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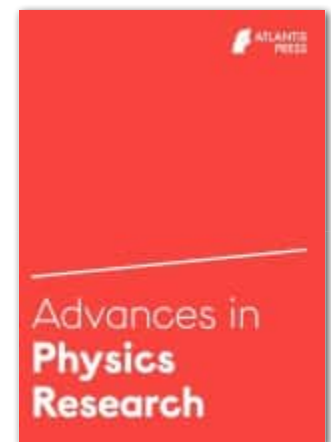
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Molecular docking approach has been successfully developed for prediction of enantioseparation of econazole on the cyclodextrin derivatives namely sulfated- β -cyclodextrin (S- β -CD) and hydroxypropyl- γ -cyclodextrin (HP- γ -CD) as chiral selectors. Molecular docking was performed using AutoDock Vina software...

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Quantitative determination of ketorolac, a nonsteroidal anti-inflammatory drug (NSAID) in water samples was reported using the micellar electrokinetic chromatography (MEKC) method. The on-line preconcentration technique at MEKC was then investigated to increase the detection sensitivity of ketorolac....

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The research studied disease mapping of dengue haemorrhagic fever (DHF) in Banyumas Regency. The generalized Poisson (GP), negative binomial (NB), and CAR-BYM models are then used to modelling the DHF. The predictor variables used in this research are the number of health worker, altitude, and population...

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Development of Ketorolac Analysis in Water Samples using Micellar Electrokinetic Chromatography

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Abstract

Quantitative determination of ketorolac, a nonsteroidal anti-inflammatory drug (NSAID) in water samples was reported using the micellar electrokinetic chromatography (MEKC) method. The on-line preconcentration technique at MEKC was then investigated to increase the detection sensitivity of ketorolac. A 6-fold increase in sensitivity factor was achieved using normal stacking mode (NSM)-MEKC. The average recovery of ketorolac in tap water samples was 102.16% (RSD = 0.06%). The current NSM-MEKC method is simple, has short analysis time, high accuracy, and uses fewer organic solvents (environmentally friendly).

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Development of Ketorolac Analysis in Water Samples using Micellar Electrokinetic Chromatography

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ABSTRACT

Quantitative determination of ketorolac, a nonsteroidal anti-inflammatory drug (NSAID) in water samples was reported using the micellar electrokinetic chromatography (MEKC) method. The on-line preconcentration technique at MEKC was then investigated to increase the detection sensitivity of ketorolac. A 6-fold increase in sensitivity factor was achieved using normal stacking mode (NSM)-MEKC. The average recovery of ketorolac in tap water samples was 102.16% (RSD = 0.06%). The current NSM-MEKC method is simple, has short analysis time, high accuracy, and uses fewer organic solvents (environmentally friendly).

Keywords: Ketorolac; Micellar electrokinetic chromatography; Water sample

1. INTRODUCTION

Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), is a drug that has been shown to have opioid-sparing effects and reduces opioid-related side effects in the treatment of postoperative pain [1]. Ketorolac was developed as a safer alternative to opioid analgesics and is now available as a generic drug. Ketorolac or known as (RS)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1 carboxylic acid is a synthetic pyrrolizine carboxylic acid derivative. Ketorolac has a different shape from other NSAIDs in that it has a stereogenic center in the pyrrole ring and has an asymmetric carbon in the 2-arylpropionic acid side chain. Ketorolac is a non-steroidal anti-inflammatory drug that includes a non-narcotic analgesic drug that has antipyretic properties 20 times stronger than aspirin and was patented in 1976 and in 1989 was approved by the USFDA for medical use. Ketorolac tromethamine is an NSAID that is used for several clinical indications

and was the first to be approved for parenteral use and postoperative therapy [2-3]. At physiological pH, ketorolac tromethamine dissociates to form the anion ketorolac. It can also be used for the treatment of pain after cesarean delivery, cancer-related pain, and in the emergency department for the treatment of renal colic pain, sickle cell crisis, migraine headaches, and musculoskeletal pain. Ketorolac has been used safely and effectively in certain pediatric populations but is not currently recommended for use in children under 17 years of age [4].

Terabe in 1984 [5], introduced hybrid electrophoresis and a chromatographic method called micellar electrokinetic chromatography (MEKC) and has become reliable in the high-efficiency separation of charged and neutral analytes using capillary electrophoresis instruments. (CE) without any changes [6-11]. Capillary electrophoresis (CE) is one of the most reliable analytical liquid phase separation

techniques due to its small sample requirements, low operating costs, and high separation efficiency. CE has the availability of a CE mode which allows separation of almost all analytes. This technique uses a voltage that is applied to a glass capillary tube containing a buffer solution that produces the driving force of the electroosmotic flow [13]. The injected sample is separated based on the electrophoretic mobility between the ions and molecules through the capillary, which is a result of the object's charge and the frictional force it experiences. MEKC belongs to the category of separation methods and is a variant of capillary electrophoresis (CE).

