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A novel and sustainable pipette-tip solid-phase microextraction testing of six carbon-based nanomaterials as proof of concept for the determination of sixteen emerging pollutants from active veterinary principles

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ABSTRACT

A new and optimized solid-phase microextraction method using pipette tips is proposed as a proof of concept for the extraction of sixteen veterinary drugs: antimicrobials (trimethoprim, enrofloxacin and sulfamethoxazole), external antiparasitics (thiamethoxam, clothianidin, imidacloprid, fipronil, clorpyrifos, lufenuron, and permethrin), internal antiparasitics (fenbendazole and albendazole), anti-inflammatories (prednisolone, diclofenac, and betamethasone), and an anticoccidial (robenidine). In this context, the device has been challenged by many analytes with very different structural and physicochemical properties, which presents a major difficulty in the simultaneous extraction of different APs. To this end, six carbon-based nanomaterials (multi-walled carbon nanotubes (MWCNTs), graphite, graphene oxide (GO), electrochemically expanded graphene (GEQE), electrochemically reduced graphene (ERGO), and commercial and synthetic graphene oxide) were evaluated packing sorbent in the extraction column. Several NMs (GEQE and ERGO) were used for the first time as sorbents in microextractions and were fabricated, synthesized, and characterized in the laboratory. Simple materials available in any laboratory were used to fabricate the devices, showing the simplicity, ease of preparation, and low cost of the proposed device. Optimization of the microextraction device (pipette tip) was performed using chemometric tools (design of experiments and reaction surface methodology) to obtain the sorbent mass and pH to improve retention rates. In addition, a comparative analysis of the extraction of single and multi-analytes and of a batch and a continuous system was performed. Real samples were examined to evaluate the proper performance of the instrument, which can be used in a preanalytical phase of sample handling to isolate analytes from complex samples. Furthermore, a very detailed and comparative study of the physicochemical properties of NM compared to the analytes was performed, providing valuable information on the interactions taking place and the experimental conditions required, which can be extrapolated to many analyses with similar properties. Additionally, the AGREE software was used to determine the environmental friendliness of the extraction methods and to compare them with the literature. Based on the latter considerations, this multi-analyte microextraction method holds great promise for future applications in the determination of novel environmental contaminants in water systems.

1. Introduction

Active Principles for veterinary use (APs) have been recognized as emerging environmental contaminants [1]. These compounds have been reported to be found in watercourses and sediments (at concentration from ng mL^{-1} to mg mL^{-1}) and to have devastating effects on living organisms and the environment. In this context, routine monitoring of the systems has become a major concern worldwide [2–4]. APs consist of an enormous group of compounds with different structures and physicochemical properties, including antibiotics, anti-inflammatory drugs, antimicrobial agents, external and internal antiparasitics agents, and anticoccidial.

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Analytical chemistry is in constant flux following the idea of improving methods by optimizing detection and quantification for the analysis of traces analytes in a variety of matrices [5–7]. In this scenario, a step of efficient extraction is required to isolate and enrich the analytes. In addition, the miniaturization of the systems over the last decade has led to the ability to achieve the same results by reducing dimensions, solvents, reagents, etc.

Among the systems, solid-phase extraction and, in particular, solid-phase microextraction (SPME) is a technique that allows high preconcentration factors and is able to isolate the analyte from the matrix, varying the conditions and properties of the sorbents [8]. Another advantage is the use of a lower volume of solvents needed to perform the procedure, while alternatively large sample volumes can be used. Nowadays, nanomaterials (NMs) are used as sorbents in extraction techniques for the determination of a variety of analytes [9]. In this sense, many NMs with different compositions and morphologies are used as sorbents, taking advantages of the intrinsic chemical properties of their components and the special effects of shape or size.

Within NMs, the best-known carbon allotropes are carbon, graphite, and diamond. In addition, other synthetics such as fullerenes (spherical), nanotubes (cylindrical), graphene, and quantum dots have also been developed. The main advantage of using carbon-based NMs is their ease of fabrication, functionalization, and interaction with samples [10]. Some of them, such as nanotubes and graphene, can be synthesized from sustainable materials or even waste [11]. Carbon-based NMs are used directly, but their structure has also been modified by oxidation or functionalization with different groups. These materials exhibit excellent adsorption properties for organic and inorganic substances. Interactions with analytes occur through non-covalent forces, such as hydrogen bonds, π-π interactions, electrostatic forces, van der Waals, and hydrophobic interactions [12].

In the present work, six carbon-based NMs, i.e., multi-walled carbon nanotubes (MWCNTs), graphite, commercial graphene oxide (CGO), synthesized graphene oxide by the Hummer method (SGO), electrochemically reduced graphene oxide (ERGO), and electrochemically expanded graphene (GEQE), were investigated as sorbents for the determination of sixteen APs. As a novelty, ERGO and GEQE were used as sorbents in a microextraction device for the first time.

Furthermore, when developing a method, not only sufficiently low limits of detection and quantification can be achieved, but optimization is also required to meet the requirements of green analytical chemistry [13,14]. For this reason, the analysis of the environmental friendliness of methods has been intensified, and various software and algorithms have been developed [14,15]. The software AGREE allows the calculation of the greenness of the method based on the 12 principles of Green Analytical Chemistry (GAC) and allows the research focus on each part of the process to observe the shortcomings of the method and analyze the possible opportunities for more greenness [14].

Several aspects come into play in the development of these systems, which can be optimized using the Response Surface Methodology (RSM). Combinations of the intervening variables and their analysis are performed. From the statistical analysis of the responses and using the Desirability function, combinations of the factors that provide a solution to the requirements imposed on the responses are determined [16,17].

