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ORIGINAL ARTICLE

Ultrasonic assisted magnetic solid phase extraction based on the use of magnetic waste-tyre derived activated carbon modified with methyltrioctylammonium chloride adsorbent for the preconcentration and analysis of non-steroidal anti-inflammatory drugs in wastewater

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Abstract In this study, a magnetic waste-tyre derived activated carbon modified with methyltrioctylammonium chloride, was successfully synthesized, characterised, and applied for the extraction and preconcentration of four non-steroidal anti-inflammatory drugs in wastewater. The scanning electron microscopy and N_2-adsorption/desorption analysis results confirmed that the synthesized nanocomposite was porous with a large specific surface area of 570 $m^2\ g^{-1}$. The significant factors affecting the Ultrasonic assisted magnetic solid phase extraction method were investigated using univariate approach and response surface methodology. The optimum conditions for the extraction and preconcentration of the target analytes were 0%, 15 min, 6.5 and 30 mg, for ionic strength, extraction time, pH and adsorbent mass respectively. The quantification of the target analytes

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was performed using high performance liquid chromatography equipped with diode array detector. Under optimum conditions, low limits of detection and quantification ranging between 0.054–0.38 µg L^{-1} and 0.18–1.27 µg L^{-1}, respectively, were obtained. A wide linearity (ranging from limit of detection – 500 µg L^{-1} with $R^2 \geq 0.99$) and precision lower than 7%, were achieved. The applicability of proposed method was evaluated for the determination of naproxen, ketoprofen and diclofenac in wastewater.

1. Introduction

Pharmaceutical drugs are an important genre of persistent emerging micropollutants which are continuously discharged into the environment (Gogoi et al., 2018). The global increase in the use of pharmaceuticals has led to the contamination of the environment by xenobiotic compounds with different functionalities physicochemical and biological properties (Fatta-kassinos et al., 2011). Most pharmaceutical drugs are administered orally, and they can either be fully metabolized by the body or remain intact. A mixture of the parent drugs and their metabolites therefore enter the municipal sewage treatment plants through metabolic excretion (Gogoi et al., 2018) and consequently enter the environment. Apart from metabolic excretion, pharmaceuticals also enter the environment through improper discarding of unused and expired drugs, hospital effluents and run-off from agricultural activities (Ribeiro et al., 2015). The environmental fate and biological effectiveness of pharmaceuticals can be projected from their special physicochemical and biological properties. These physicochemical properties include complex chemical structures, polymorphism, ionizability, acidity, hydrophobicity and solubility, amongst others (Fatta-kassinos et al., 2011). Various researchers have reported the occurrence of pharmaceuticals and their metabolites in effluent and influent wastewater (Akawa et al., 2020; Lekota et al., 2019; Mlunguza et al., 2020) and surface water (Mlunguza et al., 2020; Mtolo et al., 2019; Primrose et al., 2019) at ng L^{-1} to µg L^{-1} concentration levels. Since pharmaceutical drugs are intended to target specific metabolic and molecular pathways in humans and animals even at very low concentrations, it is quite reasonable to be concerned about their likelihood to cause adverse ecotoxicological impacts. Some of the main concerns on the existence of pharmaceuticals in the environment are the possible toxicity to sensitive organisms, reproductive impairment, synergetic effects of compound mixtures, increased incidences of cancer, development of antimicrobial resistance and abnormal physiological processes, among others (Bottoni and Caroli, 2018; Gogoi et al., 2018). Monitoring of the existence and fate of pharmaceutical pollutants in the environment is therefore important to protect human and animal health.

Due to the complexity of environmental matrices, as well as the trace concentrations of pharmaceuticals in the environment, a sample preparation is required to clean up the sample and enrich the target analytes before analysis (Gogoi et al., 2018; Rykowska et al., 2018). Therefore, the continuous demand for accurate and precise results of trace concentration of pharmaceuticals in environmental matrices has led to rapid development in areas of sample preparation. Solid phase extraction (SPE, a sorbent-based extraction) method and liquid phase extraction (LPE, a solvent-based extraction method) are two traditional sample preparation methods that were developed for the extraction of trace analytes (Andrade-Eiroa et al., 2016; Płotka-wasylka et al., 2016). However, limitations such as; multistep and time-consuming extraction procedures, use of large amount of sample, toxic organic solvents and synthetic adsorbents and difficult in phase separation, limit the scope of SPE and LLE application (Carasek et al., 2018; Płotka-wasylka et al., 2015).

Recent trends in sample preparation have targeted the miniaturization and modification of the traditional sample preparation methods. This is aimed at making the modifications to be safe, quick, rugged, cheap, easy, and effective. Various microextraction methods such as, dispersive micro-solid phase extraction (Dµ-SPE) (Behbahani, 2021; Behbahani et al., 2018), molecularly imprinted polymer solid phase extraction (MIP-SPE) (Madikizela et al., 2018; Kakavandi et al., 2017), microextraction by packed sorbent (MEPS) (D'Archivio et al., 2016; Locatelli et al., 2014), hollow fiber-solid phase microextraction (Es and Esmaeili-shahri, 2014), dispersive liquid-liquid microextraction (DLLME) (Alshana et al., 2013; Bazregar et al., 2016) and magnetic solid phase extraction (MSPE) (Akawa et al., 2020; Behbahani et al., 2019), have been applied for extraction of analytes from different matrices. Magnetic solid phase extraction (MSPE), as a miniaturized method based on SPE, has shown a wide applicability for the extraction of various classes of pharmaceutical pollutants in environmental samples (Akawa et al., 2020; Baile et al., 2019; Alinezhad et al., 2018; Pérez et al., 2017).