In MEKC, the stationary phase is the anionic surfactant as the pseudo stationary phase and the surrounding aqueous phase becomes the mobile phase. Sodium dodecyl sulfate (SDS) is the most widely used surfactant in the MEKC method [14-16]. The separation of analytes is based on the principle of partition difference between the micellar phase and the aqueous phase. Micelles in the MEKC method are added to the CE buffer solution and the stationary phase to assist in separating neutral molecules. The micelle system is chosen in such a way that the charge of the micelles results in their opposite electrophoretic mobility as opposed to electroosmotic [17-18].

The poor CE concentration sensitivity is due to the small sample size (1–10 L) and the short optical path length and capillary diameter for the absorbance detector [19-23]. Electrochemical measurements and highly sensitive detectors for laser-induced fluorescence are one possible solution. Another solution is to expand the optical path such as bubble cells or Z-type cells, while minimally lowering the resolution, which can increase sensitivity. However, all these methods take a long time and the hardware is a bit expensive and a bit complicated. Online sample preconcentration is one of the most reliable solutions for increasing the level of concentration sensitivity, where a longer-than-usual plug sample is injected and focused on the capillary prior to separation. The use of pressurized injection, also known as hydrodynamics or electrokinetic, can be used. Sample stacking and sweeping are recognized as two online sample preconcentration techniques in providing increased concentration sensitivity in MEKC [24-26].

This work aims to develop the MEKC method, which is very potent and can be used for the analysis of NSAIDs, namely ketorolac. This method was then used to evaluate the application of normal stacking mode (NSM) [27], as an online preconcentration technique to increase the concentration sensitivity of MEKC. method for the analysis of ketorolac in water samples. The MEKC method proposed for ketorolac analysis is

simple, fast analysis, high accuracy and requires minimal use of organic solvents (environmentally friendly).

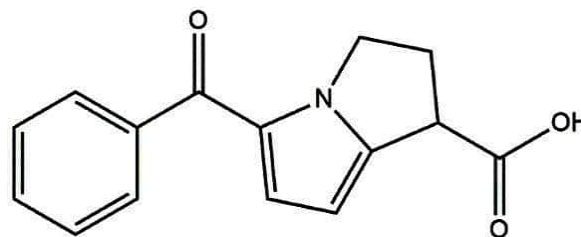


Figure 1. Chemical structure of ketorolac

2. MATERIALS AND METHODS

2.1 Materials

Ketorolac as an analyte was purchased in St. Louis, MO, USA at the Sigma-Aldrich site. The chemical structure of ketorolac is shown in **Figure 1**. Sodium hydroxide and anhydrous sodium tetraborate as solvents under the brand name “Darmstadt”, Germany purchased from Merck. Sodium dodecyl sulfate (SDS) as a chiral selector was purchased from Fischer Chemicals located in Loughborough, Leics, UK. JT Baker in Pennsylvania, USA, provided the organic solvent (HPLC grade). Deionized water (DI) was purified with Millipore Simplicity (Simpak®2) (Barnstead, USA). The standard stock solution was prepared by dilution with methanol which was used as the working standard solution. Standard stock is stored in the refrigerator until needed.

2.2 Instrumentation

A CE system from Agilent Technology (7100, Waldbronn, Germany) equipped with a DAD and operating at a wavelength of 320 nm was used for the analysis. The separation process uses uncoated fused silica capillaries, which have a total length of 64.5 cm and 56 cm for the detector size, and the inside diameter (ID) is 50 μm . The CE system (Chromatography Station CSW 1.7) was used to collect analytical data. 1.0 M NaOH was used for conditioning. DI water was used for new capillary equalization for 30 minutes, followed by 0.1 M NaOH solution for 15 minutes, DI water for 15 minutes, and finally with BGE solution for 10 minutes. Hydrodynamic injection in all cases was used to optimize separation at 50 mbar for 5 s (5 μL sample volume) at the capillary inlet.

