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# Vortex-assisted liquid-liquid microextraction of selected non-steroidal anti-inflammatory drugs using supramolecular solvent

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**ABSTRACT**

An eco-friendly efficient supramolecular solvent-based method was developed for extraction and determination of selected non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac sodium, caffeine and paracetamol in water samples followed by detection with high-performance liquid chromatography. Supramolecular solvent (SUPRAs) with composition of 400 μL of 1-undecanol as reverse micelles in dispersing solvent of 15% tetrahydrofuran (THF) solution in water at pH 4 used as extracting solvent for selected NSAIDs. Various factors affecting the extraction efficiency of NSAIDs like amount of 1-undecanol, percentage of THF, composition of SUPRA, pH, vortex time and sample amount were studied. Limit of detection (S/N = 3) and quantification (S/N = 10) were 0.02 and 0.08 μg $mL^{-1}$ for paracetamol, 0.006 and 0.02 μg $mL^{-1}$ for caffeine, 0.06 and 0.2 μg $mL^{-1}$ for diclofenac sodium with linear range of 0.1–12 μg $mL^{-1}$. The inter-day relative standard deviation (RSD) values were 3.1%–5.2%, 3.3%–4.2% and 2.2%–3.6%, while for intra-day the RSD values obtained were 2.4%–4.1%, 1.4%–3.1% and 1.5%–4.1% for paracetamol, caffeine and diclofenac sodium, respectively. The proposed method has been applied successfully to the spiked water samples and recoveries were found in the range of 89.5%–94.6% for tape water, 88.5%–92.8% for canal water and 90.0%–95.2% for industrial wastewater samples was obtained.

*Keywords:* Supramolecular solvent; Microextraction; 1-undecanol; Paracetamol; Caffeine

## 1. Introduction

A great variety of medications are currently available in the market and include many analgesics (pain-killers), antipyretics (fever reducers), antibiotics, antiseptics, hormone replacements, contraceptives, statins, mood stabilizers, antidepressants, and cytostatic. The bioactive compounds of these pharmaceuticals may have a natural origin (derived from microbes, plants or animals), or they may be solely chemically synthesized or derived from genetic engineering. All in all, over 4,000 pharmaceutical products are currently in use for medical and veterinary purposes, and in agriculture as part of growth promotion of livestock [1].

Pharmaceutical products have become recognized as relevant environmental contaminants in the course of the last decade [2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs worldwide and are used for relief of inflammatory, chronic (e.g., rheumatoid arthritis, osteoarthritis, and gout) and acute (e.g., headache, postoperative pain, and orthopedic fractures) pain conditions [3]. Among all the pharmaceutical products reported in the literature, the classes of non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently reported as environmental pollutants [4]. NSAIDs is a category of analgesic medication that reduces pain, fever and inflammation [5]. Determination

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of NSAIDs can be performed by various techniques, such as high-performance liquid chromatography (HPLC) [6–9], gas chromatography–mass spectrometry (GC–MS) [10,11], spectrophotometric method [12], micellar electrokinetic capillary chromatography (MEKC), and capillary electrochromatography (CEC) [13,14]. HPLC is the most common method that is used for separation and determination of these compounds. The analysis of drugs in a complex matrix such as urine without sample preparation is very difficult. In general, sample preparation and concentration of the target analytes are often needed before analysis. Up to now, several methods have been developed for preconcentration of NSAIDs from sample matrices including liquid–liquid extraction (LLE) [15] and solid-phase extraction (SPE) [16–18]. SPE offers unquestionable advantages compared with the traditional LLE technique, such as greater extraction efficiencies and lower consumption of organic solvents. However, it hardly reduces the large times spent for sample preparation and the large volumes of sample required for analysis [19]. Solid-phase microextraction [20,21] stir bar sorptive extraction (SBSE) [22], and liquid-phase microextraction [23–25] have been also applied for the extraction of NSAIDs.

Recently in analytical chemistry microscale methods have been used for the extraction of smaller concentrations of analytes from environmental samples. The microscale extraction methods such as liquid–liquid and liquid–solid extraction have been developed as environmentally friendly, cost effective, fast and easy to handle the samples [26–28]. Supramolecular solvents (SUPRAs) are nanostructured liquids immiscible in water made through self-assembly processes from amphiphilic molecules having outstanding properties for extraction at the microscale level. These are aggregates in three-dimensional structure having sites of different polarity with a number of interactions for analyte solubilization like hydrogen bonding, dipole–dipole interaction, $\pi$-cation interaction, hydrophobic-hydrophobic interactions, etc. to make the SUPRA solvent suitable for the extraction of organic molecules in a different polarity range. Hence, the greater number of sites for binding allow to develop efficient and ecofriendly methods for sample treatment with high efficiency of extraction [26,29,30].

In the present work, supramolecular solvent proposed for the extraction of NSAIDs has been used first time for the extraction and determination of mixture of selected NSAIDs (diclofenac sodium, caffeine and paracetamol) from water samples. The SUPRA solvent was formed from reverse micelle (1-undecanol) which were dispersed in dispersing media (tetrahydrofuran and water) having features of a range of organized aggregates with large surface area that allows extraction. It also shows the novelty of the proposed SUPRAs microextraction method. The proposed method is aimed to fabricate an extraction method for selected NSAIDs in a mixture from water samples.

