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Metal-organic frameworks as promising solid-phase sorbents for the isolation of third-generation synthetic cannabinoids in biological samples

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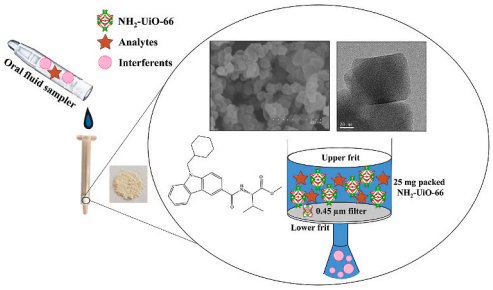
HIGHLIGHTS

- MOFs are used for the first time as SPE sorbents for isolation of synthetic cannabinoids.
- NH_2-UiO-66 has shown the best results in terms of extraction performance.
- SPE-LC-FLD provided good LODs and suitable recoveries.
- The SPE cartridges showed satisfactory reusability and low-cost (0.5 €/unit).
- The optimized protocol was successfully applied to human oral fluids.

GRAPHICAL ABSTRACT



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ABSTRACT

In this work, metal-organic frameworks (MOFs) were used for the first time as solid-phase extraction (SPE) sorbents for the isolation of synthetic cannabinoids (SCs) from oral fluids and subsequently quantified by LC-fluorescence detection (FLD). In this context, different MOF families were synthesized and tested under SPE mode. UiO-66 was the family selected, being the amino functionalized (NH_2-UiO-66) the best candidate in terms of extraction performance. After the method optimization, several analytical parameters of interest were obtained, reaching limits of detection (LODs) as low as 0.6–0.8 μg L^{-1} and precision values (expressed as RSD) lower than 10.6%. The developed method was successfully applied to the determination of 8 SCs in different oral fluids at three spiked levels with recoveries between 67 and 114%. This method claims to be a real alternative for screening purposes, being a cost-effective procedure due to the price of the sorbent (<0.5 €/cartridge) and its recyclability (up to 12 uses), among others good features.

1. Introduction

Metal-organic frameworks (MOFs) are crystalline coordination polymers composed by inorganic ions (metals or metallic clusters) and organic molecules (ligands) acting as nodes and linkers, respectively [1]. Since their outbreak in 1999 by Yaghi [2], the study of their applications

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has been exponentially growing [3] in many fields including gas separation [4], energy [5], catalysis [6], biomedicine [7] and so on. The number of available MOFs is countless due to the many possible combinations between inorganic and organic precursors [8], which lead to an enormous versatility. Particularly, MOFs have a truly potential in analytical chemistry [9,10] due to their intrinsic properties such as large surface area, porosity, chemical and thermal stability [11], and their chemical tunability and feasibility of post-synthetic modifications [12–14]. Indeed, MOFs have been used as promising sorbents in a wide range of sample preparation techniques such as (micro)solid-phase extraction (SPE) [15–17] and its dispersive modes (dSPE or magnetic-SPE) [18], solid-phase microextraction (SPME) [19], stir-bar sorptive microextraction (SBSE) [20,21], among others. Thus, microextraction techniques using MOFs have been commonly applied to determine organic compounds and metals in environmental, food and water samples.

On the other hand, the increasing consumption of new psychoactive substances (NPS), particularly synthetic cannabinoids (SCs), in the last two decades has alarmed the authorities and the population mainly due to the high number of potential derivatives with different grade of toxicity [22–24]. SCs act as receptor agonists designed specifically to mimic the cannabis effects and they are one of the largest groups of NPS reported by the United Nations Office on Drugs and Crime (UNODC) in the last decade [25]. The unawareness of their effect in the human body, especially at long-term consumption, leads to a global problem and highlights the importance of their monitoring. These compounds can be combined to CB1 and CB2 receptors of the brain and produces relaxation, drowsiness, feeling of slowness in the passage of time. Unfortunately, several challenges need to be faced including: rapid metabolism of synthetic cannabinoids (many of them provide similar metabolite structure in urine) and their presence at trace levels in biological samples [25]. Their quantification has been done in many samples such as whole blood [26], serum [27], urine [28], oral fluids [29] or hair [30]. However, the non-existent regulation has hindered their identification, requiring the use of highly sensitive procedures in most cases. Nowadays, the most common techniques employed for SCs determination are based on liquid and gas chromatography (LC and GC) coupled to sophisticated mass spectrometry (MS) [31]. Apart from these techniques, the monitoring and detection of NPS in oral fluids and other matrices still requires the development of pre-treatment/clean-up steps in order to enhance the sensitivity, being SPE with non-polar cartridges [26,32,33] and molecularly imprinted materials [28] common methodologies used for SCs enrichment. Although it has been recently reported the use of MOFs for the SC determination in the sensing field [34], the application of MOFs as efficient SPE sorbents for NPS isolation has not been reported to date.

In this work, the assessment of MOF-based materials as solid-phase extractants devoted to the retention of third generation SCs from oral fluid samples prior to their quantification by LC-fluorescence detection (FLD) is addressed. A preliminary study was performed to select the most appropriate MOF from an initial batch (MIL-101(Al, Fe), CAU-1. HKUST-1 and UiO-66). This latest MOF provided the best extraction efficiency for the target compounds, and it was chosen to explore the influence of ligand functionalization (hydroxyl and amino groups) on a series of isoreticular MOFs. As a result of this study, NH_2-UiO-66 was selected for its best analytical performance, and experimental parameters of SPE protocol affecting the extraction yield were systematically studied. Then, relevant analytical parameters (such as linear range, limit of detection (LOD) and quantification (LOQ), precision and reusability) were investigated and the method was applied to the isolation of 8 SCs in oral fluid samples. Additionally, these results were compared with those obtained with commercial C18 and HLB phases.