Magnetic nanoparticles are attractive for use as adsorbents in MSPE owing to their exceptional physicochemical properties such as high adsorption capacity towards the target analytes, high dispersibility, large surface area, as well as their excellent superparamagnetic nature and ease synthesis method (Jiang et al., 2019; Li and Shi, 2019). Magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) iron oxide nanoparticles are the most commonly used nanoparticles due to their large surface areas and small sizes (Wierucka and Biziuk, 2014). Nevertheless, the pristine iron oxide nanoparticles tend to aggregate in aqueous solutions, which therefore reduce the surface area, leading to low adsorption capacities. Also, the iron oxide nanoparticles easily oxidize and are not stable in acidic media, which can result in loss of their magnetic properties. Moreover, iron nanoparticles are not selective, and this limits their application in extraction and preconcentration (Jon et al., 2019; N. Li et al., 2018). To overcome these drawbacks, iron oxide nanoparticles are modified and functionalized with specific functional groups and coatings such as metal oxides (Qin et al., 2018), carbonaceous materials (Keramat and Zare-Dorabei, 2017), polymers (Niu et al., 2020), ionic liquids

(Abujaber et al., 2018) and surfactants (Baile et al., 2019). Functionalization and modification of the magnetic nanoparticles does not only improve the durability, but also enhances the selectivity and adsorption properties of the adsorbent (Jon et al., 2019; Vasconcelos and Fernandes, 2017). Additionally, the modification and functionalization offer unlimited possibilities of adsorbents which can be used to extract both inorganic and organic compounds.

In this study, a nanocomposite composed of magnetite (Fe_3O_4) and waste tyre derived activated carbon (WTAC) was synthesized through a co-precipitation method before it was modified with MeTOACl, an ionic liquid (IL). Activated carbon (AC) was chosen because it is economical, is highly porous, has an abundance of functional groups, high catalytic activity and large surface area which are essential properties for efficient adsorption and extraction of various analytes (Akawa et al., 2020; Dimpe and Nomngongo, 2017). Additionally, to achieve a low cost adsorbent, AC from waste tyres was used as a major component of the adsorbent, which in turn reduces the amount of waste tyres in the environment (Dimpe and Nomngongo, 2017). On the other hand, ionic liquids have several unique properties such as viscosity and miscibility with water and organic solvents, as well as good extraction ability for diverse organic compounds and metal ions (Stanisz et al., 2014). Hence, functionalising MWTAC with methyltrioctylammonium chloride is expected to improve its extraction abilities towards the target analytes. The nanocomposite was used as an adsorbent in ultrasonic assisted magnetic solid phase extraction (UA–MSPE) for the extraction and preconcentration of three common NSAIDs in environmental water samples before quantification by HPLC–DAD. To the best of our knowledge, this is the first report of an analytical method where a MWTAC@MeTOACl nanocomposite is used in UA–MSPE to determine NSAIDs in wastewater samples. The experimental parameters were optimized using a central composite design, a response surface methodology (RSM), instead of the traditional 'one at a time' method. Finally, the developed method was validated and applied to analyse the target NSAIDs in real water samples.

2. Experimental

2.1. Reagents and aqueous solutions preparation

Sodium chloride (Merck, > 98), $FeCl_3{\cdot}6H_2O$ (Sigma–Aldrich, > 98%), acetonitrile (Sigma–Aldrich, > 99%), HPLC grade), $FeCl_2{\cdot}4H_2O$ (Sigma–Aldrich, > 98%), methyltrioctylammonium chloride (Aliquat 336, $N_{25}H_{54}ClN$, Sigma–Aldrich, > 99%), NH_4OH (Sigma–Aldrich, 28%), acetic acid (Sigma–Aldrich, > 99%), methanol (Sigma–Aldrich, > 99%. HPLC grade), propanol (Sigma–Aldrich, > 99%), naproxen (NAP, Sigma–Aldrich, > 99%)), diclofenac sodium (DIC, Sigma–Aldrich, > 99%) and ketoprofen (KET, Sigma–Aldrich, > 99%). Methanol was used make up a stock solution containing 1000 mg L^{-1} of NAP, KET and DIC. The stock solution was kept at 4 °C. Ultra-pure water (Direct-Q® 3UV-R purifier system) was used for dilution of working solutions. All samples were filtered using membrane filters (0.22 μm) (Separations Scientific SA (Pty) Ltd) before analysis. **Supplementary Material Table S1** illustrates the chemical structures and properties of the studied pharmaceuticals (Aydin et al., 2019).

2.2. Instrumentation

An HPLC–DAD Agilent 1200 Infinity series (Agilent Technologies, Waldbronn, Germany) was used for chromatographic analysis. An Agilent Zorbax Eclipse Plus C18 column (150 × 4.6 mm, 3.5 μm) (Agilent, Newport, CA, USA) was operated at 25 °C and 1.00 mL min^{-1}. A mobile composed of methanol (70%) and 0.20% acetic acid (30%) was used in an isocratic mode. An X'Pert XRD (PANalytical BV, Netherlands) equipped with a Cu K_α (λ = 0.1540 6 nm) radiation was used to study the crystallinity of MWTAC@MeTOACl. The Fourier Transform Infrared spectrum of MWTAC@MeTOACl was obtained in the infrared region (400–4000 cm^{-1}) by a Shimadzu 8300 (Kyoto, Japan). Furthermore, transmission electron microscopy (TEM, JEM-2100, JEOL, Tokyo, Japan) and scanning electron microscopy (SEM) coupled with energy dispersive x-ray spectroscopy (EDS) (TESCAN VEGA 3 XMU, LMH instrument (Czech Republic)) were used for nanostructure, morphology, and elemental composition analysis. Pore diameter distribution and specific surface area of the adsorbents were measured using a Surface Area and Porosity Analyzer (ASAP2020 V4. 00 H, Micrometrics Instrument Corporation, Norcross, USA) at 77 K after degassed for 10 h at 120 °C.

2.3. Synthesis of the magnetic waste-tyre derived activated carbon (MWTAC) nanocomposite

The waste tyre-derived activated carbon (WTAC) was prepared previously in the research group (Dimpe et al., 2018). The MWTAC was prepared following a modified method reported in literature (Baile et al., 2019). Briefly, activated carbon (AC, 6.00 g), $FeCl_2{\cdot}4H_2O$ (2.85 g) and $FeCl_3{\cdot}6H_2O$ (5.35 g) were dispersed in 250 mL of water and then stirred at 90 °C under inert conditions. Thereafter, 25 mL of NH_3 solution was added and stirring continued for 1 h. An external magnet was used to isolate the MWTAC nanocomposite from the aqueous solution before the nanocomposite was washed thoroughly with deionised water until neutral pH before drying in the oven overnight at 60 °C. Finally, the adsorbent was ground to fine particles. The same procedure was followed for the synthesis of Fe_3O_4 nanoparticles, but in the absence of activated carbon.

