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Mixed-mode cationic exchange sorptive tapes combined with direct infusion mass spectrometry for determining opioids in saliva samples

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ABSTRACT

This article describes the synthesis of mixed-mode cationic exchange (MCX) tapes as sorptive phases in bioanalysis, and it faces the determination of methadone and tramadol in saliva as the model analytical problem. The tapes are synthesized using aluminum foil as substrate, which is subsequently covered with double-sided adhesive tape where the MCX particles (ca. 1.4 ± 0.2 mg) finally adhere. MCX particles allow the extraction of the analytes at the physiological pH, where both drugs are positively charged, minimizing the potential co-extraction of endogenous matrix compounds. The extraction conditions were studied considering the main variables (e.g. ionic strength, extraction time, sample dilution). Under the optimum conditions and using direct infusion mass spectrometry as the instrumental technique, detection limits as low as 3.3 $\mu g \cdot L^{-1}$ were obtained. The precision calculated at three different levels, and expressed as relative standard deviation, was better than 3.8%. The accuracy, expressed as relative recoveries, ranged from 83 to 113%. The method was finally applied to determine tramadol in saliva samples from patients under medical treatment. This approach opens the door to easily preparing sorptive tapes based on commercial (or *ad-hoc* synthesized) sorbent particles.

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1. Introduction

Thin film microextraction (TFME) is a consolidated technique in sample preparation that has been reported for the efficient extraction of a wide range of analytes in different matrices [1–5]. TFME, which evolves from solid phase microextraction, is based on the use of planar sorptive phases as extractants. The geometry change, intrinsic to this evolution, dramatically influences the extraction performance. Planar phases present a larger surface without increasing the coating thickness, thus improving the extraction kinetics [6]. Additionally, flat geometry is compatible with alternative analytical workflows opening the door to the direct analysis of the sorptive phases by spectroscopic [7,8] and spectrometric techniques [9–12]. The description of the so-called TFME dual substrates allows the combination of both types of instrumental techniques in a single sorptive phase [8], thus providing richer analytical information.

Particulate sorbents have been extensively used in solid-phase extraction and its miniaturized alternatives. In these techniques, the particles are packed in special columns/cartridges [13] or dispersed into the sample [14]. The immobilization of particulate sorbents in a planar substrate has been proposed as a miniaturization strategy in TFME [3,15]. The presence of the particles creates an unsmooth surface, thus increasing the exposed area. Depending on the target analytes, two general types of sorbents have been reported in TFME, namely: i) non-charged particles with hydrophobic [16–18] or hydrophilic-lipophilic balanced [19–21] character; and ii) particles with charged groups that allow mixed mode isolation (ion exchange plus hydrophobic/hydrophilic interactions) with the target analytes [22,23]. The latter type of sorptive phase provides an additional selectivity enhancement that is relevant in bioanalytical applications [24].

Some particle-based TFME phases, such as coated blades, are commercially available. However, the description of easy and affordable preparation approaches can popularize, even more, these sorptive phases (SP), allowing their *ad-hoc* design depending on the analytical problem to be solved. This work presents a simple approach to preparing mixed-mode cationic exchange sorptive tapes (MCX-ST). Aluminum foil is proposed as a cheap substrate

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improving the mechanical stability of the tapes and avoiding their excessive bending (which would result in reducing the exposed surface to the sample) during the extraction. The MCX particles are immobilized using a simple double-sided adhesive tape. The potential of MCX-ST was evaluated using the determination of two opioids (methadone and tramadol) in saliva as the model analytical problem. Both drugs are commonly prescribed for treating opioid addiction and severe pain, respectively. The use of MCX particles simplifies the extraction procedure as the analyte can be extracted at physiological pH where they are positively charged species.

Prescribed opioids have created a public health problem in some countries where controlling these drugs in biosamples is relevant to avoid wrong administration patterns [25–27]. Opioids are commonly tested in urine and blood, but saliva and hair are also used as specimens for their determination [28]. The isolation of opioids from biological samples is usually based on microextraction techniques that fit well with the low sample volume requirements in this type of analysis. Microextraction in packed syringe [29–31], TFME [32], and in-tube solid-phase microextraction [33] have been successfully reported in this sense. In most approaches, reversed-phase SPs are used, making necessary the adjustment of the sample pH to promote the interaction of these basic drugs with the SP. The extracted analytes are commonly determined by mass spectrometry (MS) due to its superior selectivity and sensitivity [34]. Liquid chromatography coupled with MS (LC-MS) [35–37] or direct analysis techniques such as direct analysis in real-time (DART) [38] or direct infusion mass spectrometry (DI-MS) [39,40] have been also used to monitor these compounds in biological samples.

