined with its high surface area and ordered pores. $\text{Fe}_3\text{O}_4@\text{COFs}$ -3 ($\sim 103^\circ$) were strongly hydrophobic due to methyl and methoxy group shielding. $\text{Fe}_3\text{O}_4@\text{COFs}$ -2 ($\sim 84^\circ$) was intermediate. The favorable hydrophilicity of $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 facilitates water and analyte diffusion into micropores, correlating positively with its superior adsorption performance (See Supplementary Fig. 5 for details).

Collectively, Fe₃O₄@COFs-1 demonstrated the best overall structural properties, making it the optimal candidate for SC enrichment.

2.2 Adsorption Performance Comparison

As shown in Fig. 2. Among the three materials, Fe₃O₄@COFs-1 exhibited the best comprehensive adsorption performance. It achieved the highest adsorption capacity for 5F-CUMYL-PINACA (13.93 µg/mg) and the lowest for 4CN-CUMYL-BUTINACA (13.08 µg/mg), maintaining the highest or second-highest adsorption for most SCs. Importantly, Fe₃O₄@COFs-1 showed generally lower adsorption toward the nine common drugs compared to the other three materials, demonstrating good selectivity for SCs. This selectivity is consistent with its high surface area, ordered pore structure, and chlorine-functionalized surface that may engage in specific interactions with SC molecules.

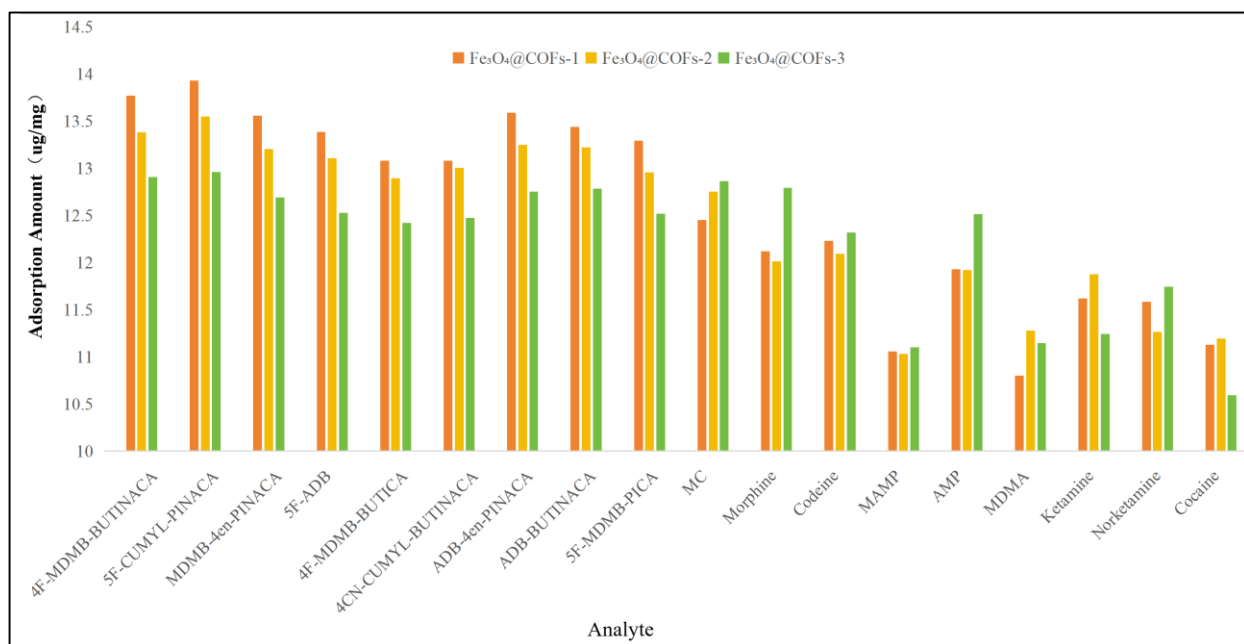


Figure 2. Adsorption capacities of three Fe₃O₄@COFs materials toward 18 analytes (9 SCs and 9 common drugs).