2.4. Synthesis of methyltrioctylammonium chloride (MeTOACl) functionalized magnetic waste-tyre derived activated carbon (MWTAC@MeTOACl) nanocomposite

Functionalization of the magnetic activated carbon was done following a modified procedure in the literature (Baile et al., 2019) Briefly, 1.00 g of MWTAC was dispersed in 20 mL ethanol containing 1% MeTOACl by stirring at room temperature for 1 h before drying at 60 °C in the oven. It is important to note that the adsorbent was prepared in triplicate and the preliminary data from adsorption studies indicated that there was no significant difference between the performance of the replicates. A composite of the three was therefore made and which was enough for the whole study.

2.5. Point of zero charge (pH_{pzc}) determination

The pH_{pzc} of adsorbent was determined following a modified method previously reported in the literature (Biata et al., 2018). The pH of 0.01 mol L^{-1} sodium chloride solutions (30 mL) in several Erlenmeyer flasks were adjusted from 2 to 10 using ammonium hydroxide and acetic acid solutions. Thereafter, 0.10 g of adsorbent was added to each flask, dispersed for 48 h and thereafter, the final pHs were measured. The pH_{pzc} was taken from a plot of (pH_f–pH_i) versus pH_i.

2.6. Sample collection

Influent and effluent wastewater samples were collected from a local wastewater treatment plant in pre-cleaned glass bottles and stored in the refrigerator at 4 °C. The samples could reach room temperature before they were put through the UA–MSPE method.

2.7. Preconcentration procedure

Briefly, the UA–MSPE procedure was carried out as follows: 30 mg of MWTAC@MeTOACl nanocomposite was added into glass bottles containing 20 mL of a sample comprising the mixture of three NSAIDs at 100 µg L^{-1} each. The pH of the sample was adjusted using acetic acid and ammonium hydroxide solutions to pH 6.5. The samples were then subjected to ultrasonication for 15 min. An external magnet was used to retrieve the adsorbent from the aqueous solution. The elution of the target compounds from the adsorbent was achieved after sonication for 5 min with 3 mL of acetonitrile acidified with 5% acetic acid. The extractant was separated from the adsorbent by a magnet and filtered with a 0.22 µm membrane filters, before the HPLC–DAD analysis.

2.8. Optimisation strategy

The choice of eluent was optimized using the "one variable at a-time" (OVAT) approach while a multivariate optimisation approach was used to optimize the rest of the parameters which were significant to the developed UA–MSPE. A central composite design (CCD) was used to optimize the method parameters such as ionic strength (IS), mass of adsorbent (MA), sample pH and extraction time (ET) in this study. The percentage extraction recoveries were used as the analytical responses which were evaluated using STATISTICA version 13 software, to determine the optimum conditions.

2.9. Method validation procedure

The proposed UA–MSPE method was validated in terms of the intraday and interday precision (expressed in terms of the relative standard deviation, % RSD), accuracy, linear range, limit of detection (LOD) and limit of quantification (LOQ), following a modified method (Lekota et al., 2020). The intraday ($n = 10$) and interday ($n = 5$ days) precision of the proposed UA–MSPE method were assessed by analysing a solution containing 100 µg L^{-1} of each analyte. The method accuracy was evaluated by a spike recovery approach. A wastewater sample was spiked at three concentration levels (10, 100, 300 µg L^{-1}) and each sample was analysed in triplicate. The method linearity was assessed by spiking a blank wastewater to prepare seven standard solutions containing 0–500 µg L^{-1} of each analyte. The standards were extracted with the developed method and a seven-point calibration curve was constructed. For each standard, three replicates were analysed. The LOD and LOQ were calculated as: LOD = (3 s/m) and LOQ = 10 s/m, where 's' is the standard deviation of peak areas of 10 replicate determinations of the lowest concentration level of the linear range and 'm' is the slope of each calibration curve.

2.10. Adsorption capacity and reusability studies of MWTAC@MeTOACl nanocomposite

The adsorption capacity of the modified sorbent was studied under optimum conditions. To evaluate the adsorption capacity of the adsorbent towards the NSAIDs, 30 mg of the MWTAC@MeTOACl nanocomposite was added to 30 mL of aqueous solution (pH 6.5) containing 100 mg L^{-1} of each analyte. The sample was ultrasonicated for 15 min. The amounts of NSAIDs adsorbed on the adsorbent were calculated as shown in equations (1).

$$q_e = \left(\frac{C_0 - C_e}{M}\right)V \tag{1}$$

Where q_e (mg/g) is the amount of KET, NAP and DIC adsorbed per gram of the sorbent, $C_{o,}$ and C_{enop} (mg/L) are the initial and equilibrium concentration of the bulk solution, V (L) is the volume of the aqueous solution and M (g) is the mass of sorbent. The reusability of the adsorbent was studied following a modified method described in literature (Dimpe and Nomngongo, 2019).

3. Results and discussion

3.1. Characterisation of nanocomposite

The functional groups present on the WTAC and MWTAC@MeTOACl adsorbent were established by the FTIR spectroscopy and the spectra are shown in Supplementary Material Fig. S1 and Fig. 1(a), respectively. The Fe—O stretching vibration peak at 597 cm^{-1} in Fig. 1(a) confirmed the presence of Fe_3O_4 nanoparticles (Kaur et al., 2015). The most common functional groups identified on WTAC and MWTAC@MeTOACl were: —OH, —CH, —C═O, —COO and —C—O. The broad peak at 3438 cm^{-1} was assigned to the stretching vibrations of the O—H groups of adsorbed water, while the C—H bond existence was confirmed by a peak at 3200 cm^{-1}. The weak peaks at 2900 cm^{-1} and 2857 cm^{-1} were ascribed to the CH_2 group symmetric and antisymmetric stretching vibration. The weak peak at 1035 cm^{-1} was ascribed to an overlap of the C—O and C—N stretching vibrations. In addition, the bands at 1623 cm^{-1} and 1386 cm^{-1} were ascribed to the C═O stretching vibrations of carboxyl and carbonyl groups and C═C stretching, respectively (Dimpe et al., 2018; Mohammadi et al., 2020). Moreover, the band at 1386 cm^{-1} could overlap with the C—N group of the methyltrioctylammonium chloride (MeTOACl), which confirmed that MWTAC was successfully functionalized with the ionic liquid. The presence of hydroxy, carbonyl,