DI-MS is an interesting strategy for drug analysis as it provides high sample throughput. Also, it can be developed on conventional LC-MS equipment without any complex instrumental modifications. However, DI-MS analysis of biofluids, even when diluted, is prone to matrix effects that adversely influence the sensitivity of the determination. In this article, a new sorptive phase based on MCX particles is proposed for the selective extraction, based on hydrophobic and electrotactic interactions, of two opioids from saliva samples. The reduction of the matrix effect and the preconcentration of the analytes contributes to a sensitivity enhancement. The extraction protocol has been also designed to preserve the high analysis rate of DI-MS. Although the extraction time is long (60 min), 45 samples can be simultaneously processed.

2. Experimental section

2.1. Reagents and samples

Unless otherwise indicated, all the reagents were provided by Sigma Aldrich (Madrid, Spain). A methanolic stock solution of the analytes (methadone and tramadol) was made at 1 $g{\cdot}L^{-1}$ and stored in the freezer at -20°C. Working solutions were built by diluting the stock in methanol or Milli-Q water (Millipore Corp., Madrid, Spain), depending on their final use. Methadone-d_3 was used as the internal standard (IS). A IS stock standard solution was prepared at a concentration of 1.25 $mg{\cdot}L^{-1}$ in methanol.

Mixed-mode cation-exchange sorbent (MCX, 30 µm of particle size, 80 Å of pore size) was purchased from Waters Corporation (Milford, Massachusetts, USA) and evaluated as the potential sorbent.

Blank oral fluid was obtained by Salivette® commercial collection devices (Sarstedt, Nümbrecht, Germany). A pool was built by mixing saliva samples from different volunteers to cover the interperson variability. This pool was used during the optimization of the extraction procedure. For sample analysis, the spiting approach was preferred as the potential interaction between basic drugs and the cellulosic pad of the Salivette® device has been reported [41].

2.2. Preparation of the MCX sorptive tape

The preparation of the MCX-ST is schematically presented in Fig. 1. A segment (30 cm) of double-sided adhesive tape (Milan, Mont-Ras, Spain) was placed over section of aluminum foil, providing the material with enhanced mechanical stability. A rectangle (1×1.5 cm) of the material was immersed in a vial containing MCX particles and vortexed. The particles adhered to the glued substrate during this step. The non-effectively attached material is finally removed by shaking the extraction unit. The amount of MCX particles loaded in the tapes are ca. 1.4 ± 0.2 mg.

Due to the low cost of the phases and the easiness of the fabrication, a fresh sorptive phase was used for each extraction. This approach also avoids cross-contamination issues.

The sorptive phase was characterized by scanning electronic microscopy (SEM). The studies were developed in a JEOL JSM 7800F microscope (Central Service for Research Support of the University of Córdoba, SCAI) and a FEI-TENEO microscope (Center of Research, Technology, and Innovation of the Sevilla University, CITIUS).

2.3. Extraction procedure

3 mL of diluted saliva sample (or standard) was placed in a 5 mL vial. The MCX-SP was immersed in the aqueous medium and incubated under continuous stirring (500 rpm) for 60 min using an orbital shaker. After the extraction, the MCX-SP was withdrawn from the sample by means of a tweezer and washed with Milli-Q before being incubated with 1 mL of methanol/ammonia (99/1 v/v) (500 rpm, 10 minutes) for analytes elution. The eluate was evaporated under vacuum during 2 h at 45°C, and the residue was dissolved in 100 µL of the elution medium. Finally, the resulting solution was placed in an insert of an HPLC vial for instrumental analysis. Forty-five samples can be simultaneously processed, thus enhancing the sample throughput.

2.4. Direct infusion mass spectrometric analysis

DI-MS/MS analyses were performed on an Agilent 1260 Infinity LC system (Agilent, Palo Alto, CA, USA). A guard column (0.2 µm filter, 2.1 mm) was used to protect the MS source from potential particles. 5 µL of the standards or the sample extracts were directly injected in the carrier phase (Milli-Q water and methanol in a 10:90 v/v ratio containing 2.2 mM of formic acid and 5 mM of ammonium formate), which was pumped at 0.2 $mL{\cdot}min^{-1}$. An Agilent 6420 Triple Quadrupole MS with an electrospray source was used to determine the target compounds. The instrumental parameters and fragmentation patterns are summarized in Table S1 and Fig. S1, respectively.