In the present work, the development of a new pipette-tip solid-phase microextraction (PT-SPME) method is proposed using different carbon-based NM. A complementary experimental design was used to optimize the critical instrument parameters: NM mass and solution pH. The optimal conditions were used for the construction of the extraction column to comprehensively analyze the feasibility of using these NM as sorbents. Besides, the greenness of the extraction method was calculated and compared with the bibliography.

Based on the latter considerations, this multi-analyte microextraction platform is very promising for future applications for determining emerging environmental pollutants in water systems of different types, improving the optimization of analytical methods. The proposed work is important for both microextraction and green analytical chemistry perspectives, as NMs provide an interesting alternative for the development of infinite of SMPE devices and complement the great potential of using chemometric tools in microextraction approaches.

2. Materials and method

2.1. Reagent

Trimethoprim (TMP), fenbendazole (FBZ), and betamethasone 17-valerate (BMV) were purchased from Vetranal (Sigma-Aldrich Inc, St Louis, USA). Imidacloprid (IMD), clothianidin (CLO), thiamethoxam (TMX), prednisolone (PSL), albendazole (ABZ), diclofenac (DCF), sulfamethoxazole (SMX), fipronil (FIP), chlorpyrifos (CPF), lufenuron (LUF) and permethrin (PER) were purchased from Sigma (Sigma-Aldrich Inc, St Louis, USA). Enrofloxacin (ENR) was purchased from Fluka (Buchs, Switzerland). Pharmaceutical grade robenidine (ROB) was provided by FACYT SRL (Santa Fe, Argentina). Sodium hydrogen phosphate and phosphoric acid were purchased from Cicarelli (San Lorenzo, Argentina). HPLC-grade acetonitrile (can) and methanol (MeOH) were obtained from Merck (Darmstadt, Germany). Milli-Q water was obtained from a Millipore system (Bedford, MA, USA). Dimethylformamide (DMF) and acetone (ACE) were purchased from Cicarelli (San Lorenzo, Argentina). Stock standard solutions were prepared by precisely weighing and dissolving a portion of each standard to reach concentrations of 1.00 mg mL^{-1} in MeOH for ENR, IMD, DCF, ROB, SMX, TMX, and CLO; canACN for TMP, BMV, PSL, FIP, PER, CPF, and LUF; and in DMF for FBZ and ABZ. These solutions were stored at 4 °C in light-resistant containers and were allowed to reach room temperature before use. When necessary, working standard solutions were prepared by diluting (1/10 or 1/100) each stock solution in buffer phosphate 10 mmol L^{-1} at the pH value given by the design. Solutions and solvents for the mobile phase were always filtered through 0.45 μm nylon membranes. Sample solutions were also filtered through syringe 0.22 μm nylon membranes before injection into the chromatographic system.

The commercial nanomaterials were obtained from multi-walled carbon nanotubes powder (MWCNT, O.D. x I.D. x L: 10 nm ± 1 nm x 4.5 nm ± 0.5 nm x 3-~6 μm; number of walls: 6–8) were acquired from Sigma-Aldrich. Co., (St Louis, USA). Commercial Graphene Oxide (CGO) was obtained from Graphenea (San Sebastian –España)

2.2. Instrumentation

Chemical structures of the nanomaterials: a) multi-walled carbon nanotubes (MWCNT), b) graphite, c) commercial graphene oxide (CGO), d) synthesized graphene oxide using the Hummer method (SGO), e) electrochemically reduced graphene oxide (ERGO), and f) electrochemically expanded graphene (GEQE) have been determined by using a Thermo Nicolet iS10 FTIR Scientific (USA). The spectra were analyzed with a resolution of 2 cm^{-1} and with 40 scans within, from a wavenumber range from 3600 to 750 cm^{-1}. Also, to characterize the nanostructures, the MicroRaman spectroscopy was performed using a HORIBA Jobin Yvon spectrometer (model HR 800 UV) working with a green laser at 532 nm, and average particle size was determined using a Zeta Sizer Nano system (Malvern Instruments).

Analytes determination was performed on an Agilent 1260 (Agilent Technologies, Waldbronn, Germany) series liquid chromatography instrument equipped with a binary pump, membrane degasser, thermostated column compartment, autosampler, UV–Vis diode array detector (DAD), and the Chemostation software package (Agilent Technologies, Waldbronn, Germany) to control the instrument, the data acquisition, and the data analysis.

The separation was performed on a 3.5 μm Zorbax Eclipse XDB-C18 analytical column (4.6 × 100 mm) (Agilent Technologies, Waldbronn, Germany). The mobile phase consisted of a mixture of acetonitrile: sodium phosphate buffer 10 mmol L^{-1} (pH = 3.50), using a gradi-

ent of 20% of ACN for 1 min, and increase to 90% of ACN in 17 min, remaining in this percentage for 4 min and returning to the initial conditions in 1 min. The mobile phase flow rate was 1.00 mL min^{-1}, the column temperature was 40 °C, and the injection volume was 100 μL The data was recollected from 200 to 400 nm and analyzed as described by Teglia et al. [18], and DAD registered the chromatographic system at 240 nm. All pH measurements were carried out with an Orion (Massachusetts, United States) 410-A potentiometer equipped with a Boeco BA 17 (Hamburg, Germany) combined glass electrode.

The extraction was performed employing a Mini Puls 3 pump (Gilson, Middleton, United States).

2.3. Synthesis of nanomaterials

2.3.1. Electrochemically expanded graphene synthesis (GEQE)

A solution of 0.50 mol L^{-1} H_2SO_4, capable of exfoliating graphite through its ions, and a two-electrode electrochemical cell was used for synthesis. A platinum electrode with a large surface area performed the functions of reference and counter electrode simultaneously and as a working electrode, and commercial graphite rods, which served as a substrate for the formation of the nanostructure, were used for the synthesis. The intercalation of the ions was driven by the action of a potential of +10 V, sustained for a given time until the total consumption of the graphite bar. Once a black colloidal solution was obtained, it was filtered and subjected to an exhaustive rinsing process. When the water in the wash reached neutral pH, the black solid obtained was collected in a ball mill to dry the synthesis product. The result was a black powder, easily manipulated.