2. Experimental Section

2.1. Reagents and solutions

Metal salts such as aluminium chloride hexahydrate, zirconium tetrachloride, iron (III) chloride hexahydrate were purchased from Merck-Sigma-Aldrich (Darmstadt, Germany). Copper (II) nitrate tetrahydrate were acquired from VWR (Leicester, United Kingdom). The organic ligands: 2-aminoterephthalic acid (2-ATA), terephthalic acid (TA), 2-hydroxyterephthalic acid (2-OTA) and trimesic acid (H_3BTC) were obtained from Merck-Sigma-Aldrich.

The SCs (5F-NPB-22, ADB-CHMICA, ADB-CHMINACA, 5F-ADB, MDMB-FUBINACA, MMB-CHMICA, MDMB-4en-PINACA, MDMB-CHMCZCA), diazepam, cocaine and methamphetamine were mainly purchased from Sigma-Aldrich (San Louis, USA) and LGC standards (Barcelona, Spain), but also provided by "Drug Control Laboratory from Valencian Community Government" (Valencia, Spain). Table S1 shows the complete names, structures and the main physical-chemical properties of the studied SCs. Stock solutions of each analyte were performed at 1000 mg L^{-1} in MeOH or MeOH:water mixtures. Then, a mixture of all of them (100–500 μg L^{-1}) was daily done by proper dilution from the stock solution in Milli-Q water. All the solutions were kept in the darkness at 4 °C until use.

All organic solvents (*e.g.* methanol (MeOH), acetonitrile (ACN), dimethylformamide (DMF)) as well as other reagents (HCl, NaOH, etc.) were of analytical grade, unless otherwise stated. For the extraction devices: empty propylene SPE cartridge (1 mL total volume) and frits (1/16", 20 μm porosity) were acquired from Análisis Vínicos (Tomelloso, Spain). Milli-Q water (Millipore, Bedford, MA, USA) with a resistivity lower than 18 MΩ cm was used.

2.2. Instrumentation

A spectrofluorometer Jasco FP-750 (Madrid, Spain) was used for extraction studies of SCs using different MOFs. The excitation (ex) and emission (em) wavelengths were fixed at 297 nm and 350 nm, respectively. A 300 μL quartz cuvette was employed to measure samples after their filtration (0.45 μm Sartorius Stedim Biotech nylon filters (Göttingen, Germany)).

On the other hand, chromatography separation of selected analytes was achieved using an Agilent 1100 Series (Santa Clara, CA, USA) equipped with a G1322A degasser, a G1311A quaternary pump and a G1328A fluorescence detector. The column was a KromaPhase 100C18 (250 × 4.6 mm, 5 μm particle size) from Scharlab (Barcelona, Spain). Analytes separation was carried out at 1 mL min^{-1} using (A) water and (B) ACN as solvents, in gradient elution mode (Table S2). The wavelengths were fixed as previously cited ($\lambda_{ex} = 297$ nm; $\lambda_{em} = 350$ nm) and the injection volume was 20 μL. All samples were filtered before their injection with 0.45 μm nylon filters.

For material characterization, scanning electron microscopy (SEM) micrographs were acquired with the microscope model Hitachi S-4800 (Ibaraki, Japan), which was coupled to an energy dispersive spectrometer (EDAX Genesis 40). A transmission electron microscope (TEM) equipped with a digital camera AMT RX80 model JEM-1010 JEOL (Akishima, Japan) was used. Powder X-ray Diffraction (p-XRD) spectra were acquired in a D8 Advance A25 diffractometer (Bruker). Adsorption-desorption nitrogen isotherms were measured with S5 Micromeritics ASAP2020 instrument (Norcross, USA) at 77 K and the specific surface area was calculated with the mathematic model Brauner-Emmet-Teller (BET). Attenuated total reflection Fourier-transform infrared (FTIR) spectra of powdered materials were recorded on a Bruker FTIR spectrometer (Bremen, Germany) model Tensor 27, equipped with a DuraSamplIR II accessory and a 9 reflection diamond/ZnSe DuraDisk plate (Smiths Detection Inc., Warrington, UK). The zeta potential measurements were performed with Zetasizer Nano ZS equipment (Malvern Instruments, Malvern, UK).

2.3. Synthesis of MOF materials

The syntheses of the following materials are deeply explained in the Supplementary information: MIL-101(Al, Fe), CAU-1, HKUST-1. The synthesis of UiO-66 analogues (the parent and those functionalized with hydroxyl and amine denoted as OH-UiO-66 and NH_2-UiO-66, respectively) were performed according to the guidelines previously reported by Hu et al. [35] with some modifications. Briefly, 3 mmol of zirconium tetrachloride and 3 mmol of 2-ATA were weighed and mixed with 150 mL of DMF (*ca.* 1937 mmol). The molar ratio Zr(IV):X-TA:DMF was approximately kept at 1:1:650. Then, the solution was homogenized 15 min in an ultrasonic bath and the mixture was introduced into a Teflon-lined stainless steel autoclave. The container was sealed and the solvothermal reaction was carried out for 48 h at 120 °C. After this period, the reaction vessel was cooled to room temperature. Note that other MOF phases can be formed if the temperatures are different or the cooling step is rapidly performed. The resulting white (UiO-66), yellow (NH_2-UiO-66) or brown (OH-UiO-66) material was washed with DMF (3 × 25 mL) in order to remove the unreacted MOF precursors. Additionally, 50 mL of MeOH were used for 8 h under vigorous stirring at room conditions to exchange the solvent. Then, the material was collected by centrifugation at 14,000 g and dried at 100 °C for 5 h. All the MOF materials were gently grinded and sieved. Several fractions were collected in the range $50 \leq x \leq 300$ μm to evaluate their analytical performance as SPE solid sorbents. The unit cell of NH_2-UiO-66 can be observed in Fig. S1.