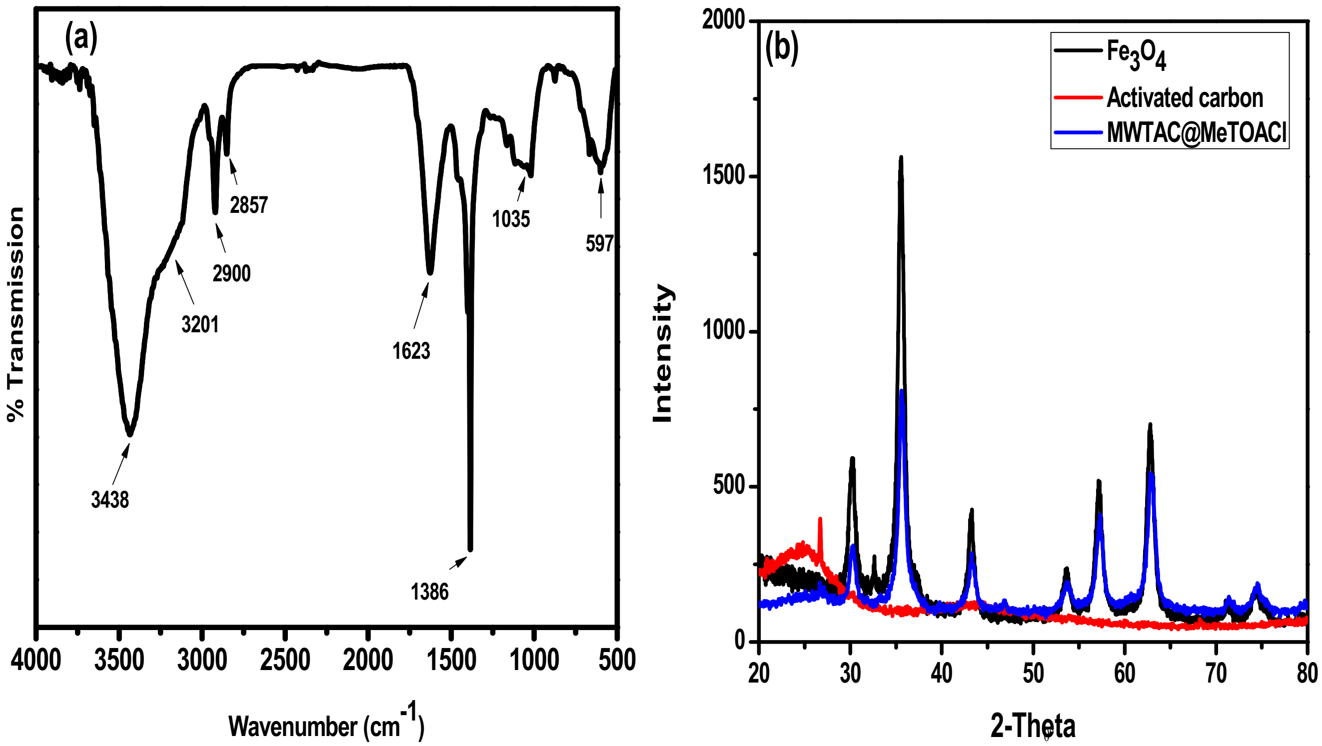

Fig. 1 (a) The FTIR spectrum of MWTAC@MeTOACl and (b) the XRD spectra of WTAC, Fe_3O_4 and MWTAC@MeTOACl nanocomposite.

carboxylic and amine functional groups as well as Fe-O in the adsorbent make it a potential adsorbent for analytes that poses either negative or positive charge. The possible adsorption mechanism might be due to electrostatic interaction, hydrogen bonding and bridging bidentate complexation (between Fe atom of the adsorbent and deprotonated analytes) (Chen and Shi, 2019).

The XRD spectra of the activated carbon, Fe_3O_4 nanoparticles and MWTAC@MeTOACl composite are illustrated in Fig. 1(b). The XRD spectrum of WTAC displayed two broad bands at 25° and 45° which are characteristic peaks for an amorphous structure of WTAC (Akawa et al., 2020; Dimpe et al., 2018). The spectrum for activated carbon was then used as reference to examine the incorporation of Fe_3O_4 nanoparticles on the WTAC surface. The characteristic diffraction peaks are clearly observed in the composite at $2\theta = 30.3°$ (220), 35.4° (311), 43.1° (400), 53.5° (422), 57.2° (511) and 62.8° (440) which correspond to the face-centred cubic structure of Fe_3O_4 nanoparticles (JCPDS no. 00-065-0731) (Munonde et al., 2018). The diffraction peaks of Fe_3O_4 indicated that the Fe_3O_4 nanoparticles retained their nanostructures in the nanocomposite.

Fig. 2(a) and (b) show the SEM images of Fe_3O_4 nanoparticles and MWTAC@MeTOACl nanocomposite, respectively. Fig. 2(a) revealed the cubic structures of Fe_3O_4 nanoparticles despite having different sizes. In addition, the Fe_3O_4 nanoparticles were evenly scattered with minimum agglomeration. The SEM image of the MWTAC@MeTOACl nanocomposite displayed in Fig. 2(b), revealed several cavities, indicating the porous nature of the WTAC, with Fe_3O_4 nanoparticles scattered on the WTAC, surface with minimum agglomeration. Agglomeration diminishes the number active sites and the surface area of the adsorbent which are available for adsorption. Thus, it is expected that the modified nanocomposite will perform optimally. The elemental composition displayed in Fig. 2 (c) determined by SEM-EDS confirmed the presence of C, O, Fe, N and Cl. The presence of N and Cl on the composite confirmed the successful functionalisation of MWTAC with MeTOACl. On the other hand, the TEM images of Fe_3O_4 nanoparticles **in** Fig. 2(e) revealed widely dispersed Fe_3O_4 nanoparticles, with cubic structures. This observation agrees with the XRD results. Fig. 2(f) shows TEM images of the MWTAC@MeTOACl which confirms the presence of Fe_3O_4 - nanoparticles on the surface of the WTAC (Fig. 2(d)). The TEM and SEM micrograms revealed a perfect morphology for the adsorption of the target analytes.

