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# Vortex-assisted supramolecular solvent dispersive liquid–liquid microextraction of ketoprofen and naproxen from environmental water before chromatographic analysis: response surface methodology optimisation

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**Abstract**

A microextraction procedure that is rapid and simple to extract and preconcentrate ketoprofen and naproxen is proposed. An environmentally friendly supramolecular solvent was applied as an extraction solvent and proved to be efficient in the extraction of ketoprofen and naproxen from environmental water. The design of experiment approach was used to screen, optimize significant parameters, and determine optimum experimental conditions. Under optimized experimental conditions, the vortex-assisted supramolecular solvent dispersive liquid–liquid microextraction provided a good linearity (0.57–700 μg $L^{-1}$), low limits of detection (0.17–0.24 μg $L^{-1}$) and extraction reproducibility below 9%. The high percentage relative recoveries (93.6–101.4%) indicated that the method is not affected by matrix. The practical applicability of the method was assessed by analysing ketoprofen and naproxen in river water and effluent wastewater samples. Both analytes were found in effluent wastewater.

**Keywords:** Dispersive liquid–liquid microextraction, Supramolecular solvent, Central composite design, Environmental water, Ketoprofen, Naproxen

## Introduction

The occurrence of emerging pharmaceutical contaminants in the aquatic environment has become a subject of interest in the global community mainly because of their potential to cause detrimental effects to both aquatic and terrestrial organisms (Gogoi et al. 2018). Pharmaceutical pollutants are introduced into the environment mainly via domestic and industrial effluents of wastewater treatment plants (WWTPs) (Han et al. 2018). This is because WWTPs do not remove pharmaceuticals effectively before discharging the effluents into the aquatic environment (Gogoi et al. 2018; Rivera-jaimes et al. 2018). Moreover, other routes of entry of pharmaceuticals into the environment include disposal of expired and left over drugs, metabolic excretion and agricultural activities run offs amongst others (Gogoi et al. 2018; Han et al. 2018). Among various classes of pharmaceuticals, non-steroidal anti-inflammatory drugs (NSAIDs), one of the most used class of analgesics and anti-inflammatory drugs globally, have proved to be one of the pharmaceutical drugs commonly detected in the aquatic environment (Cantarella et al. 2019). While NSAIDs occur in fairly low

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concentrations in environmental waters, their presence in the environment is still a major concern because pharmaceutical drugs are capable of producing biological effects even at very low concentrations (He et al. 2017; Mhuka et al. 2020). Therefore, there is a need to evaluate and monitor their occurrence in the aquatic environment.

The analysis of NSAIDs in food, biological and environmental matrices is challenging owing to their low concentrations, accompanied by the complexity of sample matrices (Baile et al. 2019; Liu et al. 2020). An appropriate sample pre-treatment method is therefore required for extraction from matrix and enrichment in order to satisfy the instrumental detection requirements (Barfi et al. 2015; Carabajal et al. 2020). Up to now, classical extraction-enrichment techniques like solid-phase extraction (SPE) and liquid–liquid extraction (LLE) have been proposed and evaluated to extract organic and inorganic analytes from numerous sample matrices (Keramat and Zare-Dorabei 2017). Nevertheless, SPE and LLE techniques are tedious, time-consuming and use big volumes of toxic, expensive, and eco-unfriendly, organic solvents (Hashemi et al. 2017; Sajid 2018). In order to overcome the limitations, microextraction methods such as magnetic solid-phase extraction (MSPE) (Akawa et al. 2021; Baile et al. 2019), solid-phase microextraction (SPME) (Liu et al. 2020; Wang et al. 2018), dispersive liquid–liquid microextraction (DLLME) (Mogaddam et al. 2021; Bazregar et al. 2016a), stir bar sorptive extraction (SBSE) (Fan et al. 2014; Wang et al. 2019) and dispersive microsolid phase extraction (DMSPE) (Asgharinezhad and Ebrahimzadeh 2015; Wahib et al. 2018) have been developed for NSAIDs prior to chromatographic analysis with satisfactory analytical performance. DLLME is among the most preferred microextraction methods for the extraction and preconcentration because of its attractive features such as simplicity, rapidity, possibility of automation, uses low volume of sample, and organic solvents (Rezaee et al. 2006). Moreover, the DLLME method results in high surface contact between the aqueous sample which enhances extraction efficiencies and results in high enrichment factors (Kocúrová et al. 2012; Rezaee et al. 2010).

