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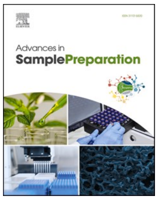

In-house metal-organic framework material for stir-bar sorptive extraction of acidic pharmaceutical compounds from environmental water samples

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ABSTRACT

Pharmaceutical residues are increasingly recognized as emerging contaminants in aquatic environments due to their widespread consumption, improper disposal, and insufficient removal in wastewater treatment plants. These compounds, often found at trace levels, pose ecological risks owing to their bioaccumulation potential and biological activity. Micro-extraction techniques, especially stir-bar sorptive extraction (SBSE), have gained widespread use for their effectiveness in preconcentration and analytical applications. However, commercial SBSE coatings show limited retention of polar analytes and suffer from poor mechanical stability as well as high purchase cost. To address these limitations, this study presents the development and evaluation of an in-house hybrid coating material for SBSE with a total cost <5€/unit, based on metal-organic frameworks (MOFs) functionalized with amine groups that provide weak anion exchange (WAX) interactions. The performance of the amino-functionalized MOF attached to a glycidyl methacrylate-based monolith (GMA@NH_2-UiO-66(Zr)) was assessed for the extraction of acidic pharmaceutical compounds from environmental water samples, followed by determination using liquid chromatography-tandem mass spectrometry (LC-MS/MS). After the proper optimization, good analytical figures were obtained for river water samples, including the method's limits of detection as low as 2 ng/L, adequate recoveries (22–41 %), matrix effect between +9 and -2 % and acceptable precision expressed as relative standard deviation below 25 %. Once validated, the method was applied for the determination of acidic pharmaceuticals from environmental water samples, which were found at ng/L level. The new material exhibited improved retention of polar pharmaceuticals, high stability, and reproducibility, demonstrating its potential as an effective tool for environmental monitoring of pharmaceutical contaminants.

1. Introduction

Pharmaceuticals are consumed worldwide by the population to improve their quality of life. After being consumed and used by the body, a part of the active pharmaceutical ingredient is excreted either unchanged or partially metabolized, resulting in its entrance into the sewage system. Also, due to the inappropriate disposal of unused pharmaceuticals and the low efficiency removal in waste-water treatment plants (WWTP), residues of these compounds have been found in influent and effluent wastewater, and therefore in surface waters [1–3]. Besides, pharmaceutical compounds have the property of interacting and accumulating in living organisms which makes them potentially hazardous for the ecosystem, thus being highly interesting compounds to be determined and assessed [4].

Most of the pharmaceutical residues found in water matrices are in trace levels (μg/L and ng/L). For this reason, a sample preparation step is required before an advanced analytical technique such as liquid chromatography coupled to mass spectrometry in tandem (LC-MS/MS), to accurately determine the compounds at low concentrations [1]. The technique most frequently used for sample preparation, clean-up, and preconcentration of trace contaminants from water matrices is solid-phase extraction (SPE). This widely known technique has undergone several modifications over the last years, which resulted in the development and use of new sorptive extraction techniques such as magnetic solid-phase extraction (MSPE), dispersive solid-phase extraction (dSPE), solid-phase micro-extraction (SPME), and stir-bar sorptive

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extraction (SBSE) [5,6]. Each of these techniques offers specific advantages depending on the analyte type and matrix complexity.

SBSE is an equilibrium-based technique that facilitates the partitioning of the analytes from the liquid sample and coating extraction material. It offers numerous benefits such as ease of operation, high reproducibility, ability to process relatively large sample volumes in a single step, and minimal use of organic solvents [7,8]. Unlike SPME, extraction capacity due to small coating volumes, SBSE employs a larger coated stir bar, allowing higher extraction yields and, hence better sensitivity, especially important when targeting trace-level analytes. To ensure the retention of target analytes the selection of the SBSE coating material is a crucial point. Nowadays, two coating materials are commercially available: ethylene glycol-silicone (EG-silicone) and polydimethylsiloxane (PDMS) [8,9]. Several studies have used these materials to determine a wide range of analytes in different matrices [10–15]. For example, the study from Gilart et al. [10] focused on a comparison of EG-silicone, PDMS, and polyacrylate (PA) materials in SBSE to determine pharmaceuticals in environmental samples. It was observed that PA and PDMS could only retain the most nonpolar analytes with low efficiency, while EG-Silicone had high recoveries with those compounds but had poor retention of the most polar ones. Moreover, several studies have reported the limited mechanical stability of these materials [9–16]. To this end, novel in-house coating materials for SBSE have been investigated and developed with higher stability, better cost-efficiency, and improved ability to extract compounds with higher polarity [5,17].

In the last few years, metal-organic framework (MOF) materials have been a subject of focus due to their unique characteristics. MOFs are formed by a metal ion center surrounded by organic ligands giving them a dimensional structure, which makes them show special characteristics as porosity, stability and high surface area [5,18]. Furthermore, recent studies have examined the incorporation of MOF microparticles into organic polymer monoliths in order to enhance the performance of those materials in terms of permeability and higher stability. One characteristic of these materials is their chemical tunability, which allows the introduction of ion-exchange moieties, such as amines or carboxylic groups, so they can selectively retain polar ionic compounds [18,19].

In this work, a hybrid stir bar coating was developed by integrating a monolithic organic phase and amino-functionalized UiO-66(Zr) onto conventional PTFE magnetic stir bars. The fabrication process began with the vinylization of the PTFE surface to enable the covalent attachment of a glycidyl methacrylate (GMA)-based polymer monolith. Subsequently, NH_2-UiO-66(Zr) was anchored onto the GMA monolith via nucleophilic epoxy ring opening. The resulting hybrid material (referred to as GMA@NH_2-UiO-66(Zr)) exhibited weak anion exchange (WAX) properties, making it a promising SBSE coating for the selective extraction of acidic pharmaceutical compounds. To the best of our knowledge, this is the first application of UiO-66(Zr)-based hybrid materials as SBSE coatings, as it only has been used in SPE or dSPE [20–22]. The developed method was successfully applied to the extraction of 6 target acidic pharmaceuticals from environmental water samples, followed by their determination using LC-MS/MS.