The textural properties of Fe_3O_4 nanoparticles, WTAC and MWTAC@MeTOACl were acquired by N_2 adsorption/desorption isotherms. The specific surface area of AC was 666 $m^2\ g^{-1}$ with an average pore size and pore volume of 4.89 nm and 0.463 $m^3\ g^{-1}$, respectively. The surface area, pore volume and pore diameter of the MWTAC@MeTOACl nanocomposite were 570 $m^2\ g^{-1}$, 0.463 $m^3\ g^{-1}$ and 5.43 nm, respectively. The N_2 adsorption-desorption isotherm curves for MWTAC@MeTOACl nanocomposite shown in **Supplementary Material Fig. S2** exhibited a type IV isotherm with a distinct H3 hysteresis loop which indicated that the MWTAC@MeTOACl nanocomposite was mesoporous (Sing, 1982). The results showed that integrating Fe_3O_4 nanoparticles (65.6 $m^2\ g^{-1}$) on WTAC and functionalization with the ionic liquid thereof, did not significantly change the textural properties of WTAC.

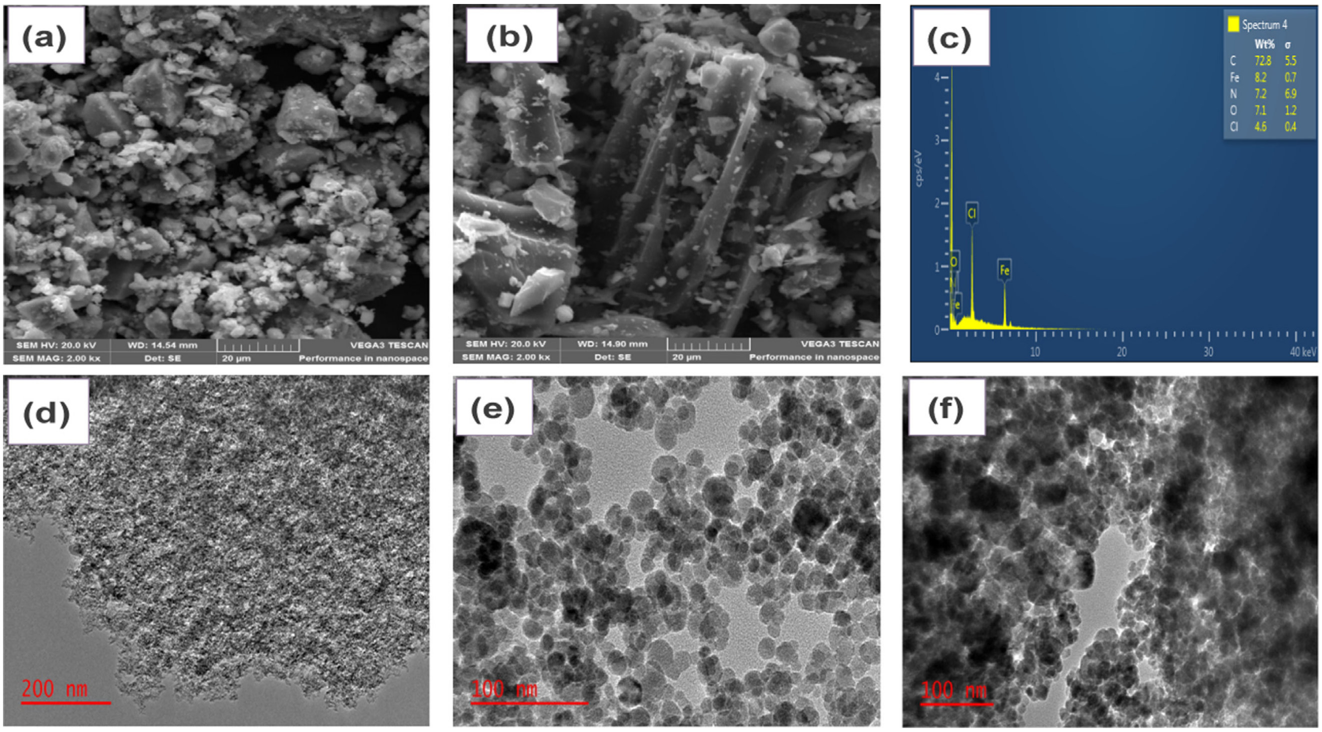

Fig. 2 The SEM micrographs of (a) Fe_3O_4 nanoparticles, (b) MWTAC@MeTOACl and (c) EDS spectrum of the composite and TEM images of (d) WTAC, (e) Fe_3O_4 nanoparticles and (f) MWTAC@MeTOACl nanocomposite.

3.2. Development and optimisation of the method

3.2.1. Preliminary study

3.2.1.1. Choice of adsorbent. Preliminary studies were carried out by subjecting the MWTAC and MWTAC@MeTOACl nanocomposites to the UA–MSPE extraction method to determine their affinity towards target analytes. **Supplementary Material Fig. S2** displays the results of the preliminary study for NAP, KET and DIC. The results obtained by the MWTAC@MeTOACl nanocomposite were much higher than MWTAC adsorbent. This could be attributed to the modification of MWTAC with the ionic liquid which resulted in the ability of the adsorbent to form strong hydrogen bonds, π–π bonds and strong hydrophobic interactions with the target analytes (Baile et al., 2019; Sun et al., 2017). The MWTAC@-MeTOACl nanocomposite was therefore used in subsequent studies.

3.2.1.2. Effect of desorption solvent. The desorption solvent type plays a significant role in the method performance and in this study, the effect of methanol, acetonitrile, and propanol, each acidified with 5% acetic acid, as desorption solvents were studied. Preliminary investigation with pure solvents resulted in low recoveries possibly due to strong bonds formed between the adsorbent and analytes. However, the addition of acetic acid to the solvent improved the extraction efficiencies. The elution results in Fig. 3 demonstrated that the desorption powers of acidified acetonitrile, a more polar aprotic solvent were stronger than that of the acidified less polar protic solvents (methanol and propanol). The use of acidified acetonitrile resulted in the protonation of the analytes and thus causing electrostatic repulsion between a positive adsorbent surface and the analytes. Therefore, acetonitrile containing 5% acetic acid was used in the subsequent analysis.