## 2. Experimental

### 2.1. Reagents and solutions

All chemicals used were of Analytical grade. HPLC-grade methanol (99.9%) purchased from BioM Laboratories, Cerritos, USA, Chemical Division (Malaysia) and acetonitrile (99.9%) provided by LabScan Analytical Sciences, Asia Co. (Pathumman, Bangkok, Thailand). 1-Undecanol and tetrahydrofuran were obtained from Merck (Schuchardt OHG 85662 Hohenbrunn) Germany and Sigma Aldrich (89555St. Louis, MO, USA), respectively. Pharmaceutical standards paracetamol (PCM), caffeine (CF) and diclofenac sodium (DIC) were gifted by a pharmaceutical company. Hydrochloric acid (HCl) was purchased from BDH Laboratory supplies Poole Bh15 1TD, England. Stock solution of 100 μg $mL^{-1}$ for each NSAID was prepared in methanol and stored at 4°C. Different concentrations of standard solutions in a mixture were prepared daily by dilution with distilled water.

### 2.2. Instruments

High performance liquid chromatography (HPLC) series 200 equipped with a reverse phase $C_{18}$ stationary phase column of 5 μm × 15 cm × 4.6 mm dimensions (California, USA), Reodyne injector fitted with a loop of 20 μL and UV-VIS detector at 254 nm was used for separation and detection of NSAIDs in SUPRA solvent. The mixture of NSAIDs, PCM, CF and DIC were separated and quantified using isocratic reverse phase HPLC analysis. Mixture of acetonitrile, water and trifluoroacetic acid (1% solution) in a ratio of 500:500:2 (Volume) was used as mobile phase at a flow rate of 1 mL $min^{-1}$. The column effluents were monitored at 254 nm using UV detector. Quantification of NSAIDs were performed by measuring peak area. Retention time of PCM, CF and DIC were 4.9, 8.06 and 10.6 min, respectively. Calibration curves for PCM, CF and DIC were constructed in the concentration range of 0.1–12 μg $mL^{-1}$.

For SUPRA solvent production and extraction of NSAIDs, vortex oscillator (Zenith lab Model-XH-C Korea) was used. pH of solutions was adjusted using WTW pH 422 lab pH meter (West Germany).

### 2.3. Sample collection and preservation

Different water samples like canal water and industrial wastewater from Hayatabad (industrial area) and laboratory tap water (University of Peshawar) were selected for the extraction study. Water samples were collected in clean containers and were filtered through filter paper for removing suspended solids. The pH of filtered water samples was adjusted to 4 using hydrochloric acid solution and stored at lower temperature. Spiking of water samples were made by adding a known concentration of 10, 15 and 20 μg $mL^{-1}$ of the working standard solution of mixture of the NSAIDs to the collected water samples and recovery experiments were performed in triplicate.

### 2.4. Supramolecular solvent formation

For the production of SUPRA, 1-undecanol (400 μL) was dissolved in tetrahydrofuran (THF) (15%) in a 50 mL falcon tube. Then, 1,700 μL of hydrochloric acid aqueous solution (pH = 4) was added and the mixture was stirred with vortex oscillator for 1.0 min. The supramolecular solvent (SUPRA) formed as an immiscible liquid into the bulk

solution and separated as an upper layer. The lower aqueous was withdrawn using a micro-syringe and transferred to a close storage tube to prevent THF losses. The resulting SUPRA solvent was stored at lower temperature for further extraction process.

### 2.5. Procedure for extraction of NSAIDs

Standard solutions of selected NSAIDs (paracetamol, caffeine and diclofenac sodium) were used to optimize the experimental conditions for SUPRA solvent extraction. Known concentrations of selected NSAIDs were transferred to falcon tube with screw cap. Solution pH was adjusted to 4 with hydrochloric acid solution then followed by 1-undecanol (400 uL) in 15% THF solution. The mixture was stirred for 1.0 min using vortex at 800 rpm agitation to increase the NSAIDs efficiency of extraction. The SUPRA solvent as a top layer was collected through microsyringe and analyzed using HPLC with UV detector.

The various experimental parameters affecting the extraction efficiency of NSAIDs (PCM, CF and DIC) such as volume and composition of the supramolecular solvent and some of the operational variables, for example, pH and vortex stirring time were studied in triplicate and selection of optimum condition was based on area values obtained from the HPLC chromatograms. The optimized conditions were then applied for the microextraction of NSAIDs from samples.

### 2.6. Method validation and quality assurance

The proposed SUPRA solvent extraction method was validated according to the quality assurance and quality control (QA/QC) protocols in terms of linearity, sensitivity, limit of detection (LOD), limit of quantification (LOQ), inter-day and intra-day precision and recoveries for accuracy. Linearity was investigated at 8 different concentration levels ranged from 0.1–12 μg $mL^{-1}$ for each NSAID. LOD and LOQ were determined as the analyte (NSAID) concentration that gave 3:1 and 10:1 mean signal-to-noise ratio, respectively.