2.3.2. Graphene oxide synthesis (SGO)

Graphene oxide (GO) was synthesized from graphite using the Hummers method [19–21]. Briefly, graphite, sodium nitrate, and potassium permanganate were added to concentrated sulfuric acid cooled to 0 °C. After heating at 35 °C for 30 min, the reaction mixture turned greenish and pasty, and when no more bubbling was observed, the reaction was carefully quenched by the slow addition of water with a pronounced temperature increase. The paste was kept at 90 °C for 15 min and turned brownish. After further dilution with water, it was allowed to cool to 40 °C for 30 min, during which it turned yellow. Hydrogen peroxide was carefully added to form colorless soluble manganese sulfate. The resulting GO was isolated while still warm by filtration, and the yellow-brown filter cake was washed with warm, 5% diluted hydrochloric acid and finally with water. The solid was solubilized in water by ultrasonication, and any insoluble residue was removed by centrifugation. Subsequently, the material was dried at 100 °C for 8 h.

2.3.3. Electrochemical reduced graphene oxide synthesis (ERGO)

A certain amount of GO (from Sigma Aldrich) was dispersed in water to prepare a 0.50 mg mL^{-1} mixture. Before modification, the glassy carbon electrode (GCE) was mechanically polished with 1.0 μm, 0.3 μm, and 0.05 μm alumina slurries sequentially and then tested by cyclic voltammetry to confirm its availability. After being sonicated in redistilled water and ethanol successively for 5 s, the GCE was prepared by casting 20 μL of as-prepared GO suspension onto the surface of the cleaned GCE with a pipette and then allowed to air dry to form a GO film for further use. Electrochemically reduced GO (ERGO) film was prepared by a surface electrochemical reduction method.

The GCE/ERGO was fabricated by immersing the GO film/GCE into an aqueous electrolyte of 0.05 M PBS and then scanning for 20 consecutive cycles at a rate of 100 mVs^{-1} from 0 to −2.0 V (versus the Ag|AgCl electrode) [22]. Subsequently, it was scraped from the surface of the electrode and dried at 100 °C until a constant mass was obtained.

2.4. Experimental design and statistical analysis

For the optimization of the extraction parameters, a central composite design (CCD) for each NM was built (see Tables SM1A-F). The selected factors were the pH values from 3.00 to 8.00 and the mass of NM from 1.00 to 2.00 mg. Consequently, a single block rotatable design ($\alpha = 1.414$), with 3 central points, was built, and the retention percentage of each analyte, computed as the area of each analyte obtained by HPLC-DAD after each experimental run was recorded as the response.

Experimental design, surface response modeling, and desirability function calculations were performed using the StatEase Design–Expert 8.0.0 (Stat-Ease, Inc, Minneapolis, USA). The artificial neural networks (ANN) were implemented using the SRO-ANN Matlab toolbox [23].

2.5. Construction of the microextraction system

Following the experimental design, the microextraction columns were built. The support holder selected for the construction were 1000 μL plastic tips, in which a fixed spun glass mass (100 mg) was mixed with the nanomaterial corresponding to each experiment and introduced into the tip (see Fig. 1).

Subsequently, a volume of 5.00 mL of a mixture of the analytes at a final concentration in the extraction of 1.00 μg mL^{-1}, at a corresponding pH, was passed through the column using a peristaltic pump at a flow rate of 2.50 mL min^{-1}. Then, the column was washed with Milli Q water for 10 min at a rate of 2.50 mL min^{-1}. Finally, to carry out the elution, 500 μL of the mixture of ACN: MeOH: ACE (1: 1: 1) was used at a rate of 1.50 mL min^{-1}. The extracts were filtered and injected.

2.6. Real samples use as proof of concept

Two real samples were used to prove the facility of the use of the PT-SPME in water. The two samples were recollected in December 2020 from the Río Salado in two different sectors: M1 31°36′15.8″S 60°44′15.9″W (pH = 6.50) and M2 31°23′04.3″S 60°54′02.4″W (pH = 6.00). In this experiment, 5.00 mL of the sample were processed as was described before. Moreover, to verify the lack of matrix effect, a mixture of the analytes at 1.00 μg mL^{-1} was added to the sample to reach a final volume of 5.00 mL and processed as enriched samples.

3. Results and discussion

3.1. Nanomaterial characterization

Full characterization was performed each nanomaterial. For example, infrared spectra, Raman spectra, and the DLS analysis provided excellent results (see *Section 1 in Supplementary Material,* for more information).

3.2. Generalities of nanomaterials: their use as sorbent

Carbon-based NMs exhibit excellent adsorption properties for organic and inorganic substances. Interactions with analytes occur through non-covalent forces, such as hydrogen bonds, π-π interactions, electrostatic forces, van der Waals, and hydrophobic interactions [12].

As a solution, more than one material can extract and subsequently release the organic molecules under study (see Figure SM1). In this scenario, the following analysis allowed the definition of the optimal conditions for each NM. To define the best conditions for the proposed system, a comparison was made between them.

3.3. Optimization of the extraction system

When working with nanomaterials, the logical tendency is to increase the amount to improve absorption, but adsorption decreases at very high concentrations of NM due to the reduction of binding sites and surface size. This phenomenon is due to the typical interaction forces of nanomaterials, which tend to agglomerate their particles in aqueous environments. Therefore, the amount of NM was defined as a factor to be analyzed in the experimental design.