The DLLME is based on a ternary solvent system in which both the disperser and the water-immiscible extractant solvents are rapidly injected into the aqueous sample with a syringe or micropipette, creating a cloudy solution of fine droplets of the extraction solvent (Marcinkowska et al. 2019). The target compounds transfer rapidly from the aqueous phase to the extraction solvent phase due to the large contact surface between the fine droplets of the extraction solvent and the aqueous phase (Hashemi et al. 2017; Mansour and Khairy 2017). The formation of the cloudy solution results in a large surface contact between the aqueous sample and the extraction solvent which leads to the method to reach the equilibrium state rapidly, making the extraction time very short. Phase separation is achieved by centrifugation (Al-Saidi and Emara 2014; Hashemi et al. 2017). A suitable disperser solvent should be miscible in both the aqueous and extraction phases for the generation of the cloudy solution (Rykowska et al. 2018). A disperser solvent plays a vital role in decreasing the interfacial tension between the organic and aqueous phases and thus reducing the sizes of the droplets and enhancing analyte recoveries (Al-Saidi and Emara 2014). Chlorinated solvents are traditionally used as extraction solvents in DLLME, however, despite the low solvent volumes used, they are toxic and eco-unfriendly (Gilberto et al. 2017; Saraji and Boroujeni 2014). Moreover, most of the chlorinated solvents are non-polar, which limits their application in extracting more polar compounds (Gilberto et al. 2017). Therefore, recent research trends have focused on developing safe, cheaper, effective and eco-friendly extraction solvents such as deep eutectic solvents (DES) (Khosrowshahi et al. 2021; Naeemullah and Tuzen 2019), supramolecular solvents (SUPRASs) (Najafi and Hashemi 2019), low density solvents (LDSs) (El-Deen and Shimizu 2019), and ionic liquids (Abujaber et al. 2019). Recently, SUPRASs have attracted increasing attention for their application as alternative, safer solvents in dispersive liquid–liquid microextraction (Ballesteros-gómez et al. 2010).

Supramolecular solvents (SUPRASs) are water immiscible liquids formed by a serial self-assembly of amphiphilic molecules at nano and molecular levels (Najafi and Hashemi 2019; Yang et al. 2017). Various types of interactions such as hydrogen bonding, ionic, π–cation, π–π, ionic and hydrophobic interactions occur between SUPRAS and target analytes. These interactions are vital for the extraction of analytes from the aqueous samples and enhancement of extraction efficiency (Ballesteros-gómez et al. 2010; Najafi and Hashemi 2019). Generally, an effective dispersion of extraction phase in the aqueous phase is of great importance in DLLME. Hence DLLME based on the use of dispersion techniques such as vortex (Wu et al. 2021), ultrasound (Haleem et al. 2017) and air agitation (Bazregar et al. 2016a) have been developed and applied for extraction and determination of various organic and inorganic compounds. Vortex mixing is a mild dispersion technique which disperses the extraction phase as fine droplets into aqueous phase effectively, which results in accelerated mass transfer of analyte from the aqueous into the extraction phase (Najafi and Hashemi 2019).

This study presents a simple, efficient, and rapid vortex-assisted supramolecular solvent dispersive liquid–liquid

microextraction technique ((VA-SS-DLLME)) for the separation and enrichment of two NSAIDs, naproxen (NAP) and ketoprofen (KET) from environmental water samples. Chromatographic analysis of the analytes was achieved by high-performance liquid chromatography-diode array detection (HPLC-DAD). A Plackett–Burman design (PBD) was applied for screening, while a central composite design (CCD) was chosen for optimization of significant parameters as well as to determine the optimal experimental conditions. Finally, the ability of the VA-SS-DLLME-HPLC-DAD to extract, enrich and determine KET and NAP in river water and wastewater samples was assessed.

## Materials and methods

### Reagents and aqueous solutions preparation

Preparation and dilutions of working solutions was done using ultra-pure and only analytical grade reagents were used. HPLC grade Acetonitrile, methyltrioctylammonium chloride (Aliquat 336, $N_{25}H_{54}ClN$,), Sodium chloride, ammonium hydroxide ($NH_4OH$, 28%), HPLC grade methanol, acetic acid, 1-octonal, naproxen (NAP), and ketoprofen (KET) were procured from Sigma-Aldrich (St. Louis MO, USA). Methanol was used to prepare stock solutions (1000 mg $L^{-1}$) of analytes before storing at 4 °C. Samples were filtered with membrane filters (0.22 µm) procured from Separations Scientific (Johannesburg, South Africa) prior to chromatographic analysis.

### Instrumentation

pH adjustments were made by using an OHAUS starter 2, 100 pH meter (Pine Brook, NJ, USA) while a Heidolph Multi-Reax vortex mixer (Separations, South Africa) was utilized for vortex-assisted extraction and Eppendorf 5702 Centrifuge (Germany) for centrifugation. An Agilent 1200 Infinity series HPLC-DAD (Agilent Technologies, Waldbronn, Germany) was used for chromatographic analysis. Separation was achieved by an Agilent C18 column (150 × 4.6 mm, 3.5 µm) (Newport, CA, USA). The sample flow was 1.00 mL $min^{-1}$ and column temperature was 25 °C. A 30:70 mobile phase of 0.20% acetic acid and methanol, respectively, and was operated in an isocratic mode. The chromatograms were recorded at 280 nm.

