Research Article

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Amine-functionalized magnetic activated carbon as an adsorbent for preconcentration and determination of acidic drugs in environmental water samples using HPLC-DAD

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Abstract: In the present study, a convenient and highly effective method was developed for the quantification of acidic drugs in wastewater and river water samples. Ultrasonic-assisted magnetic solid phase extraction employing magnetic waste tyre-based activated carbon nanocomposite functionalized with [3-(2-aminoethylamino)propyl]trimethoxysilane as a cost-effective and efficient adsorbent was used for the extraction and preconcentration of acidic drugs (naproxen [NAP], ketoprofen (KET) and diclofenac [DIC]). The quantification of target analytes was achieved by high-performance liquid chromatography with diode array detector. Under optimum conditions, the detection limit, quantification limit and relative standard deviation obtained for the analytes of interest ranged from 0.38 to 0.76, 1.26 to 2.54 $\mu g\,L^{-1}$ and 2.02 to 4.06%, respectively. The applicability of the developed method was assessed by the spike recovery tests and the relative recoveries proved that the method is reliable for the determination of acidic drugs in wastewater. Thereafter, the method was applied successfully for the determination of NAP, KET and DIC in river water, influent and effluent wastewater.

Keywords: acidic drugs, preconcentration, magnetic activated carbon, response surface methodology

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1 Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) is one of the most extensively used classes of pharmaceuticals for human and livestock medicine due to their analgesic, antipyretic and anti-inflammatory properties [1]. Although the usage of NSAIDs varies from country to country, ibuprofen, ketoprofen (KET), diclofenac (DIC), acetaminophen, aspirin and naproxen (NAP) are the most popular [2,3]. Because of their strong efficacy towards various pain and inflammation-related ailments, NSAIDs are extensively used in the health services and most of them are available over the counter without a doctor's prescription. Moreover, new NSAIDs with improved biopharmaceutical properties are developed and introduced into the market at a fast pace [3]. As a result of their high consumption accompanied by partial absorption by the body and an incomplete removal by the traditional wastewater treatment plants (WWTPs), NSAIDs have been detected in the environment. The presence of NSAIDs in the environment exacerbates their impacts on the ecosystem. Additionally, NSAIDs are considered pseudo-persistent because their degradation rates are not as high as their high rates of introduction into aquatic environment [4]. While NSAIDs are considered safe to use, an acute overdose and a chronic abuse could result in adverse cardiovascular, renal and gastrointestinal complications [3,5]. Hence, their continuous discharge into the environment may negatively impact both terrestrial and aquatic flora and fauna and unexpectedly compromise human and wildlife health.

Because of the possible impacts of NSAIDs on humans and other organisms, it is vital to monitor their occurrence and fate in the environmental matrices. Since the levels of NSAIDs in environmental matrices are generally in the trace to ultra-trace ranges ($ng\,L^{-1}$ to $\mu g\,L^{-1}$), their quantification requires sensitive analytical techniques. Analytical detection techniques, such as gas chromatography [6,7], capillary electrophoresis [8,9], liquid chromatography [10] and high-performance

liquid chromatography [11,12], have been used for the determination of NSAIDs. However, because of the low concentration of NSAIDs and the complexity of the environmental matrices, a suitable sample preparation method is required to extract and preconcentrate the target analytes before analysis [13,14]. Hence, for a proper environmental monitoring, it is important to develop sensitive, accurate and reliable sample preparation techniques for the extraction and enrichment of the NSAIDs before analysis.

Different sample preparation techniques, such as solid phase microextraction (SPME) [15], solid phase extraction (SPE) [16], dispersive micro-SPE [17], stir bar sorptive extraction (SBSE) [18], fabric phase sorptive extraction [19–22], biofluid sampler [23], molecularly imprinted polymer SPE [24,25], microextraction by packed sorbent (MEPS) [26,27], hollow fiber-SPME [28], dispersive liquid–liquid microextraction [8,29] and MSPE [30–32], have been used for the analysis of NSAIDs and other emerging pollutants in the different matrices. Among these microextraction methods, MSPE has received enormous interest because of its simplicity, rapidity, usage of low volumes of toxic solvents and has been applied for the extraction and determination of NSAIDs in the environment [1,30,32].

MSPE method is based on the use of unmodified and modified magnetic adsorbents which are dispersed directly into the solution to allow the target analytes to adsorb on the adsorbent. Adsorbents, such as metal oxides [33,34], zeolites [35,36], metal organic frameworks [37,38], carbonaceous materials [40,39] and polymers [1,41] modified with magnetic nanoparticles, have been used in the MSPE for the extraction and preconcentration of trace analytes. Among the carbonaceous materials, activated carbon (AC) has received widespread research interest because it is known to be one of the most economical and reliable adsorbents for the adsorption of organic and inorganic pollutants. This is because it is highly porous, has a large surface area and high catalytic activity which are valuable in the adsorption and extraction of various pollutants. Additionally, AC can be synthesized from various waste materials which makes the process of production economical [42]. Furthermore, the adsorption capacity of AC can be improved by modification and functionalization with additives as metal oxides [43,44], polymers [45,46], surfactants [47], and organic ligands such as EDTA [48,49] among others. Modification and functionalization of the AC enhances the sensitivity and selectivity of the adsorbent towards target analytes. Despite these advantages of AC, its usage is limited because it disperses well in aqueous solutions, making it difficult to separate [42]. Hence, modifying AC with magnetic nanoparticles allows for an easy separation from aqueous solutions.