2. Experimental

2.1. Standards and reagents

For the SBSE coating preparation, PTFE-coated stirring bars (15 mm × 1.5 mm) were sourced from VWR International Eurolab (Barcelona, Spain). The sodium naphthalene solution (FluoroEtch®) used for surface treatment of PTFE stir bars was supplied by Acton Technologies (County Limerick, Ireland). Glycidyl methacrylate (GMA) and ethylene glycol dimethacrylate (EDMA) were obtained from Sigma-Aldrich (Steinheim, Germany). Lauroyl peroxide (LPO), cyclohexanol, and 1-dodecanol were purchased from Alfa Aesar (Karlsruhe, Germany). Fluorinated ethylene-propylene (FEP) tubing (3.60 × 6.00 mm) was provided by Bohlender GmbH (Grünsfeld, Germany). Zirconium tetrachloride and 2-aminoterephthalic acid (2-ATA) (99 %) were sourced from Sigma-Aldrich. N, N-dimethylformamide (DMF) was obtained from VWR Chemicals (Fontenay-sous-Bois, France).

Eleven pharmaceuticals were chosen for the assessment of the in-house stir bar sorptive extraction (SBSE) material. Five basic compounds were selected to evaluate selectivity, atenolol (ATE), trimethoprim (TRI), venlafaxine (VEN), propranolol (PRO) and metoprolol (MTO), whereas the remaining six were acidic that are diclofenac (DICLO), fenoprofen (FEN), flurbiprofen (FLB), bezafibrate (BEZ), valsartan (VAL) and naproxen (NPX). All these pharmaceuticals were purchased as pure standards (> 96 %) from Sigma-Aldrich, and their characteristic pK_a values are shown in Table S1.

Individual standards' stock solutions were prepared in methanol (MeOH) at a concentration of 1000 mg/L and stored in the freezer at -20 °C. Working solutions of a mixture of all the analytes were prepared weekly in a combination of ultrapure water and MeOH (90/10 v/v) and stored at 4 °C in the dark. Ultrapure water was provided by a water purification system (Millipore, Burlington, United States), while "HPLC-grade" MeOH and acetonitrile (ACN) were purchased from J. T. Baker (Deventer, The Netherlands). "LC-MS grade" ACN and water were supplied by Carlo Erba (Val de Reuil, France). Formic acid (HCOOH, > 98 %) and HCl (> 37 %, reagent grade) were used to adjust the pH of the mobile phase and sample, and they were acquired from Sigma-Aldrich.

2.2. Stir bar preparation

2.2.1. Surface modification of the PTFE magnet and preparation of the monolith-coated magnet

The chemically modified magnets were prepared following a procedure taken from previous studies [18–24] with full details provided in the Electronic Supplementary Material (ESM). Notably, the structural stability of the magnetic stir bar was significantly enhanced by incorporating fused plastic into its corner regions, resulting in a dumbbell-like shape (see Fig. 1A). This design reinforces the coating attachment and improves the overall durability of the device during both stirring and handling.

2.2.2. Synthesis of NH_2-UiO-66(Zr) material

NH_2-UiO-66(Zr) was synthesized following the procedure developed by Martínez-Pérez-Cejuela et al. [25], and it is briefly detailed in the Electronic Supplementary Material (ESM).

2.2.3. Preparation of GMA@NH_2-UiO-66(Zr) coating material

The incorporation of NH_2-UiO-66(Zr) MOF into the GMA-modified magnet was adapted from a previous work [18]. Briefly, fifty milligrams of NH_2-UiO-66(Zr) previously prepared and dried (100 °C, 6 h) were weighed and dispersed in 25 mL of DMF. The dispersed solution was then transferred to a 50 mL round-bottom flask, where the GMA-modified magnet was introduced. The mixture was subjected to reflux under constant agitation (300 rpm) at 100 °C for 48 h. After the reaction, the resulting monolith@MOF hybrid material (GMA@NH_2-UiO-66(Zr)) was washed with DMF (10 mL, three times) and MeOH (10 mL) and stored in the same solvent until use in the SBSE procedure. Fig. 1B shows a cross-sectional view of the extraction device, the innermost layer being the PTFE magnet, followed by the GMA-based monolith, and the outermost layer being the yellow MOF coating.

The total estimated cost was around 4.5€ per unit of the lab-made magnet. This was calculated by summing the direct costs associated with the required chemicals and power supplies and incorporating an additional 15 % to account for indirect costs such as equipment depreciation, utilities, and general laboratory overhead.

2.3. Characterization of GMA@NH_2-UiO-66(Zr)

The coating material GMA@NH_2-UiO-66(Zr) was subjected to

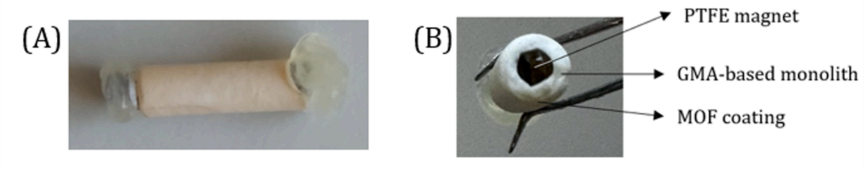


Fig. 1. Final GMA@NH_2-UiO-66(Zr) stir bar coating assembly view (A) and inner view (B).

characterization to confirm the success of the synthesis. Scanning electron microscopy (SEM) micrographs of materials were taken with a field emission scanning electron microscope with focused ion beam (FIB-SEM) model SCIOS 2 (ThermoFisher Scientific). The microscope was coupled with an energy dispersive spectrometer (Oxford Ultim Max 170) in order to provide point and area chemical analysis.. X-ray diffraction (XRD) patterns were obtained using a D8 Advance A25 X-ray diffractometer (Bruker, Berlin, Germany). Attenuated total reflection (ATR) Fourier-transform infrared (FTIR) spectra were recorded using a Cary 630 FTIR spectrometer equipped with a diamond ATR accessory from Agilent Technologies. FTIR spectra acquisitions were performed from 4000 to 400 cm^{-1} (4 cm^{-1} resolution, and an average of 25 scans). Adsorption-desorption nitrogen isotherms were measured using a S5 Micromeritics ASAP2020 instrument (Norcross, USA) at 77 K, and the specific surface area was calculated using the Brunauer-Emmet-Teller (BET) mathematical model.