### Sampling

Sampling of effluent wastewater and river water samples was done at a Pretoria Daspoort WWTP and Apies River (South Africa), respectively. Pre-cleaned glass bottles were used for sample collection and stored in the refrigerator at 4 °C. Prior to VA-SS-DLLME, all samples were allowed to cool down to room temperature.

### The VA-SS-DLLME procedure

The SUPRAS was prepared by dissolving suitable quantities of the Aliquat 336 in a fixed volume of 1-octanol before its application as an extraction solvent in the VA-SS-DLLME procedure. As a result, three SUPRAs composed of 10%, 30% and 50% Aliquat 336 in octanol were prepared. The pH of the model solution composed of 100 µg $L^{-1}$ NAP and KET each was adjusted to pH 4–9 using acetic acid and ammonium hydroxide solutions. Extraction was performed by rapidly adding a 450–800 µL of the SUPRAS into a 5 mL model solution using a syringe. This rapid addition of the SUPRAS into the sample produced a cloudy solution, which was then vortexed for 60 s and centrifuged for 3 min at 818×*g*. The aqueous phase was withdrawn, and the target analyte rich extraction solvent was analysed on the HPLC. The viscosity of the SUPRAS phase containing the target analytes was reducing by a 4 times dilution fold with methanol before injection into the chromatographic system.

### Calculation of enrichment factor, extraction recovery and relative recovery

The percentage extraction recovery (% ER) was calculated as follows:

$$\%\mathrm{ER} = \frac{C_{\mathrm{ac}} \times V_{\mathrm{ac}}}{C_o \times V_o} * 100 \tag{1}$$

where $C_{\mathrm{ac}}$ is the analyte concentration in the extraction solvent, $V_{\mathrm{ac}}$ is the extraction solvent volume, $C_o$ is the analyte concentration in the sample, and $V_o$ is the sample volume (Bazregar et al. 2016b).

The enrichment factor (EF) was calculated as follows:

$$\mathrm{EF} = C_{\mathrm{ex}}/C_0 \tag{2}$$

where $C_{\mathrm{ex}}$ is the concentration of analyte in the extraction solvent and $C_o$ is the initial concentration of the analyte.

Additionally, the percentage relative recovery (% RR) was calculated as follows:

$$\%\mathrm{RR} = \frac{(C_{\mathrm{found}} - C_{\mathrm{real}})}{C_{\mathrm{added}}} \times 100 \tag{3}$$

where $C_{\mathrm{found}}$ is the concentration of analyte in the sample after spiking, $C_{\mathrm{real}}$ is the actual analyte concentration found in real samples and $C_{\mathrm{added}}$ is the analyte concentration that was spiked in a real water sample (Ghambarian et al. 2020).

### Optimization strategy

A multivariate optimization method was used to study the significance of selected factors and to determine optimum conditions for extracting and preconcentrating

NAP and KET using VA-SS-DLLME. Firstly, Plackett–Burman design (PBD) was employed as a pre-optimization study to discover the significant parameters. The influence of the factors on the analytical response was analyzed through Pareto Charts, which graphically reveals the significance or not of the factors and their interactions. Secondly, a central composite design (CCD) (assessing the significant factors at 5 levels) and the desirability function were employed to optimize the significant factors and determine the optimum conditions, respectively. The data was evaluated by STATISTICA version 13 software.

### Procedure for method validation

The proposed VA-SS-DLLME technique was validated following the ISO/IEC 17025 (2005) standard (ISO/IEC 17025 2005). The following parameters were validated: limit of detection (LOD), limit of quantification (LOQ), linear range, accuracy, and intraday and interday precision. The LOD = $3S/M$ and LOQ = $10S/M$, '$M$' is the slope of each calibration curve and where '$S$' is the standard deviation of 10 replicates ($n = 10$) of the lowest standard. The method linearity was evaluated by preparing seven standards covering 0–1000 µg $L^{-1}$ of each analyte using a wastewater sample. The standards were extracted using the proposed VA-SS-DLLME method and used to construct a calibration curve with seven points. Three replicates ($n = 3$) of each standard were analysed. While interday precision was assessed by analysing a 100 µg $L^{-1}$ wastewater water sample in triplicate for 4 days. The intraday precision and accuracy were evaluated by spiking a wastewater water sample at three levels (50, 250, and 550 µg $L^{-1}$) and the analysis was carried in triplicates.