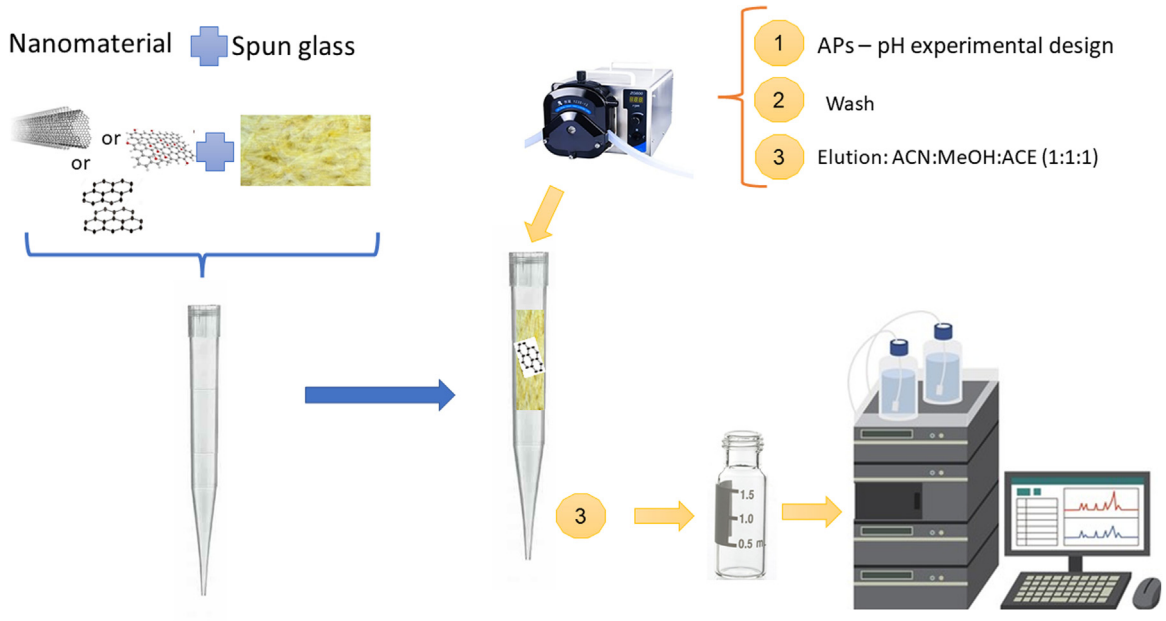

Fig. 1. Workflow of the pipette-tip solid-phase microextraction (PT-SPME) system.

On the other hand, due to the differences in the structure and propieties of both the nanomaterials and the analytes, the pH of the standard solution was an important factor to be analyzed, since these parameters determine the nature of the interaction between NM and the analytes.

Finally, a central composite design (CCD) was prepared for each nanomaterial, and the area of each analyte was recorded as response (see Tables S1A-F). Since the coefficient of determination, R^2 and the values obtained by least squares analysis (LS) were not satisfactory the responses were modeled with a radial basis function artificial neural network (RBF-ANN), which gave good results. The same training data used for modeling LS were used for the analysis. Table SM2 shows the values of R^2 for each response.

For the simultaneous optimization of the 16 responses, the desirability function was applied using the models obtained by RBF-ANN, maximizing for all sixteen responses. Fig. 2 shows the six contour plots corresponding to the global desirabilities obtained after the analysis and describing the optimal results for each NM studied. With this information, three devices were built for each NM, and the retention percentage was analyzed.

Three columns containing only the spun glass were made as extraction blanks and processes to verify the use of the spun glass as a support. After performing the procedure, it was confirmed that none of the analytes were retained on the spun glass. After determining the area of the analytes of interest, the retention percentages (%R) for each NM were calculated and summarized in Table 1. From this, it can be inferred that%R represents the ability of each nanomaterial to retain analytes. As shown in Table 1, CGO is a good candidate for use as an adsorbent in SPME because a higher number of analytes and%R observed after analysis.

3.4. Analysis of the structural characteristics of the analytes and the conditions of the interaction medium

Table 2 summarizes the design analysis performed to obtain the best extraction conditions and design of the optimized devices to select, the most appropriate conditions for single analytes, structural family, drug family, or multianalyte extraction.

Similarly, the structural characteristics of the analytes are analyzed below by the family of active principles and of the optimal experimental conditions to achieve the best performance in the extraction system.

Table 1
Retention percentage (%R) of the sixteen analytes in the six nanomaterials studied.

Analyte	% R on each nanomaterial					
	MWCNT	GEQE	Graphite	ERGO	SGO	CGO
TMP	89.7	61.1	40.9	59.5	34.5	71.5
TMX	27.0	22.1	17.8	36.8	51.3	54.2
ENR	54.8	47.6	103.0	28.2	3.8	20.8
CLO	21.8	–	23.4	22.9	49.6	35.3
IMD	25.7	–	24.7	22.9	48.7	33.6
SMX	44.3	23.6	14.6	42.3	29.0	88.5
PNS	38.3	–	17.2	37.9	64.6	104.8
ABZ	58.2	76.7	74.6	66.3	13.9	26.2
FBZ	55.3	100.3	108.9	87.0	14.8	54.1
ROB	7.8	–	62.8	4.3	1.4	60.4
DIC	28.0	18.0	15.2	30.5	18.6	79.7
BMV	76.5	84.8	45.4	72.7	66.9	88.4
FIP	29.5	16.3	6.4	29.7	26.7	68.2
CPF	27.4	33.5	17.6	21.9	10.2	53.6
LUF	–	28.3	9.7	19.5	16.7	62.9
PER	14.8	26.1	90.9	5.6	6.6	55.2

3.4.1. Antimicrobial

In particular, among the antimicrobial family, the NMs with the highest extraction capacity were MWCNT and CGO.