3.2.2. Central composite design-based optimisation of the UA–MSPE method

In this study, CCD was used to assess the main effects, quadratic effects, and interaction effects of the four selected param-

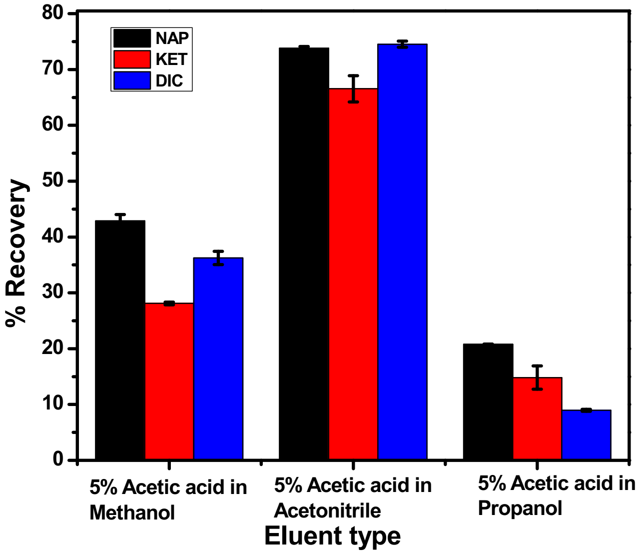

Fig. 3 Effect of type of desorption solvent on the extraction efficiency of the three NSAIDs. Conditions: extraction time: 10 min, desorption time: 5 min, pH of sample: 7, desorption volume: 2 mL and mass of adsorbent: 50 mg.

eters namely, extraction time (ET), ionic strength (IS), pH of the sample and mass of adsorbent (MA) on the % extraction recovery of each analyte. The experimental design matrix and the corresponding analytical responses are shown in **Supplementary material** **Table S2**. The significance of the main parameters and their interactions were assessed by analysis of variance (ANOVA, **Supplementary material** Table S3-5) and the data were presented as Pareto charts which indicate the parameters that are statistically significant at 95% confidence limit. It was observed from **Supplementary material Fig. S3** that the Pareto charts for NAP and DIC revealed similar responses for each parameter studied where the mass of adsorbent (MA) was the only statistically significant parameter at 95% confidence limit. However, the Pareto chart for KET revealed a different response from the others in that ionic strength was significant which may be related to the presence of the ketone functional group on KET structure, which could be shielded by the cations from the electrolyte (Baile et al., 2019; Rizzi et al., 2019). Both significant parameters showed a negative impact on the analytical responses of each analyte. It can therefore it can be concluded that increasing the ionic strength and mass of adsorbent will result in lower extraction recoveries of analytes (Rizzi et al., 2019).

In order to determine the optimum conditions for the simultaneous extraction of the selected NSAIDS, the relationship between the response and independent parameters were correlated and presented as 3-dimensional (3D) response surface plots (Fig. 4). The effect of each independent parameter on the extraction recoveries as well as the simultaneous effects of all main parameters on the extraction recoveries can be observed from the 3D plots. The effects of the sample pH with other parameters, alongside the corresponding extraction percentages of NSAIDs are presented in Fig. 4 **(a-c).** From these plots, it is evident that extraction efficiency increased when sample pH ranged from 5 to 6.5. The point of zero charge (pH_{pzc}) of the composite was found to be 6.7 suggesting that below pH_{pzc} the surface is positive while above this pH_{pzc} the surface is negative (Biata et al., 2018). Therefore, recoveries were obtained when the pH of the solution was greater than pKa values but less than pH_{pzc} value. The effect of MA was studied in the range 12.8 mg to 54.2 mg and the 3-D plots in Fig. 4 **(a, d, f)** indicated that the recoveries improved with increasing adsorbent mass. This observation can be attributed to the increase in surface area and available functional groups which acted as binding sites for the target analytes (Ahmed, 2017). Furthermore, the effect of salt addition (NaCl) or ionic strength was also studied, however it was found that the IS has a negative effect on the analytical responses. This could be because the density and viscosity of the aqueous sample increased as the salt concentration increased, which hindered the molecular mass transfer of the target analytes to the adsorbent (Liu et al., 2019). Moreover, binding sites would be surrounded by the opposite charges from the dissociation of salt resulting in inadequate contact of the analytes with the adsorbent and therefore leading to lower extraction recoveries (Liu et al., 2019). No salt was therefore used in this study.

Additionally, the desirability function (df) was used to determine the optimum conditions for the preconcentration of the NSAIDs. According to the desirability function (**See Supplementary Material Fig. S5**), the optimum conditions for the simultaneous extraction and preconcentration of DIC, NAP and KET for IS, ET, pH and MA were 0%, 15 min, 6.5 and 30 mg, respectively. The model was experimentally confirmed using the obtained optimum conditions which