## Results and discussion

### Optimization strategy

#### *Parameter screening study*

The analytical response of a method is affected by several parameters, therefore for simultaneous evaluation of parameters affecting the analytical response, a multivariate optimization approach is used (Baile et al. 2019). A Plackett–Burman design (PBD) is a method for determining or selecting statistically significant method parameters. The PBD approach assumes that the interactions between parameters are insignificant, allowing the main effects on the method to be estimated with fewer experimental runs, saving resources and time (Mousavi et al. 2018). A PBD was employed in this study to construct an experimental matrix with seven parameters at two levels which resulted in 12 experimental runs. The parameters studied were pH of sample, ionic strength (% IS), % Aliquat 336 in SUPRAS (% IL), centrifugation time (CT), extraction time (ET), centrifugation speed (CS) and SUPRAS volume (SV). The analysis of variance (ANOVA) was used to determine significant parameters and the results were presented as Pareto charts as shown in Fig. 1. The value of the standardized effect of each parameter on the extraction efficiency is represented by a bar on the Pareto chart, and the factor that crosses the 95 percent limit is considered significant (Carabajal et al. 2021). Furthermore, positive or negative values at the end of each bar signifies an enhancing or limiting influence on the analytical responses respectively, as the value of the corresponding parameter move from minimum to maximum (Baile et al. 2019).

According to Fig. 1a, b, only SUPRAS volume (SV) was statistically significant for the extraction of both KET and NAP. Furthermore, a positive effect was exerted on the

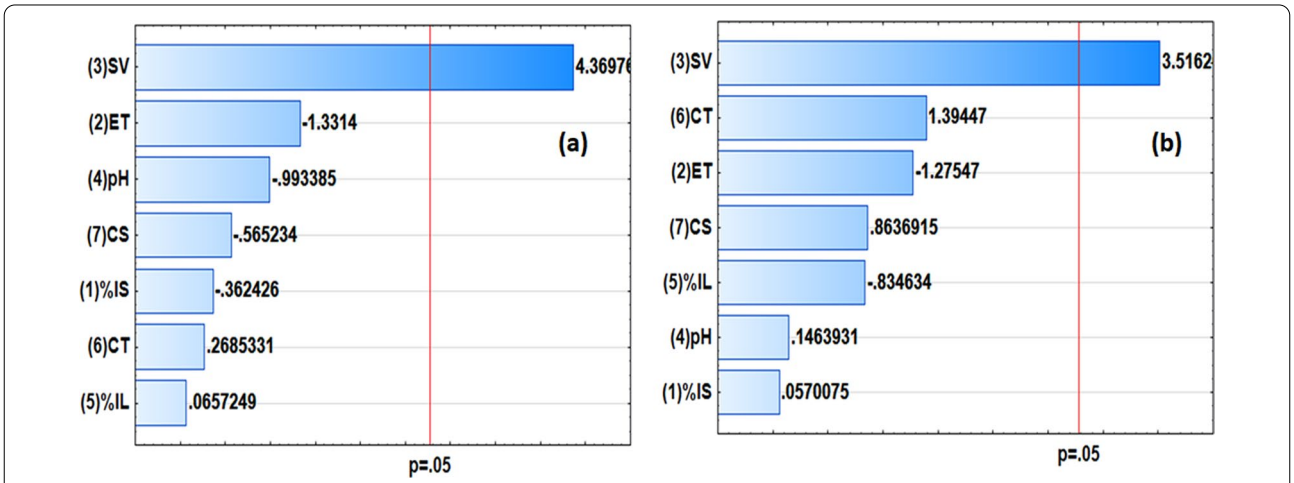


**Fig. 1** Pareto chart of the parameter effects for the desorption of: **a** NAP and **b** KET

analytical responses of both analytes by SV, indicating that the analytical response increased with increasing SV. This is due to oversaturation of the extraction solvent at lower SV. Extraction time had a negative effect on both analytes, revealing an efficient and rapid mass transfer from the sample solution to the SUPRASs (60 s were adequate for the method to reach equilibrium). Hence for further optimization and subsequent analysis, extraction time of 60 s was used. Parameters such as % IS, CT, and % IL exerted negligible effects on the method performance and were therefore fixed in subsequent studies at 0%, 3 min and 30%, respectively. pH of sample is one of the major parameters involved in the extraction efficiency of basic and acidic analytes. KET and NAP are acidic drugs, with pKa values of 4.45 and 4.19, respectively and their extraction is highly affected by the variation of sample pH (Ahmed 2017). On the other hand, overheating of the centrifuge system at high centrifugation speed could result in denaturing of the extraction solvent which could negatively affecting the interactions between the analytes and the extraction solvent. Even though sample pH and centrifugation speed being statistically insignificant at 95% confidence limit, they were further optimized together with SUPRAS volume.

#### *VA-SS-DLLME optimization by central composite design (CCD)*

In order to obtain experimental conditions that are suitable for the optimal performance of the VA-SS-DLLME technique, a CCD was applied. A CCD consists of a combination of a two-step factorial design, a star design, and a center point. The number of tests necessary for its application is expressed as $2k+2k+n0$, where $k$ is the number of parameters to optimize and $n0$ is the number of central point replicates (Baile et al. 2019; Novaes et al. 2016). The three-parameter experimental design resulted in 16 experimental runs and the matrix and analytical response values presented in Table 1.