2.4. Oral fluid collection

Oral fluid samples were used as a proof-of-concept to perform real sample analysis. This matrix was selected due to several factors including non-invasive sampling procedure, easy to collect, reduced risk of adulteration or manipulation based on the direct observation of specimen collection, presence of the parent compound instead of the metabolites, appropriate detection window to detect drugs in the "under-the-effects"phase, and well known oral fluid/blood ratio for the most common drug compounds and also to facilitate the on-site sampling. Hence, the samples were collected with commercial Salivette® kits (Sarstedt, Germany) according to the manufacturer instructions. All the volunteers provided their written consent agreeing with the ethical guidelines established by the University of Valencia on drug studies in biofluids (ref. H1454687358321). For instance, the cellulose swab was chewed for *ca.* 60 s and centrifuged to separate the liquid phase and the solid particle matter retained in the device. When not analyzed on the sampling day, oral fluid samples were stored at −20 °C.

2.5. Extraction procedure

For the isolation of the SCs from oral fluids, SPE using NH_2-UiO-66 as sorbent was performed. The protocol can be summarised as follows: 25 mg of MOF were packed between two frits into 1 mL empty polypropylene cartridges. In order to avoid sorbent losses and before introducing the MOF in the cartridge, a nylon filter was cut and placed on the top of the bottom frit. Then, the sorbent material was conditioned with 500 μL of MeOH:ACN (50:50, v/v) and 500 μL of Milli-Q water. Afterwards, the sample was loaded (500 μL) at 0.5 mL min^{-1}. The non-specific retained interferences were eliminated in the washing step with 500 μL of Milli-Q water and the analytes were eluted through the cartridge with 2 × 500 μL MeOH:ACN (50:50, v/v). The extraction device can be regenerated with 2000 μL MeOH:ACN (50:50, v/v) and 2000 μL of water. A schematic representation of the experimental procedure is depicted in Fig. 1.

3. Results and discussion

3.1. Preliminary considerations

As it has been mentioned in the Introduction section, the lack of studies of the use of MOFs in SCs extraction makes necessary the investigation of these materials as SPE sorbents. In fact, the choice of MOF can drastically affect the interactions between the sorbent and the analytes and, subsequently, i influence on the extraction performance. At this point, a large variety of parameters that affect the MOF (such as the size and organization of the pore system, surface area, and the presence of functional groups) and also the analyte (size, nature, as well as the interaction type between the MOF and the analyte) must be responsible of the efficiency of the support for both the adsorption and desorption steps. However, in many cases some of these parameters could act in opposite directions. Therefore, a selection of the most appropriate MOFs necessarily implies a general screening step for each analyte. In this sense, a screening study was carried out with several MOF families (MIL-101(Al, Fe), CAU-1, HKUST-1 and UiO-66) in order to select the best candidate. Table 1 shows a summary of several characterization features of each synthesized MOF. MDMB-CHMCZCA was selected as a representative analyte from the SC family, and these preliminary studies were performed using 25 mg of MOF, 500 μL of aqueous solution of this analyte (500 μg L^{-1}) and 500 μL of MeOH as eluting solvent.

Fig. 2A shows the results of this study, indicating that UiO-66 typology (recoveries >70%) was the most suitable sorbent to extract and subsequently elute this target analyte. In any case, it is interesting to

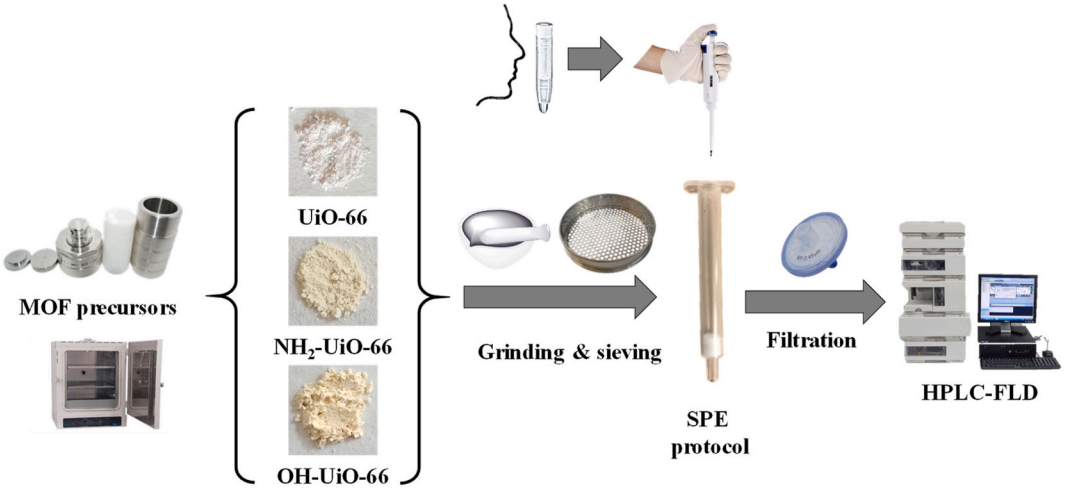

Fig. 1. Schematic representation of the experimental work followed in the present manuscript.

Table 1
Characterization features of tested MOFs.

MOF	BET Surface area (m^2 g^{-1})	Pore cavity (Å)
MIL-101(Fe)	1945	12-16 (flexible)
MIL-101(Al)	1309	12-16 (flexible)
CAU-1	1195	3–5
HKUST-1	832	9–10
UiO-66	926	7–9
NH_2-UiO-66	712	7–9
OH-UiO-66	546	7–9

highlight that different extraction values were found for the tested MOFs. The explanation of these results is not trivial, being the process influenced by many factors such as the adsorption and elution steps proposed in the SPE protocol, among others. In principle, the MOF should be able to extract efficiently the analyte from water media, and the eluting solvent, should be capable to desorb properly the analyte from the MOF. However, some problems can be found in both steps, which can hinder the effectiveness of the SPE process.