Trimethoprim (TMP) is the molecule that shows greater aromaticity compared to the others, so logically it is expected to have a more significant interaction via π staking with NMs that provide a network of C with sp^2 hybridization such as MWCNT and graphite. In contrast, the remaining NMs show a decrease in the two-dimensional network of sp^2C due to the presence of oxygen-containing functional groups and surface defects such as sp^3C, which will be present in a higher proportion in CGO and SGO and less in ERGO and GEQE. Remarkably, the difference in the structure of MWCNTs and graphite is due to the fact that the former can expose a larger effective surface area for the sorption of molecules and, at the same time, metal traces area trapped in the structure originating from the synthesis, making it a better candidate for the adsorption of a variety of molecules. The remaining NMs present a relative surface charge, that enables hydrophilic interactions.

TMP, SMX, and ENR have pKa_1 values of 7.12, 6.00, and 5.88, respectively, ENR has a pKa_2 value of 7.74, and when CGO is used as

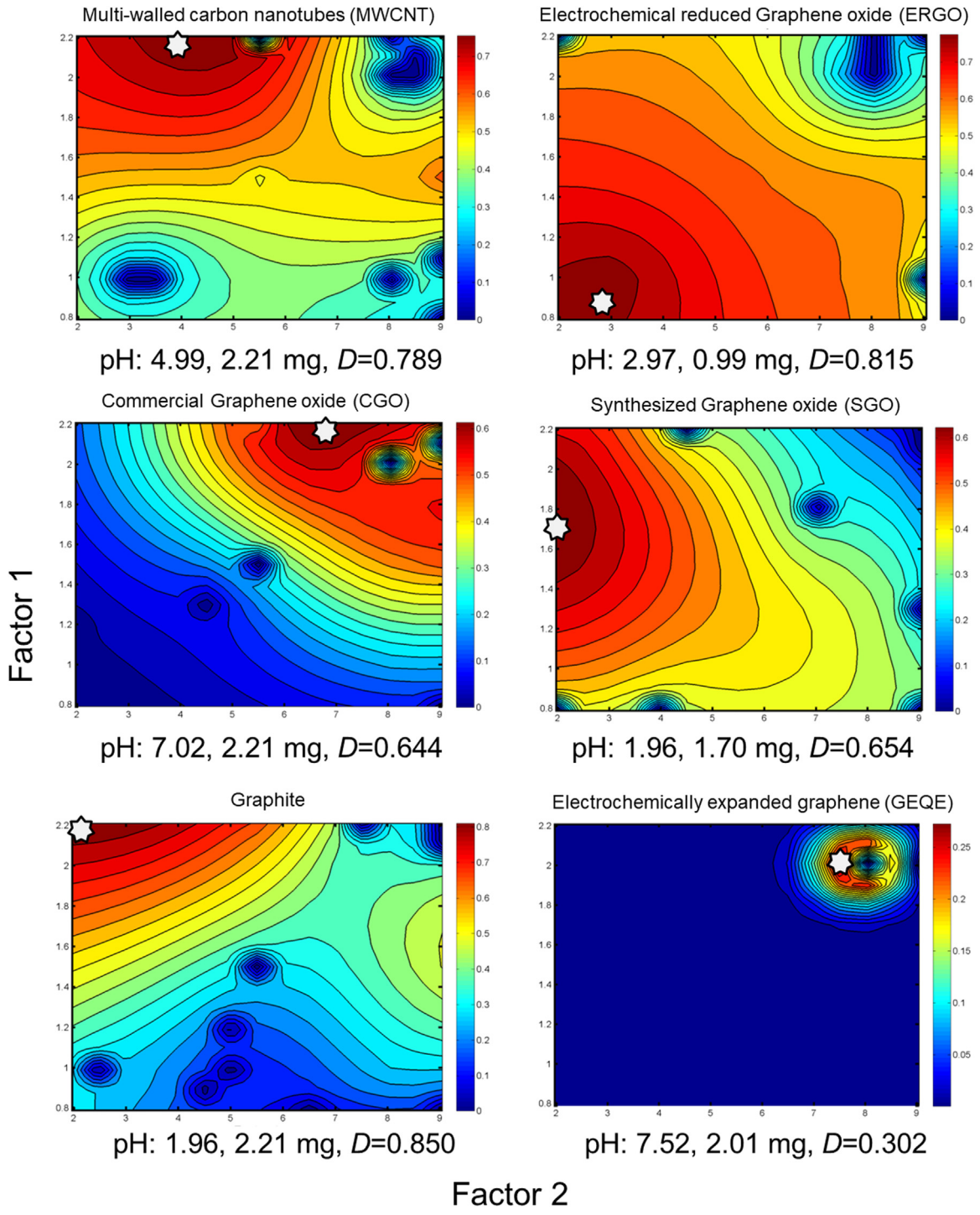

Fig. 2. Contour plots corresponding to the global desirabilities in the analysis of the 16 responses for each nanomaterial. *Starts represent the optimum conditions for each material. Factors: mass of NM (1) and pH (2).

sorbent, the working pH is 7.01; thus, under these experimental conditions, the amino groups of the molecules can expose positive charges and generate electrostatic interactions with the negatively charged oxygen groups because CGO deprotonates at a pH of 3.90, while ENR remains fairly neutral under the same conditions. For this reason, CGO is more suitable for the extraction of TMP and SMX.

3.4.2. Anti-inflammatories

BMV show a higher percentage of recovery over the NM to the other analytes in the group, which have a larger amount of sp^2C atoms arranged in a two-dimensional layer, densely packed in a hexagonal lattice. In general, the anti-inflammatories used in the present work have neutral structures or low surface charge density and are thus good candidates to be retained in NM with similar properties such as MWCNT, graphite, ERGO, and GEQE.

For the NMs with higher charge density and functional groups and/or defects (CGO and SGO in a lower percentage), it is observed that the three molecules are adsorbed in similar way. However, DIC exhibits a lower percentage of retention; this could be due to electrostatic repulsions which may be slightly reduces its adsorption compared to

Table 2
Selection of the best conditions for the construction of the PT-SPME considering the extraction of analytes belonging to the same structural family.