The correlation between the independent parameters and response was evaluated and presented as three-dimensional (3-D) response surface diagrams shown in Fig. 2. The effects of each independent parameter, as well as the simultaneous effects of all the parameters. The main facts about extraction gains can be seen in the 3-D response surface plots. The influence of the volume of SUPRAS between 0 and 901 µL was examined and Fig. 2a, c shows that quantitative recoveries between 400 and 800 µL of SUPRAS were achieved. Furthermore, the analytical response increased as the extraction solvent volume increased. At lower SV, oversaturation of the extraction solvent may be responsible for lower extraction efficiencies while lower recoveries at high SV could be related to the dilution effects (Bazregar et al. 2016a). The semi-circular contour plots observed in Fig. 2a suggest there are no interactions between pH and centrifugation speed. However, Fig. 2a, b indicates that the analytical response was high when the centrifugation speed is low (1000–1500 rpm) and it decreases with increased centrifugation speed. On the other hand, Fig. 2a, c shows that high extraction efficiencies were achieved at pH values between 3 and 4 and this is because at pH lower than the pKa value, KET and NAP are predominantly in their molecular forms which enhances their hydrogen bond interaction with the extraction solvent (Shishov et al. 2018).

**Table 1** The CCD experimental design and the resultant % ER

| Run | pH | CS | SV | KET | NAP |
|---|---|---|---|---|---|
| 1 | 4 | 1500 | 100 | 92.0 | 82.9 |
| 2 | 4 | 1500 | 800 | 96.0 | 102.9 |
| 3 | 4 | 3500 | 100 | 82.0 | 85.7 |
| 4 | 4 | 3500 | 800 | 88.0 | 101.7 |
| 5 | 9 | 1500 | 100 | 80.6 | 88.6 |
| 6 | 9 | 1500 | 800 | 82.5 | 85.7 |
| 7 | 9 | 3500 | 100 | 71.3 | 74.3 |
| 8 | 9 | 3500 | 800 | 75.0 | 91.4 |
| 9 | 3.3 | 2500 | 450 | 93.1 | 102.9 |
| 10 | 9.7 | 2500 | 450 | 65.3 | 87.8 |
| 11 | 6.5 | 1213 | 450 | 93.6 | 96.4 |
| 12 | 6.5 | 3787 | 450 | 91.5 | 86.8 |
| 13 | 6.5 | 2500 | − 0.5 | 0.0 | 0.00 |
| 14 | 6.5 | 2500 | 900 | 95.9 | 96.5 |
| 15 | 6.5 | 2500 | 450 | 100.2 | 99.6 |
| 16 | 6.5 | 2500 | 450 | 98.0 | 102.9 |

#### *Optimization by desirability function (DF)*

The DF is used to simultaneously estimate optimal conditions for all the significant parameters studied. Determining the optimization conditions depends on the target value for the response which can be maximum, minimum, or central value. The DF value always fall within the 0–1, where a value close to one signifies satisfactory conditions for a preferred response while a value close to 0 signifies the least desired results (Bazregar et al. 2016b) The optimal conditions for the three parameters as determined by DF (Fig. 3) were found to be: sample pH: 4, SUPRAS volume (SV): 800 µL and centrifugation speed (CS): 1200 rpm. The overall optimal conditions of the developed method were: 4, 800 µL, 1200 rpm, 0%, 60 s, 30% and 3 min for sample pH, extraction solvent volume, centrifugation speed, % ionic strength, extraction time, % Aliquat in extraction solvent and centrifugation time, respectively. These conditions were verified experimentally in triplicate and the experimental values