From the structure and cavity size of MOFs (see Table 1) and the molecular size of MDMB-CHMCZCA (molecular width less than 6.5 Å, length less than 12.2 Å, Fig. 2B), it can be derived that MIL-101 family can host this analyte due to their network flexibility, whereas for other MOFs such as HKUST-1 and UiO-66, a partial penetration process of this drug may happen into these structures, or even it could not enter inside the pores as in the case of CAU-1, where small triangular windows with a free aperture of 3–5 Å is present. However, the results showed that the MOFs with larger cavities (as MIL-101) led to lower extraction efficiencies. This fact could be explained by the pronounced adsorption of this hydrophobic analyte within the hydrophobic MIL-101 framework, which may produce an incomplete desorption of this compound when polar solvent as MeOH was tested. In the case of HKUST-1 and UiO-66, the cavity size was almost similar in both materials (7–10 Å); however, the water stable Zr(IV)-based MOF provides larger adsorption sites for π-and hydrogen bonding interactions. Indeed, these multiple H-bond anchoring positions (as the bridging hydroxyls reside at the corners of the MOF's tetrahedral cavity [36–38]) are key for the interaction of the analyte with several H-acceptor groups.

Taking into account these considerations, the introduction of different functionalities in UiO-66 network was studied. In so doing, the organic ligand (TA) was changed by 2-ATA and 2-OTA, introducing an amino and hydroxyl groups, respectively. Some characterization figures including SEM images and p-XRD are depicted in Figs. S2 and S3. The recoveries from this study were shown in Table S3. In comparison to the bare MOF, the recoveries showed a 10% enhancement when NH_2-UiO-66 was tested; however, OH-UiO-66 gave recovery values 5% lower. This finding cannot be explained by the capability of both MOFs to establish hydrogen bonds. Turning the attention to the BET surface areas of these functionalized MOFs, the value of UiO-66 was reduced by introducing $–NH_2$ groups, although not morphological changes were shown (Fig. S2), which is in agreement with previous studies [39–41]. On the other hand, adding –OH groups to UiO-66 significantly decreased the surface area, which is consistent with the large sizes of the particles of this MOF (Fig. S2) compared to the NH_2-UiO-66. This trend could be explained due to the higher polarity of the hydroxyl functional groups and the strong interaction with metal ions and solvents. Hence, the removal of the linker molecules (2-OTA) from the structure and the formation of pores will be retarded, resulting in a much lower surface area [39,40]. In addition to this hypothesis, which could justify the lower BET area of the OH-UiO-66 material from the point of view of MOF formation, it is necessary to analyze how the particle size would affect the adsorption/desorption of the analytes. As expected, the larger the crystal size, the larger the pores and, consequently, slower diffusion processes. Moreover, if the surface-analyte interaction is strong, a certain blockage of the pores cannot be excluded. Therefore, the problems detected for nitrogen adsorption can increase more markedly for other species, such as the analytes of interest in this article.

3.2. Characterization of NH_2-UiO-66

Once the most appropriate MOF was selected, characterization studies were performed in order to corroborate the synthesis process, to explore its morphology and chemical/structural properties.

First, the morphology was investigated by SEM and TEM micrographs (Fig. 3A and B). A pseudo-polyhedral shape (octahedrons) is found, concretely face-centered cubic (fcc) topology, matching with other reported contributions elsewhere [42,43]. The particle size diameter of the NH_2-UiO-66 is comprised between 76 and 107 nm (n = 50). Also, the elemental composition of this MOF from EDX analysis was obtained. As shown in Fig. S4, typical peaks of Zr, O and C were observed. Furthermore, the atomic percentages of these elements for UiO-66, OH-UiO-66 and NH_2-UiO-66 can be checked at Table S3.

Also, the FTIR and p-XRD spectra were employed to corroborate the successful synthesis of NH_2-UiO-66. The FTIR spectra depicted in Fig. 3C show the peaks from 1750 to 1300 cm^{-1}, which can be assigned to C=C and O–C–O stretching vibrations, and the broad band appearing at 2750-3500 cm^{-1} can be attributed to C–H bond vibration in the aromatic and aliphatic modes. The MOF also shows the characteristic peak related to the C–N stretching at 1275 cm^{-1}, and the NH_2 vibration typically around 3400-3500 cm^{-1}. This spectrummatched with previously published FTIR spectrum of NH_2-UiO-66 [44].

The p-XRD pattern of this material is depicted in Fig. 3D and showed

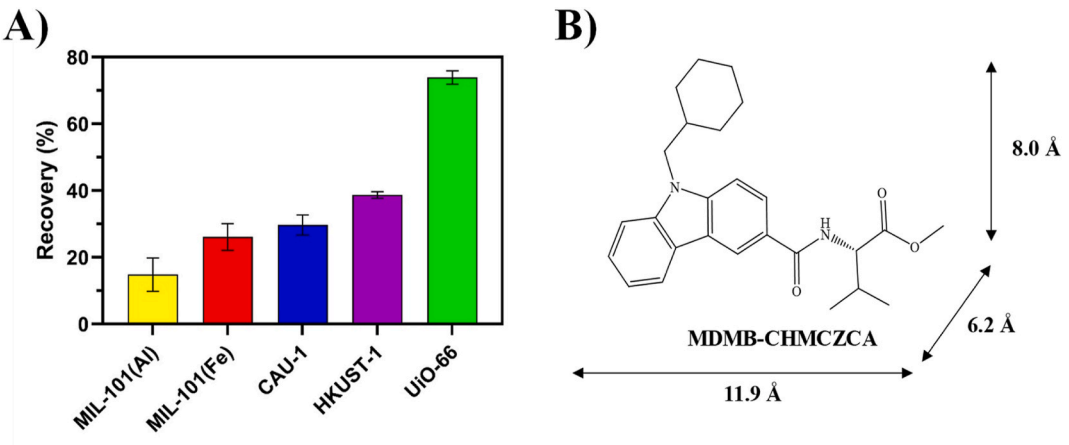

Fig. 2. A) Influence of the MOF nature on the extraction efficiency of MDMB-CHMCZCA at 500 μg L^{-1} as representative SCs.; B) Molecular dynamics from MDMB-CHMCZCA. The structure has been represented using ChemDraw® Professional software and the sizes have been obtained with Chem3D.