2.3 Optimization of Adsorption and Elution Conditions

Binding solvent. During the adsorption extraction process, it's necessary to ensure the COF material is evenly distributed and used in a consistent amount, and to choose the right reagent for distributing the material. We studied methanol, acetonitrile, and isopropanol as binding liquids for the material to

maximize adsorption of synthetic cannabinoids. By testing the content of drugs in the supernatant after the microspheres adsorbed them, the results are shown in Figure 3a. Methanol gave the best adsorption recovery for synthetic cannabinoids, with an 76% adsorption rate for 5F-CUMYL-PINACA, while the adsorption rate for MAMP was 6%.

Wastewater pH. The suitable solution pH is a key factor and usually affects the adsorption effect, as it influences the existing form and stability of the target analytes. The effect of wastewater sample pH was studied by adjusting the solution pH between 4 and 11 using 1.0 mol/L HCl and 1.0 mol/L NaOH. Adsorption recovery was relatively low under strongly acidic or basic conditions, likely due to pH-induced changes in surface charge properties of the adsorbent and analyte speciation. Optimal adsorption occurred at pH 8 (weakly alkaline), with recoveries ranging from 71% (ADB-BUTINACA) to 85% (5F-CUMYL-PINACA) across the nine SCs (Fig 3b).

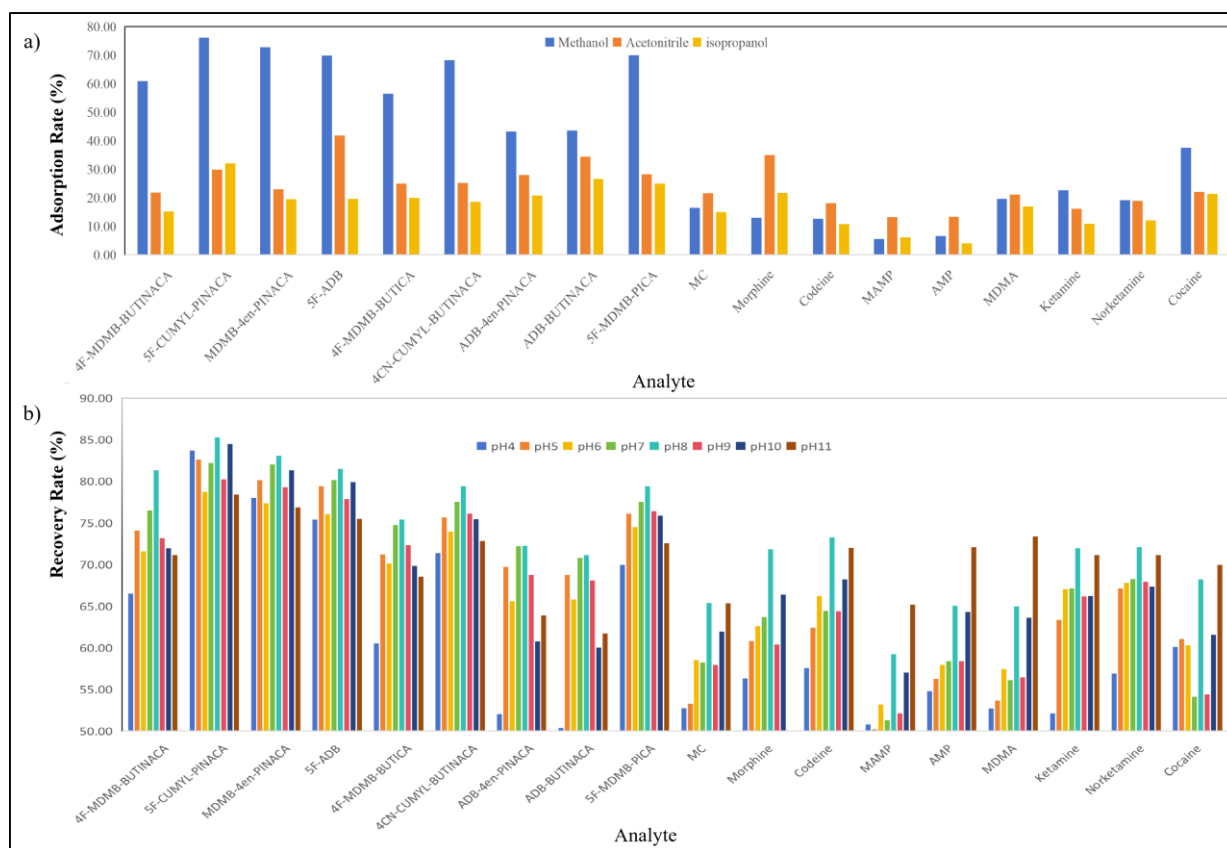


Figure 3. a) Effect of binding solvent on adsorption recovery; b) Effect of wastewater pH on adsorption recovery.

Adsorption time. Adsorption time not only affects the performance of adsorption extraction but also impacts the analysis time. To achieve the best adsorption extraction efficiency, a suitable adsorption time is needed. The adsorption time was optimized between 10 and 180 minutes. Adsorption increased rapidly within the first 40 min and gradually plateaued thereafter. At 120–180 min, slight decreases were observed, suggesting partial desorption. Considering efficiency, 40 min was selected as the optimal adsorption time (See Supplementary Fig. 6a for details).

