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ELECTROPHORESIS

RESEARCH ARTICLE

Rapid determination of NSAIDs by capillary and microchip electrophoresis with capacitively coupled contactless conductivity detection in wastewater

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[Correction added on 28 November 2022, after first online publication: IReL funding statement has been added.]

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Abstract

A simple, rapid method using CE and microchip electrophoresis with C^4D has been developed for the separation of four nonsteroidal anti-inflammatory drugs (NSAIDs) in the environmental sample. The investigated compounds were ibuprofen (IB), ketoprofen (KET), acetylsalicylic acid (ASA), and diclofenac sodium (DIC). In the present study, we applied for the first time microchip electrophoresis with C^4D detection to the separation and detection of ASA, IB, DIC, and KET in the wastewater matrix. Under optimum conditions, the four NSAIDs compounds could be well separated in less than 1 min in a BGE composed of 20 mM His/15 mM Tris, pH 8.6, 2 mM hydroxypropyl-beta-cyclodextrin, and 10% methanol (v/v) at a separation voltage of 1000–1200 V. The proposed method showed excellent repeatability, good sensitivity (LODs ranging between 0.156 and 0.6 mg/L), low cost, high sample throughputs, portable instrumentation for mobile deployment, and extremely lower reagent and sample consumption. The developed method was applied to the analysis of pharmaceuticals in wastewater samples with satisfactory recoveries ranging from 62.5% to 118%.

KEYWORDS

capacitively coupled contactless conductivity detection, CE, environmental water, microfluidics, nonsteroidal anti-inflammatory drugs

1 | INTRODUCTION

Recently, pharmaceuticals have been increasingly used by humans and animals. Despite their effectiveness in treating a wide range of diseases, they pose a risk to aquatic environments [1, 2]. Among these pharmaceuticals, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely detected in environmental water due to their nonmedical use and abuse of prescription drugs. In addition, during the pandemic, NSAIDs are frequently used to treat COVID-19-related inflammation, fever, or pain symptoms. Consequently, it is likely that the COVID-19 pandemic has increased demand for pharmaceuticals and this trend

Abbreviations: ASA, acetylsalicylic acid; DIC, diclofenac sodium; HP-β-CD, hydroxypropyl-beta-cyclodextrin; IB, ibuprofen; KET, ketoprofen; NSAIDs, nonsteroidal anti-inflammatory drugs; WWTPs, wastewater treatment plants.

will continue as highly transmissible variants are developed [3]. The more frequent drugs consumed of this group are ibuprofen (IB), ketoprofen (KET), diclofenac (DIC), and acetylsalicylic acid (ASA) [4–6]. The pKa values for IB, KET, DIC, and ASA are 4.60, 4.00, 4.15, and 3.15, respectively.

There are many routes for pharmaceutical contaminants to enter the environment, mainly by human and veterinary excretion, hospital and municipal wastewater, or disposal from pharmaceutical production [7]. After their released into the environment, and as a result, they have been detected in surface water, wastewater, and groundwater.

Conventional wastewater treatment plants (WWTPs) have never been able to eliminate these compounds completely because they were not designed to do so [8, 9]. This problem is expected to become more difficult during a pandemic when such drugs are extensively prescribed and significant amounts of unmetabolized drugs are excreted [3]. Recently, Thalla and Vannarath reported that the concentration of DIC, IB, KET, and ASA in wastewater ranged from 22.7 to 2747.3 μg/L [10]. Other studies report the concentration of IB in different countries between 0.004 and 603 μg/L [11]. Therefore, their concentrations can differ widely across countries, depending on the amount of drugs that are consumed, the size of the population, and the effectiveness of the treatment plants [12]. These substances present at higher concentrations in WWTPs. Thus, a number of NSAIDs are discharged into the environment. It is essential to develop fast, simple, and reliable analytical methods for detecting NSAIDs in environmental water.