3. Results and discussion

Basic drugs are positively charged at the physiological pH of oral fluid (ranged between 6.5 and 7.5). The extraction of the most hydrophobic ones can be performed by reversed phase sorptive phases although a previous pH adjustment, which is challenging due to the low sample volume, is needed. This adjustment can be omitted when mixed-mode sorbents, involving cation exchange interactions, are used. Also, this double interaction mechanism allows the extraction of more polar drugs extending the analytical applicability. In this work, we aimed to simplify the preparation of mixed-mode planar SP. This simplification, which is achieved by using low-cost and highly available materials, positively affects the affordability and versatility of the material.

Very recently, He and coworkers have highlighted the relevance of adhesive tapes in different scientific fields [42]. However, their

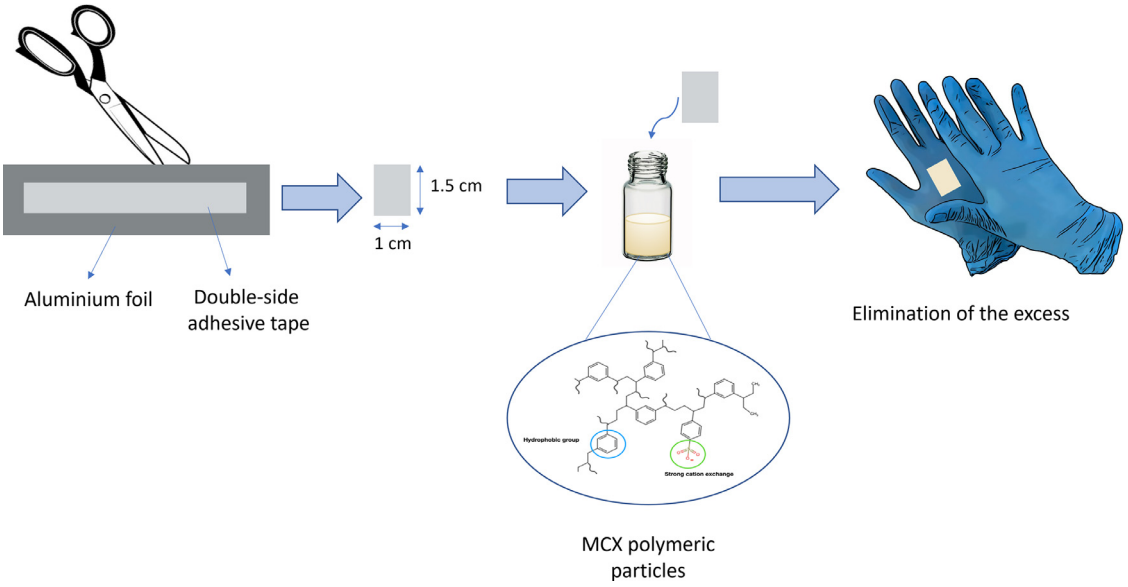

Fig. 1. Schematic representation of the synthesis of the sorptive tape.

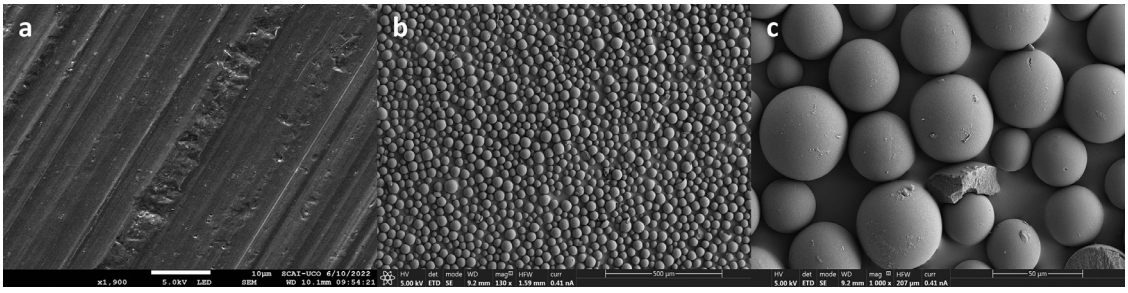

Fig. 2. SEM micrographs of the a) aluminum foil; b-c) MCX-based sorptive phase. For comparison purposes, the scale is visible in the different panels.