Elution solvent. The choice of elution reagent determines the elution effect. To elute 9 synthetic cannabinoids and 9 drugs, the elution solution for the microspheres was optimized. Five control groups were set up: methanol, 0.1% formic acid in methanol, 0.2% formic acid in methanol, acetonitrile, 0.1% formic acid in acetonitrile, and 0.2% formic acid in acetonitrile. Among six eluents tested, 0.1% formic acid in acetonitrile provided the highest elution efficiency (91% for 5F-CUMYL-PINACA), outperforming methanol-based eluents and pure acetonitrile (See Supplementary Fig. 6b for details).

Elution time. The elution performance affects the adsorption properties of the prepared COF materials, and elution time also plays an important role, so it was optimized. Using 0.1% formic acid in acetonitrile as the eluent, it was added to the magnetic multi-walled carbon nanotubes containing the target substance, followed by ultrasonic cleaning for 10, 20, 30, 40, 50, and 60 minutes. The magnetic multi-walled carbon nanotubes were collected with an external magnet. As the ultrasonic time increased, the extraction rate increased, with the elution rate of 4CN-CUMYL-BUTINACA reaching 94%. Considering the time, an elution time of 30 minutes was found to be ideal. (See Supplementary Fig. 7 for details).

2.4 Adsorption Capacity and Reusability

The study optimized factors like the material binding solution, pH of the wastewater sample solution, adsorption time, elution solvent, and elution time using a single-factor experimental method, and the best conditions were obtained. Under optimized conditions, Fe₃O₄@COFs-1 achieved a maximum adsorption

capacity of 18.11 $\mu\text{g}/\text{mg}$ for 5F-CUMYL-PINACA, with an average of 16.45 $\mu\text{g}/\text{mg}$ across nine SCs (minimum: 15.70 $\mu\text{g}/\text{mg}$ for 4CN-CUMYL-BUTINACA) (Fig. 4a).

The reusability of a material is one of the key factors in judging its adsorption performance. Reusability testing demonstrated that $\text{Fe}_3\text{O}_4@\text{COFs-1}$ retained over 65% average adsorption efficiency for the nine SCs after five consecutive adsorption-elution cycles, indicating good stability and reusability (Fig. 4b).