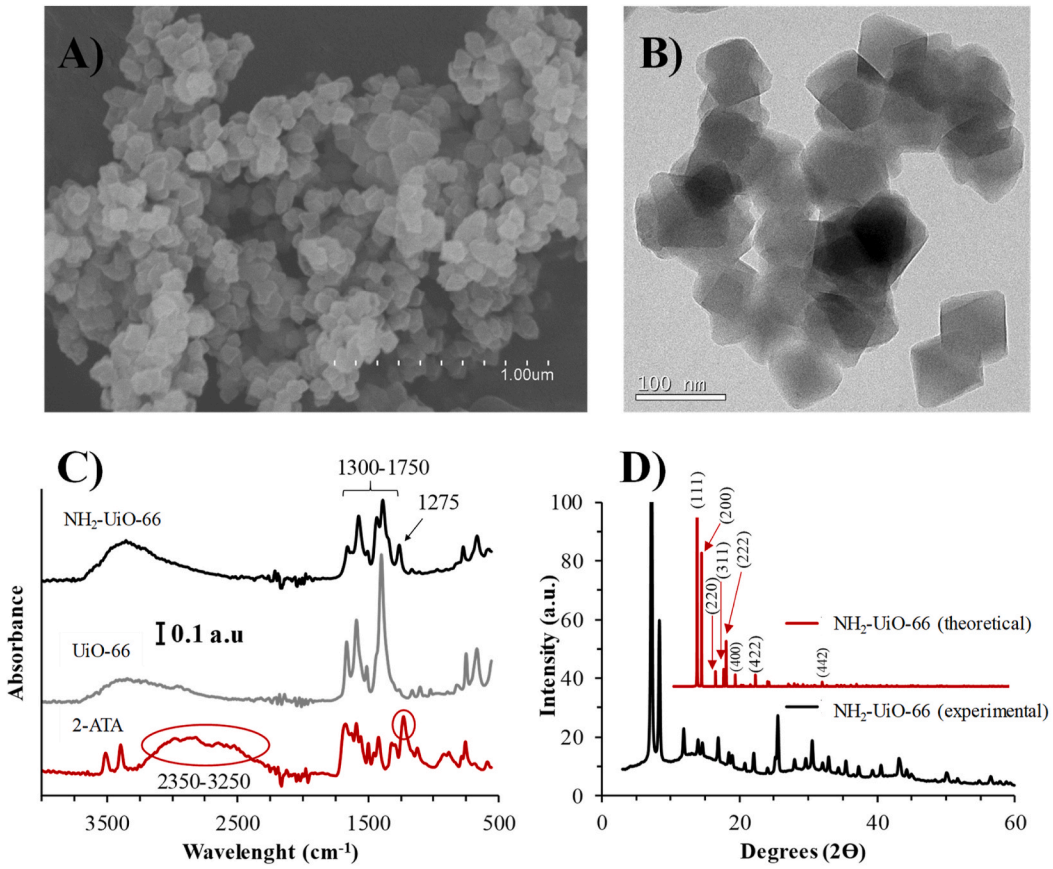

Fig. 3. NH_2-UiO-66 characterization studies. A) SEM image; B) TEM image; C) FTIR spectra from 4000 to 50 cm^{-1} and D) p-XRD spectra (theoretical and experimental) from 5 to 60° with the main reflections (hkl).

the main diffraction peaks at (111), (200), (222) and (422), which matched well with the theoretical pattern of this MOF (also shown in Fig. 3D) and with those reported in the literature [45]. All these results suggest that the synthesis was successfully performed and the typical cubic close packed structure is corresponding to NH_2-UiO-66.

Besides, the adsorption/desorption nitrogen isotherms were measured to obtain the porosity of NH_2-UiO-66 and the surface area (Fig. S4B). Thus, a typical type IV adsorption/desorption isotherm was observed. As expected, the presence of micropores corresponding to the MOF intracrystal (structural) pores is detected as an abrupt adsorption step that occurs at very low relative pressure values in the range of 0–0.2 P/P_0. The small size of the N_2 molecules favours the quick filling of these cavities by capillarity. In addition, a second adsorption step is detected in the N_2 adsorption-desorption isotherms. This step, which occurs significantly in a more slowly way, is detected at P/P_0 values greater than 0.9. So, this latter phenomenon can only be attributed to large meso/macroporous interparticle voids (generated through aggregations of individual NH_2-UiO-66 nanocrystals), as was also previously observed in SEM/TEM images. Thus, this aggregation of nanocrystals provides a hierarchical porosity to the MOF grains (combining small micropores and large textural pores) that can be beneficial for analytical purposes. The resulting BET surface area was 712 $m^2\ g^{-1}$, which was similar to those found by other authors [41]. In summary, the combination of a bimodal pore system, a high BET surface area and adequate functionalization to interact with target analytes makes NH_2-UiO-66 material, a promising MOF for this study.

Finally, the Z-potential of the material was measured in order to explore the net charge on the surface during the loading process. In so doing, NH_2-UiO-66 was dispersed in nanopure water (1000 mg L^{-1}) and sonicated for 5 min. The measurements (n = 3) were performed at atmospheric conditions and the final zeta potential value was 17.3 ± 3.5 mV (estimated from the particle mobility using the Smoluchowski model), indicating that the surface is slightly positively charged. This is consistent with the presence of amino moieties on the MOF surface, which repeals analytes such as cocaine (positively charged at pH 7) and does not affect to SCs (without ionizable moieties in their structures).

3.3. SPE protocol optimization

Sample volume was fixed to the maximum value that could be collected from volunteers. In this case, and considering the relatively small sample volumes that are usually collected, 500 μL was selected as sample volume. On the other hand, oral fluid has a pH normal range of 6.8–7.3 [46], an average electrolyte composition including bicarbonate (14 mM), sodium (18 mM), potassium (20 mM), calcium (0.5 mM) and phosphate (3 mM) [47]; and a considerable buffer capacity, mainly attributed to the higher bicarbonate concentration [48]. For these reasons and to minimize sample pretreatment, parameters such as ionic strength or pH were not considered.