There are many analytical methods that have been reported for the determination of pharmaceutical contaminants in different environmental matrices using GC and HPLC coupled with MS [13–16]. These techniques, however, are expensive, require sample preparation, and generate large amounts of organic waste. In recent years, microchip electrophoresis (ME) has received a lot of attention because it is a highly effective platform for detecting numerous analytes due to its rapid analyzing time, low cost, high sample throughputs, portable instrumentation for mobile deployment, extremely lower reagents and samples consumption, and low-power requirement (the maximum voltage can be used 3 kV) [17, 18]. Additionally, all separation modes available in CE could be used in the ME, allowing for a broad range of applications [19]. ME allows for integrating multiple functions such as injection, separation, and detection on a single microchip with typical channel lengths of 1–10 cm [20].

ME has been coupled to different detection methods, including laser-induced fluorescence detection [21], mass spectrometric detection, and chemiluminescence [22]. Although the majority of the analytical techniques mentioned above provide high sensitivity, they require derivatization reactions, which are laborious and time consuming. On the other hand, electrochemical detection proved to be simple and low cost when combined with ME. Furthermore, it has the potential to enable miniaturization, automation, portability, and real-time analysis [23, 24].

Among electrochemical detection, C^4D has received significant attention in monitoring on-chip separations owing to its superior advantages compared to other electrochemical detection [25]. C^4D has the potential to eliminate problems that are frequently encountered in electrochemical detection systems when an electric field is applied during the electrophoretic run, such as electrode surface fouling and electrical interferences [26]. This is due to the sensing electrodes of the C^4D being located outside of the microchannels.

The separation and determination of NSAIDs have been reported by using CE–C^4D either individually or in combination with other drugs [27–31] in the environmental matrix, biological sample, and pharmaceutical formulation. In the literature, there are few papers that reported detecting NSAIDs by ME. ME with electrochemical detection was used to determine salicylic acid, acetaminophen, diflunisal, and DIC [24]. ASA, DIC, and IB have also been determined by microchip isotachophoresis-zone electrophoresis with contact conductivity detection [32]. To the best of our knowledge, there has been no study conducted to determine NSAIDs using ME–C^4D, except for Tanyanyiwa and Hauser's work [33]. They examined three model compounds, acetaminophen, IB, and salicylic acid, using ME–C^4D in the pharmaceutical formulation. In the present study, we applied, for the first time, ME with C^4D detection to the separation and detection of ASA, IB, DIC, and KET in the wastewater matrix. This method demonstrated excellent repeatability, good sensitivity, and a rapid analysis time of less than 1 min.

The aim of this study is to develop a simple, rapid method for the analysis and determination of four NSAIDs in the environmental sample using CE–C^4D and ME–C^4D.

2 | MATERIALS AND METHODS

2.1 | Instrumentation

CE electropherograms were obtained by Agilent CE 7100(Waldbronn, Germany) equipped with C^4D (TraceDec, Austria). A fused-silica capillary (Composite Metal Services, Shipley, UK) with 50 μm id and 375 μm od was used for all experiments. The new bare capillary was preconditioned using 1 M sodium hydroxide (NaOH)

for 30 min, DI water for 30 min, and finally with BGE for 30 min. The hydrodynamic injection was used to inject the samples for 2 s at 25 mbar. All experiments were carried out at 20 kV. ChemStation CE software (Agilent Technologies) was used to control the CE instrument and to collect the analytical signals. The pH meter (Metrohm 654) with microelectrode (Metrohm 6.0234.100) was used for all pH measurements.

All microchip electrophoretic measurements were carried out using a Quad HV microchip electrophoresis system (model ER455) supplied by Edaq (Denistone East, NSW, Australia). Glass chips with a double-T injector of 9 mm cross arm length, a 40 mm long separation channel, and a 33 mm effective length (from the intersection to the sensing electrodes) manufactured by Micronit Microfluidics BV (Enschede, The Netherlands) were purchased. More details about the layout of ME and preconditioning of the chips have been given elsewhere [34].