Therefore, the aim of this study was to develop a simple ultrasonic-assisted magnetic SPME (UA-MSPME) method employing waste tyre-based AC decorated with magnetic nanoparticles and functionalized with [3-(2-aminoethylamine)propyl]trimethoxysilane (APTMS) (APTMS@WTMAC) as a valuable adsorbent. MSMPE was then used for the simultaneous extraction and enrichment of three NSAIDs (KET, NAP and DIC) in wastewater and river water, prior to high-performance liquid chromatography with diode array detector (HPLC-DAD) quantification. To the best of our knowledge, this is the first report of an analytical method in which APTMS-functionalized magnetic tyre-based AC is used in the MSPME method for analysing NSAIDs in environmental samples. Both univariate and multivariate designs were used to optimize and determine optimum conditions for the optimal performance of the method. Lastly, the method was successfully applied for the analysis of KET, NAP and DIC in real river water and wastewater.

2 Experimental

2.1 Reagents and materials

Unless otherwise stated, all chemicals used were of analytical reagent grade. Sodium chloride and sodium nitrate were ordered from ACE (Johannesburg, South Africa). Methanol (HPLC grade), APTMS, acetonitrile (HPLC grade), ammonium hydroxide solution (30%), ferric chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), acetic acid (99.7%) and ferrous chloride tetrahydrate ($FeCl_2{\cdot}4H_2O$) were purchased from Sigma-Aldrich (St. Louis, MO, USA). NAP, KET and DIC sodium salts were purchased from Sigma-Aldrich (St. Louis, MO, USA). A stock solution of 1,000 mg L^{-1} of each analyte was prepared by dissolving an appropriate amount of the analyte in methanol and stored at 4°C. The working solutions were prepared immediately before the experiments by dilution of the stock solution with ultra-pure water (Direct-Q® 3UV-R purifier system). PVDF membrane filters (0.22 µm) (Separation Scientific SA (Pty) Ltd) were used to filter the samples prior to HPLC analysis.

2.2 Synthesis and functionalization of magnetic AC composite

The magnetic AC (Fe_3O_4/AC) nanocomposite was prepared via a co-precipitation method, as reported in the literature [44], with some modifications. The AC was previously prepared in our research group from waste tyres [45]. A 6 g of AC was dispersed in 200 mL solution of $FeCl_3{\cdot}6H_2O$ (2 mol) and $FeCl_2{\cdot}4H_2O$ (1 mol). The mixture was vigorously stirred using a magnetic stirrer under nitrogen at 90°C. Thereafter, 30 mL of ammonia (NH_3) solution was quickly added into the above suspension and left to stir for 1 h before it was cooled to room temperature. The synthesized Fe_3O_4/AC nanocomposite was separated using a magnet and washed repeatedly with deionized water until pH was neutral. The resultant adsorbent was left to dry in the oven overnight at 60°C and ground to fine particles using a pestle and mortar. Magnetic nanoparticles were synthesized using the same procedure, but in the absence of AC. For functionalization, 1 g of Fe_3O_4/AC was dispersed in 30 mL of ethanol for 30 min and 0.6 mL of APTMS was added. This mixture was then stirred for 1 h and left to dry at room temperature. The functionalized composite is referred to as Fe_3O_4/AC-NH_2.

2.3 Characterization of the synthesized adsorbents

The functional groups present on the adsorbents were studied with a Shimadzu FTIR model 8300 (Kyoto, Japan). The spectra were recorded in the 400–4,000 cm^{-1} range. The XRD (PANalytical X'Pert X-ray Diffractometer [PANalytical BV, Netherlands]) was used to study the crystallinity of the adsorbents. The morphology and elemental composition were examined using scanning electron microscopy (SEM, TESCAN VEGA 3 XMU LMH instrument [Czech Republic]) coupled with energy dispersive X-ray spectroscopy (EDS). The nanostructures of the adsorbents were studied using transmission electron microscopy (TEM, JEM-2100, JEOL, Tokyo, Japan).

2.4 Preparation of samples

The environmental water (influent, effluent and river water) samples were collected in clean, glass bottles from a local WWTP and river and kept in the refrigerator. The collected samples were equilibrated to room temperature and subjected to the MSPE method.

2.5 Chromatographic conditions

Chromatographic analysis was carried out using an Agilent 1200 Infinity series HPLC equipped with a diode array detector (Agilent Technologies, Waldbronn, Germany). The mobile phase consisting of 0.2% acetic acid and methanol in a ratio of 30:70 (v/v), respectively, was pumped through an Agilent Zorbax Eclipse Plus C18 column (3.5 µm × 150 mm × 4.6 mm) (Agilent, Newport, CA, USA). The flow rate and injection volume were maintained at 1.00 mL min^{-1} and 10 µL, respectively. The chromatograms were recorded at 280 nm. A set of standards (n = 8) prepared by serial dilution of the stock solution with methanol were used for the instrument calibration.