use in sample preparation is scarcely developed. The mechanical stability of the tape is a relevant characteristic for sample preparation. On the one hand, it must be high enough to avoid excessive bending during the extraction that would result in reducing the exposed surface to the sample. On the other hand, a certain grade of flexibility would improve its agitation into the sample. Aluminum foil fulfills both criteria, and it was selected as substrate. As can be seen in Fig. 2a, it presents a smooth surface. Aluminum foil presents a negligible capacity to adhere particulate sorbent, but this capacity is boosted if a double-sided adhesive tape is employed. One of the sides adheres to the aluminum foil while the other allows the immobilization of the sorbent. The SEM pictures of the resulting MCX-tape are presented in Fig. 2b-c. The particles are distributed over the surface and their sizes fit well with the values provided by the manufacturer. In order to check the stability of the particles during the extraction process (isolation and elution), the MCX-tapes were immersed in an aqueous solution (pH 6) and agitated at 500 rpm during 30 min. No particle leaching was observed at naked eyes. Notwithstanding this, a guard column was used in the instrumental analysis to prevent blockage due to eventual MCX particles losses during the analyte elution. The system backpressure was stable during the analysis indicating that the particles are not present in the final eluates.

To be sure that the extraction capacity was mainly due to the MCX particles, the potential contribution of the components of the extraction unit (aluminum foil, adhesive, and MCX particles) in the isolation of the analytes, was initially scrutinized. For this purpose, an aqueous standard solution (pH 6) containing the analytes at 50 $\mu g \cdot L^{-1}$ was extracted using three different materials: i) aluminum foil; ii) adhesive tape supported over aluminum foil; and iii) the MCX-tape. Three different media: methanol, methanol/ammonia (99/1 v/v), and methanol/formic acid (99/1 v/v) were used as eluent.

The results, expressed as absolute extraction recovery, are presented in Fig. 3a (for methadone) and Fig. 3b (for tramadol). According to the data, the extraction capacity of the adhesive tape is negligible compared to that provided by the MCX particles. Also, the presence of the MCX particles (which, according to the SEM micrographs, cover the adhesive tape homogenously) reduces, even further, the potential interaction of the analytes with the glued film.

The effect of the eluent composition on the absolute extraction recovery corroborates the role of the MCX particles in the extraction. MCX sorbent extracts the analytes by combining hydrophobic (hydrophobic moieties of the analytes with the polymeric backbone) and electrostatic (positively charged analytes with the negative sulfonic group) interactions. Methanol can only break the hydrophobic interactions, and its elution capacity (alone or mixed with formic acid) is limited. The presence of ammonia improves the elution because it can neutralize the analytes (their pKa are in the 9.1-9.2 range), breaking the electrostatic interactions.

3.1. Study of the main variables of the extraction procedure

Once the sorbent and the eluent were selected, the main variables of the extraction procedure were studied. The effect of the ionic strength, the extraction time, and the sample dilution were