2.2 | Chemicals

ASA (≥99.0%), IB, DIC, KET, histidine (His), 2-(N-morpholino)ethanesulfonic acid (Mes), tris(hydroxymethyl)aminomethane (Tris), lactic acid, hydroxypropyl-beta-cyclodextrin (HP-β-CD), sodium hydroxide (NaOH), hydrochloric acid (HCl), and methanol were purchased from Sigma-Aldrich (Dublin, Ireland). In this experiment, analytical reagent-grade chemicals were used. Ultrapure DI water with a resistivity of 18.2 MΩ·cm was obtained from a Milli-Q (Millipore, Molsheim, France) water purification system.

2.3 | Sample preparation

The stock solutions of ASA, KET, DIC, and IB were prepared individually in methanol at a concentration of 100 mg/L and stored at 4°C. Appropriate quantities of Mes, His, and Tris were dissolved in DI water to make stock solutions at a concentration of 100 mM. They were mixed and diluted at a required ratio to give final concentrations for running buffers. Different concentrations of HP-β-CD were weighed and added to BGEs.

2.4 | Real sample

Wastewater samples were collected from the effluent of Cork, Ireland region. The sample was filtered through 0.45 μm filter paper (Millipore, Ireland) and stored in the refrigerator (4°C) until analysis.

3 | RESULTS AND DISCUSSION

3.1 | Optimization of CE parameters

Different BGEs at different pH from 6.0 to 8.7 were used to optimize the separation of NSAIDs. The type of BGE has an enormous influence on the peak shape of the sample and the S/N. To optimize BGE type, three BGEs, including Tris/lactic acid, Mes/His, and His/Tris, were tested. It was found that His/Tris BGE presented the best (S/N) in relation to other tested BGEs. In addition to providing higher sensitivity, it also provides good peak shape and high efficiency. Furthermore, His/Tris BGE has the fastest analyzing time (less than 2 min) compared to other tested BGEs. For this reason, His/Tris BGE was considered to be the optimal BGE for these NSAIDs analytes.

The pH of the BGE is known to be essential in CE experiments that utilize charged analytes, as it affects the amount of dissociation of weak acids, as a result influencing their effective mobilities [35]. The pH value of the BGE can be adjusted by varying the His to Tris ratio. The pH of 8.6 was chosen as the optimal pH for His/Tris BGE.

To achieve the best performance in terms of efficiency separation, resolution (resolution > 1.5), and S/N for NSAIDs, other parameters were investigated, including the concentration of HP-β-CD, organic solvent percentage, separation voltage, and injection time. Four NSAIDs analytes could be completely separated in less than 2 min with a BGE composed of 20 mM His/15 mM Tris, pH 8.6, 2 mM HP-β-CD, 10% methanol (v/v) at a separation voltage of 20 kV, and a hydrodynamic injection of 25 mbar for 2 s.

3.1.1 | The addition of cyclodextrin

Cyclodextrins have been increasingly used to enhance the resolution and separations of NSAIDs in chromatographic and CE techniques [36]. This is mainly due to the relatively hydrophobic cavity in comparison to the hydrophilic external surface, which can form inclusion complexes with a broad range of drugs resulting in the improvement of aqueous solubility [37].

HP-β-CD has been widely used as an effective resolving modifier for anions [38]. HP-β-CD is neutral, and after forming an inclusion complex with the analyte, the charge-to-size ratios of the analyte ion are decreased. Furthermore, HP-β-CD could form hydrogen bonds with the analytes because of its hydroxyl groups [30].

To examine the influence of HP-β-CD concentration on separation of NSAIDs, several experiments were performed in the range of 0–3 mM of HP-β-CD. The addition of HP-β-CD had the greatest effect on the electrophoretic