2.6 Preconcentration procedure

The preconcentration studies were performed using a model solution containing a known concentration of the target analytes and 0–23% NaCl at pH 4–9. Twenty-five milliliters of the model solution was mixed with 20–50 mg of the adsorbent in glass bottles and the adsorbent was dispersed in the solution by means of ultrasonication for 10 min. Magnetic decantation was thereafter used to separate the adsorbent from the aqueous solution. The analytes were then desorbed from the adsorbent using 2 mL of acidified methanol after ultrasonication for 5 min. The sample was filtered before HPLC analysis.

2.7 Chemometric optimization

In order to obtain the best results from an analytical method, the conditions should be optimized. A multivariate optimization approach was used to optimize the developed UA-MSPME. In this study, the optimization was carried out using a central composite design (CCD). Parameters, such as mass of adsorbent (MA), sample pH and ionic strength (IS), were considered as parameters which may have a significant effect on the extraction and

Table 1: Factors and levels used in the CCD for the preconcentration of the NSAIDs

Parameters	Low point (−1)	Central point (0)	High point (+1)
pH	4	6.5	9
% Ionic strength (IS)	0	2.5	5
Mass of adsorbent (MA, mg)	20	35	50

preconcentration of NAP, KET and DIC. Factors and levels used in the optimization of the method are presented in Table 1. The type of elution solvent and choice of adsorbent were screened univariately and solvents, such as methanol, acetonitrile, acidified methanol and acidified acetonitrile, were evaluated for their abilities to desorb the analytes from the adsorbent.

Ethical approval: The conducted research is not related to either human or animal use.

3 Results and discussion

3.1 Characterization

The XRD patterns of Fe_3O_4 nanoparticles and Fe_3O_4/AC-NH_2 nanocomposite are displayed in Figure 1. According to Figure 1(a), the characteristic peaks of the Fe_3O_4 nanoparticles were located at 2θ = 30.25° (220), 35.37° (311), 43.14° (400), 53.48° (422), 57.18° (511) and 62.82° (440) [50,51], which are in agreement with the JCPDS no. 00-065-0731. According to Figure 1(b), the diffraction patterns of the Fe_3O_4 nanoparticles on the nanocomposites are the same as those of the pure Fe_3O_4 nanoparticles, indicating that depositing Fe_3O_4 nanoparticles on the AC and functionalization thereof, had no effect on the Fe_3O_4 nanoparticles' structure.

The morphologies of adsorbents were investigated using TEM. Before analysis, the samples were dispersed in ethanol by sonication, drop coated on a copper grid and dried. Figure 2 shows the TEM images of (a) Fe_3O_4 nanoparticles, (b) AC, (c) Fe_3O_4/AC-NH_2 composite and (d) EDS spectrum of the Fe_3O_4/AC-NH_2 composite. Figure 2(a) shows a highly uniform pattern of the Fe_3O_4 nanoparticles. The cubic structures of the Fe_3O_4 nanoparticles were observed, with no agglomeration. The morphology of the Fe_3O_4/AC-NH_2 nanocomposite, shown in Figure 2(c), indicated dissimilar contrast of the adsorbent. The darker areas could be attributed to the presence of carbonic, while the lighter areas were attributed to the presence of Fe_3O_4 nanoparticles. The TEM image confirms the successful modification of AC with Fe_3O_4 nanoparticles. The elemental composition of the composite was confirmed by SEM-EDS. The EDS spectrum of the Fe_3O_4/AC-NH_2 composite, presented in Figure 2(d), exhibited peaks assigned to Fe, O, C and N. The presence of N in the nanocomposite confirmed the successful amine functionalization of the nanocomposite.

The functional groups on Fe_3O_4, Fe_3O_4/AC and amine-functionalized Fe_3O_4/AC nanocomposite were investigated by FTIR spectroscopy and the spectra are presented in Figure 3. The broad peaks at 3,442 cm^{-1} were assigned to the stretching vibrations of the O–H