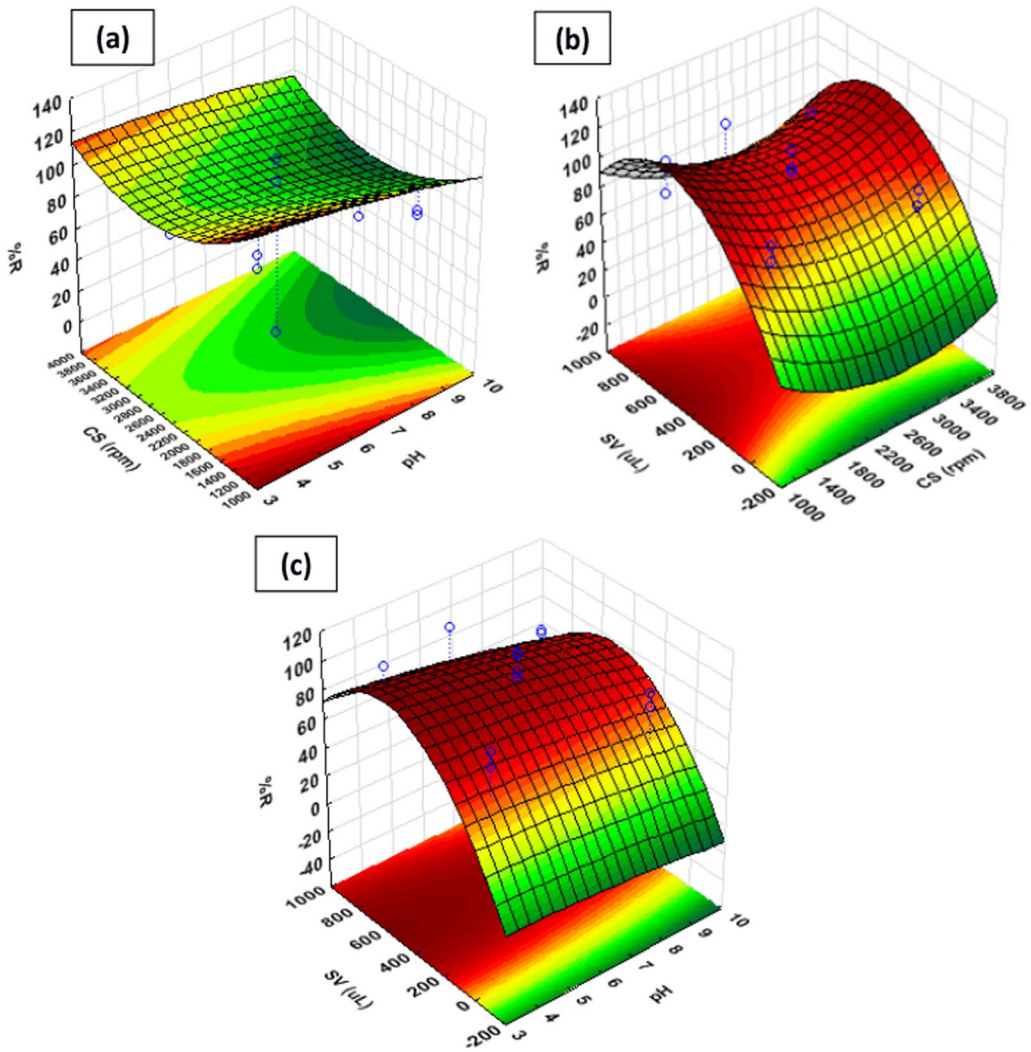


**Fig. 2** The 3D response surface plots of KET **a** centrifugation speed vs sample pH, **b** SUPRAS volume vs centrifugation speed and **c** SUPRAS volume vs sample pH

(97.8 ± 2.1% and 102.3 ± 2.3%) were found to agree fully with the model predicted values (100.2 and 102.9%). This signified the validity of the model, and these conditions were therefore used in subsequent investigations.

#### Analytical performance of the method

The figures of merit of the VA-SS-DLLME-HPLC-DAD method displayed in Table 2 showed a wide linear range (LOQ –700 μg $L^{-1}$) for the target analytes. The resulting calibration curves showed high level of linearity with a coefficient of determination ($R^2 = 0.9989$) for KET and ($R^2 = 0.9966$) for NAP. The method repeatability and reproducibility given as percentage relative standard deviation (% RSD) ranged from 3.1–8.9% and 7.3–8.6% respectively. The relatively low % RSDs revealed a highly precise method. Relatively low method LODs and LOQs of 0.17–0.24 μg $L^{-1}$ and 0.57–0.80 μg $L^{-1}$ respectively, indicated that the method is sensitive. The proposed method resulted in relatively high EFs ranging between 41 and 46. The obtained figures of merit showed a simple, efficient and suitable method for extracting KET and NAP from water matrices and can be efficiently applied for the analysis of NSAIDs.

The method accuracy was studied using a spike recovery method. Effluent samples spiked at three different levels (50, 250 and 550 μg $L^{-1}$) were each analyzed in triplicate. The % RR obtained ranged from 93.6% to 101.4% with % RSD values ranging between 1 and 7% (Table 3). The relatively good recoveries revealed that