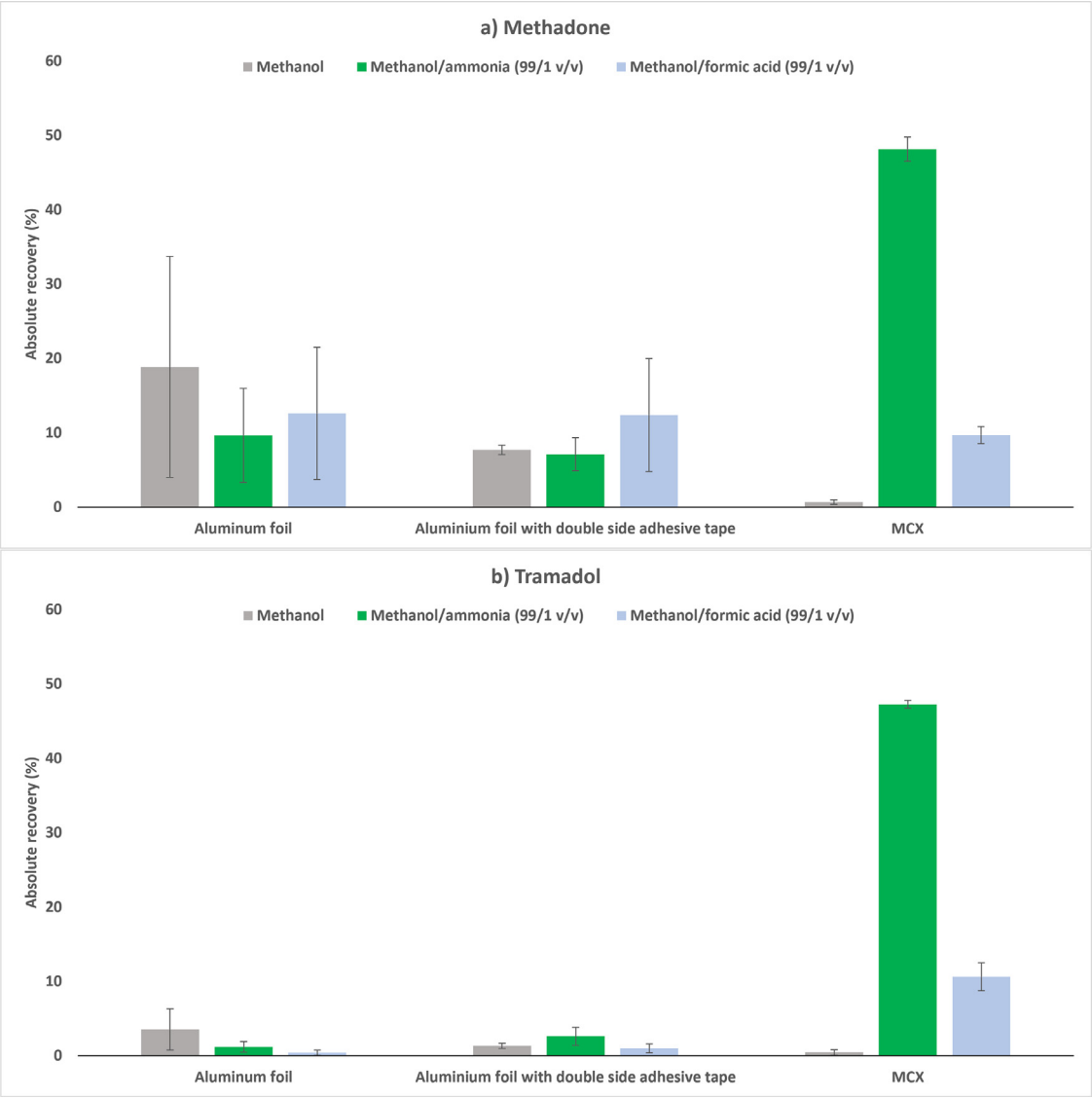

Fig. 3. Evaluation of the extraction ability of the different components of the sorptive phases, namely: aluminum foil, adhesive tape over aluminum foil and the MCX-based planar sorptive phase. The results expressed as absolute extraction recovery were obtained for extractions (in triplicate) of an aqueous standard containing tramadol (panel A) and methadone (panel B) at 50 µg L^{-1}. The pH of the standard was fixed at 6 to promote the mixed interaction of the analytes with the MCX particles.

evaluated. The pH was fixed at 6 since the analytes remained positively charged (the pKa for methadone and tramadol are 9.2 and 9.4, respectively), thus boosting the interaction with the sorbent. In most cases, this pH is within the normal physiological interval making the pH adjustment unnecessary. Based on our previous experience a stirring speed of 500 rpm was enough to facilitate the contact between the analyte in the sample and the sorbent.

3.1.1. Ionic strength

The ionic strength may have a double and contradictory effect on the microextraction process. On the one hand, it reduces the solubility of the analytes in water, thus improving their extraction by a salting-out effect. On the other hand, it can increase the viscosity of the sample reducing the diffusion rate of the analytes. This effect was evaluated at five conductance levels using NaCl as a model electrolyte. The results, shown in Fig. S2, indicate a negligible impact of the ionic strength on the extraction of the analytes. Also, this effect can be corrected using an internal standard, as reported in the literature [21].

3.1.2. Extraction time

To fully understand the kinetic of the process, the extraction time was evaluated at six different levels (Fig. 4). The absolute extraction recovery increases with time until the equilibrium of extraction is achieved (ca. 60 min). Although the extraction time is long, the simultaneous extraction of several samples (up to 45 in this work) provides a good sample throughout.