Drug classification	Analyte	Structural family	Nanomaterial*	PT-SPME system: sample pH/mass of nanomaterial
Antimicrobials	Enrofloxacin	Fluoroquinolones	1. Graphite 2. MWCNT 3. GEQE	pH 2.0 2.2 mg of graphite
	Trimethoprim	Diaminopyrimidine	1. MWCNT 2. CGO 3. GEQE	pH 5.0 2.2 mg of MWCNT
	Sulfamethoxazole	Sulfonamide	1. CGO 2. MWCNT 3. ERGO	pH 7.0 2.2 mg of CGO
External antiparasitic agents	Imidacloprid, thiamethoxam, clothianidin	Neonicotinoids	1. SGO 2. CGO 3. ERGO	pH 2.0 1.7 mg of SGO
	Fipronil	Phenylpyrazole insecticides	1. CGO 2. ERGO 3. MWCNT	pH 7.0 2.2 mg of CGO
	Chlorpyrifos	Organophosphate insecticides	1. CGO 2. GEQE 3. MWCNT	pH 7.0 2.2 mg of CGO
	Lufenuron	Benzoylurea pesticide	1. CGO 2. GEQE 3. ERGO	pH 7.0 2.2 mg of CGO
	Permethrin	Pyrethroids	1. Graphite 2. CGO 3. GEQE	pH 2.0 2.2 mg of graphite
Internal antiparasitic agents	Internal antiparasitic agents	Benzimidazole	1. Graphite 2. GEQE 3. ERGO	pH 2.0 2.2 mg of graphite
Anti-inflammatories	Betamethasone 17-valerate and prednisolone	Glucocorticoids	1. CGO 2. SGO 3. MWCNT	pH 7.0 2.2 mg of CGO
	Diclofenac		1. CGO 2. ERGO 3. MWCNT	pH 7.0 2.2 mg of CGO
Anticoccidial	Robenidine		1. Graphite 2. CGO	pH 2.0 2.2 mg of graphite

* The numbering refers to the nanomaterials with the highest extraction (from highest to lowest).

PNS and BMV, since DIC has a pKa of 4.15 and, at pH 7 (optimal pH for extraction with CGO), both DIC and CGO expose mainly negative charges.

On the other hand, both PNS and BMV are structurally similar, and it is reasonable to assume that they exhibit similar behavior toward the various NMs. This could be due to the fact that it is easier to form hydrogen bonds with the NMs that have oxygen-containing groups, and generally, with all NMs through non-covalent forces, such as van der Waals forces.

3.4.3. Internal antiparasitics

Both ABZ and FBZ remain practically neutral at a pH less than 7.00. Therefore, it is reasonable to assume that a lower retention percentage is observed on NMs that have negative surface charges with a higher percentage of sp^3C and surface defects (CGO and SGO) than on NMs that have a more pristine nature (MWCNT, graphite, ERGO, and GEQE).

Comparing the structures of the two analytes, FBZ has higher aromaticity than ABZ. Therefore, higher adsorption is expected through π stacking interaction and via van der Waals and hydrophobic interactions.

3.4.4. External antiparasitics

In general, this group has a lower aromaticity than the analytes of the other groups, so that a lower retention or adsorption to the NMs can be expected. Nevertheless, differences between them can be observed. Within this functional group, a structural subfamily belongs to the neomycid (TMX, CLO and IMD), of which TMX shows a slightly higher retention. This subfamily shows greater affinity for NM with more surface oxygen groups (CGO and SGO). Nevertheless, in a general analysis of all analytes forming the external antiparasitics, a clear preference for CGO is observed, since they have at least twice the adsorption capacity compared to the other NM.

3.4.5. Anticoccidial

The two best materials for obtaining ROB are graphite and CGO. When CGO is used as a NM sorbent, expected hydrogen bond-type interactions, π-π interactions, electrostatic and van der Waals forces are expected. Electrostatic interactions predominate, because CGO has a high density of negative charge at a pH of 7.00, while ROB has a high density of negative charges, due to its pKa value of is 3.56, and therefore interactions and subsequent adsorption are favored.

In the case of graphite (pH 1.96), the interactions that dominate adsorption are non-covalent forces of the π-π, type van der Waals forces, and hydrophobic interactions.

In summary, when the goal is the extraction of multianalytes, as in the case of this work, where the extraction of sixteen analytes from different families, both structural and active principles, was performed, the optimized condition to obtain the highest overall extraction yield was the use of commercial graphene oxide (CGO) at a pH of 7.00.

However, if, for example, the analysis of fluoroquinolones in water is to be performed, the PT-SPME must be prepared using 2.2 mg graphite and the sample brought to a pH of 2.0. If glucocorticoids are

to be extracted, the best conditions are to use 2.2 mg CGO at a pH of 7.0.

3.5. Study of the system in batch or continuous form

A comparative study of the extraction capacity of the continuous (column) and batch method using multi-walled carbon nanotubes (MWCNTs), graphite, and commercial graphene oxide (CGO) as NMs was then performed. The extraction of sixteen analytes was analyzed using batch and continuous systems, under the same operating conditions (mass of NMs, sample volume, and elution of the developed system). In the discontinuous approach, the NM was stirred for one day in contact with the aqueous solution of the analyte mixture at optimal pH.

In this sense, when analyzing the capacity of each NM in both extraction systems (continuous vs. batch), the batch approach was more effective only in a few situations, while the continuous method showed similar or better recovery percentages in most of the experimental conditions analyzed.