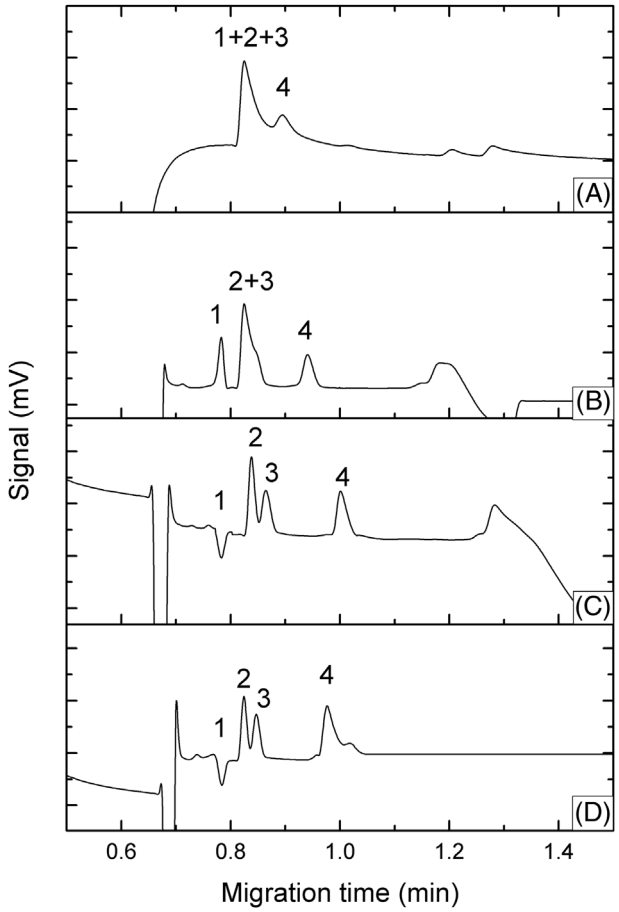

FIGURE 1 CE–C^4D electropherograms show the effect of using different concentrations of hydroxypropyl-beta-cyclodextrin (HP-β-CD) on the separation of nonsteroidal anti-inflammatory drugs (NSAIDs); (A) 0 mM, (B) 1 mM, (C) 2 mM, and (D) 3 mM. Capillary: 50 μm id 16 cm (effective length) 40 cm (total length); Peak: 1—ibuprofen (IB) (3 mg/L), 2—ketoprofen (KET) (1 mg/L), 3—diclofenac sodium (DIC) (1 mg/L), and 4—acetylsalicylic acid (ASA) (1 mg/L); temperature: 25°C; BGE: 20 mM His/15 mM Tris; separation voltage: 20 kV