3.1.3. Study of the sample dilution

Biofluids present complex matrices that may affect the extraction of the analytes. This complexity is also ascribed to oral fluid samples due to their inherent viscosity. The matrix effect in the oral fluid can be easily overcome by diluting the sample before the extraction. This dilution factor was studied at two different levels (1/2 and 1/4), and the results are presented in Fig. S3. As observed, the absolute extraction recovery increases with the sample dilution, and a 1/4 dilution was selected as the optimum value. In this case, as the effect is not dramatic, no dilution could also be chosen for better sensitivity.

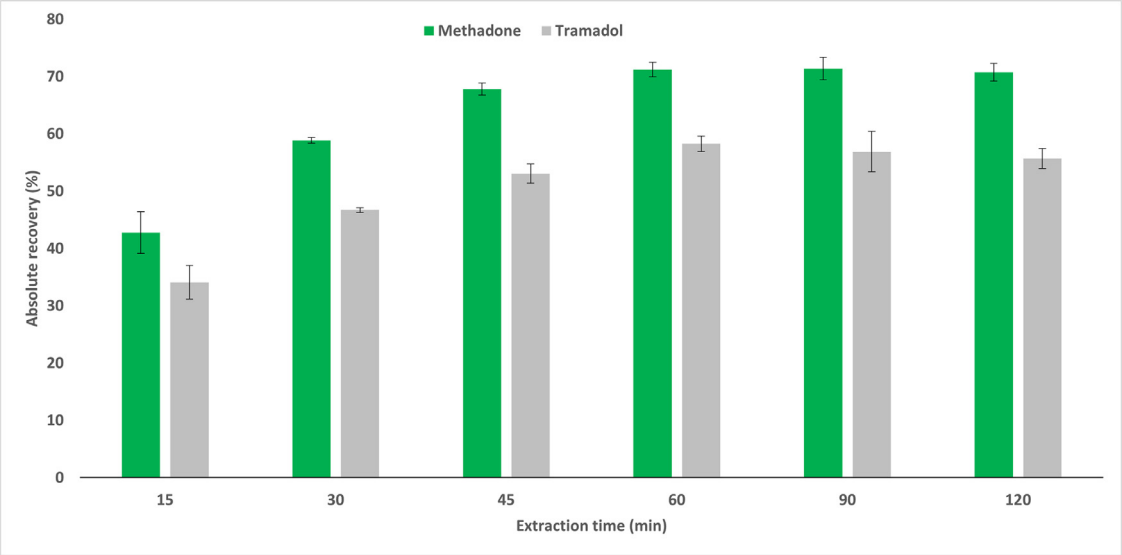

Fig. 4. Effect of the extraction time on the absolute recovery of the analytes.

Table 1
Analytical figures of merit of the proposed method for the determination of opioids in saliva samples.

Analyte	LOD ($\mu g \cdot L^{-1}$)	LOQ ($\mu g \cdot L^{-1}$)	R^2	Linear range ($\mu g \cdot L^{-1}$)	RSD intra-day (%, n=5)			Accuracy (% RR)		
					10 $\mu g \cdot L^{-1}$	50 $\mu g \cdot L^{-1}$	250 $\mu g \cdot L^{-1}$	10 $\mu g \cdot L^{-1}$	50 $\mu g \cdot L^{-1}$	250 $\mu g \cdot L^{-1}$
Methadone	3	10	0.9986	LOQ - 500	0.6	3.8	1.7	83 ± 3	113 ± 1	99 ± 3
Tramadol	3	10	0.9984	LOQ - 500	2.6	1.4	2.3	94 ± 3	104 ± 4	87 ± 13

LOD, limit of detection; LOQ, limit of quantification; RSD, relative standard deviation; RR, relative recovery.

Table 2
Comparison of the proposed method with others reported in the literature.

Analytes	Matrix	Pre-treatment	Instrumental technique	Extractant	LOD ($\mu g \cdot L^{-1}$)	RSD intra-day (%)	Accuracy (% RR)	Reference
Methadone	Urine	SPME	DART-MS	C18 particles	0.5	<1.6	100.6-103.1	[18]
Methadone	Saliva	TFME	GC-MS	Paper coated polyimide	3	<14.6	86.9-107.8	[32]
Methadone	Saliva	NTME	HN-ESI-MS/MS	Polydopamine	1.2	<13.6	99-123	[33]
Methadone	Saliva	µ-SPE	DI-MS/MS	Nylon-6	1.5	<9.1	93-98	[43]
Methadone	Dried Saliva	Dried saliva spots sampling	GC-MS/MS	Filter paper /cellulose	5	<10.99	89-108.1	[44]
Methadone Tramadol	Urine	SHS-HLLME	GC-FID	Dipropylamine/water	2.4	<7.1	78.7-81.3	[45]
Tramadol	Saliva	AA-dµ-SPE	GC-FID	Fe_3O_4@Cu-Fe-LDH	1.5	-	93.1-94.7	[46]
Methadone Tramadol	Saliva	TFME	DI-MS/MS	MCX	3	<3.8	83-113	This work