For MWCNT an increase in percent recovery of 1.77, 1.74, 1.44, 1.26, and 3.26 times, respectively, was observed when extraction was performed in batch mode. On graphite, improvement was observed for four of the sixteen analytes when extraction was performed in batch mode, with an increase in percent recovery of 1.25-, 1.75-, 3.31-, and 2.38-fold for TMP, IMD, CPF, and DIC, respectively. When CGO was used as adsorbent, an increase of 2.50- and 1.72-fold was obtained only for two analytes (ABZ and FBZ).

The increase in recovery for these particular analytes may be due to the adsorption-desorption kinetics of the analytes with NM, as the adsorption process take more time to occur. This could be due to the structural characteristics, lower aromaticity of these analytes, and physicochemical conditions, that make the batch extraction method lightly better for this small group of analytes. In general, similar results were obtained for continuous and discontinuous strategies for most analytes. In particular, the continuous method showed significant improvements for ENR over MWCNT and graphite, for TIA and PER over MWCNT and graphite and CGO, for PNS on MWCNT and CGO, and for DIC and SMX on CGO. On the other hand, batch systems have some disadvantages, such as the time required and the loss of NM due to precipitation, resulting in a low possibility of NM reuse.

3.6. Comparative analysis: individual vs. multi-analyte extraction

Complementarily, to corroborate the capacity of the system as an extraction method for multiple analytes, the performance of graphite as a sorbent was evaluated by comparing the percent recovery of six analytes (representatives of each group of APs, i.e., TMP, IMD, CPF, FBZ, BMV and ROB) that performed the extraction individually and in a mixture under the same operating conditions (mass of NMs, sample volume, and elution of the developed system).

Analysis of the results showed that, only two of the six analytes' studies had higher recoveries in the single extraction (TMP and IMD). In particular TMP showed about a twofold higher recovery rate in single extraction; a threefold a recovery rates were obtained for IMD. In contrast, recoveries for the other analytes showed no significant changes. When analyzing the capacity of the extraction method, several factors must be analyzed and considered. These include, the affinity of the different analytes for the analyzed NM, physicochemical properties, structure, adsorption-desorption kinetics, and active area for adsorption (steric hindrances).

When comparing the six analytes in terms of structure, physical chemical properties, and the possibility of interaction with the graphite surface, TMP, IMD, and CPF exhibit the lowest affinity for the surface of NM, either due to structure, aromaticity, and interaction via non-covalent labile forces that allow for greater retention capacity.

Table 3
Analytical figures of merit of the proposed method.

Analyte	Linear working range (μg mL^{-1})	γ (mL μg^{-1})	LOD (μg mL^{-1})	LOQ (μg mL^{-1})
TMP	0.062 – 12.06	112.6	0.022	0.066
ENR	0.030 – 10.81	163.1	0.010	0.030
TMX	0.082 – 10.20	98.5	0.027	0.082
CLO	0.075 – 9.89	102.5	0.025	0.075
IMD	0.095 – 10.53	36.4	0.032	0.095
SMX	0.110 – 10.58	24.5	0.037	0.110
PSL	0.121 – 9.85	20.5	0.040	0.121
ABZ	0.072 – 10.25	89.8	0.024	0.072
FBZ	0.075 – 10.35	85.2	0.025	0.075
ROB	0.059 – 10.01	112.3	0.019	0.059
DCF	0.098 – 10.20	89.6	0.033	0.098
BMV	0.123 – 9.58	30.5	0.041	0.123
FIP	0.089 – 10.58	55.8	0.030	0.089
IBU	0.111 – 10.00	98.5	0.037	0.111
LUF	0.084 – 9.46	68.7	0.028	0.084
CPF	0.095 – 10.25	56.8	0.032	0.095
PER	0.125 – 10.58	25.3	0.042	0.125

γ: analytical sensitivity.

Therefore, based on the latter considerations, it could be argued that this multi-analyte microextraction method is promising for future applications.

3.7. Analytical parameters

The analytical performance of the system was determined as described by Teglia *et al.* [18]. Table 3 summarizes the results.

In addition, Fig. SM2 shows the chromatographic profiles registered at 240 nm of a standard solution of 1.00 μg mL^{-1} of each analyte after it has been run through the procedure PT-SPME.

3.8. Analysis of real samples

The extraction device was tested with real river water. Data analysis showed that the presence of CPF was present in M2 at a concentration of 0.05 μg mL^{-1} (see Fig. SM3). In turn, the sample spiked with the 16 analytes at 1.00 μg mL^{-1} showed recovery percentages between 85 and 95% for CGO as absorbent material, clearly showing that there is no nuancing effect. This evaluation proves the efficiency of the developed extraction system for the analysis of real samples.

3.9. Green analytical chemistry evaluation

The Green Metric Tool [14] was used to obtain a green certificate. The criteria to be evaluated are related to the 12 principles of Green Analytical Chemistry (GAC). The scale assigns a value of 1.00 points to the ideal green analysis, and the corresponding penalty points are subtracted from this value, analyzing each principle separately. A general value of 0.75 was obtained (see Table 4), showing satisfactory green" performance of the method. Values were determined for each principle as described in *Section 2* in the *Supplementary Material*. For comparison, all methods were analyzed using the same parameters described in this section. In the development of PT-SPME, the lowest individual values were obtained for GAC principles 3 and 10, i.e., due to the *ex situ* extraction (item 3) and the use of NM in the design of the system (item 10). Nevertheless, it can be concluded that the development method follows the principles of the GAC.

3.10. Comparison among extraction methods that use different nanomaterials as sorbents

Table 4 summarizes various extraction systems using carbon nanomaterials as sorbents that have been reported in the last 10 years.

Table 4
Recent applications of different nanomaterials as sorbent for pharmaceutical drugs.