2.4. SBSE procedure

The SBSE procedure began with a conditioning step by introducing the stir bars into 25 mL glass screw-cap vials containing 5 mL of MeOH for 10 min, followed by 5 mL of ultrapure water adjusted to the same pH as the sample (pH 7) for another 10 min, both under constant agitation. A fixed sample volume of 10 mL, adjusted to pH 7 with HCl, was then extracted for 3 h under constant agitation at 600 rpm at room temperature. After that, a clean-up step was performed by adding 3 mL of MeOH for 2 min in an ultrasonic (US) bath. Then, the elution was carried out using 3 mL of 5 % NH_4OH in MeOH for 10 min, also in a US bath. The elution volume was evaporated until dryness using a centrifuge evaporator miVac Duo (Genevac, Ipswich, UK) and then reconstituted with 1 mL of ultrapure water/MeOH (90/10 v/v). All the reconstituted solutions were filtered with 0.22 µm polytetrafluoroethylene (PTFE) syringe filters (Scharlab). After each use, the stir bars were cleaned by rinsing two times with the elution solution (5 % NH_4OH in MeOH) and two additional rinses with MeOH in the US bath, for 10 min each step. The cleaned stir bars were stored in Eppendorf tubes filled with ultrapure water until their next use. SBSE devices were reused up to 20 times, without any significant decrease in extraction efficiency.

Prior to extraction, river water samples were filtered using 0.47 µm nylon membrane filters (Scharlab).

2.5. Chromatographic conditions

The optimization of the SBSE procedure was performed with an Agilent 1100 LC instrument equipped with a binary pump, an autosampler, an automatic injector, an oven, and a diode array detector (DAD) (Agilent, Waldbronn, Germany). The mobile phase was a mixture of ultrapure water (solvent A) and ACN (solvent B), both with 0.1 % of HCl (v/v). A Luna Omega 5 µm Polar C18 100 Å (150 × 3.0 mm, 5 µm particle size) was used as chromatographic column with a precolumn (4 mm × 3 mm), both supplied by Phenomenex (Torrance, CA, United States). The oven temperature was set at 30 °C, the flow rate was 0.4 mL/min, and the injection volume was 20 µL. The separation was performed using a gradient elution starting at 10 % of B, increasing to 45 % within 6 min, then to 50 % in 18 min, and finally reaching 100 % in 2 min. The % of B was held at 100 % for 4 min, after it was returned to initial conditions in 1 min. These conditions were held for 3 min for the stabilization of the column. TRI, MTO, PRO, BEZ, VAL, FEN, FLB, and DICLO were measured at 210 nm, whereas ATE, VEN and NPX were measured at 230 nm.

Once the SBSE process was optimized, an LC-MS/MS was used to validate the method and to analyze samples. Particularly, an Agilent 1200 instrument equipped with an autosampler and a quaternary pump. This LC was coupled to a 6460 QqQ mass spectrometer (MS/MS) (Agilent, Waldbronn, Germany). The same chromatographic conditions were used, except that HCOOH was used instead of HCl, and the injection volume was changed to 5 µL. Regarding the MS detection, electrospray ionization (ESI), working in both negative and positive modes, was selected as the ionization source in the MS for the acidic and basic compounds. The MS optimum parameters for the acquisition of all the compounds were the following: a source gas temperature of 320 °C, a nebulizer pressure of 50 psi, a nitrogen flow rate of 12 L/min, a capillary voltage of 3000 V for positive mode and 3500 V for the negative mode, a fragmentor voltage between 100 and 80 V, and a collision energy between 2 and 25 eV. Data acquisition was performed in MRM mode, with the selection of a precursor ion and two product ions of each analyte. The most abundant transition was selected as quantification and the other transitions as confirmation in multiple reaction monitoring (MRM). To observe the corresponding transitions, collision energies and fragmentor voltages, see Table S1.

2.6. Validation parameters

The analytical performance of the SBSE-LC-MS/MS method was assessed using standard mixtures. Instrumental linearity was plotted and used to calculate SBSE extraction recoveries and the sample's concentration. The target compounds showed good linearity ($R^2 > 0.9995$) across a concentration range of 0.5 to 500 µg/L for all acidic compounds, except FEN and FLB, whose linearity ranged between 1 and 500 µg/L. Instrumental limits of quantification (LOQ) were established as the lowest concentration from the calibration curve, while the limits of detection (LOD) were defined as the lowest concentration with a signal-to-noise ratio (S/N) of at least 3. LOQs and LODs were 0.5 and 0.1 µg/L, respectively for all acidic compounds, except FEN and FLB, whose LOQs and LODs were 1 and 0.25 µg/L, respectively.

Apparent recovery ($\%R_{app}$) was assessed by spiking the sample with a mixture of analytes at a concentration of 20 µg/L prior to SBSE and comparing the measured concentration to the theoretical value. To account for the background signal, non-spiked river water samples were also analyzed, and their signal was subtracted from that of the spiked sample.

Matrix effects (%ME) were evaluated by spiking at a concentration of 200 µg/L into the blank sample extract after all the SBSE protocol. The %ME was calculated using the equation: $\%ME = [(C_{exp} / C_{theo}) \times 100] - 100$, where C_{exp} is the concentration obtained from the calibration curve, and C_{theo} is the expected (theoretical) concentration. Positive %

ME values indicate signal enhancement, whereas negative values correspond to signal suppression.

Method precision was determined in terms of repeatability, including intra-day (using a single extraction device, $n = 3$) and inter-day (over three consecutive days, using a single extraction device, $n = 3$), both expressed as the relative standard deviation (%RSD) of peak areas at a concentration of 20 µg/L. Furthermore, the reproducibility (using different magnet batches) was also assessed ($n = 3$).