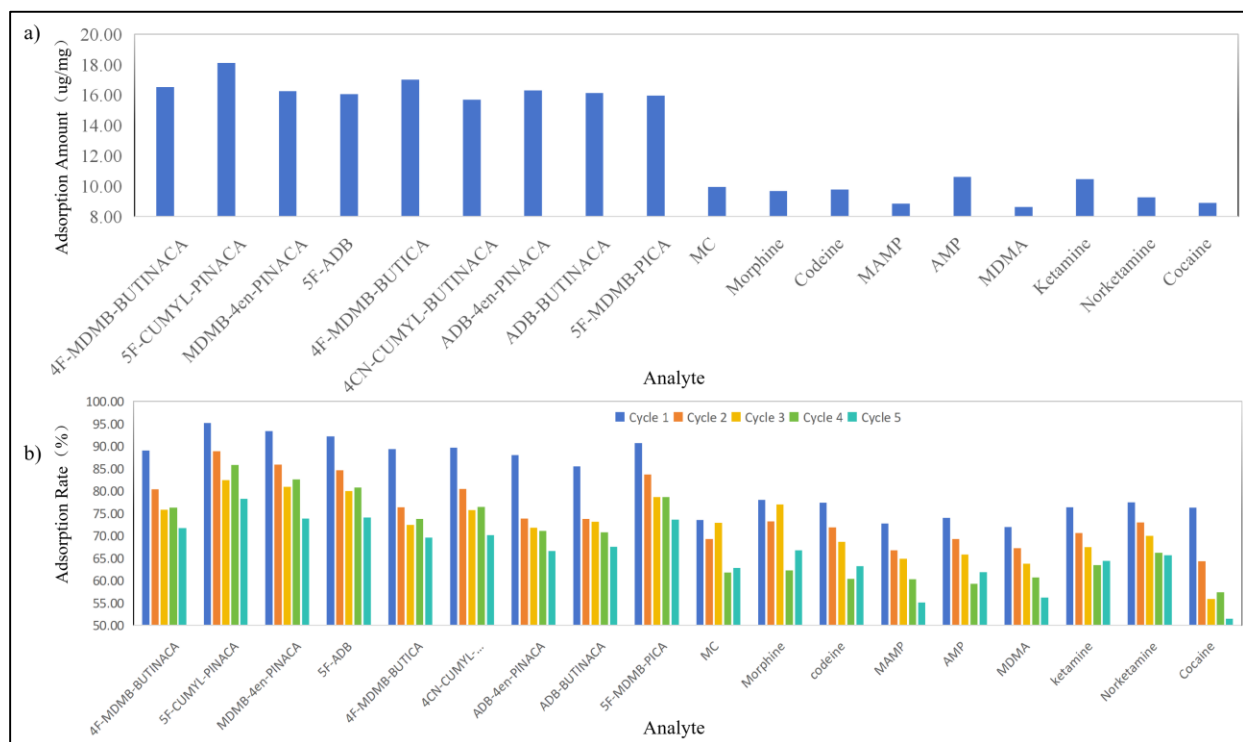


Figure 4. a) Adsorption capacity of $\text{Fe}_3\text{O}_4@\text{COFs-1}$ under optimized conditions; b) Reusability of $\text{Fe}_3\text{O}_4@\text{COFs-1}$ over five adsorption-elution cycles.

2.5 Method Validation

The UPLC-MS/MS method was validated for linearity, sensitivity, precision, matrix effect, and extraction recovery.

Linearity, LOD, and LOQ. Calibration curves were constructed at eight concentration levels (0, 1, 5, 10, 20, 50, 100, 150 $\mu\text{g}/\text{L}$). All 18 analytes exhibited good linearity within 1-150 $\mu\text{g}/\text{L}$ with coefficients of

determination (r^2) greater than 0.99. The limit of detection (LOD, S/N = 3) was 0.5 $\mu\text{g/L}$, and the limit of quantification (LOQ, S/N = 10) was 1 $\mu\text{g/L}$, satisfying the requirements for trace SC detection in wastewater (See Supplementary Fig. 8 for details).