Carbon-based nanomaterial	Additives -functionalization	Analyte	Extraction Technique	Green analytical chemistry assessment	Ref.
MWCNTs		Sulfonamides	dSPE		[24]
		Moxifloxacin, lomefloxacin, danofloxacin, ciprofloxacin, levofloxacin, marbofloxacin, enrofloxacin, difloxacin, pefloxacin, oxolinic acid and flumequine	dSPE		[25]
	Fe_3O_4 -nanocomposite	Doxorubicin	MSPE		[26]
		Lomefloxacin and Ofloxacin	Dispersive μ-SPE		[27]
	Polymer coated Fe_3O_4 -nanocomposite	Naproxen	MSPE		[28]
	PAC	Nitrofurazone	Batch adsorption		[29]
	Poly(ethylene glycol)	Ibuprofen, naproxen and diclofenac	SPME		[30]
	-COOH grafted	Phenobarbital	SPME		[31]
MWCNT with selected properties: pristine, hydroxylated, thin-walled with large inner diameter, aminated, and high-purity		Triclosan, prometryn, 4-acetylamino-antipyrine, carbendazim, caffeine, ibuprofen, acetaminophen, carbamazepine	Membrane filter		[32]

(*continued on next page*)

Table 4 (*continued*)

Carbon-based nanomaterial	Additives -functionalization	Analyte	Extraction Technique	Green analytical chemistry assessment	Ref.
Activated carbon, carbon xerogel and CNT		Ciprofloxacin	Batch		[33]
GO		Tetracycline, oxytetracycline, and doxycycline	Batch		[34]
	Polymer coated	Dopamine	HF-SPME		[35]
	Polyethylene glycol nanocomposite	Fluoroquinolones	SBSE		[36]
	Magnetite composites	Ciprofloxacin and norfloxacin	Batch		[37]
		Ibuprofen	DMSP in micro-channel		[38]
	Polyaniline nanocomposite	Nicotine	HF-SPME		[39]
Graphene		Sulfadimidine sodium, sulfa-monomethoxine sodium, sulfachloropyrazine sodium and fluorescamine	PT-SPE		[40]
		Aspirin, acetaminophen, and caffeine	Batch		[41]
Porous graphene		Atenolol, carbamazepine, ciprofloxacin, diclofenac, gemfibrozil and ibuprofen	Batch		[42]

(*continued on next page*)

Table 4 (*continued*)

Carbon-based nanomaterial	Additives -functionalization	Analyte	Extraction Technique	Green analytical chemistry assessment	Ref.
MWCNT, graphite, GEQE, ERGO, SGO and CGO		Trimethoprim, enrofloxacin, sulfamethoxazole, thiamethoxam, clothianidin, imidacloprid, fipronil chlorpyrifos, lufenuron, permethrin, fenbendazole, albendazole, prednisolone, diclofenac, betamethasone robenidine	PT-SPME		This work

MSPE: Magnetic solid phase extraction; dSPE: dispersive solid phase extraction; HF-SPME; Hollow fibber solid phase microextraction; MSPD: matrix solid-phase dispersion; PT-SPE: tip solid-phase extraction; FL: spectrofluorometric; MWCNT: multi-walled carbon nanotubes; CGO: commercial graphene oxide, SGO: synthesized graphene oxide using the Hummer method; ERGO; electrochemically reduced graphene oxide; GEQE: electrochemically expanded graphene; GO: graphene oxide; PAC: power active carbon; DMSP: dispersive micro-solid phase extraction.

The first conclusion from the analysis of Table 4 allows us to note that, unlike most published extractive systems, only the absorption capacity of one or some of the most common NM, such as carbon nanotubes (CNTs) or graphene, is analyzed. In this sense, 70% of the reports describe CNTs (multi- or single-walled), 10% use GO, 10% graphene, and 10% other nanomaterials. Moreover, only two works compare different NM: one is nanotubes with different properties [32], the other is the use of activated carbon, carbon xerogel and CNT [33].

Moreover, the works focus on the extraction and absorption of a limited number of analytes, all belonging to the same family with similar physicochemical properties. In addition, only three works determine a maximum of 8 analytes belonging to different families [32,42,43].

Otherwise, the Green Analytical Chemistry score was calculated for each extraction method (for more information, see *Section 2* of the *Supplementary Material*). According to the analysis, although in general the worst individual scores are those expressing the non-direct analysis (item 1), the use of a larger sample size (item 2), the ex - situ measurements (item 3), and the use of no renewable source (item 10) the present work is greener than the others due to the final score of 0.75.

4. Conclusions

The manuscript proposes an innovative solid-phase microextraction (SPME) approach using various carbon-based nanomaterials (multi-walled carbon nanotubes, graphite, graphene oxide, electrochemically expanded graphene, electrochemically reduced graphene, commercial and synthesized graphene oxide), some of them are used for the first time as sorbents, since they can be synthesized in the laboratory at low cost, as sorbents for the determination of sixteen veterinary active ingredients in water and using chemometric tools for the optimization of the studied system. In addition, the optimization of the device was carried out through an experimental design to obtain the mass of the sorbent and the working pH to improve the retention.

In addition, the analytical performance was evaluated for sixteen emerging contaminants used in veterinary medicine belonging to five different families of active ingredients, and the interactions between nanomaterials and different active ingredients were discussed in detail. The study revealed the optimal conditions for each case, achieving at the same time an efficient multi-analyte extraction. Moreover, the developed work allows the selection of different NM for each analyte or family, providing important information for the selection of a NM for each individual system. Finally, after the comparative extraction analysis single vs. multianalyte and batch vs. continuous system, it was concluded that the commercial graphene oxide turned out to be the NM that allowed the extraction of the largest amount of analytes with the highest retention percentages (%R) and offered advantages in terms of simplicity, low cost, and high solubility.

To complete the analysis, the microextraction devices were tested with real river water samples (complex matrices), proving the efficiency of the developed extraction system for real samples analysis.

In addition, the Green Metric Tool was used to define the environmental friendliness of the method, showing that the developed method follows the principles of Green Analytical Chemistry.

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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.greeac.2023.100060.

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