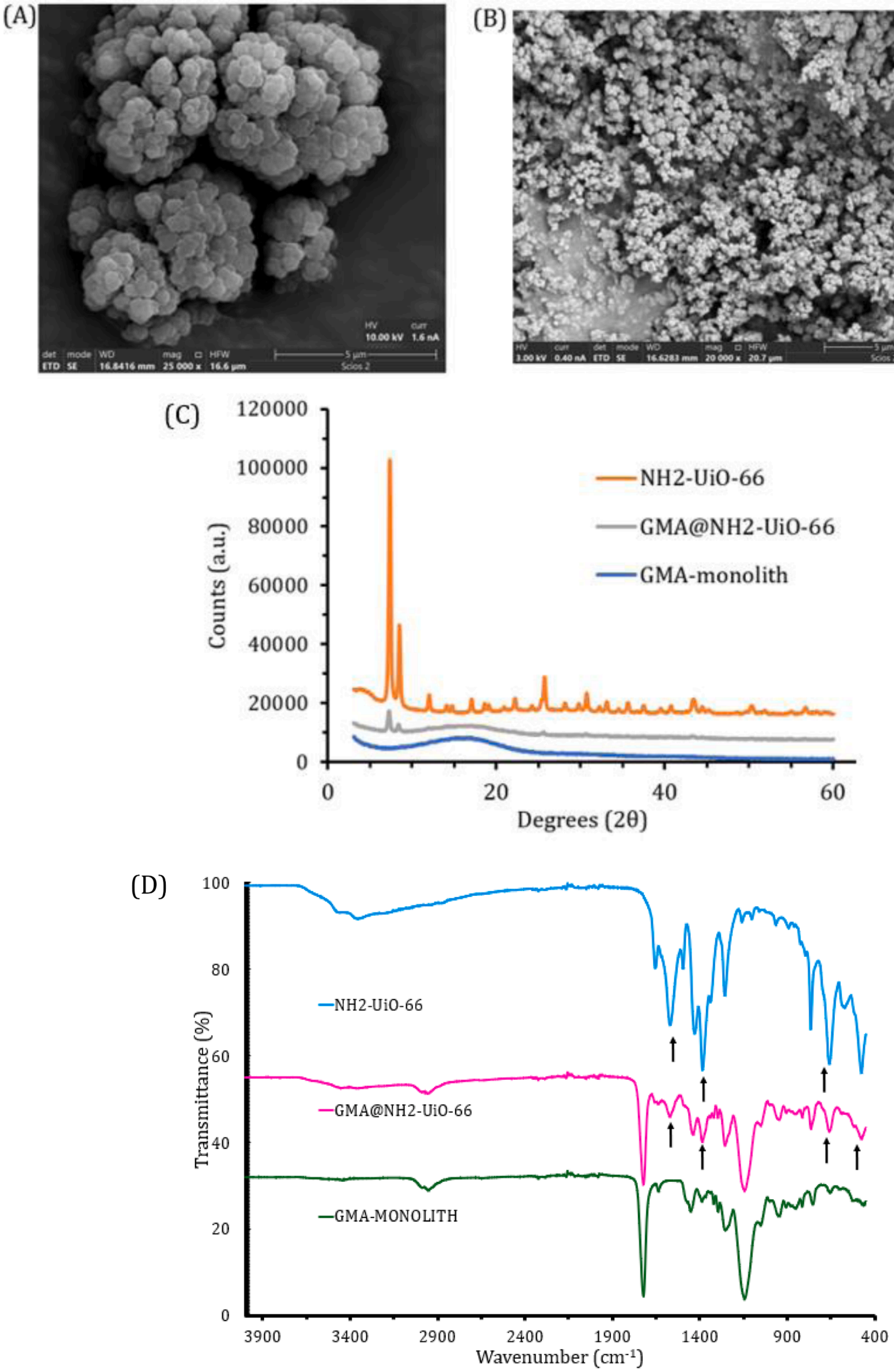


Fig. 2. SEM images of GMA-monolith (A) and GMA@NH_2-UiO-66(Zr) (B). XRD patterns of (from top to bottom) NH_2-UiO-66(Zr), GMA@NH_2-UiO-66(Zr) and GMA-monolith (C). FT-IR spectra of (from top to bottom) NH_2-UiO-66(Zr), GMA@NH_2-UiO-66(Zr) and GMA-monolith (D).

The method limits of quantification (MQLs) and the method limits of detection (MDLs) were estimated from the instrumental ones.

3. Results and discussion

3.1. Preparation and characterization of GMA@NH$_2$-UiO-66(Zr) stir bar coating material

As described in Section 2.2, the surface of the PTFE magnet must be activated prior to incorporating the MOF into the monolith, in order to ensure an effective bonding between this surface and the monolith material. To achieve this, a sodium naphthalene solution (Fluoroetch) was used to chemically etch the surface of the magnet, introducing hydroxylic functional groups needed for subsequent vinylization with GMA. Following this treatment, the GMA monolith-modified magnet was synthesized, and the NH$_2$-UiO-66(Zr) was incorporated using DMF as dispersing solvent. The resulting material, GMA@NH$_2$-UiO-66(Zr), is shown in Fig. 1A, where the characteristic yellow color of the MOF can be observed. As it was already observed by S. Zatrochová et al. [18], the monolith layer tends to be thicker than the outer MOF layer, which complicates the characterization process. As a result, characterization was carried out directly on the assembled stir bar. In fact, N_2 adsorption–desorption isotherm data reveal that the presence of MOF is reduced because the surface area only increased from 0.5984 ± 0.0138 $m^2\ g^{-1}$ to 0.6378 ± 0.0040 $m^2\ g^{-1}$, after the MOF impregnation (being the surface area of the MOF powder around 700$m^2\ g^{-1}$ [25].

Firstly, the morphology of the hybrid material (GMA@NH$_2$-UiO-66 (Zr)), the neat polymeric monolith, and the MOF powder was investigated using SEM. Fig. 2A depicts the GMA-monolith showing the typical network structure composed of clusters of rounded microglobules, whereas Fig. 2B displays the polymer after MOF coating. As can be observed, the polymer surface became roughened, where MOF crystal particles (see Fig. S1) were evidenced, suggesting a successful attachment of MOF to the polymer surface. Figure S1 displays smaller structures corresponding to the MOF (NH$_2$-UiO-66(Zr)) porous material. Furthermore, EDX analysis was conducted to further confirm the presence of the MOF on the surface of the monolith (Figure S2). By comparing Figure S2A and S2B, it can be verified that the zirconium metal originates solely from the MOF, thus indicating that the zirconium content found in Figure S2C is attributable to NH$_2$-UiO-66(Zr). This finding, together with mapping analysis (Figure S3), further demonstrates the successful assembly of NH$_2$-UiO-66(Zr) to the GMA-based monolith.

Further evidence of the successful formation of the coating hybrid material was demonstrated by XRD analysis, which provides crystallographic structure information about our materials. Fig. 2C shows the characteristic diffraction peaks of the crystalline MOF powder (orange line), compared to the broad band corresponding to the amorphous monolith (blue line). The hybrid material (gray line) displayed small diffraction peaks corresponding to the relatively low amount of MOF on the stir bar surface compared to the larger contribution of GMA-based monolith in the resulting material.