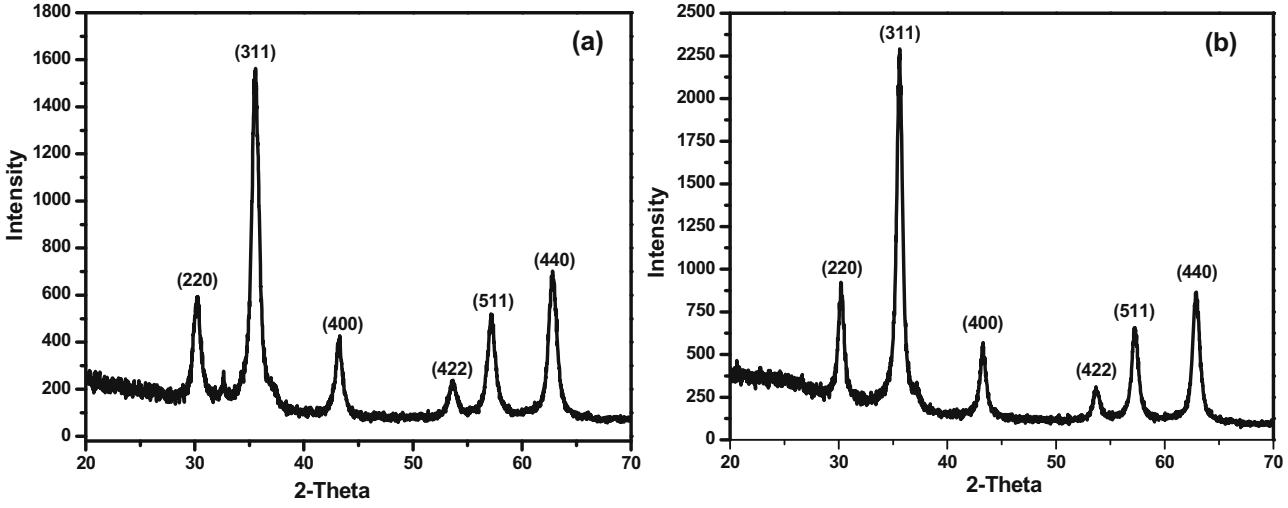

Figure 1: The XRD diffraction patterns of (a) Fe_3O_4 nanoparticles and (b) Fe_3O_4/AC-NH_2 composite.

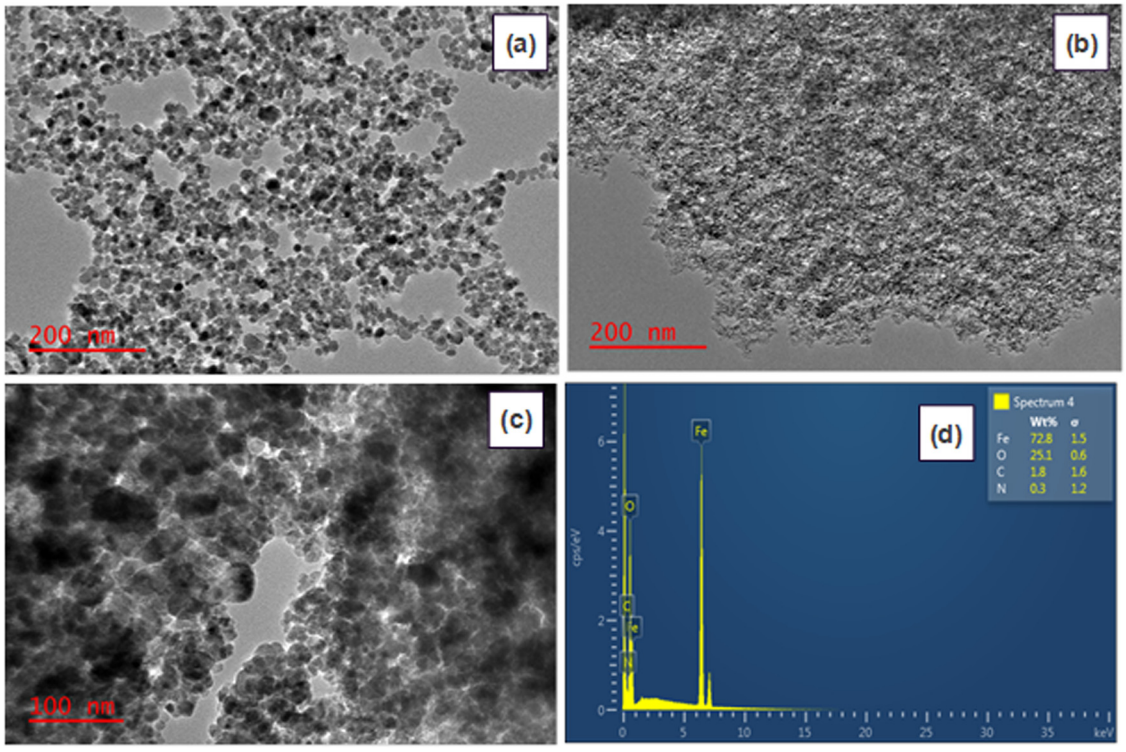

Figure 2: The TEM images of (a) Fe_3O_4 nanoparticles, (b) activated carbon, (c) Fe_3O_4/AC-NH_2 composite and (d) EDS spectra of Fe_3O_4/AC-NH_2.