3. RESULTS AND DISCUSSIONS

It is known that the low sensitivity of MEKC concentration is caused by several factors, including the

small number of samples injected (1-10 L sample volume) [28-33]. This study uses the normal stacking mode applied to the optimized MEKC system to increase the detection sensitivity of ketorolac. The stacking process is performed when the conductivity of the sample is significantly lower than that of the running buffer. The sampling procedure in the normal mode under MEKC conditions is referred to as normal stacking mode (NSM). The application of the NSM method on the MEKC system uses a lower conductivity of the sample solution compared to the micellar/separation solution. Pure water is used to dilute the sample stock solution [34-36].

The NSM method is used to optimize the sample injection time and the best sample injection time is 80

seconds. The decrease in peak height occurred when there was an increase in sample injection time (more than 80 seconds), while the peak area did not increase significantly (data not shown). After confirming that no ketorolac was found in the tap water sample, the NSM-MEKC method was used to analyze the ketorolac in the spiked tap water sample. **Figure 2** shows an electropherogram of 0.75 g/mL of ketorolac in a spiked tap water sample and a tap water sample using the optimized NSM-MEKC method. There is no interference matrix peak with a standard rejection peak.

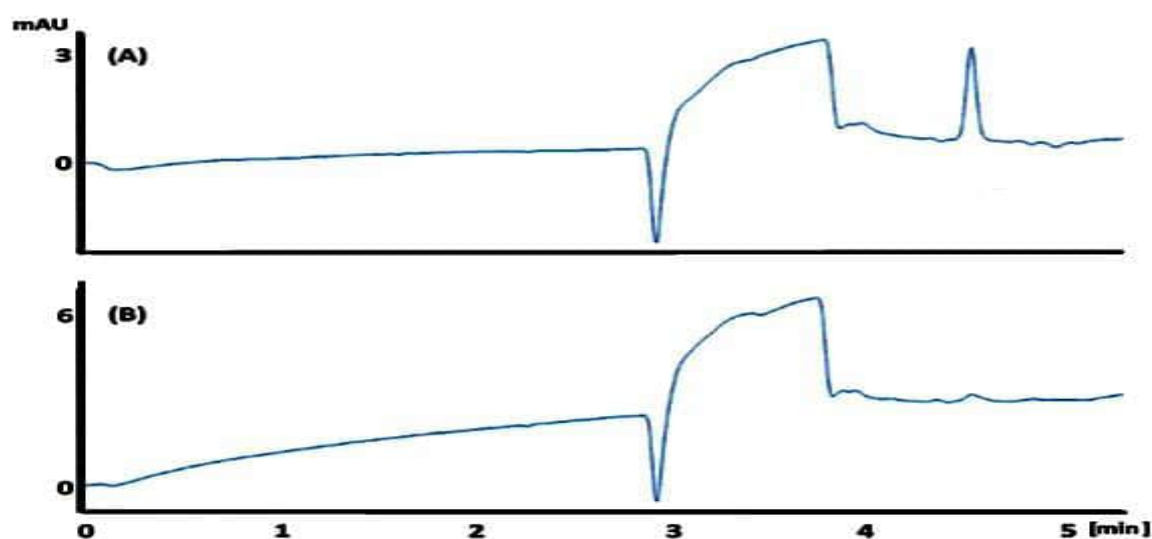


Figure 2. Electropherogram (A) 0.75 $\mu\text{g/mL}$ ketorolac in spiked tap water samples; and (B) tap water samples; with the optimized NSM-MEKC method.

The average recovery of ketorolac in spiked tap water samples was 102.16% (RSD = 0.06%, $n=3$). The NSM-MEKC method increased the detection sensitivity of ketorolac 6-fold when compared to the conventional MEKC injection method. These results indicate that NSM-MEKC tends to improve the detection of ketorolac.

4. CONCLUSIONS

Analysis of ketorolac in water samples has been reported using the micelle electrokinetic chromatography (MEKC) method. The on-line preconcentration technique at MEKC using the normal stacking mode suggests an increased possibility of detection of ketorolac. The results obtained can be used as a reference in a preliminary study for further studies

on the application of other online preconcentration techniques at MEKC for ketorolac analysis.

AUTHORS' CONTRIBUTIONS

DH performed CONCEPTUALIZATION, METHODOLOGY, SUPERVISION, and REVIEW. C did INVESTIGATION, DATA CURATION, WRITING and EDITING. AF made VALIDATION, SOFTWARE, PROJECT ADMINISTRATION, and SUPERVISION. S performed SUPERVISION, PROJECT ADMINISTRATION, and VALIDATION. WAWI did CONCEPTUALIZATION, SUPERVISION, FORMAL ANALYSIS, and VALIDATION. HYA contributed to CONCEPTUALIZATION, SUPERVISION, FORMAL ANALYSIS, AND VALIDATION.

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