Finally, FT-IR was performed as further confirmation of MOF incorporation. Fig. 2D shows the characteristic absorption bands of both the neat MOF, the monolith, and the final hybrid material. For instance, the GMA-based monolith shows the carbonyl group stretching band around 1700 cm^{-1} and the ester stretching band near 1150 cm^{-1}. Regarding the MOF, characteristic amine bending bands around 1500 cm^{-1} are present in both the MOF and the GMA@NH$_2$-UiO-66(Zr) material. Additionally, recognizable peaks from C—N stretching absorption of aromatic amines (1335–1250 cm^{-1}) and characteristic vibrational bands of the framework (O—C-O) groups around 1400 cm^{-1} and 1550 cm^{-1} are present in both MOF and hybrid material. A broad band observed between 2750 and 3500 cm^{-1} in the NH$_2$-UiO-66(Zr) spectrum likely corresponds to O–H and N–H stretching vibrations, while N–H wagging modes are observed at 750 and 650 cm^{-1}.

All the above results confirm that NH$_2$-UiO-66(Zr) was successfully incorporated into the GMA-based monolith SBSE coating, as evidenced not only by naked-eye (visible color change), but also through comprehensive characterization.

3.2. SBSE optimization

In order to obtain the best stir bar performance, the different steps of an SBSE procedure must be optimized. These steps are extraction pH and volume of sample, extraction time, the inclusion or not of a cleaning step, and elution time. The starting conditions to optimize were adopted from a previous study conducted by our research group. Briefly, a stir bar was conditioned with 5 mL of MeOH for 10 min followed by 5 mL of ultrapure water adjusted to pH 7 for another 10 min. An extraction volume of 10 mL of ultrapure water spiked at 0.5 mg/L, adjusted to pH 7 with HCl. This solution was extracted for 3 h, under agitation at 600 rpm at room temperature. The following step was a clean-up by adding 3 mL of MeOH for 2 min in an ultrasonic (US) bath. After, the elution step with 3 mL of 5 % NH_4OH in MeOH for 10 min, also by US bath. Finally, the eluate was evaporated until dryness with the help of a vacuum evaporator and then reconstituted with 1 mL ultrapure water/MeOH (90/10 v/v), which was injected into an LC-DAD instrument.

3.2.1. Sample pH

The extraction pH was first evaluated since the SBSE material was functionalized with amino moieties that have weak anion exchange character, which become ionically charged only under neutral or acidic conditions. To achieve selective extraction of acidic analytes, it was essential to operate at pH values where these compounds were negatively charged, thus allowing electrostatic interactions with the positively charged extraction phase. According to their pK_a values (Table S1), the acidic analytes are predominantly in their anionic form at pH values above 4.5. For this purpose, sample pH values of 5, 6, and 7 were tested, while keeping all the other extraction parameters as those described in Section 3.2. Fig. 3 shows similar results across the three assessed pH values. It can also be observed that at pH 5, FEN, FLB, and DICLO recoveries were slightly higher than at pH 7, whereas VAL, BEZ and NPX showed contrary behavior. Nevertheless, the basic compounds exhibited very low recoveries (between 2 and 9 %) across all tested pH values, which can be attributed to their minimal retention onto the amino-functionalized material and the high selectivity of the sorbent toward acidic analytes. Overall, the best results were observed for pH 7, hence being the one chosen as optimal.

At optimal pH conditions (pH 7), the contribution of the MOF component to the extraction performance was evaluated by testing an unmodified GMA-coated stir bar (without MOF anchoring) under identical conditions. Negligible acidic analyte retention was observed for the unmodified device (recoveries around 2 %), confirming that the polymeric backbone itself does not significantly contribute to the extraction process. In contrast, the GMA@NH$_2$-UiO-66(Zr) stir bar exhibited retention of the acidic compounds (recoveries ranging between 48 and 54 %), indicating that the MOF coating provides the predominant interaction sites responsible for acidic analyte retention.

3.2.2. Cleaning step

The cleaning step was assessed to check the selectivity of the method by removing interferences or compounds retained by reverse-phase or other non-specific interactions. In the initial conditions, a clean-up step with 3 mL of MeOH was used, a volume that ensured the stir bar was covered. Then, this step was evaluated by including it or not in the SBSE procedure. Similar recoveries were observed in both cases for acidic compounds, between 48–54 % using clean-up and 41–54 % without this step, indicating that for acidic compounds, the ionic interaction is the predominant one. In contrast, as expected, basic analytes were not retained, resulting in very low recoveries (below 10 %) under all conditions, reflecting the high selectivity of the amino-functionalized

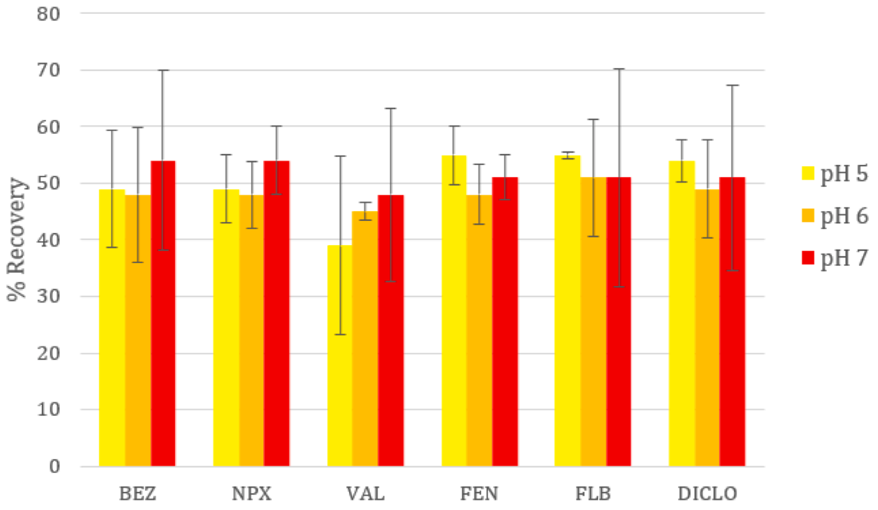


Fig. 3. Recovery values (%) for acidic compounds using GMA@NH_2-UiO-66(Zr) coating SBSE material, for different sample pHs.

sorbent toward acidic compounds. Given these results, this step was included in the optimum conditions to prevent interference retention when dealing with complex samples.

The cleaning step has been rarely used in SBSE, since it is only used to enhance the selectivity of the method and disrupt non-specific interactions when working with mixed-mode ion-exchange sorbents. Some studies [26,27] reported the use of ultrapure water to rinse the stir bars before elution which is less effective. However, to the best of our knowledge, this is the first time that an established clean-up step with MeOH is used in SBSE.