Regarding the method optimization, several parameters were investigated in order to maximize the analytical performance of the method including sorbent particle size (Fig. S5), elution solvent composition and volume (Fig. 4).

The particle size is a key aspect on the efficiency of SPE protocol. Presumably, packing materials with lower particles should confer improved efficiency to the SPE process, but can produce backpressures problems and a slow SPE flow-rate. Furthermore, a particle leaking can occur during SPE process if the particles are too small. To overcome this problem, SPE cartridges were prepared using a bottom frit together with a nylon filter (0.45 μm) as commented in Experimental Section. Then, the MOF material was grinded and sieved in three different ranges (50–100, 100–200 and 200–300 μm). The results are depicted in Fig. S5.

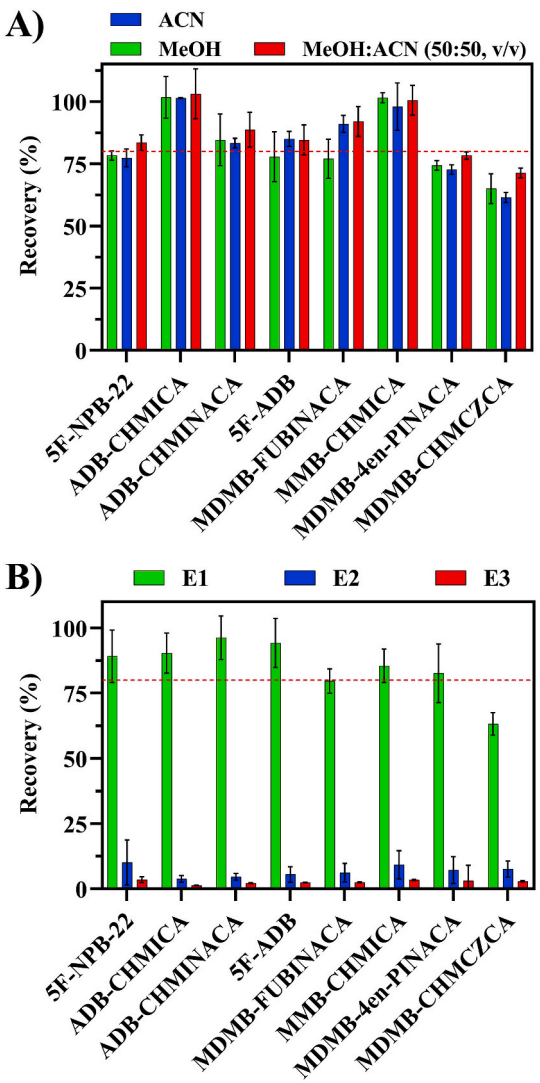

Fig. 4. Optimization of elution solvent using the NH_2-UiO-66 as SPE sorbent for the isolation of SCs in MQ water at 250 μg L^{-1}: A) Solvent composition and B) number of elution steps (0.5 mL each).

In general, for identical sorbent nature, the recoveries of analytes showed better values when the particle size decreases. Apart from providing extra adsorption sites for extraction, the cartridges packed with the 50–100 μm showed a uniform and suitable flow rate. Furthermore, in order to assess possible losses and leaching of NH_2-UiO-66 particles in SPE protocol, different cartridges (5 replicates with particle sizes in the selected range) were weighed (25 ± 0.5 mg) before and after analyte extraction. The resulting sorbent masses were statistically similar with a 95% of confidence level (T-test).

Next, the influence of the elution solvent on extraction efficiency was performed in terms of nature (Fig. 4A) and volume (Fig. 4B). In the former study, the use of a mixture MeOH:ACN (50:50,v/v) showed, in most cases, a slight increase in extraction performance (*ca.* 5%) compared to the individual solvents probably due to the synergistic effect of hydrogen-bonding ability of MeOH with the polar groups of the SCs, and the ability of disrupting the π-interaction between SCs and NH_2-UiO-66 by the presence of ACN. Then, the number of elution steps using this mixture was evaluated. In each elution step, 0.5 mL of MeOH:ACN (50:50, v/v) were tested. The best results were obtained when eluting two consecutive times with 0.5 mL of this mixture (Fig. 4B), being selected for the following experiments. The third eluting step was discarded since less than 4% of the analytes were eluted in this fraction, which did not pay off the extra effort in terms of time and waste of reagents.

3.4. Quality parameters of the method

After optimization, the analytical features of the developed SPE-LC-FLD protocol were evaluated. Table 2 summarizes several quality parameters. As it can be seen, the calibration plots of the individual analytes (average of 3 independent calibration plots) showed a linear range comprised between 2 and 200 μg L^{-1}, with correlation coefficients higher than 0.99 in all cases. Also, the limits of detection (LODs) and quantification (LOQs) were calculated at signal-to-noise ratio (S/N) of 3 and 10, respectively. The LODs and LOQs were found to be 0.6–0.8 μg L^{-1} and 2.1–2.7 μg L^{-1}, respectively. Furthermore, the precision of the method (intra- and inter-units), expressed as relative standard deviation (RSD) was also evaluated (Table 2). Intra-batch experiments were performed using cartridges from the same MOF synthesis by analyzing three replicates within a day, whereas inter-batch experiments were carried out using cartridges from different MOF syntheses (three extractions in three independent days). The precision of the method, which was calculated for standard concentrations of 100 μg L^{-1}, varied between 6.6 and 10.6%.