Repeatability and precision were investigated with the help of relative standard deviation (RSD) calculated from extractions of spiked samples with NSAIDs and then analyzed by the proposed SUPRA solvent extraction method. The inter-day precision (repeatability) was calculated at three concentrations, 5 μg $mL^{-1}$ ($n$ = 3), 10 μg $mL^{-1}$ ($n$ = 3) and 15 μg $mL^{-1}$ ($n$ = 3). The intra-day (intermediate) precision was also calculated at three different concentrations, 5 μg $mL^{-1}$ ($n$ = 3), 10 μg $mL^{-1}$ ($n$ = 3) and 15 μg $mL^{-1}$ ($n$ = 3) daily for three consecutive days. Each sample was analyzed by HPLC. Accuracy of the method was estimated by samples spiked with mixture of NSAIDs at three concentration levels of 2 μg $mL^{-1}$ ($n$ = 3), 5 μg $mL^{-1}$ ($n$ = 3) and 10 μg $mL^{-1}$ ($n$ = 3). The value of accuracy was calculated by the difference between observed/calculated concentrations and the known spiked concentration multiplied by 100.

Recovery experiments were analyzed by spiking the collected water samples. Recovery (%) of the proposed analytical method was calculated using ratio of the peak areas of the spiked samples of known concentration of NSAID to those of unspiked aqueous solutions. Calculated NSAIDs concentrations were divided by the known spiked concentration and multiplied by 100 to obtain % recovery. All experiments were performed in triplicate.

## 3. Results and discussion

### 3.1. Selection of solvent for supramolecular solvent formation

The selection of an appropriate extraction solvent as supramolecular solvent is of major importance for the optimization of the extraction process. For this purpose, three solvents of alkanol (octanol, 1-decanol and 1-undecanol) were investigated with THF (15%) solution. The final selection of solvent was based on extraction efficiency and chromatographic behavior. The results are given in Fig. 1 as an average peak area for the solvents. The results show that 1-undecanol-THF (%15) has higher extraction efficiency than other solvents. 1-undecanol is an alkanol and contained eleven carbon atoms as compared to 1-decanol (10 carbon atoms) and octanol (8 carbon atoms). With increasing the number of carbons in the hydrocarbon chain (carbon from 8 to 11) in response the driving forces (hydrogen bonding and dispersion) increases for extraction process. As well as 1-undecanol present in the molecular form at pH of solution for extraction (pKa = 16.84) and retains its ordered structure throughout the pH range. The structure and nature of the functional groups present in PCM, CF and DIC molecules suggests thepotentials of different types of interactions. The interactions of NSAID with SUPRA solvent is important to understand for an efficient extraction process. These three NSAIDs (PCM, CF, DIC) are relatively polar hydrophilic compounds containing hydrogen donors and acceptors atoms. Therefore, 1-undecanol reverse micelle solubilize NSAIDs mainly due to mixed-mode mechanism and multiple binding sites availability on hydrophobic interactions in the hydrocarbon tail and hydrogen bonds of the alcoholic polar groups with NSAIDs. Hence, 1-undecanol was preferred for further experiments.

### 3.2. Optimization of extraction process

The different experimental conditions which effect the extraction of selected NSAID recoveries were investigated including composition of SUPRA and volume of SUPRA solvent, pH, sample volume and extraction time to achieve good precision and sensitivity.

pH of solutions is important for the formation of supramolecular solvent as well as it also affect the dissociation constant of selected NSAIDs (PCM, CF, DIC) with acid-base properties. The pKa of PCM is 9.5, DIC is 4.2 and CF is 14.0 therefore, the pH was adjusted with hydrochloric acid (HCl) and studied in the range of 1–6 for the formation of SUPRA solvent as immiscible aggregates from water solution and extraction of selected NSAIDs (Fig. 2). The hydrophobic attractive forces are responsible for stabilization of reverse micelle and as a result, increases the formation of reverse micelle. Therefore, pH values 4 was selected for further extraction process.

The volume of THF as dispersion solvent was studied from 5% to 35% (v/v) for the NSAIDs extraction efficiency,

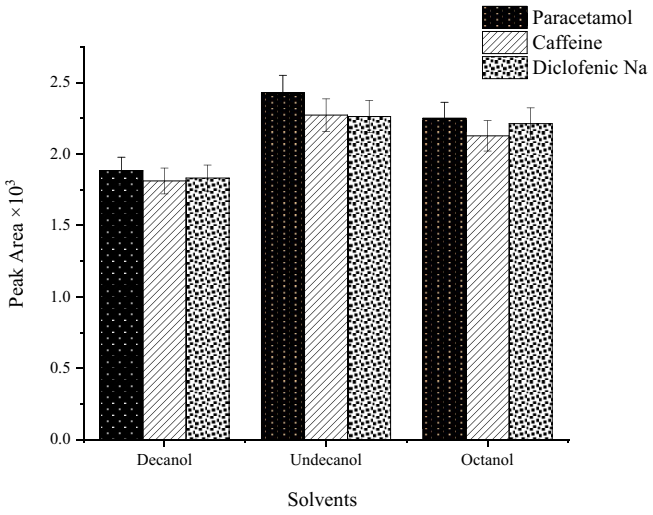


Fig. 1. Selection of solvent for preparation of supramolecular solvent (pH = 4, vortex time 0.5 min, 15% THF, $n$ = 3).