3.2.3. *Elution conditions*

The elution step was optimized by evaluating three parameters: solvent, volume and time. Regarding the elution solvent, two alternatives were evaluated: 5 % NH_4OH in MeOH, that promotes protonation of acidic analytes, and 5 % HCOOH in MeOH, which neutralizes the amino moieties within the coating. Both solvents effectively disrupted the ionic interactions between analytes and the coating, yielding comparable recovery values – between 40–56 % for 5 % HCOOH and between 48–54 % for 5 % NH_4OH. Nevertheless, 5 % NH_4OH in MeOH was selected as the elution solvent, as prioritizing analyte neutralization was expected to preserve better the coating integrity. This approach was believed to allow for extended reuse of the stir bars without compromising analytical performance.

The elution volume was not further evaluated, as the objective was to maintain the minimum volume necessary to cover the stir bar during the elution step. This approach ensured reduced solvent consumption and minimized waste generation, in line with green analytical principles. Additionally, increasing the elution volume would have extended the subsequent vacuum evaporation step, thereby prolonging the overall analysis time. For these reasons, the lowest effective elution volume was selected and maintained throughout the study.

Finally, elution time was assessed by increasing the initial 10 min to 15 and 20 min, to evaluate potential improvements in recoveries. Recovery values ranged between 48–54 %, 43–58 %, 36–50 % for 10, 15 and 20 min, respectively. Overall, no significant differences were detected among the tested times, indicating that prolonged elution time did not enhance recovery efficiency. Thus, 10 min was established as the optimal elution time, ensuring the shortest analysis time without compromising efficiency.

In contrast to previous studies, such as those by Kole et al. [11] and Tanwar et al [26]., which required up to 40 min in an ultrasonic bath to achieve effective elution from PDMS-coated commercial stir bars (Twister®), the present study achieved effective elution in only 10 min.

3.2.4. *Extraction time*

To optimize this parameter, several extraction times were tested in order to determine at which point the recoveries remained constant. Consequently, 1, 2, 3, 4, and 6 h of extraction were tested. It was observed that acids' recoveries increased up to 3 h, after which they remained relatively constant, meaning that the equilibrium had been reached between analytes and SBSE's coating. At 4 h, the recoveries of FEN, FLB, DICLO slightly increased, whereas BEZ, NPX and VAL recoveries remained unchanged. Fig. 4 presents the effect of the studied extraction times in the recoveries for three representative acidic compounds with different behaviors, which correspond to the overall trend of all the model acidic analytes (Figure S4 presents the behaviors for the remaining acidic analytes). It was decided that the little enhancement in recoveries observed in three of the analytes was not significant enough to extend the extraction time by one additional hour. Thus, fixing 3 h as the optimal extraction time.

An extraction time of 3 h was not considered excessively long, as the method allows multiple samples to be processed in parallel, mitigating the effect of extraction time on overall efficiency. Similar (3 – 4 h), and even longer (24 h) extraction times have been reported in other studies for several SBSE coatings for common analytes: PDMS [10–28], EG-Silicone [26,28], GMA-based monolith [16], poly(MAA-co-DVB) [29], poly(VPD-*co*-DVB) [30]. Probably, due to the low kinetics/diffusion rates of the analytes through the stationary phase.

3.2.5. *Sample volume*

Finally, the last parameter to optimize was the sample volume, so as to improve the sensitivity of the method. Until now, the volume tested had been 10 mL; hence, 25 and 100 mL were also evaluated. It was observed that increasing the volume led to a decrease in total recoveries for acidic compounds, reaching around 17–27 % using 25 mL and 13–22 % using 100 mL for all the analytes, while using 10 mL of sample, recoveries of 48–54 % were obtained. This behavior was due to the low quantity of MOF coating material, as shown in the characterization studies, resulting in fewer interactions with the analytes and consequently lower recoveries were obtained when increasing sample volume. Thus, the selected optimum volume was 10 mL.

Comparable results were obtained in Nadal et al. study [16], in which WAX mixed-mode materials were assessed for SBSE of acidic pharmaceuticals from environmental water samples. They also optimized the extraction procedure, and for the optimal volume, 10 mL, NPX, FEN, and DICLO recoveries were 37, 44, and 63 %, whereas in the present study, 54, 51, and 51 %, respectively. Since higher recoveries were not expected due to the non-exhaustivity of the procedure, we considered that the recoveries were acceptable.

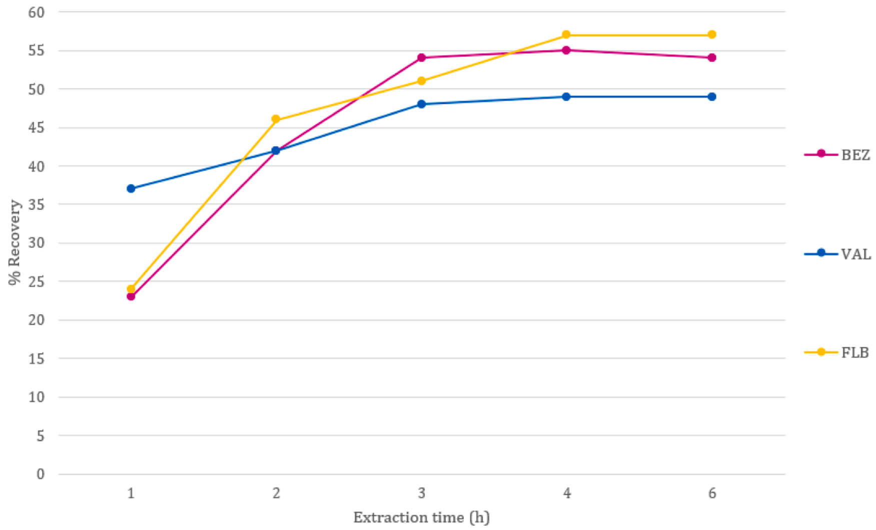


Fig. 4. Extraction time (h) effect in recovery values (%) for BEZ, VAL and FLB using GMA@NH$_2$-UiO-66(Zr) coating SBSE material.

Additionally, sample volumes of up to 100 mL have been reported in SBSE procedures for the determination of pharmaceuticals in environmental water samples, depending on the coating material and stir bar length. For example, 10 mm stir bars with PDMS or EG-Silicone coatings required sample volumes ranging from 40 to 100 mL [26,28], while 20 mm bars coated with PDMS, PU, or C$_{18}$-protected phases used lower volumes between 20 and 25 mL [31,32]. On the other hand, the present study employed a stir bar of intermediate length (15 mm) and achieved effective extraction using only 10 mL of sample.

