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-aminooethyl-amino)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 µg 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

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 µg 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,
rpacity, 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]
imodified 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. MSPE
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 environ-
mental samples. Both univariate and multivariate de-
signs 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, acetoni-trile
(HPLC grade), ammonium hydroxide solution (30%),
ferric chloride hexahydrate (FeCl3·6H2O), acetic acid
(99.7%) and ferrous chloride tetrahydrate (FeCl2·4H2O)
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\(^{\circledast}\)
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 (Fe₃O₄/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 FeCl₃·6H₂O (2 mol) and FeCl₂·4H₂O (1 mol). The mixture was vigorously stirred using a magnetic stirrer under nitrogen at 90°C. Thereafter, 30 mL of ammonia (NH₃) solution was quickly added into the above suspension and left to stir for 1 h before it was cooled to room temperature. The synthesized Fe₃O₄/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 Fe₃O₄/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 Fe₃O₄/AC-NH₂.

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
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 Fe₃O₄ nanoparticles and Fe₃O₄/AC-NH₂ nanocomposite are displayed in Figure 1. According to Figure 1(a), the characteristic peaks of the Fe₃O₄ 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 Fe₃O₄ nanoparticles on the nanocomposites are the same as those of the pure Fe₃O₄ nanoparticles, indicating that depositing Fe₃O₄ nanoparticles on the AC and functionalization thereof, had no effect on the Fe₃O₄ 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) Fe₃O₄ nanoparticles, (b) AC, (c) Fe₃O₄/AC-NH₂ composite and (d) EDS spectrum of the Fe₃O₄/AC-NH₂ composite. Figure 2(a) shows a highly uniform pattern of the Fe₃O₄ nanoparticles. The morphologies of the Fe₃O₄/AC-NH₂ 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 Fe₃O₄ nanoparticles. The TEM image confirms the successful modification of AC with Fe₃O₄ nanoparticles. The elemental composition of the composite was confirmed by SEM-EDS. The EDS spectrum of the Fe₃O₄/AC-NH₂ 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 Fe₃O₄, Fe₃O₄/AC and amine-functionalized Fe₃O₄/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

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**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              |

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**Figure 1:** The XRD diffraction patterns of (a) Fe₃O₄ nanoparticles and (b) Fe₃O₄/AC-NH₂ 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$_3$O$_4$/AC-NH$_2$ were assigned to the C–N vibrations which confirms the successful functionalization of the adsorbent with APTMS.

Figure 2: The TEM images of (a) Fe$_3$O$_4$ nanoparticles, (b) activated carbon, (c) Fe$_3$O$_4$/AC-NH$_2$ composite and (d) EDS spectra of Fe$_3$O$_4$/AC-NH$_2$.

Figure 3: The FTIR of Fe$_3$O$_4$, AC and Fe$_3$O$_4$/AC-NH$_2$ composite.
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 Fe₃O₄, Fe₃O₄/AC and Fe₃O₄/AC-NH₂ towards the target acidic drugs. Figure 4 shows the extraction efficiencies obtained with Fe₃O₄, Fe₃O₄/AC and Fe₃O₄/AC-NH₂ for all analytes. The % ER obtained by Fe₃O₄/AC-NH₂ are much higher than Fe₃O₄ and Fe₃O₄/AC adsorbents. This could be attributed to the modification of Fe₃O₄/AC with the amine groups which resulted in increased sensitivity and therefore provided a high affinity towards the target analytes. Fe₃O₄/AC-NH₂ 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

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   | 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 |
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<sub>a</sub> values of <5 [51], it is understandable that the highest extraction efficiencies are obtained at lower pH. Because at pH ≤ pK<sub>a</sub>, the target analytes appear in their unionized forms and are easier to extract as compared to pH higher than the pK<sub>a</sub> 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
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 3: Analytical figures for the analysis of NSAIDs using the proposed UA-MSPME procedure

| Analyte | Linear range (µg/L) | R² | 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            |