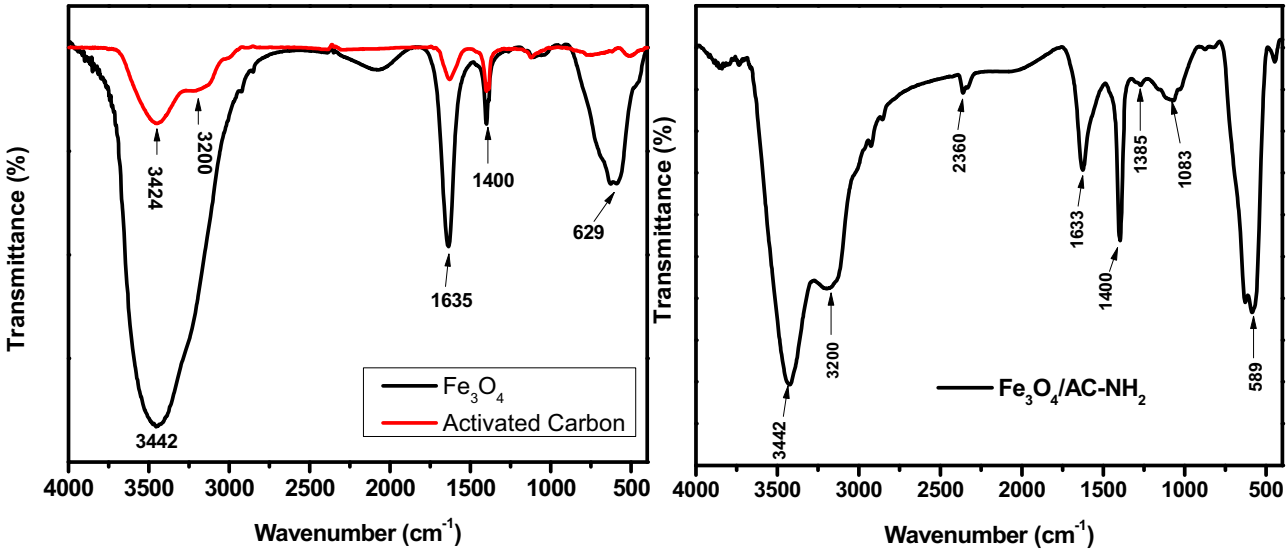

Figure 3: The FTIR of Fe_3O_4, AC and Fe_3O_4/AC-NH_2 composite.

groups, while the adsorption band at 3,200 cm^{-1} reflected the presence of the C–H bond. In addition, the bands at 1,633 and 1,386 cm^{-1} were attributed to the C=O stretching vibrations of carbonyl and carboxyl groups and C=C stretching respectively [45]. The modification of the AC with magnetic nanoparticles was confirmed by the presence of the bands at 583 cm^{-1} which was allocated to the Fe–O stretching vibrations. In addition, the peaks at 2,360 and 1,083 cm^{-1} on the Fe_3O_4/AC-NH_2 were assigned to the C–N vibrations which confirms the successful functionalization of the adsorbent with APTMS.

3.2 Method development and optimization

3.2.1 Choice of adsorbent and choice of elution solvent

The preliminary studies were conducted to select the ideal adsorbent and elution solvent. The selection of the best adsorbent to be used in the study was done by evaluating the affinity of Fe_3O_4, Fe_3O_4/AC and Fe_3O_4/AC-NH_2 towards the target acidic drugs. Figure 4 shows the extraction efficiencies obtained with Fe_3O_4, Fe_3O_4/AC and Fe_3O_4/AC-NH_2 for all analytes. The % ER obtained by Fe_3O_4/AC-NH_2 are much higher than Fe_3O_4 and Fe_3O_4/AC adsorbents. This could be attributed to the modification of Fe_3O_4/AC with the amine groups which resulted in increased sensitivity and therefore provided a high affinity towards the target analytes. Fe_3O_4/AC-NH_2 was therefore chosen as an absorbent of choice for further studies. The preliminary experiments indicated that between methanol, acidified methanol, acetonitrile and acidified acetonitrile, the use of acidified methanol as elution solvent resulted in better recoveries and acidified methanol was therefore used in subsequent analysis.

3.2.2 Optimization of the preconcentration procedure

The evaluation of the parameters, which could significantly affect the extraction and preconcentration of KET, NAP and DIC from aqueous solution, was achieved by using the CCD, a response surface methodology. Parameters, such as MAs, sample pH and % IS, were evaluated. The three factors were each studied at three levels (minimum, central point and maximum) and a total of 16 experimental run were conducted. The matrix and analytical response obtained from these experiments are presented in Table 2.

The analysis of variance was used to evaluate the significance of the main parameters and their interactions at 95% confidence limit and the data were presented as Pareto charts (Figures 5) and 3D response surface plots (Figure 6). The reference line in the Pareto chart is helpful in the comparison of the relative importance of the parameter and the interactions between the parameters. The length of each bar in the Pareto chart is proportional to the relative effect of the corresponding parameter and the bar that crosses the reference line is considered to be statistically significant at 95% confidence level. Furthermore, the positive and negative values at the end of the bars indicate whether the analytical responses increase or decrease, respectively, when moving from the low to high level of the corresponding parameter. According to the Pareto chart (Figure 5), IS was statistically significant for both NAP and DIC. Even though IS was not significant for KET, it exerted a positive effect on all target analytes. IS can affect the extraction recoveries, either by the "salting out" effect or by the "salting in" effect. The effect of IS on the preconcentration of KET, NAP and DIC was studied ranging from 0 to 22% and it was observed from the 3D response plots in Figure 6(a and c) that the highest

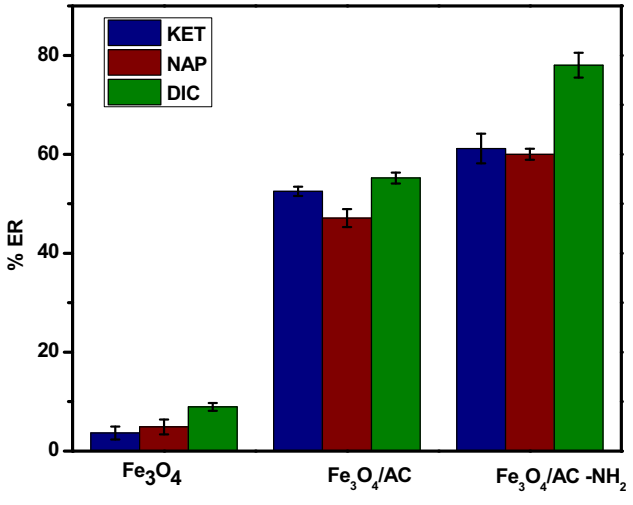

Figure 4: Affinity of the adsorbents towards KET, NAP and DIC. Parameters used were: sample pH: 6.5, adsorbent mass: 20 mg, desorption time: 5 min, extraction time: 10 min and desorption volume: 2 mL.

