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Development of an Analytical Method Based on Capillary Electrophoresis for Simultaneous Quantification of Memantine and Donepezil in Anti-Alzheimer's Pharmaceuticals

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Abstract

In the study, a capillary electrophoresis method utilizing capacitively coupled contactless conductivity detection (CE-C⁴D) was developed and evaluated for the simultaneous analysis of memantine (MEM) and donepezil (DON) in pharmaceutical samples for Alzheimer's disease treatment. The analytical conditions were established, including a background electrolyte (BGE) composed of 1.0 M acetic acid, a separation voltage of -22 kV, and siphonic sample injection at a height of 10 cm for 60 seconds. Under these conditions, the limits of detection (LOD) for MEM and DON were 0.59 mg/L and 1.39 mg/L, respectively. The relative standard deviations (RSD) for peak area and migration time were less than 6% and 1%, respectively, in intra-day repeatability assessments (n = 7), and less than 8% and 4%, respectively, in inter-day reproducibility assessments (n = 5) for mixed standard samples at a concentration of 20 mg/L. The recovery efficiency for both analytes in spiked standard matrices ranged from 94 to 108%. The CE-C⁴D method was applied to analyze two real pharmaceutical samples containing DON as the main active ingredient, and the results indicated that the difference between the content determined by CE-C⁴D and the manufacturer's labeled content was less than 10%.

Keywords: Alzheimer, capillary electrophoresis, donepezil, memantine, pharmaceuticals.

1. Introduction

Alzheimer's disease is a neurodegenerative disorder commonly affecting individuals over 65 years of age [1]. It leads to the destruction of myelin and a reduction in acetylcholine, a key neurotransmitter involved in memory and learning, resulting in memory loss, cognitive decline, and loss of motor function [2, 3]. These symptoms worsen over time and ultimately lead to death. Alzheimer's disease is the most prevalent among neurodegenerative diseases. As of 2016, there were approximately 43.8 million cases and 2.4 million deaths worldwide due to Alzheimer's disease; in Vietnam, the figures were about 655,000 cases and nearly 42,400 deaths [4].

The increasing number of patients has led to a growing demand for Alzheimer's medications. Two main groups of drugs are used: glutamate modulators such as memantine (3,5-dimethyladamantan-1-amine, MEM) and cholinesterase inhibitors such as donepezil (2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one, DON) [5]. MEM blocks excitotoxic stimulation arising from excessive glutamate release and is typically indicated for moderate to severe stages of Alzheimer's disease. In contrast, DON inhibits cholinesterase activity, the enzyme that degrades acetylcholine, and is approved for all stages (mild, moderate, and severe) of Alzheimer's disease [6]. The chemical structures of MEM and DON are illustrated in Fig. 1.

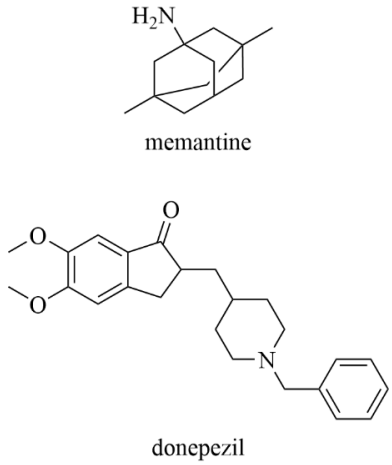

Fig. 1. Chemical structures of memantine and donepezil

Common Alzheimer's medications in Vietnam include Aricept (main ingredient: DON), Nemanda (main ingredient: MEM), and Namzeric (containing

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both DON and MEM). The high demand for these drugs necessitates the development of methods for simultaneous quantification of the main active ingredients (MEM and DON) to ensure quality control. However, accurate and rapid analysis of these compounds in practice remains challenging, especially for on-site determination.