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.
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 Fe₃O₄/AC-NH₂ 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 Fe₃O₄/AC-NH₂-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 MSPMME method for the extraction and enrichment of acidic drugs (KET, NAP and DIC) in environmental water samples. The prepared amine-functionalized Fe₃O₄@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

### Appendix: Table 6

| 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] |
| SSBSE-HPLC-UV         | River water, sediments        | NAP, KET | 2.0–1,000       | 0.35–0.38  | 11.0–11.8 | [50] |
| SSBSE-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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**Authors’ contributions:** MNA: execution of all laboratory experiments, except synthesis of AC, synthesized by MKD. MNA and PNN: data analysis. MNA: data interpretation and writing of the manuscript. PNN: conceptualization of the research project. The manuscript was thoroughly reviewed by all authors before submission.

**References**

1. Wahib SMA, Ibrahim WAN, Sanagi MM, Kamboh MA, Keyon ASA. Magnetic sporopollenin-cyanopropyltriethoxysilane-dispersive micro-solid phase extraction coupled with high performance liquid chromatography for the determination of selected non-steroidal anti-inflammatory drugs in water sample. J Chromatogr A. 2018;1532:50–7.

2. Altman R, Bosch B, Brune K, Patrignani P, Young C. Advances in NSAID development: evolution of diclofenac products using pharmaceutical technology. Drugs. 2015;75(8):859–77.

3. He B, Wang J, Liu J, Hu X. Eco-pharmacovigilance of non-steroidal anti-inflammatory drugs: necessity and opportunities. Chemosphere. 2017;181:178–89.

4. Bottoni P, Caroli S. Presence of residues and metabolites of pharmaceuticals in environmental compartments, food, commodities and workplaces: a review spanning the three-year period 2014–2016. Microchem J. 2018;136:2–24.

5. Baile P, Vidal L, Canals A. A modified zeolite/iron oxide composite as a sorbent for magnetic dispersive solid-phase extraction for the preconcentration of nonsteroidal anti-inflammatory drugs in water and urine samples. J Chromatogr A. 2019;1603:33–43.

6. Lee CH, Shin Y, Nam MW, Jeong KM, Lee J. A new analytical method to determine non-steroidal anti-inflammatory drugs in surface water using in situ derivatization combined with ultrasound-assisted emulsification microextraction followed by gas chromatography – mass spectrometry. Talanta. 2014;129:552–9.

7. Racamonde I, Rodil R, Benito J, José B, Kabir A, Furton KG. Fabric phase sorptive extraction: a new sorptive micro-extraction technique for the determination of non-steroidal anti-inflammatory drugs from environmental water samples. Anal Chim Acta. 2015;865:22–30.

8. Alshana U, Gőger NG, Ertaş N. Dispersive liquid–liquid microextraction combined with field-amplified sample stacking in capillary electrophoresis for the determination of non-steroidal anti-inflammatory drugs in milk and dairy products. Food Chem. 2013;138(2–3):890–7.

9. Ahmad SM, Almeida C, Neng NR, Nogueira JMF. Bar adsorptive microextraction (BAMPE) coated with mixed sorbent phases – enhanced selectivity for the determination of non-steroidal anti-inflammatory drugs in real matrices in combination with capillary electrophoresis. J Chromatogr B. 2016;1008:115–24.

10. Saleh A, Larsson E, Yamini Y, Jönsson JÅ. Hollow-fiber liquid phase microextraction as a preconcentration and clean-up step after pressurized hot water extraction for the determination of non-steroidal anti-inflammatory drugs in sewage sludge. J Chromatogr A. 2011;1218(10):1331–9.

11. Shishov AY, Chislov MV, Nechaeva DV, Moskvin LN, Bulatov AV. A new approach for microextraction of non-steroidal anti-inflammatory drugs from human urine samples based on in situ deep eutectic mixture formation. J Mol Liq. 2018;272:738–45.