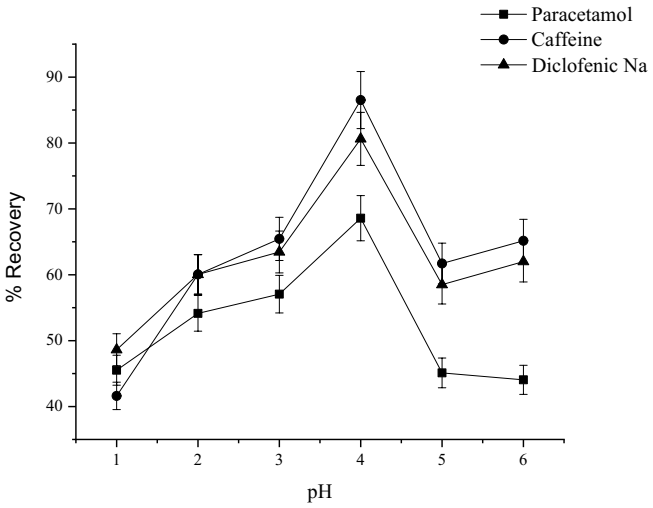


Fig. 2. Recovery of NSAIDs using SUPRA solvent extraction at different pH values.

SUPRA solvent aggregate of 1-undecanol in a reverse micelle forms aqueous cavities spontaneously which is then surrounded by the polar groups of 1-undecanol with the hydrocarbon chain dissolved in THF. As dispersion solvent THF plays a dual role, as a dispersing solvent and also causing self-assembly of 1-decanol in SUPRA solvent in which both hydrogen bonding and dispersing are included. In Fig. 3a, the extraction efficiency gradually increases along with the increasing percentage of THF in SUPRA solvent and reaches the highest value when 15% of THF was used. THF provide an excellent reaction media for the extraction process of organic compounds. Thus, 15% concentration of THF as the optimum percentage of dispersive solvent in SUPRA solvent was selected. The effect of THF percentage on formation of SUPRAs was also studied. THF were added to make its ratio in solution from 10% to 40%. It was shown from recoveries that the extraction efficiency increased with increase in THF concentration up to 15%, which leads to improved dispersion and solubilization of 1-undecanol, after that it decreased (Fig. 3a).

For the formation of supramolecular solvent (SUPRAs) containing 1-undecanol as reverse micelles in THF phase, different volume of 1-undecanol were optimized in the range between 250–500 μL and the extraction recoveries obtained are shown in Fig. 3b. The extraction efficiency of selected NSAIDs increased with the use of lower amount of 1-undecanol (400 μL), with increase in amount of 1-undecanol there is decrease in extraction efficiency due to the reduction of micellar solubilization sites.

The effect of volume of SUPRA solvent was investigated for the recovery of selected NSAIDs, different volumes were added to analyte solution from 200 to 700 μL. Recoveries equal to or above 95% were obtained using 400 μL volume of SUPRA solvent (Fig. 4a). Volume of SUPRA solvent less than 400 μL was not sufficient for the NSAIDs extraction and large volume of SUPRA solvent makes the phase more diluted making detection signal decreased. The percent recoveries of selected NSAID were also studied using the effect of composition of SUPRA solvent. At constant amount of 1-undecanol (400 μL) dispersed in variable ratio of THF/water continuous phase. The peak recoveries were obtained with ratio 15:85 of THF:$H_2O$ (Fig. 4b). Supramolecular solvent extraction of the selected NSAIDs from aqueous solution was assisted by vortex to expedite the extraction and also to improve the diffusion of NSAIDs to acceptor phase from the donor phase.

The vortex time was investigated in the range of 0.5 min to 5.0 min to study its effect on recoveries of NSAIDs. Fig. 5 shows the extraction recovery from 1.0 to 5.0 min of all selected NSAIDs. The results show that maximum recoveries achieved at a minimum of 1.0 min vortex time. Therefore 1.0 min extraction time was selected as an optimum value. The experimental parameters having highest recoveries are given in Table 1.

### 3.3. Validation of the proposed method

The proposed SUPRA solvent extraction method was evaluated under the investigated extraction conditions for linear range, limit of detection (LOD), limit of quantification (LOQ), precision and accuracy. At peak recovery of extracted NSAIDs, various analytical parameters like linearity range, correlation coefficient, limits of detection (LOD), limit of quantification (LOQ) and precision calculated as relative standard deviation (RSD %) for inter-day and intra-day were determined at three different concentrations. Calibration curves for all three selected NSAIDs were made using standard solutions (0.1–12 μg $mL^{-1}$) prepared in water and obtained by least squares linear regression analysis of the peak area against concentration of each drug. Table 2 summarizes various parameters. Linearity range with correlation coefficient of 0.9975 to 0.9985, indicated good correlation. The limit of detection (LOD) was determined by analyzing four blank samples on signal to noise ratio of three. The method showed a low detection limit of 0.02, 0.006 and 0.06 μg $mL^{-1}$ for PCM, CF and DIC, respectively. While limit of quantification (LOQ) was calculated by analyzing four blank samples on signal to noise ratio of ten and LOQ values of 0.08, 0.02 and 0.2 μg $mL^{-1}$