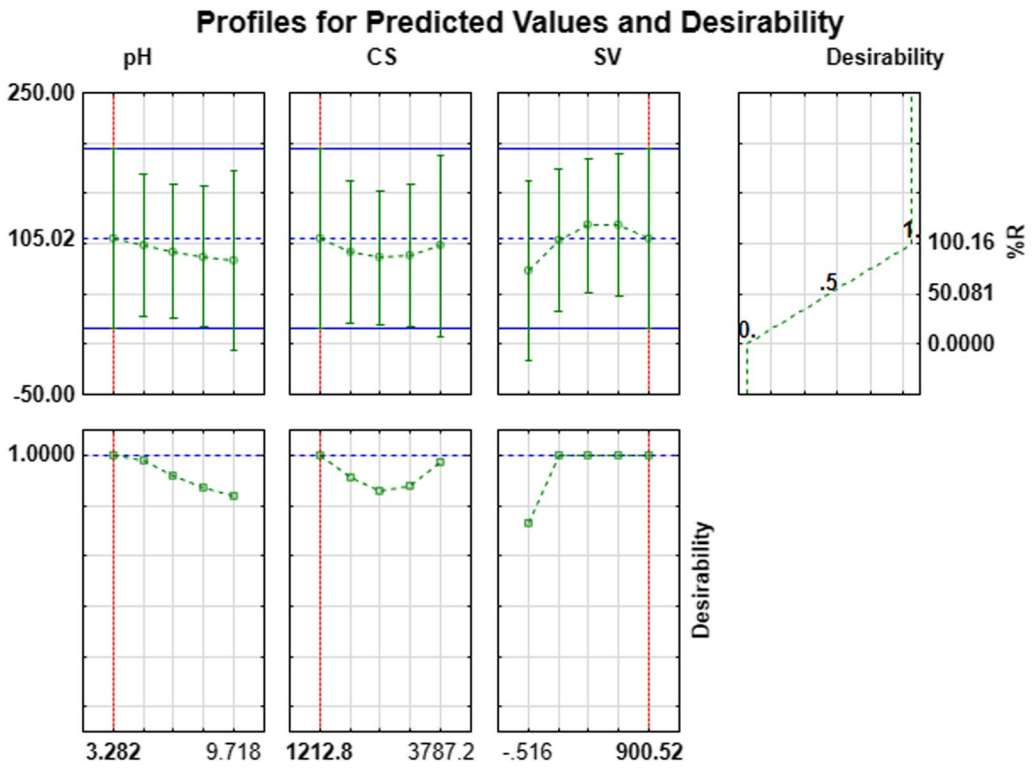


**Fig. 3** The desirability plot of the parameter effects of ketoprofen

**Table 2** VA-SS-DLLME-HPLC-DAD method figures of merit

| Parameters | KET | NAP |
|---|---|---|
| Linear range (μg $L^{-1}$) | 0.57–700 | 0.80–700 |
| $R^2$ | 0.9989 | 0.9966 |
| LOD (μg $L^{-1}$) | 0.17 | 0.24 |
| LOQ (μg $L^{-1}$) | 0.58 | 0.81 |
| Intraday (% RSD, $n=8$) | | |
| 50 μg $L^{-1}$ | 8.98 | 7.38 |
| 250 μg $L^{-1}$ | 3.10 | 3.33 |
| 550 μg $L^{-1}$ | 3.50 | 4.08 |
| Interday(% RSD, $n=4$ days) | 8.64 | 7.30 |
| EF | 46 | 41 |
| % ER | 97.8 ± 2 | 102.3 ± 2 |

**Table 3** Real water analysis of KET and NAP

| NSAID | Added (μg $L^{-1}$) | % RR | % RSD |
|---|---|---|---|
| KET | 50 | 98.2 | 7 |
| | 250 | 93.6 | 3 |
| | 550 | 101.4 | 3 |
| NAP | 50 | 97.0 | 6 |
| | 250 | 97.9 | 4 |
| | 550 | 100.9 | 1 |

the developed VA-SS-DLLME method performance was not affected from matrix effects.

### Comparison with analytical methods in literature

The developed VA-SS-DLLME method was compared with methods reported in literature for the determination of NSAIDs in various matrices. Aspects such as LOD, sample volume and % ER were considered for comparison of the methods. In comparison to the other methods. Table 4 revealed that the performance (LOD and % RR) of the VA-SS-DLLME-HPLC-DAD is generally better or similar to methods in literature. In addition, the VA-SS-DLLME-HPLC-DAD method required much less sample volume as compared to (Akawa et al. 2021; Alinezhad et al. 2018; Baile et al. 2019; Han et al. 2019; Li et al. 2018), which makes the developed method simple and easy to handle. Moreover, the rapidity of the method and use of eco-friendly extraction solvent add to the advantages of the VA-SS-DLLME.

### Determination of ketoprofen and naproxen in real water samples

The proposed method reliability and applicability was assessed by determining ketoprofen and naproxen in river water and effluent wastewater. This was done by analyzing non-spiked and spiked (10 μg $L^{-1}$) samples

**Table 4** Comparison of proposed VA-SS-DLLME-HPLC-DAD method with published methods for the extraction of NSAIDs

| Method | Matrix | Sample volume (mL) | LOD (μg $L^{-1}$) | Recovery (%) | Ref |
|---|---|---|---|---|---|
| SPE-UHPLC-UV | Hospital wastewater, tap, river water | 10 | 0.13–0.82 | 93–100 | Li et al. (2018) |
| IL-DLLME-UHPLC-UV/FP | River & Tap water | 5 | 17.0–95.0 | 90–103 | Toledo-Neira and Álvarez-Lueje (2015) |
| MSPE-UHPLC-DAD | Influent and effluent wastewater | 20 | 0.05–0.38 | 82–98 | Akawa et al. (2021) |
| MDSPE-LC-DAD | Wastewater, urine and tap water | 20 | 0.50–3.0 | 86–107 | Baile et al. (2019) |
| MSPE-UHPLC-UV | Urine, Serum, River water | 10 | 0.20–0.40 | 85–114 | Han et al. (2019) |
| DLLME-LC–MS | River water, tap water | 6 | 0.10–3.0 | 73–80 | Zgola-Grzeskowiak (2010) |
| MSPE-HPLC–UV | wastewater, tap and river water | 50 | 0.05–0.08 | 70–84 | Alinezhad et al. (2018) |
| VA-SS-DLLME-HPLC-DAD | River water | 5 | 0.17–0.24 | 96–102 | This study |