12. Ramos-Payan M, Maspoch S, Llobera A. An effective micro-fluidic based liquid-phase microextraction device (µLPEM) for extraction of non-steroidal anti-inflammatory drugs from biological and environmental samples. Anal Chim Acta. 2016;946:56–63.

13. Khedazi T, Daneshfar A. Development of dispersive micro-solid phase extraction based on micro and nano sorbents. Trends Anal Chem. 2017;89:99–118.

14. Dimpe KM, Nomngongo PN. Current sample preparation methodologies for analysis of emerging pollutants in different environmental matrices. Trends Anal Chem. 2016;8:199–207.

15. Wang R, Li W, Chen Z. Solid phase microextraction with poly (deep eutectic solvent) monolithic column online coupled to HPLC for determination of non-steroidal anti-inflammatory drugs. Anal Chim Acta. 2018;1018:111–8.

16. Muzikis L, Tawanda N, Chimuka L. Applications of molecularly imprinted polymers for solid-phase extraction of non-steroidal anti-inflammatory drugs and analgesics from environmental waters and biological samples. J Pharm Biomed Anal. 2018;147:624–33.

17. Asgharinezhad AA, Ebrahimzadeh H. Coextraction of acidic, basic and amphiprotic pollutants using multiwalled carbon nanotubes/magnetite nanoparticles@polypropylene composite. J Chromatogr A. 2015;1412:1–11.

18. Mao X, He M, Chen B, Hu B. Membrane protected C-18 coated stir bar sorptive extraction combined with high performance liquid chromatography-ultraviolet detection for the determination of non-steroidal anti-inflammatory drugs in water samples. J Chromatogr A. 2016;1472:27–34.

19. Racamonde I, Rodil R, Quintana JB, Sieira BJ, Kabir A, Furton KG, et al. Fabric phase sorptive extraction: a new sorptive microextraction technique for the determination of...
non-steroidal anti-inflammatory drugs from environmental water samples. Anal Chim Acta. 2015;865(1):22–30.

[20] Tartaglia A, Kabir A, D’Ambrosio F, Ramundo P, Ulusoy S, Ulusoy H, et al. Fast off-line FPSE-HPLC-PDA determination of six NSAIDs in saliva samples. J Chromatogr B Anal Technol Biomed Life Sci. 2020;1144(122082):1–9.

[21] Tartaglia A, Kabir A, Ulusoy S, Sperandio E, Piccolantonio S, Ulusoy H, et al. FPSE-HPLC-PDA analysis of seven paraben residues in human whole blood, plasma, and urine. J Chromatogr B Anal Technol Biomed Life Sci. 2019;1125(121707):1–10.

[22] Locatelli M, Tartaglia A, D’Ambrosio F, Ramundo P, Ulusoy Hl, Furton KG, et al. Biofluid sampler: a new gateway for mail-in-analysis of whole blood samples. J Chromatogr B Anal Technol Biomed Life Sci. 2020;1143(122055):1–9.

[23] Gülle S, Ulusoy Hl, Kabir A, Tartaglia A, Furton KG, Locatelli M, et al. Application of a fabric phase sorptive extraction-high performance liquid chromatography-photodiode array detection method for the trace determination of methyl paraben, propyl paraben and butyl paraben in cosmetic and environmental samples. Anal Methods. 2019;11:6136–45.

[24] Tartaglia A, Kabir A, Ulusoy S, Ulusoy Hl, Merone GM, Savini F, et al. Novel MIPs-parabens based SPE stationary phases characterization and application. Molecules. 2019;24(18):3334.

[25] Madikizela LM, Tavengwa NT, Chimuka L. Applications of molecularly imprinted polymers for solid-phase extraction of non-steroidal anti-inflammatory drugs and analgesics from environmental waters and biological samples. J Pharm Biomed Anal. 2018;147:624–33.