For Alzheimer's medications, research on quantifying active ingredients in drugs or biological samples is still limited. Published studies mainly employ high-performance liquid chromatography (HPLC) or ultra-performance liquid chromatography (UPLC) coupled with ultraviolet (UV) or mass spectrometry (MS) detectors. Ralf Koeber *et al*. (2012) developed a method for DON analysis in human plasma using HPLC-UV, with a retention time of 12.1 minutes, calibration range of 5.0 – 160 µg/L, and limits of dectection (LOD) of 1.7 µg/L [7]. Muriel Noetzli *et al*. (2012) developed a simultaneous analysis method for MEM, DON, galantamine, rivastigmine, and metabolite NAP 226-90 using UPLC-MS/MS, with calibration ranges for DON and MEM of 1.0 – 300 µg/L and an analysis time of about 4.5 minutes [8]. Manisha Bhateria *et al*. (2015) used LC-MS/MS to simultaneously determine MEM and DON in mouse serum, with an LOD of 0.20 µg/L and a linear range of 0.20 – 400 µg/L, using amantadine as an internal standard [9]. G.H. Ragab *et al*. (2019) developed an HPLC biochemical method for simultaneous determination of DON and citalopram in drug and human serum samples, with an optimal analysis time of about 6 minutes, calibration range of 0.10 – 10 mg/L, and LOD of 17 µg/L for DON [10]. Recently, Shourya Tripathi *et al*. (2025) simultaneously analyzed DON and quercetin using UPLC-PDA with an analysis time of about 10 minutes [11].

Recently, several studies employing spectroscopic and electrochemical methods have been developed for the quantification of DON and MEM. A thin-layer chromatography (TLC) method combined with digital image analysis tools, including densitometry, ImageJ software, and smartphone color picker apps, for quantifying DON and MEM from chromatograms was developed by Eman Moaaz *et al*. (2024) [12]. Due to the absence of conjugated π systems, MEM exhibits very weak UV-Vis absorption and requires derivatization with Dragendorff's reagent to generate color (brown for DON and dark yellow for MEM). The results showed optimal linear ranges of 1 – 20 µg/band for DON and 1 – 30 µg/band for MEM, respectively. Additionally, advanced electrochemical methods utilizing ion-selective electrodes (ISEs) integrated with molecularly imprinted polymers (MIPs) have been developed. The lowest LODs achieved were 19.0 µg/L for DON and 40.2 µg/L for MEM [13].

In pharmaceutical analysis, capillary electrophoresis (CE) is often used as an alternative to HPLC. However, there have been no studies on the analysis of these active ingredients in Alzheimer's medications using CE. Furthermore, in Vietnam, no research has been conducted on quantitative analysis of DON and MEM in pharmaceutical products, and the Vietnamese Pharmacopoeia does not provide corresponding methods for determining DON or MEM.

The most common method for simultaneous quantification of active pharmaceutical ingredients is HPLC/UPLC, which is also recommended in pharmacopoeias. However, the main drawbacks of HPLC are high cost, the need for skilled operators, and difficulty in on-site implementation. To address these challenges, CE offers a reasonable alternative, requiring fewer chemicals, relatively simple operation, and ease of on-site deployment, especially with miniaturized CE devices. The application of CE with capacitively coupled contactless conductivity detection (C^4D) in pharmaceutical analysis has developed significantly over the past 20 years [14, 15], and recently, CE-C^4D has been used for simultaneous quantification of three main active ingredients in Parkinson's disease medications, another common neurodegenerative disorder [16]. Therefore, this study focuses on addressing the issue of quality control for Alzheimer's medications by quantifying the main active ingredients (MEM and DON) using CE-C^4D. To the best of our knowledge, the use of CE-C^4D for the simultaneous quantification of MEM and DON in anti-Alzheimer's medications has not been previously reported. This study, for the first time, develops and validates a CE-C^4D method for this purpose. The novelty of this work lies in providing a simple, rapid, and cost-effective analytical method that is suitable for on-site quality control of these pharmaceuticals, offering a practical alternative to the more complex and expensive HPLC-based methods.

2. Materials and Methods

2.1. Chemicals

Standard substances of MEM and DON (as hydrochloride salts, purities > 98.0 %) were purchased from Tokyo Chemical Industry (Tokyo, Japan). Acetic acid (Ace, ≥ 99.7 %), formic acid (For, ≥ 95 %), and lactic acid (Lac, ≥ 85.0 % in H_2O) used for preparing the background electrolyte (BGE) solutions were obtained from Merck KGaA (Darmstadt, Germany). Other chemicals, including solid NaOH and 37% (w/w) HCl solution of analytical grade, were supplied by Sigma-Aldrich (Taufkirchen, Germany).

Single stock standard solutions at a concentration of 1000 mg/L of MEM and DON were freshly prepared monthly in 0.1 M HCl solution. Mixed working standard solutions containing both analytes at different levels were prepared daily by mixing and diluting the stock solutions with deionized water. BGE solutions were also obtained daily and sonicated for 10 minutes to remove air bubbles before use. All prepared solutions were stored in a refrigerator at 4 °C if not used immediately.