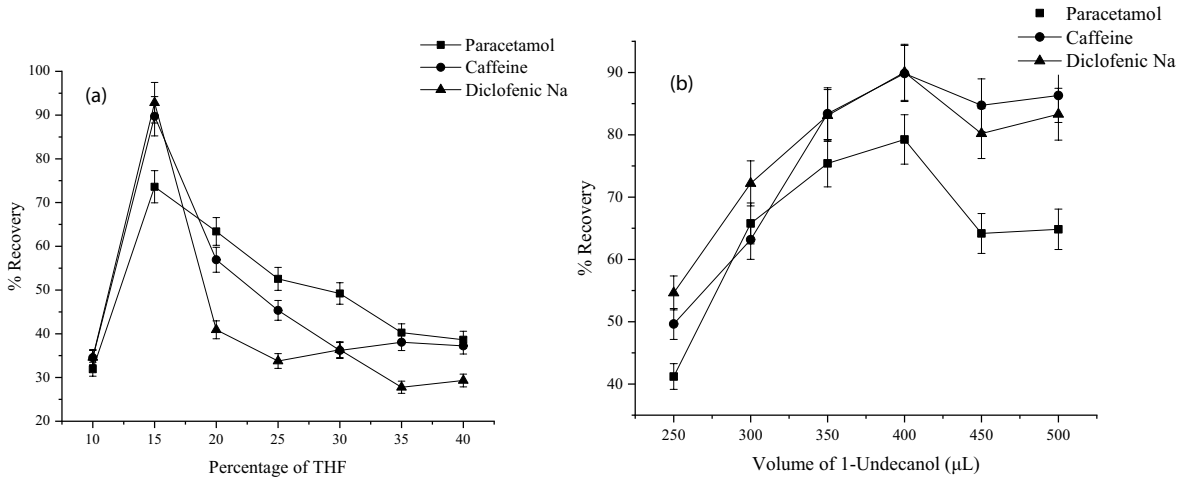


Fig. 3. Recovery of NSAID at (a) different THF % solution and (b) various volume of 1-undecanol for the formation of SUPRA solvent.

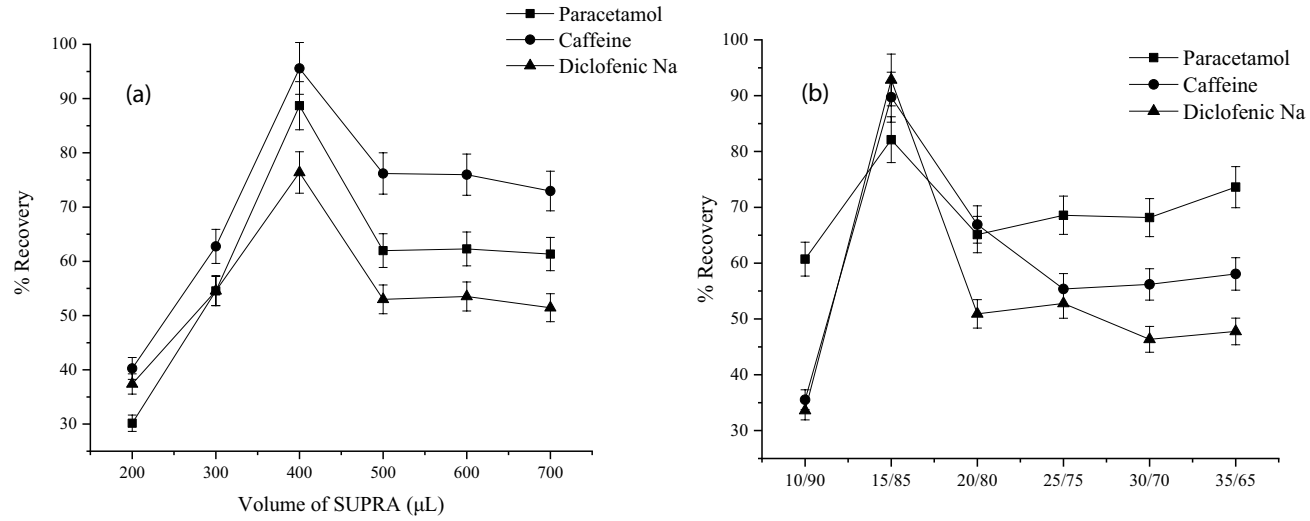


Fig. 4. Effect of (a) SUPRA solvent volume and (b) THF water ratio on the extraction of NSAIDs.

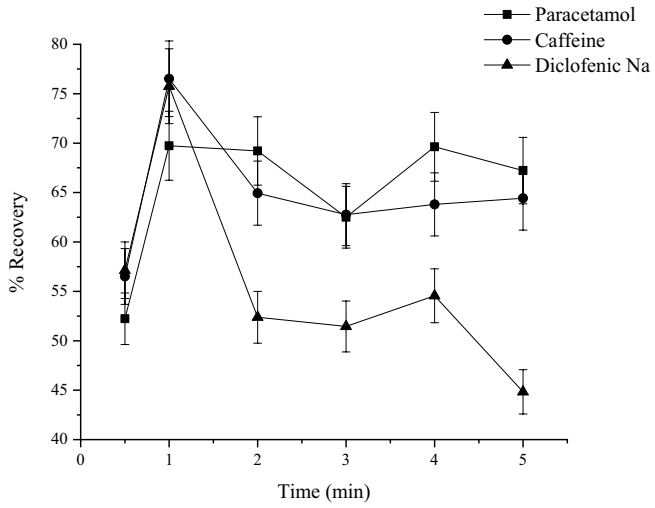


Fig. 5. Effect of vortex time on the extraction of NSAIDs.

was found for PCM, CF and DIC, respectively. No appreciable differences in retention times were observed for the selected NSAID injected in methanol or SUPRA solvent.