[26] Locatelli M, Ferrone V, Cifelli R, Carmine R, Carlucci G. Microextraction by packed sorbent and high performance liquid chromatography determination of seven non-steroidal anti-inflammatory drugs in human plasma and urine. J Chromatogr A. 2014;1367:142–51.

[27] D’Archivio AA, Maggi MA, Ruggieri F, Carlucci M, Ferrone V, Carlucci G. Optimisation by response surface methodology of microextraction by packed sorbent of non-steroidal anti-inflammatory drugs and ultra-high performance liquid chromatography analysis of dialyzed samples. J Pharm Biomed Anal. 2016;125:114–21.

[28] Es Z, Esmaili-shahri E. Sol-gel-derived magnetic SiO2/TiO2 nanocomposite reinforced hollow fiber-solid phase microextraction for enrichment of non-steroidal anti-inflammatory drugs from human hair prior to high performance liquid chromatography. J Chromatogr B. 2014;973:142–51.

[29] Bazregar M, Rajabi M, Yamin Y, Asghari A, Hemmati M. Tandem air-agitated liquid-liquid microextraction as an efficient method for determination of acidic drugs in complicated matrices. Anal Chim Acta. 2016;917:44–52.

[30] Liu S, Li S, Yang W, Gu F, Xu H, Wang T. Magnetic nanoparticle of metal-organic framework with core-shell structure as an adsorbent for magnetic solid phase extraction of non-steroidal anti-inflammatory drugs. Talanta. 2019;194:514–21.

[31] Mirzajani R, Kardani F, Ramezani Z. Preparation and characterization of magnetic metal–organic framework nanocomposite as solid-phase microextraction fibers coupled with high-performance liquid chromatography for determination of non-steroidal anti-inflammatory drugs in biological fluids. Microchem J. 2019;144:270–84.

[32] Alinezhad H, Amir A, Tarami M, Maleki B. Magnetic solid-phase extraction of non-steroidal anti-inflammatory drugs from environmental water samples using polyamidoamine dendrimer functionalized with magnetite nanoparticles as a sorbent. Talanta. 2018;183:149–57.

[33] Qin S, Fan Y, Mou X, Li X, Qi S. Preparation of phenyl-modified magnetic silica as a selective magnetic solid-phase extraction adsorbent for polycyclic aromatic hydrocarbons in soils. J Chromatogr A. 2018;1568:29–37.

[34] Liu L, Lv J, Wang X, Lou D. Magnetic solid – phase extraction of tetracyclines using ferrous oxide coated magnetic silica microspheres from water samples. J Chromatogr A. 2018;1534:1–9.

[35] Gaffar A, Al Kahlawy AA, Aman D. Magnetic zeolite-natural polymer composite for adsorption of chromium(Ⅵ), Egypt. J Pet. 2017;26(4):995–9.

[36] Mthombeni NH, Onyango MS, Aoyi O. Adsorption of hexavalent chromium onto magnetic natural zeolite-polymer composite. J Taiwan Inst Chem Eng. 2015;50:242–51.

[37] Bazregar M, Rajabi M, Yamin Y, Aghnavi-beydokhti S. Centrifugelless dispersive liquid–liquid microextraction based on salting-out phenomenon followed by high performance liquid chromatography for determination of Sudan dyes in different species. Food Chem. 2018;244:1–6.

[38] Liu L, Zhang X, Hao J, Lv J, Wang X, Zhu B. Magnetic solid-phase extraction of fluoroquinolones from water samples using titanium-based metal-organic framework functionalized magnetic microspheres. J Chromatogr A. 2018;1579:1–8.

[39] Li N, Chen J, Shi Y. Magnetic polyethyleneimine functionalized reduced graphene oxide as a novel magnetic sorbent for the separation of polar non-steroidal anti-inflammatory drugs in waters. Talanta. 2019;191:526–34.