LOD, limit of detection; RSD, relative standard deviation; RR, relative recovery.
Pretreatment: SPME, solid phase microextraction; TFME, thin film microextraction; NTME, needle trap microextraction; µ-SPE, micro-solid phase extraction; SHS, switchable hydrophilicity solvent; HLLME; homogeneous liquid-liquid microextraction; AA-dµ-SPE, air-assisted dispersive micro solid phase extraction.
Instrumental technique: DART, direct analysis in real time; MS, mass spectrometry; GC, gas chromatography; HN, hypodermic needles; ESI, electrospray ionization; DI, direct infusion; FID, flame ionization detector.
Extractant: Fe_3O_4@Cu–Fe–LDH, layered double hydroxide coated on a magnetic nanoparticle.

3.2. Analytical figures of merit

The analytical method was validated in terms of linearity, sensitivity, precision, and accuracy using matrix-matched calibration models (blank oral fluid samples with a known concentration of the target analytes). The analytical figures are summarized in Table 1. The limit of detection (LOD) and limit of quantification (LOQ) were calculated for a signal-to-noise ratio of 3 and 10, respectively. The LOD was 3.3 $\mu g \cdot L^{-1}$ for both analytes. The linear range ($R^2 > 0.9984$) was calculated at seven concentration levels, and it spanned from the LOQ to 500 $\mu g \cdot L^{-1}$ for both opioids. The precision was calculated at 10, 50, and 250 $\mu g \cdot L^{-1}$ using 5 independent extractions at each concentration level. The precision, expressed as relative standard deviation (RSD), was better than 3.8%. Finally, the accuracy (% relative recovery) was evaluated at the same concentration levels using an independent pool of blank saliva samples. The results were in the range of 83-113 %, fulfilling the typical validation criteria. The enrichment factors were 2.9 and 4.8 for tramadol and methadone, respectively.

The MCX-SPs were not reused to avoid cross-contamination and the use of large volumes of solvents during their cleaning. The price of each MCX tape (approximately 0.07 €) makes this approach affordable. As each extraction was performed with a new MCX-SP, the precision of the analytical method involved the tape-to-tape variation.

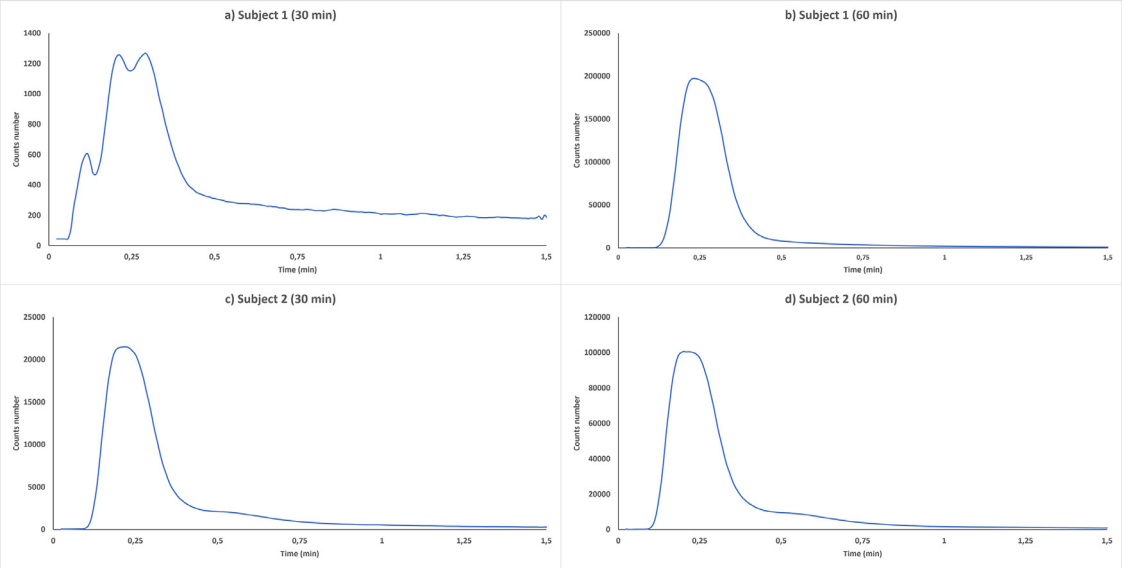

Fig. 5. Chronograms obtained for the analysis of two saliva samples (subjects 1 and 2) after 30 and 60 min of drug intake. For details, see the text.