**Table 5** The determination of NSAIDs and recoveries in the studied effluent wastewater and river water ($n = 3$)

| Analyte | Added (μg $L^{-1}$) | River water | | Effluent wastewater | |
|---|---|---|---|---|---|
| | | Found (μg $L^{-1}$) | % RR | Found (μg $L^{-1}$) | % RR |
| KET | 0 | N.D | – | 3.61 ± 0.38 | – |
| | 10 | 9.87 ± 0.36 | 98.7 | 13.2 ± 0.86 | 95.9 |
| NAP | 0 | N.D | – | 4.28 ± 0.32 | |
| | 10 | 9.42 ± 0.81 | 94.2 | 13.5 ± 0.74 | 92.2 |

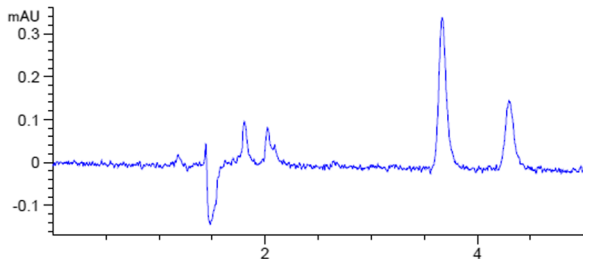


**Fig. 4** A chromatogram of a wastewater sample after VA-SS-DLLME method spiked with 10 μg $L^{-1}$ of KET and NAP

after extraction and the results are shown in Table 5. Recovery values for the spiked river and effluent samples were 94.2–98.7% and 92.2–95.9%, respectively. These results demonstrated acceptable precision and accuracy. In addition, none of the target analytes were detected in river water, however KET and NAP were detected in effluent wastewater at 3.61 and 4.28 μg $L^{-1}$, respectively. These results indicated the ineffectiveness of the wastewater treatment plants to remove these pollutants before discharging effluents into the environment.

A chromatogram of a spiked effluent sample at 10 μg $L^{-1}$ is displayed in Fig. 4. The chromatogram displays good resolution, with no interfering peaks. This indicated that the proposed method was effective in cleaning up and extracting the analytes from matrix.

## Conclusion

A rapid, accurate, and simple supramolecular solvent based dispersive liquid–liquid microextraction method for the extraction of ketoprofen and naproxen from environmental water samples was presented for the first time. The obtained results indicated that the VA-SS-DLLME method provided a noticeable matrix removal and analytes enrichment in a short time. The developed method showed high extraction efficiencies and satisfactory repeatability. This convenient method was successfully used to extract and preconcentrate two NSAIDs in river water and effluent samples. In overall, VA-SS-DLLME method revealed great capability to analyse ketoprofen and naproxen in real water samples.

#### Abbreviations

ANOVA: Analysis of variance; CCD: Central composite design; CS: Centrifugation speed; CT: Centrifugation time; DES: Deep eutectic solvents; DF: Desirability function; DLLME: Dispersive liquid–liquid microextraction; DMSPE: Dispersive microsolid phase extraction; EF: Enrichment factor; HPLC-DAD: High-performance liquid chromatography-diode array detection; IL: Ionic liquid; IS: Ionic strength; KET: Ketoprofen; LDSs: Low density solvents; LLE: Liquid–liquid extraction; LOD: Limit of detection; LOQ: Limit of quantitation; MSPE: Magnetic solid-phase extraction; NAP: Naproxen; NSAIDs: Non-steroidal anti-inflammatory drugs; PBD: Plackett–Burman design; RR: Relative recovery; RSD: Relative standard deviation; SBSE: Stir bar sorptive extraction; PE: Solid-phase extraction; SPME: Solid-phase microextraction; SUPRAS: Supramolecular solvent; SV: Supramolecular solvent volume; VA-SS-DLLME: Vortex-assisted supramolecular solvent dispersive liquid–liquid microextraction; WWTP: Wastewater treatment plant.

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#### Author contributions

PNM, MKD, and MNA contributed to study conceptualization. MNA was in charge of the technique, validation, data analysis and interpretation, and manuscript writing. PNM contributed to data analysis utilizing software, supervision, funding, paper editing, review, and final approval. All authors read and approved the final manuscript.

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**Availability of data and materials**
The raw data used to support the findings of this study will be made available to anyone who requests it.

## Declarations

**Competing interests**
No conflict of interests is declared by the authors.

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