[40] Salam MA. Preparation and characterization of chitin/magnetic/multiwalled carbon nanotubes magnetic nanocomposite for toxic hexavalent chromium removal from solution. J Mol Liq. 2017;233:197–202.

[41] Saravanan P, Vinod VTP, Sreedhar B, Sashidhar RB. Gum kondagou modified magnetic nano-adsorbent: an efficient protocol for removal of various toxic metal ions. Mater Sci Eng C. 2012;32(3):581–6.

[42] Dimpe KM, Nompongno PN. A review on the efficacy of the application of myriad carbohydrate materials for the removal of toxic trace elements in the environment. Trends Environ Anal Chem. 2017;16:24–31.

[43] Munonde TS, Masakato NW, Nompongno PN. Preparation of magnetic Fe3O4 nanocomposites modified with MnO2, Al2O3, Au and their application for preconcentration of arsenic in river water sample. J Environ Chem Eng. 2018;6(2):1673–81.

[44] Jain M, Yadav M, Kohout T, Lah tinten M, Kumar V, Sillanpää M. Development of iron oxide/activated carbon nanoparticle composite for the removal of Cr(Ⅵ), Cu(Ⅱ) and Cd(Ⅱ) ions from aqueous solution. Water Resour Ind. 2018;20:54–74.

[45] Dimpe KM, Nompongno PN. Application of activated carbon-decorated polyacrylonitrile nanofibers as an adsorbent in dispersive solid-phase extraction of fluoroquinolones from wastewater. J Pharm Anal. 2019;9(2):117–26.

[46] Pawar RR, Kim ML, Kim JG, Hong SM, Sawant SY. Efficient removal of hazardous lead, cadmium, and arsenic from aqueous environment by iron oxide modified clay-activated carbon composite bead. Appl Clay Sci. 2018;162:339–50.
[47] Arumugam TK, Krishnamoorthy P, Rajagopalan NR, Nanthini S, Vasudevan D. Removal of malachite green from aqueous solutions using a modified chitosan composite. Int J Biol Macromol. 2019;128:655–64.

[48] Keyvani F, Rahpeima S, Javanbakht V. Synthesis of EDTA-modified magnetic activated carbon nanocomposite for removal of permanganate from aqueous solutions. Solid State Sc. 2018;83:31–42.

[49] Liu Y, Chen M, Hao Y. Study on the adsorption of Cu (ii) by EDTA functionalized Fe3O4 magnetic. Chem Eng J. 2013;218:46–54.

[50] Jalilian N, Ebrahimzadeh H, Asgharinezhad AA. Determination of acidic, basic and amphoteric drugs in biological fluids and wastewater after their simultaneous dispersive micro-solid phase extraction using multiwalled carbon nanotubes/magnetite nanoparticles/poly(2-aminopyrimidine) composite. Microchem J. 2018;143:337–49.

[51] Madikizela LM, Chimuka L. Synthesis, adsorption and selectivity studies of a polymer imprinted with naproxen, ibuprofen and diclofenac. J Env Chem Eng. 2016;4(4):4029–37.

[52] Wang Y, Jia M, Wu X, Wang T, Wang J, Hou X. PEG modified column MIL-101 (Cr)/PVA cryogel as a sorbent in stir bar solid phase extraction for determination of non-steroidal anti-inflammatory drugs in water samples. Microchem J. 2019;146:214–9.

[53] Han X, Chen J, Li Z, Qiu H. Combustion fabrication of magnetic porous carbon as a novel magnetic solid-phase extraction adsorbent for the determination of non-steroidal anti-inflammatory drugs. Anal Chim Acta. 2019;1078:78–89.

[54] Hu C, He M, Chen B, Hu B. Simultaneous determination of polar and apolar compounds in environmental samples by a polyaniline/hydroxyl multi-walled carbon nanotubes composite-coated stir bar sorptive extraction coupled with high performance liquid chromatography. J Chromatogr A. 2015;1394:36–45.