Next, the reusability of the SPE sorbent was assessed. This parameter is an important aspect of SPE sorbents since it reduces waste generation and saves costs related to the use of a single SPE cartridge (25 mg). As shown in Fig. S6A, no significant loss of analytical performance was observed up to 12 reuses (considering 80% as acceptable recovery value), which proves the suitable reusability of extraction devices. To further confirm the stability and robustness of the SPE sorbent, p-XRD patterns of MOF were measured before and after the 12 re-uses of the material (Fig. S6B). As it can be seen, XRD diffraction spectrum did not change significantly, which reveals that the MOF crystallinity/integrity remained unaltered.

Adsorption capacity of the material was studied using a mixture of 10 mg L^{-1} of individual components by diluting the stock solution with water and subjected to the proposed protocol. Then, 1 mL was loaded (80 μg total mass) into 25 mg of NH_2-UiO-66 cartridge. No analytes were found in the percolated fraction suggesting that the mixture was totally retained. The adsorption capacity of the material was higher than 3.2 mg g^{-1}. Taking into consideration that in previously published studies the concentration of SCs in oral fluids ranged from 0.8 to 40 μg L^{-1} (0.4–20 ng) [49], the obtained adsorption capacity assures a complete retention of SCs from oral fluids.

Finally, selectivity studies using different families of common psychoactive substances were also included. By doing so, three new analyte families were assessed including diazepam (benzodiazepine), cocaine (tropane alkaloid) and methamphetamine (amphetamine). The optimum SPE protocol was carried out and the obtained recoveries for each drug were lower than 50% in all cases, which suggests that not all the drugs are retained in the same way by this material.

3.5. Application to field samples

The feasibility of the proposed method was demonstrated by its application to the isolation of SCs in oral fluids. The samples were analyzed in order to find any potential presence of the analytes, but any target SC was detected in these samples. Then, each matrix was spiked at different concentration levels (5, 10 and 50 μg L^{-1}) with the target analytes in order to evaluate the accuracy of the method. The results of this study are shown in Table 3 and the resulting chromatograms are depicted in Fig. 5. As it can be seen in this table, the recoveries are comprised between 67 and 114%, with RSD values below 16% in all cases.

Furthermore, the performance of commercial packed C18 and HLB was compared to the NH_2-UiO-66 extraction efficiency by using the optimized SPE protocol. In this respect, the sorbent amount of

Table 2
Analytical figures of SPE-LC-FLD method using NH_2-UiO-66 as sorbent in the analysis of synthetic cannabinoids.

Analyte	Linear range (μg L^{-1})	LOD[a] (μg L^{-1})	Calibration plot	Precision (RSD, %)	
				Intra-batch	Inter-batch
5F-NPB-22	2–200	0.7	Y = (0.858 ± 0.008) x – (1.2 ± 0.8)	5.9	10.5
ADB-CHMICA		0.7	Y = (0.859 ± 0.009) x – (1.3 ± 0.9)	6.6	8.9
ADB-CHMINACA		0.8	Y = (0.622 ± 0.012) x – (1.5 ± 1.1)	6.6	8.7
5F-ADB		0.7	Y = (0.743 ± 0.013) x – (1.4 ± 1.2)	6.2	9.5
MDMB- FUBINACA		0.7	Y = (0.93 ± 0.05) x – (5 ± 4)	3.0	10.8
MMB-CHMICA		0.7	Y = (1.74 ± 0.02) x – (3 ± 2)	3.2	10.6
MDMB-4en-PINACA		0.7	Y = (0.318 ± 0.005) x – (0.6 ± 0.4)	4.4	6.3
MDMB-CHMCZCA		0.6	Y = (0.751 ± 0.010) x – (1.4 ± 0.9)	2.3	3.8

[a] Intrumental values.

Table 3
Recovery assessment of SCs in spiked oral fluid samples using MOF-based SPE protocol. Recovery (%) ± SD (n = 3)[a].

Oral fluid	Spiked level (μg L^{-1})	Recoveries (%) ± RSD[a]							
		5F- NPB-22	ADB-CHMICA	ADB-CHMINACA	5F-ADB	MDMB-FUBINACA	MMB-CHMICA	MDMB-4en-PINACA	MDMB-CHMCZCA
V1	5	78 ± 2	91 ± 3	106 ± 1	109 ± 4	110 ± 16	105 ± 14	114 ± 7	106 ± 3
V2	10	95 ± 4	88 ± 12	93 ± 7	92 ± 15	79 ± 3	83 ± 8	99 ± 10	67 ± 5
V3	50	99 ± 10	96 ± 9	93 ± 7	98 ± 5	102 ± 11	97 ± 4	89 ± 6	76 ± 9

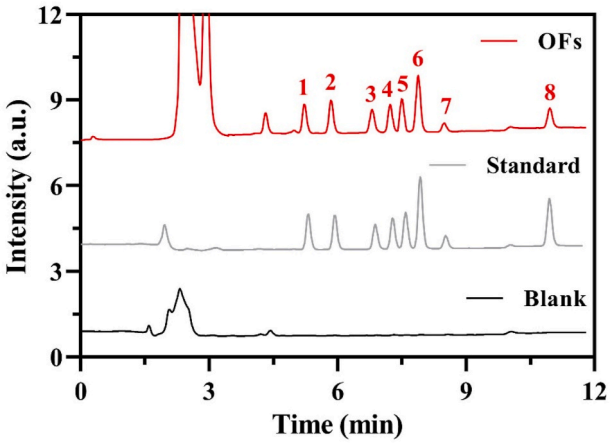

Fig. 5. HPLC-FLD chromatograms of a standard solution of SCs (grey line), a oral fluid blank (black) and spiked at 50 μg L^{-1} (red) after SPE protocol. Peak identification: 1) 5F-NPB-22; 2) ADB-CHMICA; 3) ADB-CHMINACA; 4) 5F-ADB; 5) MDMB-FUBINACA; 6) MMB-CHMICA; 7) MDMB-4en-PINACA; 8) MDMB-CHMCZCA. Chromatographic conditions can be found at Experimental Section. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

commercial cartridges was downscaled to 25 mg to be comparable with our MOF cartridge. As shown in Fig. S7, in most cases, the recoveries of these commercial sorbents were slightly lower than those found by the MOF sorbent, being the proposed approach a cost-effective alternative.