2.2. Instrumentation

In this study, all CE experiments were conducted by using a manually operated CE instrument at the Center for Environmental Technology and Sustainable Development (CETASD), VNU University of Science, Vietnam National University, Hanoi. This system used a EMCO high-voltage (HV) power from XP Power (Rungis Cedex, France) with the maximum HV supply of ±25 kV. The C^4D detector in this system was a commercial product ET-120 from eDAQ (New South Wales, Australia). Data from the C^4D detector were acquired by an eDAQ e-corder 410 system.

A fused-silica capillary (Agilent Technologies, California, USA) with dimensions of 50 µm internal diameter, 365 µm outer diameter, 50 cm total length, and 42 cm effective length was used for all separations. Before the first analysis of each day or following a change of BGE, the capillary was conditioned sequentially by flushing with 0.1 M NaOH (5 min), then deionized water (10 min), and finally fresh BGE (15 min). Between consecutive runs with the same BGE, the capillary was rinsed with BGE for 5 min to ensure reproducibility. Besides, all analyses were conducted at a controlled ambient temperature of 25 °C maintained by air conditioning.

2.3. Sample Preparation

Pharmaceutical samples containing DON as the main active ingredient, including sample S1 (Lupipezil 5 mg) and S2 (Yradan 10 mg), were purchased from major pharmacies in Hanoi. Five tablets of each type were finely ground and mixed thoroughly. An accurately weighed amount of powder corresponding to the average tablet weight (145.6 mg for sample S1 and 151.6 mg for sample S2, equivalent to 5 mg and 10 mg of DON, respectively) was dissolved in 100 mL of 0.1 M HCl solution and was sociated for 10 minutes. HCl solution was used to completely dissolve the tablet powder and maintain a low pH to ensure the stability of the active ingredients, as well as to create a sample matrix similar to the standard solutions. The resulting solution was then diluted with 0.1 M HCl to a final DON concentration of approximately 20.0 mg/L. Finally, the diluted solution was filtered through a 0.45 µm nylon membrane filter before injection into the CE system.

For the recovery studies, the pre-spiked samples prepared as described above served as the 100% recovery level (working concentration). Matrix-matched samples were generated by diluting these 100% solutions at different factors (0, 2, and 4 times). Analytes were then spiked into the matrices at three concentration levels (10, 20, and 40 mg/L for MEM; 5, 10, and 20 mg/L for DON), achieving final concentrations twice those in the corresponding matrices (for DON).

2.4. Method Validation

The LOD and quantification (LOQ) for the analytes were determined as the concentrations corresponding to signal-to-noise ratios (S/N) of 3 and 10, respectively. Repeatability was assessed by performing seven consecutive measurements of a 20.0 mg/L standard solution of each analyte within a single day (n = 7). Moreover, the inter-day reproducibility was evaluated by repeated measurements of the 20.0 mg/L standard solution over five days (n = 5). Finally, the method accuracy was assessed using spiked samples at concentrations of 10.0 – 40.0 mg/L for MEM and 5.00 – 20.0 mg/L for DON in real sample matrices (pharmaceutical samples containing DON). The concentration ranges for the recovery study were chosen to represent the lower, middle, and upper range of the expected concentrations in the final sample solutions.

2.5. Software

The operating conditions (frequency 800 kHz, amplitude 100%, and headstage gain ON) of the C^4D detector were set using C^4D Profiler V2 v. 2.5.2 software (eDAQ). Detector data were recorded, and information on migration time, peak height, and peak area was processed using eDAQ Chart v. 5.27. Electropherograms were visualized using Wavemetric Igor Pro v. 9.05 (Oregon, USA). Other statistical analyses and graphs were performed using Microsoft Excel 365 and RStudio v. 2025.09.1 (Posit PBC, Massachusetts, USA) with R v. 4.5.1 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results and Discussion

3.1. Optimization of Analytical Conditions

The primary consideration in CE analysis is the selection of a suitable BGE to ensure that all analytes are in ionic form, enabling electrophoretic separation. The pH of the BGE is a critical parameter in CE as it determines the ionization state of the analytes and the electroosmotic flow (EOF). Based on the chemical structures of the two analytes (Fig. 1), the presence of primary amine (in MEM) and tertiary amine (in DON) groups suggests that these compounds can exist as cations in acidic media due to protonation of the amine groups (forming $–NH_3^+$ and $–NH^+$). For such compounds, the use of weak organic acid solutions as BGE has been demonstrated to be appropriate for electrophoresis. In this study, three organic acids were investigated to evaluate their ability to simultaneously separate MEM and DON, including Ace, For, and Lac, at concentrations ranging from 0.5 to 3.0 M with pH in the range of 2.53 – 2.14, 2.04 – 1.64, and 2.08 – 1.69, respectively.