The inter-day precision was carried out over four daily replicates, spiked at three different concentration levels (Table 2) for 3 d and the intra-day precision was made over four replicates, spiked at three concentration levels (Table 2) within 1 d. The inter-day and intra-day precision (RSD, %) were in the range of 2.2%–5.2% and 1.4%–4.1%, respectively. The results show low variation between measurements.

### *3.4. Analysis of real environmental samples*

The applicability and selectivity of the proposed method was evaluated by standard addition method to check that the co-extractants from water samples have any effect on the SUPRA solvent based extraction of NSAIDs. Three concentrations of NSAIDs (PCM, CF, DIC) solutions 2.0, 5.0 and 10.0 μg $mL^{-1}$ were added to tap water, canal water

and industrial wastewater samples before extraction and each of the water sample in triplicate was analyzed by the proposed method of SUPRA solvent extraction. The results (Table 3) show that the recoveries of PCM, CF and DIC in selectivity study were found to be 90.0%–92.6%, 88.5%–90.0% and 91.0%–95.0% for PCM in tap water, canal water and industrial wastewater, respectively. The recovery of CF in tap water ranged from 92.5%–94.6%, for canal water ranged from 90.6%–92.0% while for industrial wastewater ranged from 90.0%–93.5%. Similarly, the recovery of DIC from tap water, canal water and industrial wastewater ranged from 89.5%–92.8%, 90.6%–92.8% and 91.4%–95.2%, respectively. The results indicated that there were no significant interferences produced by the co-extractants of water samples using the proposed method for the analysis of PCM, CF and DIC non-steroidal anti-inflammatory drugs. Chromatograms obtained after analysis of samples demonstrating good separation for NSAIDs of interest (Figs. 6 and 7). High values of recoveries from all water samples revealed that the matrix from real samples had no significant effects on the extraction of selected drugs.

Table 1
Optimized parameters for the extraction of NSAIDs drugs using SUPRA solvent microextraction method

| Parameter | Optimized values |
|---|---|
| pH | 4.0 |
| Vortex time (min) | 1.0 |
| 1-undecanol volume (μL) | 400 |
| THF (%) | 15 |
| Volume of SUPRA (mL) | 0.4 |
| THF:$H_2O$ ratio | 15:85 |

#### *3.4.1. Matrix effect*

The percent matrix effect (%), can be calculated by comparing slopes of calibration.

Table 2
Analytical parameters of the proposed method

| Analyte | Linear range (μg mL$^{-1}$) | Equation (Regression) | $R^2$ | Retention time (min) | LOD (μg mL$^{-1}$) | LOQ (μg mL$^{-1}$) | Conc. (μg mL$^{-1}$) | Precision (%RSD) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Inter-day | Intra-day |
| Paracetamol | 0.1–12 | $Y = 0.0534 + 0.0966X$ | 0.9975 | 4.9 | 0.02 | 0.08 | 5.0 | 3.1 | 2.4 |
| | | | | | | | 10.0 | 3.2 | 4.1 |
| | | | | | | | 15.0 | 5.2 | 3.5 |
| Caffeine | 0.1–12 | $Y = 0.0534 + 0.0559X$ | 0.9984 | 8.0 | 0.006 | 0.02 | 5.0 | 3.3 | 1.4 |
| | | | | | | | 10.0 | 4.2 | 3.1 |
| | | | | | | | 15.0 | 3.6 | 2.5 |
| Diclofenac sodium | 0.1–12 | $Y = 0.0557 + 0.054X$ | 0.9672 | 10.2 | 0.06 | 0.2 | 5.0 | 2.3 | 1.5 |
| | | | | | | | 10.0 | 2.2 | 4.1 |
| | | | | | | | 15.0 | 3.6 | 2.5 |

LOD: limit of detection, LOQ: limit of quantification, RSD: relative standard deviation