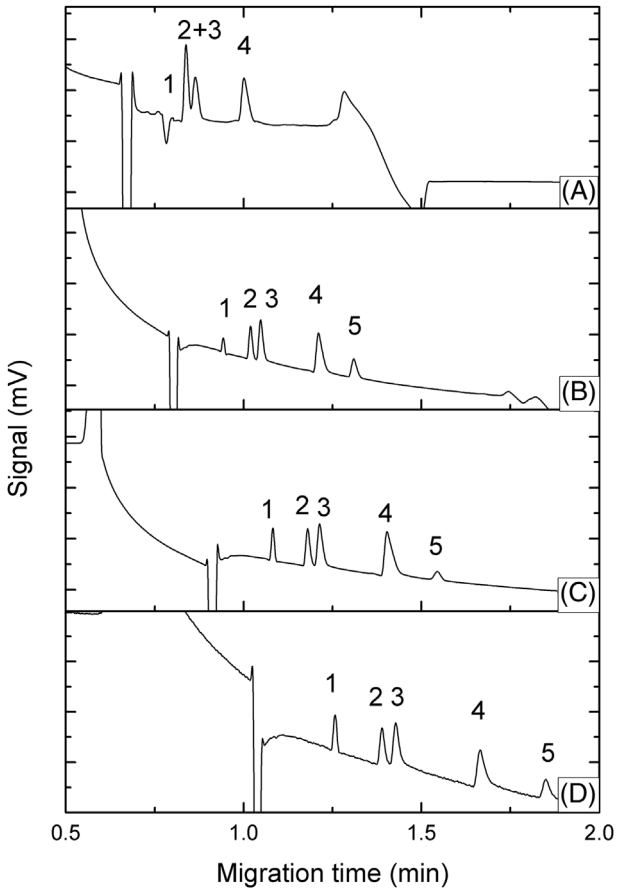

FIGURE 2 CE–C^4D electropherograms show the effect of using different methanol concentrations on the separation of nonsteroidal anti-inflammatory drugs (NSAIDs); (A) 0%, (B) 5%, (C) 10%, and (D) 15% (v/v). Capillary: 50 μm id 16 cm (effective length) 40 cm (total length); Peak: 1—ibuprofen (IB) (3 mg/L), 2—ketoprofen (KET) (1 mg/L), 3—diclofenac sodium (DIC) (1 mg/L), 4—acetylsalicylic acid (ASA) (1 mg/L), and 5—impurity; temperature: 25°C; BGE: 20 mM His/15 mM Tris, 2 mM hydroxypropyl-beta-cyclodextrin (HP-β-CD); separation voltage: 20 kV

mobilities of IB, DIC, and KET; without this complexing reagent, these peaks overlapped. As illustrated in Figure 1B, at a concentration of 1 mM HP-β-CD, the resolution occurred between IB and KET, but it was poor between KET and DIC. When the concentration of HP-β-CD was 2 mM, the resolution improved between KET and DIC (Figure 1C). Although the HP-β-CD is neutral and does not possess any charge, increasing the concentration of HP-β-CD greater than 1 mm (in our case) resulted in detected IB as a negative peak (Figure 1C,D).

Higher concentrations of HP-β-CD resulted in no further improvement in resolution. Furthermore, increasing the HP-β-CD concentration to 3 mM resulted in broad distorted peaks (Figure 1D). Therefore, 2 mM of HP-β-CD was chosen as the optimum concentration.

Due to the inability to obtain baseline separation by adding only HP-β-CD to the BGE, the use of organic solvents concurrently was tested in order to achieve better resolution between KET and DIC.

3.1.2 | Organic solvent

The effect of organic modifier on the separation of NSAIDs was examined by gradually adding 0–15% (v/v) of methanol to His/Tris BGE (pH 8.6). A general increase in both resolution and selectivity was observed upon the addition of methanol to the BGE. It can be noticed that (Figure 2) the IB peak turned to a positive peak when the methanol was added to the BGE. Although the mechanism

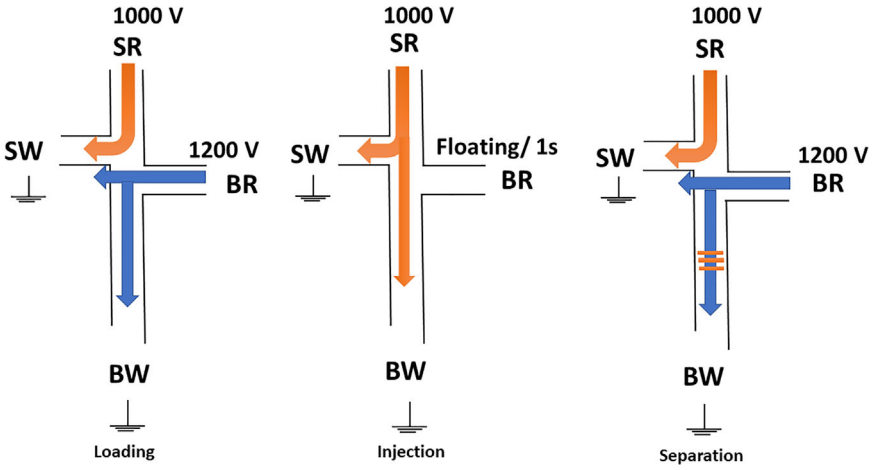

FIGURE 3 Schematic illustration of the injection in a double-T microchip. There are four reservoirs SW, SR, BR, and BW for sample waste, sample reservoir, BGE reservoir, and BGE waste, respectively

of the IB complex is not clear, the most important effect is probably due to the change in the conductivity of the IB complex in the presence of methanol.