Table 2: The experimental design and the percentage extraction recoveries (% ER) of the UA-MSPME method of optimization

Experimental run	pH	% IS	MA (mg)	KET	NAP	DIC
1	4	0	10	72.7	63.7	70.0
2	4	0	40	65.5	53.1	50.4
3	4	20	10	77.0	72.0	100.2
4	4	20	40	75.2	68.7	84.7
5	9	0	10	62.5	59.5	65.0
6	9	0	40	61.5	49.3	41.9
7	9	20	10	69.1	67.8	72.8
8	9	20	40	68.6	59.5	57.6
9	3	10	25	72.5	65.3	69.4
10	10	10	25	65.5	62.5	62.9
11	7	−3	25	65.3	58.4	47.4
12	7	23	25	68.9	64.9	65.8
13	7	10	6	49.8	53.3	56.5
14	7	10	44	70.9	63.0	58.3
15 (C)	7	10	25	76.2	70.3	68.4
16 (C)	7	10	25	73.8	68.3	65.2

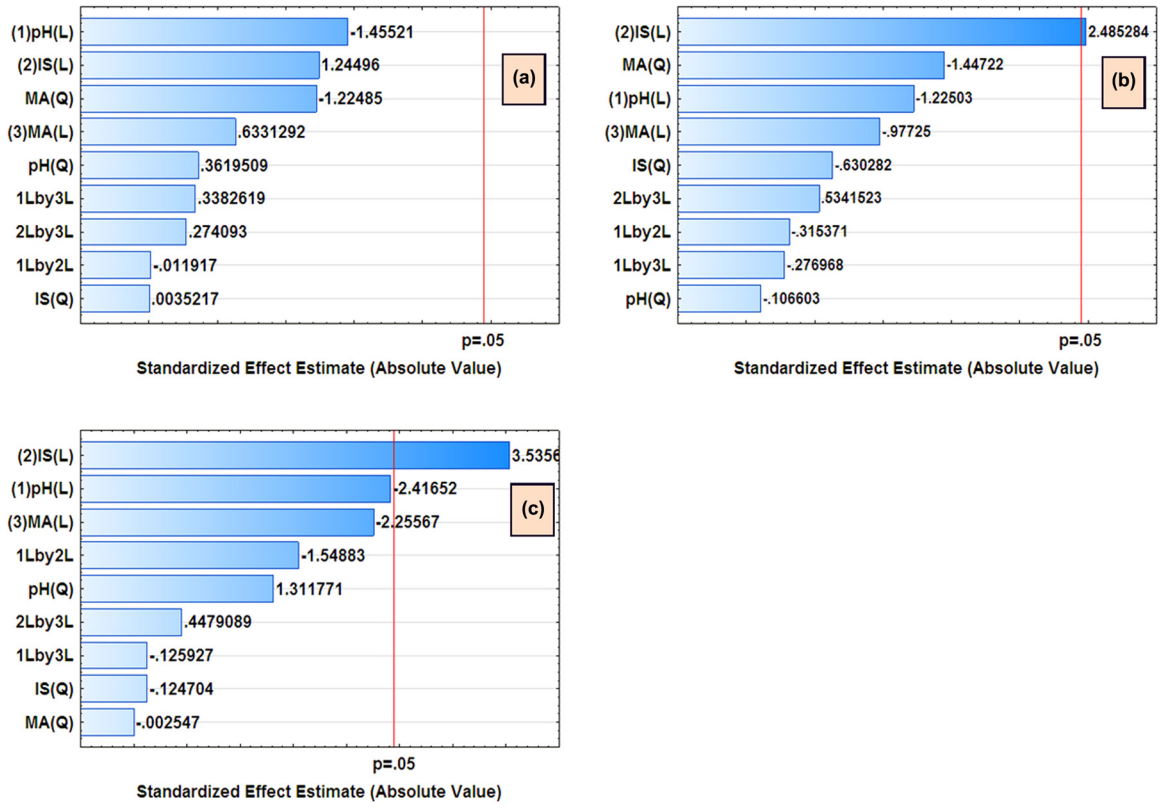

Figure 5: Pareto chart of the standardized effects of the factors for the extraction and preconcentration of: (a) KET; (b) NAP and (c) DIC. IS = % ionic strength, MA = mass of adsorbent and pH of sample.

extraction efficiencies were achieved at high salt content, >20%. This means, in the presence of salt, the target analytes became less soluble in aqueous solution (salting out effect) and can easily be adsorbed by the adsorbent [50].

Furthermore, the effects of the interaction of adsorbent mass and pH of the sample on the preconcentration of the NSAIDs were investigated between 4–44 mg and 3.28–9.72, respectively. Figure 6(b) indicates that the extraction recoveries of the studied NSAIDs increased when pH was below 5 while the adsorbent mass was between 15 and 40 mg. Considering that the target analytes are acidic, with pK_a values of <5 [51], it is understandable that the highest extraction efficiencies are obtained at lower pH. Because at pH ≤ pK_a, the target analytes appear in their unionized forms and are easier to extract as compared to pH higher than the pK_a values where KET, NAP and DIC are ionized. On the other hand, the highest extraction recoveries observed at lower masses could be ascribed to the high surface area of the adsorbent, which provided adequate binding sites for the target analytes. The optimum conditions for the extraction of the NSAIDs from the optimization model for pH, MA and % IS were 4.5, 20 mg and 23%, respectively, and these were then used for further analysis.