3.3. *Validation of the method*

The optimized method was validated for river water samples using an LC-MS/MS instrument, in terms of apparent recovery (%R$_{app}$), matrix effect (%ME), linear range, method detection and quantification limits, and the precision as repeatability intra-day and inter-day and reproducibility.

The %R$_{app}$, %ME, MDLs and MQLs obtained for river water samples are presented in Table 1. The %R$_{app}$ was calculated by spiking samples at a concentration of 20 μg/L. As Table 1 shows, the apparent recoveries ranged between 21 and 41 %, which are comparable to those reported by Nadal et al. [16], who obtained apparent recoveries between 20 and 47 % for common acidic analytes under similar extraction conditions.

The %R$_{app}$ values obtained for the samples diminished compared to those achieved during the optimization phase, likely due to the complexity of the sample's matrix. Furthermore, as has been aforementioned, SBSE is a non-exhaustive technique, and high recoveries are not typically expected.

The %ME in the analyzed river water remained below 10 %, indicating the high selectivity employed by the SBSE phase. In particular, as Table 1 presents, most of the selected acidic analytes displayed signal enhancement, with values ranging from + 2 to + 9 %. The only exception was FEN, that exhibited a slight suppression (– 2 %). A larger %ME had been reported by other studies using other extraction techniques with mixed-mode properties [16,33–35], such as Borrull et al. [33] that used SPE with amphoteric properties for acidic and basic drugs in Ebre river water samples, which obtained signal suppression between -6 and -31 % for VAL, FEN and DICLO.

Table 1
Validation parameters in terms of %R$_{app}$, %ME, MDLs and MQLs for the acidic target compounds.

	Ebre river water			
	%ME[a]	%R$_{app}$[b]	MDL (ng/L)	MQL (ng/L)
NPX	+3	39	4	20
BEZ	+9	23	2	10
VAL	+6	22	2	10
FEN	-2	41	10	40
FLB	+4	39	10	40
DICLO	+5	31	3	15

[a] spiked at 200 μg/L.
[b] spiked at 20 μg/L.

Method linearity was estimated from the instrumental one and considering the extraction factor and recoveries. It corresponded to MQL–20,000 ng/L for FEN, FLB and NPX, MQL–15,000 ng/L for DICLO, and MQL–10,000 μg/L for BEZ and VAL. MDLs and MQLs for all the acidic compounds are indicated in Table 1. As shown, MDLs and MQLs are in the low ng/L range, except for FEN and FLB which were slightly higher (i.e., 40 ng/L as MQL for both) likely due to their low ionization yield.

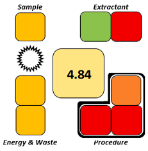
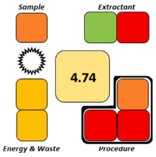
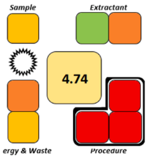
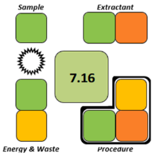
The repeatability intra-day ($n = 3$), in terms of three extractions with one device within the same day, and inter-day ($n = 3$), in terms of extraction in three consecutive days using the same device, were evaluated. The values of %RSD were between 5 and 12 % for intra-day tests, and between 4 and 13 %, except for DICLO, which showed 25 %, in inter-day tests. Furthermore, reproducibility between stir bar devices was also assessed with values below 19 % for all selected acidic compounds.

A comparison of the SBSE-LC-MS/MS method with other reported SBSE methods used for the determination of pharmaceutical compounds, has been performed in terms of extraction time, sample volume, R$_{app}$ (%), and precision (RSD, %), which data are compiled in Table 2. As can be seen in Table 2, the extraction time in the present study (3 h) is comparable to that reported in several previous studies [16–35], although faster extractions have been achieved in few studies [36]. The present study employed a relatively low sample volume (10 mL), demonstrating greater efficiency compared to earlier reports using 40 mL [26] and 100 mL [28].

Recoveries (R, %) in this study ranged from 22 to 41 %, which are comparable to those reported in other studies [16–35]. Higher recoveries have also been reported; however, these values are relative recoveries and cannot be compared to the present work, that presented apparent recoveries.

As observed in Table 2, the MLDs for common analytes (FEN, NPX and DICLO) of the developed method were lower than those achieved by SBSE/LC-MS/MS using EG-Silicone and PDMS [26,28], and PAN-I/MWCNTs [36]; nevertheless they were comparable when using GMA-based with EDA modifications [16], and MEC-18/SAX and

Table 2
Comparison of the proposed SBSE-LC-MS/MS method based on GMA@NH_2-UiO-66(Zr) coating with other reported studies for common analytes.

Common analytes	Sample matrix	Sorbent material[a]	Instrument	Extraction time (h)	Sample volume (mL)	R (%)	MDL (ng/L)	Precision (RSD, %)	Reuse times	Green assessment by SPMS	Ref
FEN; NPX; DICLO	River water	GMA-based with EDA modification	LC-MS/MS	3	10	31; 20; 47	10; 5; 5	< 9	25		[16]
NPX; DICLO	River and effluent wastewater	EG-silicone and PDMS	LC-MS/MS	3	40	22; 78 5; 18	71; 11	< 16	n.a.		[26]
NPX; DICLO	Tap and surface water	EG-silicone	LC-MS/MS	24	100	71–104; 112–83*	10–30; 6–10	< 20	50		[28]
FEN; NPX; DICLO	River and effluent wastewater	MEC—C18/ SAX and MEC—C18/ SCX	LC-MS/MS	3	25	47; 21; 69	0.3–4.8	< 21	30		[35]
NPX	River water and sediment	PANI/ MWCNTs-OH-	HPLC-UV	0.8	10	82–106*	350	< 15	20		[36]
FEN; NPX; DICLO	River water	GMA@NH_2-UiO-66(Zr)	LC-MS/MS	3	10	41; 38; 34	10; 4; 3	< 25	20		Present study

* relative recoveries.

[a] EDA: Ethylenediamine, PANI/MWCNTs-OH: Polyaniline/hydroxyl multi-walled carbon nanotubes, APTS: 3-aminopropyl triethoxysilane, LDH: layered double hydroxide; MEC: Microextraction capsule with C-18 strong anion exchange and strong cation exchange properties.