The addition of organic solvent had a great effect on separation and baseline. As can be shown in Figure 2C, symmetric peaks and baseline separation were achieved with the BGE containing 10% of methanol. No further improvement in the resolution between KET and DIC was obtained by increasing the percentage of methanol in this BGE. Furthermore, increasing the concentration of methanol led to an increase in migration times might be attributed to the decreased electroosmotic flow [39]. Therefore, the optimum percentage of methanol was 10%, as all studied drugs exhibited the best resolution and efficiency.

3.2 | Optimization of ME parameters

ME results from the miniaturization of CE, and thus the separation process on the chip is based on the same principle as in the capillary. However, introducing the sample plug into the channels in the ME is different from the conventional CE. In ME separation, introducing the sample is usually by electrokinetic injection when the electric field applies across the microchannels.

There are many injection modes in ME, such as pinched, floating and gated injection. For all experiments in this work, the gated injection was used. As shown in Figure 3, the voltages were applied to the sample reservoir (SR) and BGE reservoir (BR), and the other reservoirs were grounded. During the sample loading phase, the sample flows from SR to sample waste (SW), while the BGE flows from BR to BGE waste (BW) for 5 s. There is also a flow of BGE from BR to SW, which prevents sample leakage into the separation channel. In the sample injection phase, the BR is floated for 1 s to allow a sample plug to move into the separation channel. Then the voltage is added again at BR to move the plug of the sample into the separation channel (Figure 3). Separation and detection happened during the sample movement.

In order to determine the optimum voltage, analyses at different voltages were carried out. From Figure 4D, it can be seen that higher resolutions, efficiency, and short migration time were obtained for all the analytes when 1000 V (SR) and 1200 V (BR) were used. However, when the voltage was decreased to 400 V (SR) and 600 V (BR), the overlapping peaks occurred, resulting in a loss in resolution and poor efficiency (Figure 4A). When 600–800 V were applied to (SR) and (BR), respectively, there was a distorted peak, and the resolution between KET and DIC was still not ideal (Figure 4B). There was an improvement in peak shapes and the selectivity when 800 V (SR) and 1000 V (BR) were used, but the resolution between KET and DIC was less than 1.5 (Figure 4C). Based on these findings, separation voltages of 1000–1200 V were found to be ideal (Figure 4D).

To achieve optimal sensitivity, the frequency and voltage of the excitation signal were optimized. The best results were obtained using 700 kHz and 60 Vpp. For this reason, 700 kHz and 60 Vpp were used for all subsequent measurements.

3.3 | Calibration

The calibration curves of the proposed method were linear and ranged from 0.25 to 10 mg/L for KET, ASA, and DIC and 1 to 20 mg/L for IB for both CE and ME measurements. The results of both CE and ME methods shown in Table 1 exhibited excellent correlation coefficients (R^2) values (>0.99). Good RSDs for all studied analytes were less than 2.5% (for migration time) and less than 9 (for peak area). The LOD for this method (S/N = 3) ranged from 0.062 to 0.6 mg/L for all compounds without sample preconcentration.