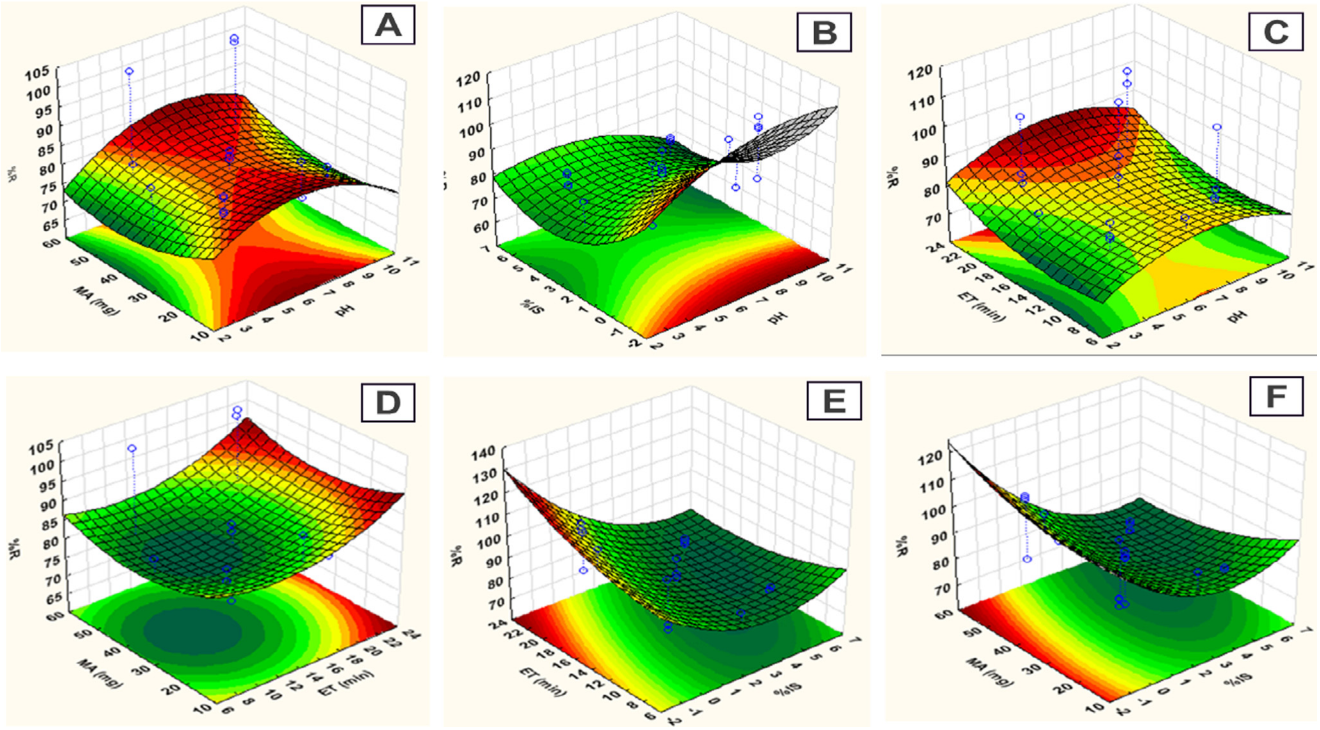

Fig. 4 The 3D response surface plots of the extraction of NSAIDs). (MA = mass of adsorbent, IS = % ionic strength, ET = extraction time, pH of sample).

resulted in satisfactory extraction recoveries of 93.3%, 82.1% and 94.1% for KET, NAP and DIC, respectively, which proved that the model was valid. These optimum conditions were then used in further analysis.

3.2.3. Analytical performance of the method

Method validation is very imperative for establishing its analytical performance. The analytical figures of merit of the proposed UA–MSPE method obtained under the optimal experimental conditions are shown in Table 1. A wide linear dynamic range (LOQ–500), with the coefficient of determination (r^2) greater than 0.992 was obtained for KET, NAP and DIC. The repeatability and reproducibility of the method expressed as relative standard deviation (% RSD) were 3.8–6.3% and 4.9–8.3%, respectively. Low % RSDs indicated the high precision of the method for the preconcentration of KET, NAP and DIC. Low LODs and LOQs of the method were 0.054–0.38 μg L^{-1} and 0.18–1.3 μg L^{-1}, respectively, which indicated a sensitive method. The analytical figures of merit indicated that the developed method was simple, efficient, and sensitive for the extraction of DIC, KET and NAP in wastewater samples can be used for the detection and quantitative analysis of NSAIDs.

The spike recovery method was used to measure the accuracy of the developed method. Wastewater (influent and effluent) samples were spiked at three levels, (10, 100 and 300 μg L^{-1}), with each sample analysed in triplicate. The percentage relative recoveries (% RR) (Table 2) obtained in the range of 82.3–98.2%. These recoveries indicated that the matrix effects did not affect the performance of the developed UA–MSPE method and that the method is suitable for the extraction and preconcentration of the target analytes.

Table 3 Concentrations (in μg L^{-1}) of NSAIDs in effluent and influent wastewater samples obtained using UA–MSPE method.

Samples	KET	NAP	DIC
Effluent	12.1 ± 0.2	7.50 ± 1.0	9.68 ± 0.8
Influent	19.3 ± 0.5	18.6 ± 0.6	20.4 ± 0.3

3.2.4. Validation and application of the method

As shown in Table 3, naproxen, ketoprofen and diclofenac were detected in both effluent and influent samples at 7.50–12.05 μg L^{-1} and 18.6–20.4 μg L^{-1}, respectively. A similar study on the preconcentration of naproxen, ketoprofen and diclofenac in wastewater and river water revealed the presence of ketoprofen at concentrations ranging from 23 to 159 μg L^{-1} in the same wastewater treatment plant (Akawa et al., 2020). The difference in the occurrence of these analytes could be attributed to seasonal changes and flow conditions. The findings of the two studies indicating the presence of NSAIDs in effluents may indicate the inefficiencies of the WWTP to effectively remove the pollutants before discharging not the environment. The concentrations of NSAIDs obtained in the current study were compared with global concentrations (Table 4). The concentrations found in this study were comparable with reported results from samples collected from different parts of South Africa but were higher than the other parts of the world. The relatively high levels of NSAIDs concentrations in environmental water systems in South Africa and other developing countries could be credited to the availability of conventional/traditional wastewater treatment plant technologies which may not be able efficiently remove or degrade micropollutants such as NSAIDs (Awad et al., 2019).

Table 1 UA–MSPE method analytical figures of merit.

Parameters	KET	NAP	DIC
Linear range (μg L^{-1})	1.3–500	0.18–500	0.80–500
Regression line	$y = 0.196(\pm 0.002)x - 0.45(\pm 0.005)$	$y = 0.841(\pm 0.009)x - 5.57(\pm 0.09)$	$y = 0.103(\pm 0.001)x - 1.28\ (\pm 0.08)$
R^2	0.9955	0.9976	0.9926
LOD (μg L^{-1})	0.38	0.054	0.24
LOQ (μg L^{-1})	1.3	0.18	0.80
Intraday (% RSD, n = 10)	4.5	3.2	4.0
Interday(% RSD, n = 5 days)	5.2	4.4	6.7

Table 2 Analysis of effluent and influent wastewater samples with % RSD in parentheses.

Sample	**Added μg L^{-1}**	**% RR[a]** **KET**	**% RR** **NAP**	**% RR** **DIC**
Effluent	10	92.2 (4)	86.0 (8)	98.0 (6)
	100	89.1 (3)	82.3 (3)	91.1 (5)
	300	96.0 (1)	83.0 (3)	86.1 (3)
Influent	10	88.1 (6)	91.1 (10)	98.2 (3)
	100	88.0 (4)	90.7 (3)	87.6 (9)
	300	98.1 (4)	88.2 (6)	87.6 (9)

[a] Relative recovery.

Table 4 Global concentrations (μg L^{-1}) of NSAIDs in effluent wastewater.

Study site	**Maximum concentration detected (μg L^{-1})**			**Ref**
	KET	**NAP**	**DIC**	
China	3.18	0.92	–	(Guan et al., 2016)
Iran	–	–	27.3	(Rezaei et al., 2013)
South Africa	5.34	–	20.8	(Madikizela and Chimuka, 2016)
China	0.0094	0.0012	0.026	(Ashfaq et al., 2017)
South Africa	3.50	–	–	(Zunngu et al., 2017)
Turkey	0.46	5.61	0.47	(Aydin et al., 2019)
Chile	2.30	1.44	1.30	(Manzo et al., 2014)
Spain	0.38	0.11	0.45	(Racamonde et al., 2015)
South Africa	12.1	7.50	9.68	This study

Table 5 Comparison of proposed UA–MSPE method with reported studies for the extraction of NSAIDs in environmental samples.