3.6. Comparison with other reported works

In order to corroborate the suitability of the developed SPE-LC-FLD compared to the most recent reported contributions, a comparison has been carried out in Table 4. Concretely, all the selected applications are focused on the analysis of biological samples, including oral fluids [29,32,33], hair [30], urine [28] and blood [26]. The nature of sorbent used was quite diverse highlighting from commercial phases [26,32,33] to home-made silica-based particles [29], MIPs [28] or MOFs (our contribution). In terms of recoveries, the developed sorbent presented similar values to those found in home-made sorbents [28–30]; however, studies based on commercial phases presented recoveries as low as 30% [32,33] or even 16% [26]. Besides, the commercial sorbents presented lower precision than those synthesized in the laboratory. Concerning the LODs, our values were similar to those using LC-FD [29], but these values were generally higher compared when more sophisticated and expensive MS systems (or detectors) [26,28,33] were used. In any case, the possibility to achieve better LODs can be done using more sensitive analytical instruments.

Other advantage of our sorbent is the low amount of material required (25 mg), even 5 times lower than home-made cyclodextrin-

Table 4
Comparison between the proposed method and similar reported methods published recently. LOD: limit of detection; RSD: relative standard deviation.

Analytes	Material (amount, mg)	Format	Method	Sample matrix	Recoveries (%)	RSD (%)	LOD (μg L^{-1})	Reuses	Reference
16	OMIX C18 (–)	Tip	μ-SPE-HPLC-MS/MS	Human whole blood	16–70	<27	0.075–0.3	–	[26]
31	C18 sorbent (–)	Syringe	μ-SPE-HPLC-MS/MS	Human oral fluids	31–97	<25	0.005–0.85	–	[33]
72	PS-DVB polymeric (–)	Cartridge	Online-SPE-HPLC-MS/MS	Human oral fluids	33–153	<20	0.4–3.8	–	[32]
3	Cyclodextrin-silica (150)	Cartridge	SPE-HPLC-FLD	Human oral fluids	76–96	<6	0.11–0.73	–	[29]
19	MIP (50)	Conic filter	μSPE-HPLC–MS/MS	Human urine	80–120	<10	0.032–0.75	27	[28]
4	Hexapeptide resin (30)	Cartridge	SPE-UHPLC-MS/MS	Human hair	65–85	-< 15	–	100	[30]
8	NH_2-UiO-66 (25)	Cartridge	SPE-HPLC-FLD	Human oral fluids	67–114	<11	0.6–0.8	12	This work

Abbreviations: MIP, molecularly imprinted polymer; PS-DVB, Polystyrene divinyl benzene; HLB, hydrophilic lipophilic bound, UiO: University of Oslo, SPE: solid-phase extraction; FLD, fluorescence detection; MS: mass spectrometry.

based sorbent (150 mg) [29] and, consequently, the cost of sorbent is much lower. For instance, typical commercial phases such as *Supelclean™ ENVI™-18 SPE Tube* and *Supelclean™ LC-SAX SPE Tube/Supelclean™ LC-SCX SPE Tube* have a cost ranged from 2.3 to 3.22€/unit, whereas the cost estimate of our cartridges of NH_2-UiO-66 is lower than 0.50€/unit taking into account the convenient, simple and low-cost synthesis. This fact combined with the satisfactory reusability of our sorbent (see data above), information that commonly is not evaluated or missing (see Table 3), makes that this protocol represents a real attractive alternative for screening purposes of SCs in biological samples, being highly recommendable when MS detectors are not available.

4. Conclusions

In the present work, a straight-forward and simple method for the extraction and determination of SCs in oral fluid samples has been investigated. For the first time, MOFs have been used for the isolation of these drugs as SPE sorbents, due to the well-known capabilities of these materials to retain organic molecules at trace levels in complex matrices. In this regard, the suitability of different MOFs as SPE phases was initially investigated, being the UiO-66 the best candidate able to extract and elute the tested analytes. Then, the effect of ligand functionalization of this MOF and its influence on extraction performance was carried out. The NH_2-UiO-66 gave the best extraction efficiencies, and it was characterized in order to establish its morphological and chemical properties. The SPE method was adequately optimized including aspects such as particle size, elution solvent and volume. The main analytical features of SPE-LC-FLD were also evaluated giving LODs as low as 0.6–0.8 μg L^{-1}; suitable precision (RSD lower than 11%), low sample and reagents volumes (<5 mL) and easy sample preparation. The optimized protocol was successfully applied to the isolation of 8 SCs at different levels in oral fluids with suitable recoveries (67–114%). Also, other important advantages of the developed protocol are the good reusability (up to 12 re-uses) of the sorbent and the low estimated cost of cartridge preparation (<0.5€). Despite the good performance of SPE protocol, further studies focused on the preparation of greener MOFs (mainly in the synthesis step) will carried out in the coming years in order to develop attractive extraction methodologies of hazardous drugs in biological samples. In any case, the results of this study give a step forward in the field of the simultaneous isolation and analysis of NPS in biological samples.

Notes

The authors declare that they have no financial/commercial conflicts of interest.

CRediT authorship contribution statement

Héctor Martínez-Pérez-Cejuela: Conceptualization, Formal analysis, Investigation, Methodology, design, Writing – original draft. **Mónica Conejero:** Formal analysis, Investigation. **Pedro Amorós:** Writing – review & editing, Funding acquisition, Resources. **Jamal El Haskouri:** Formal analysis, Investigation. **Ernesto Francisco Simó-Alfonso:** Writing – review & editing, Funding acquisition, Resources. **José Manuel Herrero-Martínez:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition, Resources. **Sergio Armenta:** Conceptualization, Methodology, design, Writing – review & editing, Supervision, Funding acquisition, Resources.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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