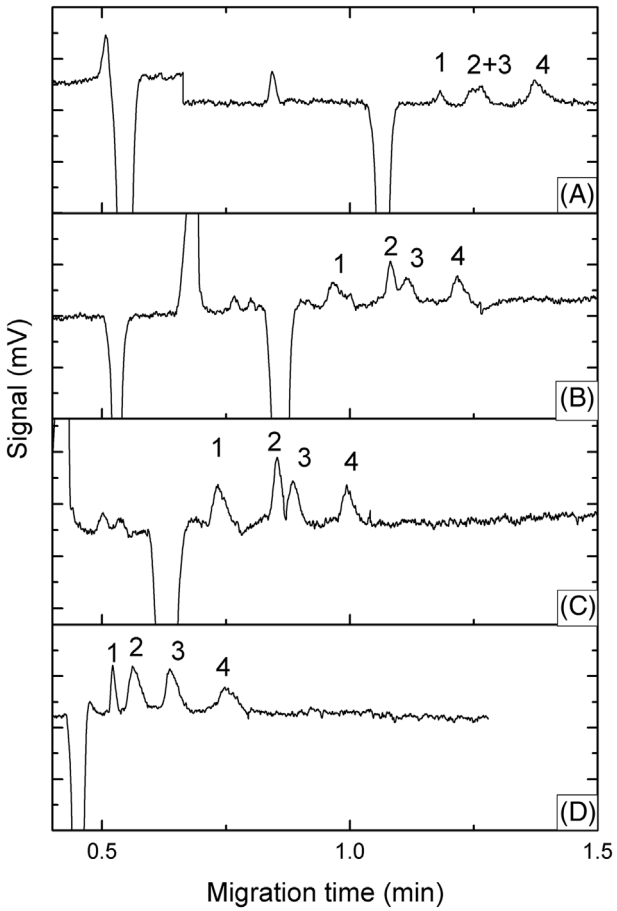

FIGURE 4 Microchip electrophoresis (ME)–C^4D electropherograms show the effect of using different voltages on the separation of nonsteroidal anti-inflammatory drugs (NSAIDs); (A) 400 V (SR)–600 V (BR), (B) 600 V (SR)–800 V (BR), (C) 800 V (SR) 1000 V (BR), and (D) 1000 V (SR)–1200 V (BR). Peak: 1—ibuprofen (IB) (3 mg/L), 2—ketoprofen (KET) (1 mg/L), 3—diclofenac sodium (DIC) (1 mg/L), and 4—acetylsalicylic acid (ASA) (1 mg/L); BGE: 20 mM His/15 mM Tris, 2 mM hydroxypropyl-beta-cyclodextrin (HP-β-CD); 10% (v/v) methanol

3.4 | Analysis of real sample

For the extraction of NSAIDs from wastewater samples, a Sep-Pak C18 3 cc column (Waters, Ireland) was used. Cartridges were washed with 3 ml methanol and 6 ml DI water (adjusted to pH 2 with HCl to keep the four NSAIDs analytes in their protonated forms) before loading the samples. It should be noted that 10 ml of wastewater (pH 2 with HCl) was spiked with 1 mg/L of IB and 0.25 mg/L of each (KIT, DIC, and ASA). To maximize the retention of analytes, spiked wastewater samples were loaded at a constant and low flow rate of 1 drop/s. Subsequently, the cartridge was washed with 3 ml DI water (without adjustment) and 3 ml of methanol–water (30:70, v/v). To elute the target analytes from the sorbent, 2 ml of methanol was used. The resulting eluates were reduced to 0.5 ml using a gentle stream of nitrogen gas. The nonspike wastewater sample was prepared following the same procedure used for spiked wastewater samples.

The described method was applied to extract the target analytes from wastewater using CE and ME with C^4D detection (Figure 5A,B). As illustrated in Table 2, the recoveries for KET, IB, and DIC in spiked wastewater obtained with CE and ME were in the range of 62.5%–118%, with RSD < 17% (n = 3), indicating satisfactory recoveries of these compounds, except for ASA. The low affinity of ASA to C18 sorbent could be the reason for low recovery.

4 | CONCLUDING REMARKS

We have demonstrated a simple, rapid, and efficient method for the determination of NSAIDs in environmental water using CE and ME with C^4D. Under the optimum conditions, the proposed method showed excellent R^2 (>0.99), good repeatability of migration time, and

TABLE 1 Calibration of the four nonsteroidal anti-inflammatory drugs (NSAIDs)

Technique	Analytes	Linearity range (mg/L)	R^2	LOD (mg/L)	$RSD_{n=6}$ (peak area)	$RSD_{n=6}$ (migration time)
CE–C^4D	ASA	0.25–4	0.9962	0.062	5.3	1.3
	DIC	0.25–4	0.9965	0.125	5.2	1.1
	IB	1–16	0.9951	0.5	3.7	1
	KET	0.25–4	0.9979	0.125	4.9	1.2
ME–C^4D	ASA	0.625–10	0.9901	0.156	8.8	2.4
	DIC	0.625–10	0.9909	0.156	6	0.92
	IB	1.25–20	0.9911	0.625	7.4	2
	KET	0.625–10	0.9956	0.156	6.7	0.9

Abbreviations: ASA, acetylsalicylic acid; DIC, diclofenac sodium; IB, ibuprofen; KET, ketoprofen; ME, microchip electrophoresis.