Precision, matrix effect, and recovery. Intra-day ($n = 18$) and inter-day ($n = 18$, over three consecutive days) precision and accuracy were within 15.6%, meeting conventional bioanalytical acceptance criteria. After internal standard calibration, matrix effects ranged from 0.86 to 14.8 with RSD < 15%, indicating negligible matrix interference. Extraction recoveries ranged from 88.73% to 110.39% with RSD < 11.5%, demonstrating high extraction efficiency and method stability (See Supplementary Fig. 9 for details).

3. Experimental

3.1 Materials and Reagents

Ferric chloride (FeCl_3 , anhydrous), sodium citrate (anhydrous), sodium acetate (anhydrous), ethylene glycol, acetic acid (glacial), methanol, ethanol, acetonitrile, isopropanol, formic acid, ammonium acetate, hydrochloric acid, and sodium hydroxide were of analytical or chromatographic grade. 2,5-Dimethoxyterephthalaldehyde (DMTP), 2,5-dichloroterephthalaldehyde, [1,1'-biphenyl]-2,2'-dicarboxaldehyde, 2,5-dimethylterephthalaldehyde, and 1,3,5-tris(4-aminophenyl)benzene (TAPB) were purchased from Sigma-Aldrich. Ultrapure water was used throughout.

Nine synthetic cannabinoid standards (purity $\geq 99\%$): 4F-MDMB-BUTINACA, 5F-CUMYL-PINACA, MDMB-4en-PINACA, 5F-ADB, 4F-MDMB-BUTICA, 4CN-CUMYL-BUTINACA, ADB-4en-PINACA, ADB-BUTINACA, and 5F-MDMB-PICA. Nine common drug standards (purity $\geq 99\%$): methcathinone hydrochloride (MC), morphine monohydrate, codeine, methamphetamine hydrochloride (MAMP), amphetamine (AMP), 3,4-methylenedioxymethamphetamine hydrochloride (MDMA), ketamine, norketamine hydrochloride, and cocaine. Internal standards: methamphetamine- d_5 (MAMP- d_5 , $100.0 \pm 0.6 \mu\text{g/mL}$) and THC- d_3 ($100.0 \pm 0.15 \mu\text{g/mL}$), purchased from Cerilliant Corporation.

Standard stock solutions (10 mg/mL) were prepared in methanol based on purity and salt correction. Working solutions (1 mg/mL) were obtained by diluting stock solutions with methanol.

3.2 Instrumentation

UPLC-MS/MS analysis was performed on a Shimadzu LCMS-8050 system equipped with LabSolutions workstation. Other instruments included Sartorius Secura 125-1CN and Quintix 124-1CN analytical balances, Eppendorf Research plus pipettes (0.5-10, 10-100, 100-1000 μ L), Scientific Industries VORTEX GENIE 2 vortex mixer, and Merck Millipore Synergy UV water purification system.

3.3 Preparation of Fe_3O_4 Nanospheres

Fe_3O_4 nanospheres were synthesized *via* a solvothermal method. 7.0 g anhydrous $FeCl_3$ and 5.0 g anhydrous sodium citrate were dissolved in 240 mL ethylene glycol with 3.0 mL deionized water under magnetic stirring. 24.0 g anhydrous sodium acetate was dissolved in 160 mL ethylene glycol. The two solutions were combined and stirred for 1 h, then transferred to a 500 mL Teflon-lined stainless steel autoclave and heated at 200 $^{\circ}C$ for 15 h. After cooling to room temperature, the black product was collected by magnetic separation, washed three times each with deionized water and ethanol, and dried under vacuum at 60 $^{\circ}C$ for 12 h.

3.4 Preparation of $Fe_3O_4@COFs$ Composites

As shown in Fig. 6, magnetic COF composites were prepared *via* in situ growth. In a typical procedure, 97 mg dialdehyde monomer and 122 mg TAPB were dissolved in 500 mL ethanol and 100 mL deionized water under stirring (200 rpm) with ultrasonication for 30 min. Separately, 50 mg Fe_3O_4 nanospheres were dispersed in ethanol by ultrasonication for 30 min and added to the monomer solution, followed by additional ultrasonication for 30 min. A solution of 3 mL glacial acetic acid in 30 mL deionized water was added dropwise over 1–2 h under constant stirring. The reaction was continued at room temperature for 24 h. The product was collected magnetically, washed three times each with ethanol and deionized water, and dried under vacuum at 60 $^{\circ}C$ for 12 h.