3.3 Evaluation of the developed UA-MSPME performance

Under optimum conditions, the analytical figures of merit, such as limit of detection (LOD), limit of quantitation (LOQ), linearity, precision and repeatability for the developed method, were evaluated and are presented in Table 3. The linearity of the method was evaluated by preparing eight standard solutions in water and extracted with the developed method. The calibration curve method for each analyte was constructed by plotting the peak areas (y-axis) against the concentration (x-axis) acquired using the HPLC-DAD. For each standard, three replicates were performed. The developed method displayed a relatively wide linearity for the studied analytes ranging from 1.3 to 850 µg/L. The LODs were defined as three times the standard deviation of the lowest concentration signal divided by the slope of the

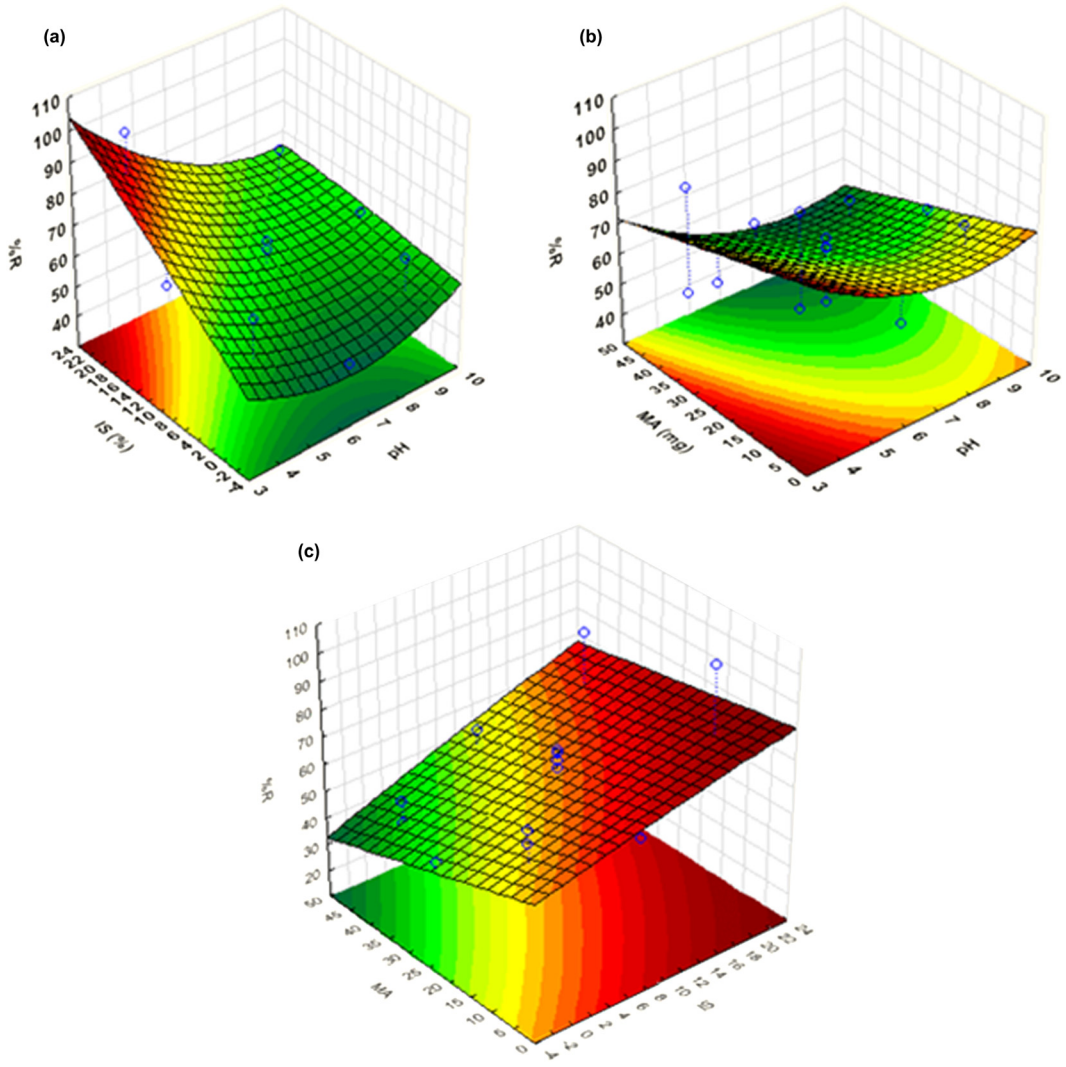

Figure 6: The 3D response surface plots describing the effects of the interactions between (a) ionic strength and pH, (b) mass of adsorbent and pH, and (c) mass of adsorbent and ionic strength on the extraction of the target analytes.