MEC—C18/SCX [35]. Precision, expressed as relative standard deviation percentage (RSD, %), was below 25 %, slightly higher than in the other studies, yet still considered acceptable.

Additionally, the reusability of the present study's stir bar was observed to be consistent with values reported in other studies, which range between 20 and 30 reuses [16–36], without any noticeable loss of recovery values. An excellent reusability was reported by Aparicio et al. [28], in which the stir bar was reused up to 50 times.

Overall, the present study achieves adequate recoveries with an appropriate extraction time, low sample volume and high sensitivity, with acceptable precision.

3.4. Analysis of real samples

A total of three Ebre river water samples were collected from different locations and dates and were analyzed in duplicate by LC-MS/MS.

Table 3 presents the concentration ranges of the target acidic compounds found in the river samples. Most of the acidic compounds were quantified, except for FEN and FLB, whose concentrations were not detectable. High occurrence (up to 1160 ng/L) had been found in one of the samples, while the other two showed lower levels. Overall, slightly higher concentrations were found in this study compared to other studies evaluating common analytes in environmental water samples using different extraction techniques [2–34]. For instance, Salas et al. [34] did not detect FEN in Ebre river waters, which is consistent with

Table 3
Range of concentrations (ng/L) of the selected acidic analytes found in Ebre river water samples.

Analytes	Concentration in Ebre river water (ng/L)
NPX	130 - 445
BEZ	25 - 240
VAL	35 - 210
FEN	< MDL - MQL
FLB	< MDL
DICLO	115 - 1160

this study. However, they also did not detect DICLO, whereas in this work, it was found at a higher concentration. In addition, Ma et al. [2] detected FLB in river water samples from China, while in this study, it was not detected.

3.5. *Greenness and practicality assessment*

The sample preparation metric of sustainability (SPMS) was selected as the greenness assessment tool. This metric, which provides a score of up to 10, exclusively evaluates the sustainability of the sample preparation step by considering four categories: sample information, extractant information, sample preparation procedure and energy consumption and waste [37].

The present study achieved an SPMS value of 5.74 (see Table 2), which is considered acceptable and higher than those estimated for several other SBSE procedures [26–35]. This improved score is mainly attributed to the use of a smaller sample volume (10 mL) and an alternative extractant of lower environmental impact. Table 2 also summarizes the SPMS scores calculated from the available data for each study. A common positive feature among all SBSE methods is the reusability of the extractant and the ability to process multiple samples simultaneously, which reduces waste generation and increases sample throughput. However, most procedures share similar sample preparation procedure information, energy consumption and waste generation that diminishes the final SPMS score, including extraction times exceeding 1 h, multi-step workflows (< 6 steps), and the need for an evaporation step to achieve the desired enrichment factor and sensitivity.

Among the methods compared, Nadal et al. [35] obtained one of the lowest scores (4.74) because of the use of two different extractants, that even though provided strong anion- and cation-exchange properties, increased the number of preparation steps and waste generation. In contrast, Hu et al. [36] demonstrated the greenest approach, achieving a score of 7.16 through a simplified preparation, a low number of steps, and minimal waste generation, owing to the omission of device conditioning and direct injection after desorption.

Regarding practicality, it was assessed using the blue applicability grade index (BAGI) metric tool. It scores methods according to some attributes observed in Figure S5 between values of 25 to 100, being 25 the worst method performance and 100 the excellence. Therefore, BAGI has been used to assess the practicality of this report's analytical method. As Figure S5 shows, the overall score for this analytical method was 60, which is the minimum score to be considered practical according to Manousi et al. [38]. Several factors contribute to this mark. First, although simultaneous preparation of more than two samples is possible, the overall sample throughput results in ≤ 1 sample per hour, which could increase if a higher number of simultaneous samples are carried out. Second, despite the fact that NH_2-UiO-66(Zr) MOF must be synthesized in the laboratory, the procedure is straightforward, inexpensive (<5 €/unit), and the resulting stir bars are reusable up to 20 times, reducing waste. Third, SBSE is coupled with LC–MS/MS, which in this method was necessary to achieve the trace levels typically found in environmental samples, ensuring high sensitivity and reliable quantification. Finally, preconcentration steps are needed, enhancing the method's sensitivity and enabling the reliable detection of trace analytes in environmental samples. Overall, this BAGI score is consistent with another study with similar analytical performance and method (score of 55.0) [39,40].

4. Conclusions

A cost-effective in-house hybrid SBSE coating material (GMA@NH_2-UiO-66(Zr)) was successfully synthesized. The material consisted of the incorporation of a metal–organic framework UiO-66(Zr), further functionalized with amino groups, onto glycidyl methacrylate (GMA)-based polymer, which was immobilized onto commercial PTFE magnetic stir bars. So far as we can ascertain, this is the first study to employ GMA@NH_2-UiO-66(Zr) as an SBSE coating.

After the proper optimization and validation, the developed method resulted in a simple, and selective method to determine acidic pharmaceuticals, obtaining adequate recoveries (22–41 %), especially considering the non-exhaustivity of SBSE. In addition, even though the extraction requires 3 h, sample throughput remains unaffected because simultaneous extractions are feasible. Furthermore, thanks to the amino-functionalization, the hybrid coating provides WAX properties (a systematic MeOH clean-up step is presented), which greatly improve the retention of acidic and polar pharmaceuticals in environmental water samples, overcoming the poor performance of commercial PDMS and EG-silicone coatings for polar analytes. No significant matrix effects were observed, also confirming the selectivity of the GMA@NH_2-UiO-66 (Zr) coating. Additionally, GMA@NH_2-UiO-66(Zr) was applied to Ebre river water samples, demonstrating its suitability for the analysis of environmental matrices. Finally, from a sustainability perspective, the method achieved a BAGI practicality value of 60, indicating acceptable operational feasibility, and an SPMS greenness score that is both acceptable and higher than those reported for other SBSE procedures.

CRediT authorship contribution statement

Abril Trullàs: Writing – original draft, Validation, Methodology, Investigation. **Héctor Martínez-Pérez-Cejuela:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Francesc Borrull:** Methodology, Conceptualization. **Mónica Catalá-Icardo:** Writing – review & editing, Investigation, Conceptualization. **José Manuel Herrero-Martínez:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Rosa Maria Marcé:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Núria Fontanals:** Writing – review & editing, Supervision, Methodology, 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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.sampre.2025.100224.

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