Three composites were prepared by varying the dialdehyde monomer: $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 (2,5-dichloroterephthalaldehyde), $\text{Fe}_3\text{O}_4@\text{COFs}$ -2 ([1,1'-biphenyl]-2,2'-dicarboxaldehyde), and $\text{Fe}_3\text{O}_4@\text{COFs}$ -3 (2,5-dimethylterephthalaldehyde).

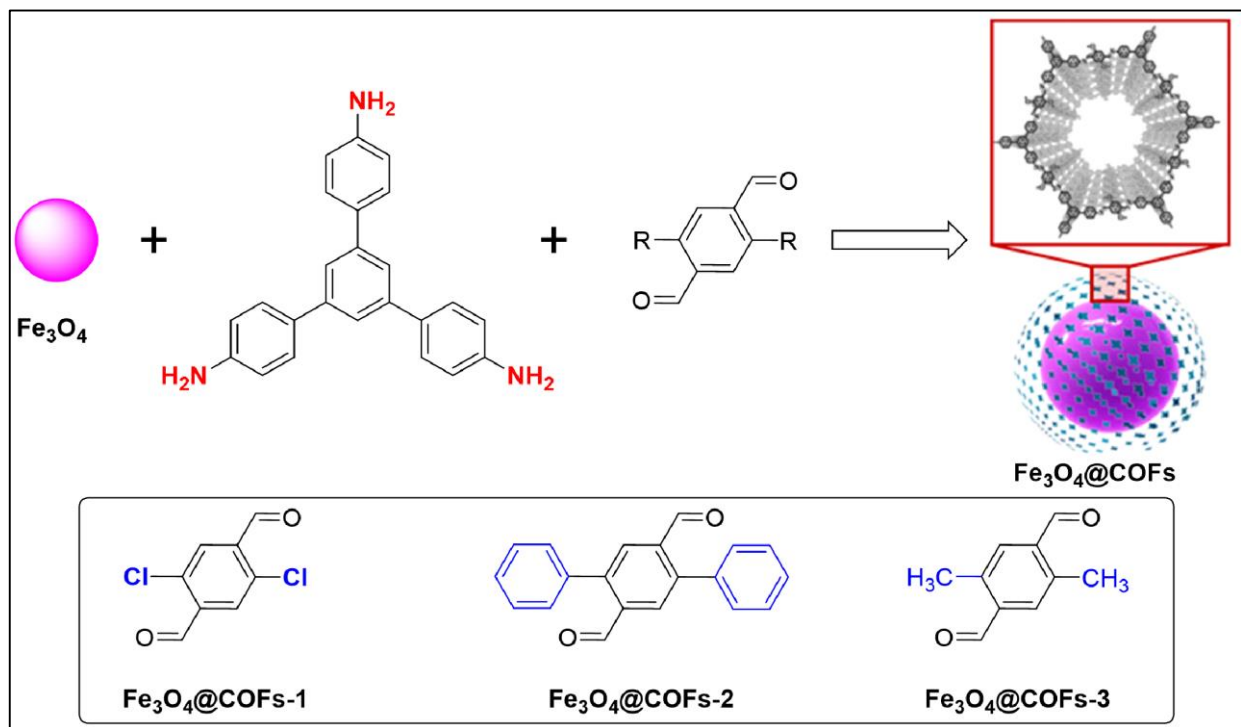


Figure 5. Schematic diagram of the synthesis procedure of the $\text{Fe}_3\text{O}_4@\text{COFs}$ composites.