Table 3
Determination of NSAIDs drugs and recoveries for tap, canal and industrial wastewater samples

| Drugs | Spiked (μg mL$^{-1}$) | Tap water | | Canal water | | Industrial wastewater | |
|---|---|---|---|---|---|---|---|
| | | Found | $R$ (%) | Found | $R$ (%) | Found | $R$ (%) |
| Paracetamol | 0.0 | n.d | – | n.d | – | n.d | – |
| | 2.0 | 1.82 | 91.0 | 1.80 | 90.0 | 1.86 | 93.0 |
| | 5.0 | 4.63 | 92.6 | 4.45 | 89.6 | 4.75 | 95.0 |
| | 10.0 | 9.0 | 90.0 | 8.85 | 88.5 | 9.1 | 91.0 |
| Caffeine | 0.0 | n.d | – | n.d | – | n.d | – |
| | 2.0 | 1.86 | 93.0 | 1.84 | 92.0 | 1.80 | 90.0 |
| | 5.0 | 4.74 | 94.6 | 4.53 | 90.6 | 4.62 | 92.3 |
| | 10.0 | 9.25 | 92.5 | 9.15 | 91.5 | 9.35 | 93.5 |
| Diclofenac sodium | 0.0 | n.d | – | n.d | – | n.d | – |
| | 2.0 | 1.86 | 92.8 | 1.81 | 90.6 | 1.83 | 91.4 |
| | 5.0 | 4.57 | 91.3 | 4.64 | 92.8 | 4.73 | 94.6 |
| | 10.0 | 8.95 | 89.5 | 9.14 | 91.4 | 9.52 | 95.2 |

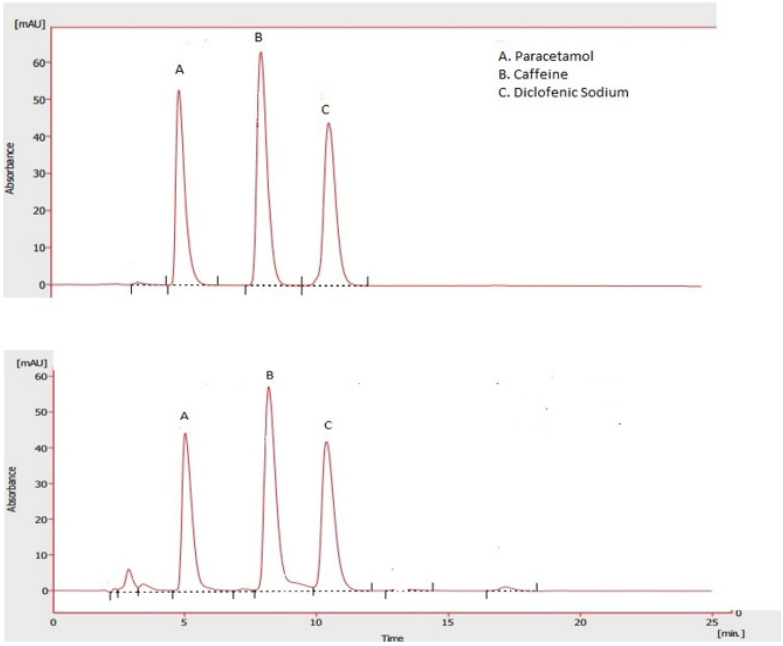


Fig. 6. Chromatograms obtained from spiked with 5 and 10 μg $mL^{-1}$ of mixture of selected NSAIDs drugs using SUPRAs microextraction.

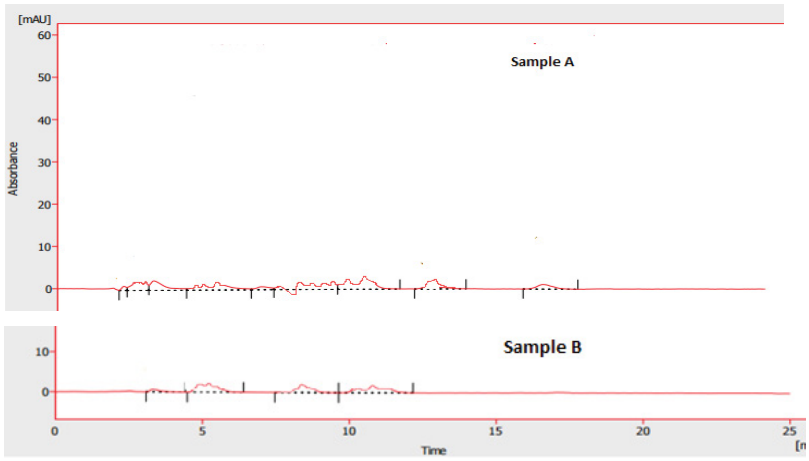


Fig. 7. Chromatograms obtained from water samples, canal water (Sample A) and tap water (Sample B).

Table 4
Effect of matrix from real samples

| Samples | Drugs | Matrix effect (%ME) | Extent of ME |
|---|---|---|---|
| Tap water | Paracetamol | –3.50 | Mild |
| | Caffeine | –1.40 | Mild |
| | Diclofenac sodium | 2.38 | Mild |
| Canal water | Paracetamol | –5.64 | Mild |
| | Caffeine | –3.21 | Mild |
| | Diclofenac sodium | –1.86 | Mild |
| Industrial estate water | Paracetamol | –23.54 | Medium |
| | Caffeine | –24.67 | Medium |
| | Diclofenac sodium | –28.38 | Medium |