Table 3
Analysis of real samples containing tramadol.

Subject	Sex	Tramadol dose (mg)	Time since consumption (min)	Concentration found ($\mu g \cdot L^{-1}$)
1	Female	37.5	30	below LOQ
			60	>500
2	Female	50	30	52.1 ± 0.7
			60	272 ± 6

Table 2 compares the proposed method with other methods published in the literature for the determination of the same analytes in complex biosamples [18,32,33,43–46]. The precision and accuracy levels are comparable with other counterparts. The sensitivity levels for all the methods, except the method proposed by combining magnetic solid phase extraction and dispersive liquid-liquid microextraction, are in the low $\mu g \cdot L^{-1}$. The proposed method is simple, cheap and a rapid procedure since it combines the simultaneous extraction of the samples (45 samples in 60 min) with the fast (less than 2 min) and selective determination by direct infusion mass spectrometry.

Finally, the greenness of the approach was evaluated using the analytical greenness metric for sample preparation tool (AGREEprep) [47]. This metric evaluates the complete analytical procedure, and the final rate is not exclusive for the sample preparation step. A good score of 0.55 (Fig. S4) was obtained.

The proposed method was finally applied for the analysis of saliva samples from two patients who were medically treated with tramadol. Informed consent was obtained from all individual participants involved in the study. The study, which is in the framework of the PID2020-112862RB-I00 project, has been approved by the appropriate ethics committee (Comité de Ética de la Investigación de Córdoba) and has been performed in accordance with the ethical standards. Each volunteer provided two samples after 30 and 60 min of drug intake. The results of these analyses are summarized in Table 3. Furthermore, Fig. 5 shows the chronogram for the samples where the intensity of the quantification transition for tramadol is represented against the acquisition time. The obtained results align with reported values in the literature [48]. The differences observed for the concentration of tramadol in both patients depend on pharmacokinetics factors.

4. Conclusions

In this article a planar SP based on particulate MCX sorbent is proposed for the determination of methadone and tramadol in saliva samples. The preparation of the SP is very simple, and it only requires the use of a double-sided adhesive tape over one of its sides, MCX particles are attached by adhesive forces. In order to increase the mechanical stability, aluminum foil was adhered to the other side. The experiments carried out demonstrated that the MCX particles are responsible for the extraction, with a negligible contribution of the supports (aluminum foil plus the adhesive tape). The distribution of the MCX sorbent in a thin film permits to reduce the amount of sorbent needed in each extraction (ca. 1.4 ± 0.2 mg) making the extraction unit affordable (ca. 0.07 €). This aspect, together with the good extraction ability of the materials, is essential to transfer and apply the idea to other laboratories.

The MCX-tape allows a mixed mode interaction with the target compounds (methadone and tramadol) without needing the adjustment of the sample pH. The mixed-mode mechanism improves the selectivity of the extraction, complementing the features of DI-MS as regards the expeditiousness of the analysis. The analytical workflow combines rapid sampling, the simultaneous extraction of the samples (45 samples in 60 min), and the fast (less than 2 min) determination by direct infusion mass spectrometry. This is crucial when rapid decision-making is needed in clinical/toxicological analysis. All these favorable analytical features allow facing the main challenge of bioanalysis (processing many samples and providing high metrological quality results).

The extraction procedure described in this article includes several steps. The main objective was to demonstrate the potential of the material. The procedure can be adapted to other analytical problems by considering the sensitivity level required for their resolution. In cases where the sensitivity improvement is not critical, the evaporation and reconstitution step can be avoided.

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.

CRediT authorship contribution statement

Carlos Calero-Cañuelo: Investigation, Methodology, Writing – original draft. **Francisco Antonio Casado-Carmona:** Supervision, Conceptualization, Writing – original draft. **Rafael Lucena:** Conceptualization, Funding acquisition, Writing – review & editing. **Soledad Cárdenas:** Project administration, Funding acquisition, Writing – review & editing.

Data availability

Data will be made available on request.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.chroma.2023.464097.

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