3.5 Characterization

Transmission electron microscopy (TEM) was used to examine morphology. Fourier transform infrared spectroscopy (FTIR) was employed for chemical structure analysis. Thermogravimetric analysis (TGA) was performed to evaluate thermal stability and composition. X-ray diffraction (XRD) was conducted for crystal structure analysis. Raman spectroscopy was used to assess framework order and defects. Nitrogen adsorption-desorption measurements were carried out to determine BET surface area and pore size distribution. Static water contact angle measurements were performed to evaluate surface wettability.

3.6 Adsorption and Elution Experiments

For initial screening, 5 mg of each magnetic material was added to 5 mL wastewater spiked with 18 analytes at 20 µg/mL. After vortex adsorption for 30 min and magnetic separation for 180 s, the supernatant was analyzed by UPLC-MS/MS.

Single-factor optimization was performed for Fe₃O₄@COFs-1, including binding solvent (methanol, acetonitrile, isopropanol), wastewater pH (4-11), adsorption time (10-180 min), elution solvent (methanol, 0.1% formic acid in methanol, 0.2% formic acid in methanol, acetonitrile, 0.1% formic acid in acetonitrile, 0.2% formic acid in acetonitrile), and elution time (10-60 min).

Under optimized conditions, adsorption capacity was determined using 100 µL of 10 mg/mL material suspension in 900 µL wastewater (pH= 8, 20 µg/mL analytes) with 40 min adsorption, followed by elution with 0.1% formic acid in acetonitrile for 30 min. Reusability was evaluated over five consecutive adsorption-elution cycles, with material washed three times with 0.1% formic acid in acetonitrile between cycles.

3.7 UPLC-MS/MS Conditions

Chromatographic separation was performed on a Restek Allure PFP Propyl column (5 µm, 2.1 mm × 100 mm) at 40 °C. Mobile phase A was water containing 10 mM ammonium acetate and 0.05% formic acid; mobile phase B was acetonitrile-water (90:10, v/v) containing 10 mM ammonium acetate and 0.05% formic acid. The gradient program was: 0-4 min, 20-95% B; 4-6 min, 95% B; 6-6.1 min, 95-20% B; 6.1-10.0 min, 20% B. Flow rate was 0.35 mL/min and injection volume was 10 µL.

Mass spectrometry was operated in electrospray ionization positive mode with multiple reaction monitoring (MRM). Interface temperature: 300 °C; desolvation temperature: 526 °C; heat block temperature: 400 °C; drying gas flow: 10 L/min; nebulizing gas flow: 3 L/min; heating gas flow: 10 L/min.

4. Conclusions

Three functionalized magnetic covalent organic framework composites ($\text{Fe}_3\text{O}_4@\text{COFs}$ -1 to -3) were successfully prepared and evaluated for the enrichment of synthetic cannabinoids in wastewater. $\text{Fe}_3\text{O}_4@\text{COFs}$ -1 (chlorine-functionalized) exhibited the highest BET surface area ($1194 \text{ m}^2/\text{g}$), best crystallinity, superior thermal stability, and favorable hydrophilicity, translating to the highest adsorption capacity and selectivity toward SCs. Under optimized conditions (methanol binding solvent, pH 8, 40 min adsorption, 0.1% formic acid in acetonitrile elution for 30 min), the maximum adsorption capacity reached $18.11 \text{ }\mu\text{g}/\text{mg}$, with over 65% efficiency retained after five reuse cycles. The coupled MDSPE-UPLC-MS/MS method demonstrated good linearity ($1\text{--}150 \text{ }\mu\text{g}/\text{L}$, $r^2 > 0.99$), low LOD ($0.5 \text{ }\mu\text{g}/\text{L}$), satisfactory precision ($<15.6\%$), and high recovery ($88.73\text{--}110.39\%$). This work provides an efficient, convenient, and reliable approach for monitoring synthetic cannabinoids in urban wastewater.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the Publications website at <http://pubs.acs.org>.

Author Information

Corresponding Author

*E-mail: liuwenbin@shxky.cn

*E-mail: zhaoxuejun@shxky.cn

Notes

The authors declare no competing financial interest.

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