Analytes	Matrix	Extraction type	Detection technique	LOD (μg L^{-1})	% RSD	Recovery (%)	Ref
KET, NAP, DIC	River, tap water, hospital wastewater	SPE[a]	UHPLC–UV	0.13–0.38	0.3–9.4	89.4–98.7	(W. Li et al., 2018)
KET, NAP, DIC	River & Tap water	IL–DLLME[b]	HPLC–UV/FP	17–95	2.0–3.0	90–103	(Toledo-Neira and Álvarez-Lueje, 2015)
KET, DIC, NAP	Hospital wastewater, river water, sewage treatment plant	SPE[c]	GC–MS	0.004–0.02	0.9–3.4	90.6–95.8	(Mohiuddin et al., 2021)
KET, NAP, DIC	Water	SB–SPE[d]	HPLC–MS/MS	0.019–0.035	0.5–1.9	77.4–102.3	(Wang et al., 2019)
KET, NAP, DIC	Urine, Serum, River water	MSPE[e]	HPLC–UV	0.2–0.4	2.0–4.0	84.7–113.7	(Han et al., 2019)
KET, NAP, DIC	River water, tap water	DLLME[f]	LC–MS	0.1–3.0	5.0–9.0	73–80	(Zgola-Grzeskowiak, 2010)
KET, NAP, DIC	River water, effluent and influent wastewater	MSPE[g]	HPLC–DAD	0.38–0.76	2.0–4.1	86–110	(Akawa et al., 2020)
KET, NAP, DIC	Wastewater	MSPE[h]	HPLC–DAD	0.05–0.38	4.4–6.7	82–98	This study

SPE[a]: Self-assembling covalent organic framework functionalized poly (styrene-divinyl benzene-glycidylmethacrylate); IL–DLLME[b]: (1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF6]); SPE[c]: Starch-Mg/Al layered double hydroxide; SB–SPE[d]: PEG modified column MIL-101(Cr)/PVA cryogel; MSPE[e]: magnetic porous carbon; DLLME[f]: Chloroform; MSPE[g]: Fe_3O_4/AC-NH_2, MSPE[h]: MWTAC@MeTOACl.

A comparative study between the current and previously developed sample preparation methods for the extraction and determination of diclofenac, naproxen and ketoprofen in environmental samples was done to comprehensively assess the performance of the developed method. Table 5 shows that the analytical performance (LOD, % RSD and % RR) of the UA–MSPE method is generally similar to the other methods reported in literature. These results confirmed that the UA–MSPE method based on the use of MWTAC@MeTOACl nanocomposite is a reliable and efficient technique for extracting and preconcentrating NSAIDs in environmental water samples.

3.3. Adsorption capacity, mechanisms, and adsorbent reusability studies

The ability of the MWTAC@MeTOACl nanocomposite to adsorb KET, NAP and DIC was evaluated in this study. The calculated adsorption capacities of the adsorbent were 45.3, 56.4 and 54.0 mg g^{-1} for DIC, NAP and KET, respectively. Other researchers reported similar results using activated carbon adsorbents, derived from various sources (Ahmed, 2017). The adsorption mechanisms between the adsorbent and adsorbates are described below. Several mechanisms between the adsorbent and the target analytes are expected. The first adsorption mechanism involved the electrostatic interactions between the positively charged MeTOACl and the negatively charged NSAID molecules (Baile et al., 2019). This is a pH dependant mechanism, that is at pH below the pKa of analytes, the analytes are in a neutral form, whereas at pH values above the pKa, the analytes are negatively charged. It is important to note that the optimum pH for this method was 6.5 while the pKa values of the target NSAIDs range between 4 and 5 (Mlunguza et al., 2019) and hence electrostatic interactions between the NSAIDs and the positively charged MeTOACl played a major role in the adsorption. The second mechanism resulted from the hydrogen bonding between the nitrogen atoms (hydrogen bond acceptors) of the MeTOACl and the carboxylate groups (hydrogen bond donors) of the NSAIDs. Furthermore, cation interactions between the quaternary ammonium groups of the ionic liquid and aromatic rings of the NSAIDs as well as the π–π interactions between the aromatic rings of the NSAIDs and activated carbon occurred. Consequently, in this study, the main mechanisms governing the adsorption of the analytes onto MWTAC@MeTOACl nanocomposite were electrostatic interactions, hydrogen bonding, the π–π interactions, cation interaction and hydrophobic interactions.

Additionally, regeneration studies revealed that MWTAC@MeTOACl nanocomposite was reusable up to the 3rd adsorption-desorption cycle (**See Supplementary material Table S6**) without significant decrease in the analytical response. After the 4th cycle, a noticeable reduction of around 13% in the analytical response was observed. The loss of affinity of the adsorbent towards the target analytes could be due to the removal of the ionic liquid from the adsorbent during the repeated elution step. Moreover, the repeated washing and elution led to the loss of binding sites on the adsorbent due to the leaching of the ionic liquid. Since the adsorbent could be used up to the third cycle without loss of affinity, the MWTAC@MeTOACl nanocomposite was considered to be stable with good reusability properties.

4. Conclusion

An efficient and eco-friendly MWTAC@MeTOACl nanocomposite was successfully prepared and applied for the first time as an adsorbent in the UA–MSPE method for the extraction and preconcentration of NSAIDs in wastewater. The magnetic properties enabled the effortless separation of MWTAC@MeTOACl nanocomposite from the aqueous sample, thus making the method simple and time saving, because the centrifugation and filtration steps are eliminated. Moreover, the adsorbent is economically viable, because the activated carbon was synthesized from low-cost waste materials. The UA-MSPE method was successfully developed and validated and the method was found to be highly sensitive and reproducible for the quantification of ketoprofen, diclofenac and naproxen in environmental water samples. Satisfactory analytical performance was achieved under optimum conditions which indicated that the MWTAC@MeTOACl nanocomposite is efficient and effective for the extraction and preconcentration of ketoprofen, naproxen and diclofenac in wastewater.

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.

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Data availability statement

The data seconding the conclusions of this article shall be availed upon request without reservation.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2021.103329.

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