Table 5
Comparison of proposed method with other reported methods for extraction of NSAIDs drugs

| NSAIDs drugs | Extraction method | Detection technique | Extraction time/ analysis (min) | Solve. vol. (mL) | Samp. vol. (mL) | Linear range | LOD | RSD % | Sample type | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Inter-day Intra-day | | |
| Ketoprofen Naproxen Ibuprofen Diclofenac | SPE, Oasis HLB | HPLC-DAD | SPE + 20 | | | 0.1–50 μg $mL^{-1}$ | 0.0058–0.0354 μg $mL^{-1}$ | | Water | [32] |
| Naproxen Indomethacin Diclofenac Ibuprofen | SPE, MNPs + CTAB | HPLC-UV | 20 | | 20 | 2.5–400 ng $mL^{-1}$ | 2–7 ng $mL^{-1}$ | | Water urine | [33] |
| Diclofenac<br>Ibuprofen<br>Carbamazepine | SUPRAs | UHPLC-UV | 30 | 0.7 | | 0.5–25 μg $mL^{-1}$<br>0.05–5 μg $mL^{-1}$ | 0.42 μg $mL^{-1}$<br>0.017 μg $mL^{-1}$ | | Sediment water | [34] |
| Diclofenac Ibuprofen Carbamazepine | SPE | LC-MS | SPE + 45 | 1 | | 0.05–10 μg $mL^{-1}$ | 0.3–30 ng $g^{-1}$ | | Water | [35] |
| Ketoprofen Naproxen Ibuprofen Diclofenac | SPE, Sorbent Strata TM X | GC-MS | 16 × 60 | | 50 | 0.02–0.25 mg $mL^{-1}$ | 2–6 ng $mL^{-1}$ | | Water | [36] |
| Ketoprofen Naproxen Ibuprofen Diclofenac | SPE | HPLC-DAD | SPE + 10 | | | 1–800 μg $mL^{-1}$ | 0.2 μg $mL^{-1}$ | | Water | [37] |
| Seven NSAIDs drugs | Ultrasonic-assisted emulsify micro extract | GC-MS | 20 | 0.1 | 10 | 0.02–50 ng $mL^{-1}$ | 0.005–0.01 ng $mL^{-1}$ | | Water | [38] |
| Twelve acidic NSAIDs | SPE, MWCNT | HPLC-QqQMS/MS | SPE + 20 | | 100 | 1–1,000 ng $L^{-1}$ | 0.01–1.3 ng $L^{-1}$ | | Surface water, tap water | [39] |
| Diclofenac Paracetamol Caffeine | SUPRAs | HPLC-UV | 1.0 | 0.4 | 20 | 0.1–12 μg $mL^{-1}$ | 0.006–0.06 μg $mL^{-1}$ | 2.2%–5.2%<br>1.4%–4.1% | Water samples | Present method |

Solid-phase extraction (SPE); High-performance liquid chromatography with diode-array detection (HPLC-DAD); Magnetic nanoparticles (MNPs); Cetyltrimethyl ammonium bromide (CTAB); High-pressure liquid chromatography with ultraviolet detector (HPLC-UV); Ultra-high performance liquid chromatography-ultraviolet; Liquid chromatography–mass spectrometry (UHPLC-MS); Gas chromatography–mass spectrometry (GC-MS); Multi-walled carbon nanotubes (MWCNTs); Triple quadruple tandem mass spectrometry detector (HPLC-QqQ-MS/MS).

Curves of standards in pure solvent with matrix spiked with standards was performed.

The matrix effects (% ME) for samples were calculated using equation [31].

$$\mathrm{ME}(\%) = \left[\frac{(\mathrm{Slope})_{\mathrm{matrix}}}{(\mathrm{Slope})_{\mathrm{solvent}}} \times 100\right] - 100 \quad (1)$$

where $(\mathrm{Slope})_{\mathrm{matrix}}$ is the slope in matrix and $(\mathrm{Slope})_{\mathrm{solvent}}$ is the slope in solvent. The results of calculations ranked on a scale 0% ME shows no matrix effect, 20 to − 20% ME indicate mild matrix effect, 20 to 50 or (−20) to (−50) % is a medium matrix effect, and above value shows strong matrix effect. The negative values indicate signal suppression due to matrix while the positive values are a sign of signal enhancement.

The % ME calculated for studied matrices (tap water, canal water and industrial estate water) are given in Table 4. These obtained values represent very little matrix effect for tap water and canal water while medium for industrial estate water sample.

### *3.5. Comparison of SUPRA with other reported methods*

The proposed method were compared with other reported methods for the determination of NSAIDs drugs in real samples (Table 5). The reported methods mostly involved high volume of solvents and extraction time while lower volume of sample. The current method presented low volume of solvent and extraction time as well as high volume of solvent. Extraction of selected NSAIDs drugs with SUPRAs microextraction has the advantage of low solvent consumption for the extraction, good values of LOD and LOQ which helps in quantitative determination of drugs in real samples.

## 4. Conclusions

Supramolecular (SUPRA) solvents contain nanostructures of amphiphiles which have a variety of polarity range and gives multiple binding sites (i.e., hydrogen bonds, hydrophobic, cation-π interaction, dispersion, etc.). These properties of multiple bonding make the SUPRA solvent one of the appropriate solvent for the microextraction. Therefore, these properties of SPRA solvent have been engineered for the microextraction of selected NSAIDs drugs in water samples. The method is rapid, green, eco-friendly and the requirement of using organic solvents was also eliminated in the microextraction. High extraction recoveries (%) were achieved in 1.0 min for all drugs using low SUPRA solvent (400 μL) volume.

## Conflict of interest

The authors have no conflict of interest.

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