Table 3: Analytical figures for the analysis of NSAIDs using the proposed UA-MSPME procedure

Analyte	Linear range (µg/L)	R^2	Regression equation	LOD (µg/L)	LOQ (µg/L)	Intra-day % RSD	Inter-day % RSD
KET	LOQ – 750	0.9954	$Y = 0.1382x + 0.609$	0.38	1.3	2.0	2.8
NAP	LOQ – 800	0.9951	$Y = 0.0734x + 0.083$	0.60	2.0	2.1	2.7
DIC	LOQ – 850	0.9964	$Y = 0.2158x - 2.965$	0.76	2.5	4.1	3.3

calibration (3 sd/m). While the LOQs were expressed as 10 times the standard deviation (sd) of the signal-to-noise ratio divided by the slope (m) of the calibration (10 sd/m). The LODs and LOQs were found to be 0.38–0.76 and 1.3–2.5 µg/L, respectively. The repeatability (intra-day precision) expressed as the percentage relative standard deviation (% RSD) of the method was evaluated by five successive replicates of 10 µg/L and was found to range from 2.02 to 4.06%. Whereas, the reproducibility of the method evaluated by analysing 10 µg/L standard over 5 working days ranged from 2.8 to 3.3%.

In the absence of certified reference materials for the NSAIDs in water, the trueness of the developed method was evaluated by the spike recovery approach. Water samples were spiked at two levels, the low (30 µg/L) and

Table 4: Relative recoveries and spiked levels obtained from the spike recovery test.

Analyte	Spiked level (µg/L) $n = 3$	% RSD	% R	% Relative bias
KET	30	2.5	94.5	−5.5
	50	3.3	89.4	−10.6
NAP	30	3.9	110.0	10.0
	50	5.3	107.0	7.0
DIC	30	4.1	88.9	−11.1
	50	86.4		3.1

Table 5: Results of the determination of target analytes using the proposed method

Sample	KET Found (µg/L)	NAP	DIC
Influent	159	<LOQ	<LOQ
Effluent	91.1	<LOQ	<LOQ
River	23.8	<LOQ	<LOQ

the high (50 µg/L), and samples were analysed in triplicate. The percentage relative recoveries ranged from 86.4 to 110%. The trueness of the method is demonstrated by the low % RSDs that ranged between 2.5 and 5.3% and % relative bias ranging from −11.1 to 10.0%, as presented in Table 4. The low % RSD and good recoveries showed that the developed method was reliable for the analysis of NSAIDs in different water matrices.

3.4 Analysis of real water samples

The proposed analytical method was used for the extraction of three NSAIDs (KET, NAP and DIC) in river and wastewater and the results are presented in Table 5. Among the three target analytes, only KET was found in river water, effluent and influent. The presence of KET in real water samples could signify the incomplete removal of NSAIDs by the WWTPs which could eventually pose adverse effects to living organisms.

3.5 Comparison of the proposed method to literature

Some related results for the comparison of the analytical performance between the Fe_3O_4/AC-NH_2 nanocomposite and reported methods in the literature [1,5,26,50,52–54] for the extraction of NSAIDs in various matrices are presented in Table 6. The results indicated that the current Fe_3O_4/AC-NH_2-based MSPE method was comparable or displayed a better performance, compared to some of the reported extraction methods in terms of RSDs, linearity and LODs. The analytical figures of merit, accompanied with the low cost and ease of synthesis of the adsorbent, indicated that the developed method was simple, sensitive and efficient for the determination of NSAIDs in environmental water samples.

4 Conclusion

The amine-functionalized magnetic AC was successfully synthesized and applied as an adsorbent in the MSPME method for the extraction and enrichment of acidic drugs (KET, NAP and DIC) in environmental water samples. The prepared amine-functionalized Fe_3O_4@AC nanocomposite had many advantages such as low cost and simple preparation method and high extraction efficiency for simultaneous extraction of NSAIDs. Satisfactory analytical performance of the method was

Table 6: Comparison of the developed method with reported

Analytical method	Matrix	Analyte	Linearity (µg/L)	LOD (µg/L)	% RSD	Ref.
D-µSPE-HPLC-UV	River, lake, tap and wastewater	DIC, KET	0.5–1,000	0.24–0.45	1.1–4.5	[1]
SB-SPE-HPLC-MS/MS	Water	KET, NAP, DIC	0.1–10	0.019–0.035	0.5–1.9	[52]
MEPS-HPLC-PDA	Human plasma, urine	KET	100–10,000	30	≤7.3	[26]
MSPE-LC-DAD	Water, urine	DIC, KET	3.3–400	1.0–2.0	2.0–5.0	[5]
MSPE-HPLC-UV	Urine, serum, river water	KET, NAP, DIC	1.0–1,200	0.2–0.4	2.0–4.0	[53]
SBSE-HPLC-UV	River water, sediments	NAP, KET	2.0–1,000	0.35–0.38	11.0–11.8	[50]
SBSE-HPLC-UV	Sewage and lake water	NAP, KET	20–2,000	6.90–7.69	4.9–9.2	[54]
MSPE-HPLC-DAD	Wastewater, River water	KET, NAP, DIC	1.3–850	0.38–0.76	2.0–4.1	This work

achieved under optimum conditions. The presence of KET in river water may indicate that the WWTPs do not efficiently remove these organic pollutants before discharging the water into the environment. This could negatively affect aquatic and terrestrial organisms. It would be interesting to study the distribution of NSAIDs in river water over a period of time.

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