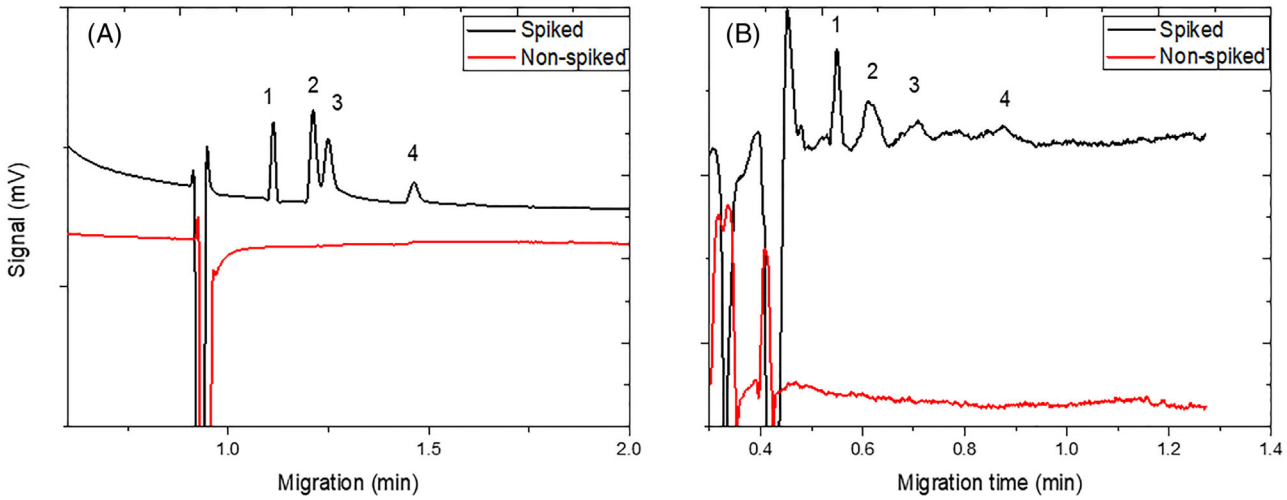

FIGURE 5 Electropherograms corresponding to (A) SPE for wastewater using CE-C^4D and (B) SPE for wastewater using microchip electrophoresis (ME)-C^4D. Peak: 1—ibuprofen (IB) (3 mg/L), 2—ketoprofen (KET) (1 mg/L), 3—diclofenac sodium (DIC) (1 mg/L), and 4—acetylsalicylic acid (ASA) (1 mg/L); BGE: 20 mM His/15 mM Tris, 2 mM hydroxypropyl-beta-cyclodextrin (HP-β-CD); 10% (v/v) methanol

TABLE 2 The recoveries of investigated compounds in wastewater samples

	Recovery (RSD%)	
	CE–C^4D	ME–C^4D
Analyte	Wastewater sample	Wastewater sample
IB	115.3 (5%)	114 (9%)
KET	118 (8%)	69.2 (8%)
DIC	92.3 (5.6%)	62.5 (6.7%)
ASA	26.7 (10%)	23 (16.2%)

Abbreviations: ASA, acetylsalicylic acid; DIC, diclofenac sodium; IB, ibuprofen; KET, ketoprofen; ME, microchip electrophoresis.

peak areas <2.5% and <9%, respectively, and LOD ranged from 0.062 to 0.6 mg/L. Even though this LOD is comparable with their concentrations in wastewater, further improvement in detection sensitivity is necessary. Thus, online electrophoretic preconcentration methods [40] will be the focus of future research. Clear advantages of ME–C4D method over conventional CE are rapid analysis time, low cost, high sample throughputs, portability, extremely lower reagent, and sample consumption. The ME–C^4D method presented in this study can be used to determine NSAIDs in environmental applications.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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