The results shown in Fig. 2 demonstrate that all selected acid solutions are suitable BGEs for the separation of MEM and DON, as both analytes were clearly detected and separated under all tested BGE concentrations. Additionally, the migration time of the analytes tended to increase with increasing acid concentration for Ace and Lac. This can be explained by

the increased viscosity of the solution at higher acid concentrations, leading to reduced electrophoretic mobility of the analyte ions. In contrast, the migration time for For exhibited the opposite trend, similar to previous findings using For for the analysis of major active ingredients in Parkinson's disease medications [16], and may result from a combination of increased ion density and analyte-ion interactions outweighing the viscosity effect, as For is a medium-strength acid (pK_a = 3.75) with strong hydrogen bonding capability. Nevertheless, the obtained analysis times were satisfactory, remaining below 10 minutes in all cases, even at high acid concentrations.

Changes in peak area and resolution between MEM and DON peaks are presented in Fig. 3. There is a clear trend of decreasing peak areas for both MEM and DON with increasing BGE concentration for all three acids. This is attributed to the increased background conductivity at higher acid concentrations, resulting in reduced conductivity differences between the analyte ions and the background. Conversely, resolution tended to improve with increasing BGE concentration, indicating that higher acid concentrations enhance analyte separation. A concentration of 1.0 M Ace (pH = 2.38) was selected as the optimal condition, providing the largest peak areas (183 mV·s for MEM and 118 mV·s for DON), relatively short analysis time (about 6 minutes), and good resolution (4.41). At this pH, both MEM and DON are fully protonated, maximizing their electrophoretic mobility and allowing for their effective separation within a short analysis time.

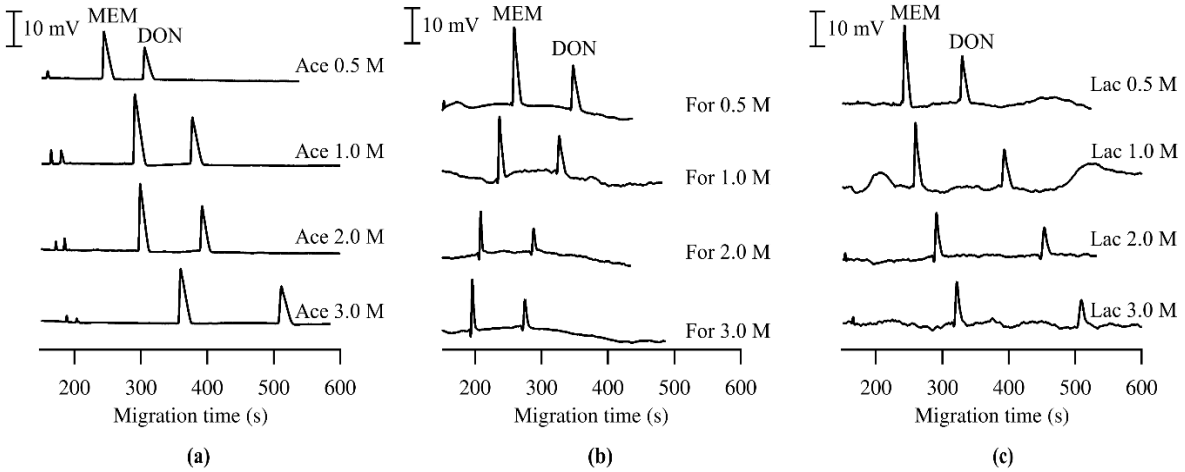

Fig. 2. Electropherograms of memantine and donepezil mixtures using BGEs containing (a) acetic acid; (b) formic acid; and (c) lactic acid at various concentrations. Other CE conditions: separation voltage -22 kV; fused-silica capillary with 50 µm inner diameter, total length 50 cm, effective length 42 cm; siphoning injection at a height of 10 cm for 60 seconds. Analyte concentration: 20 mg/L.

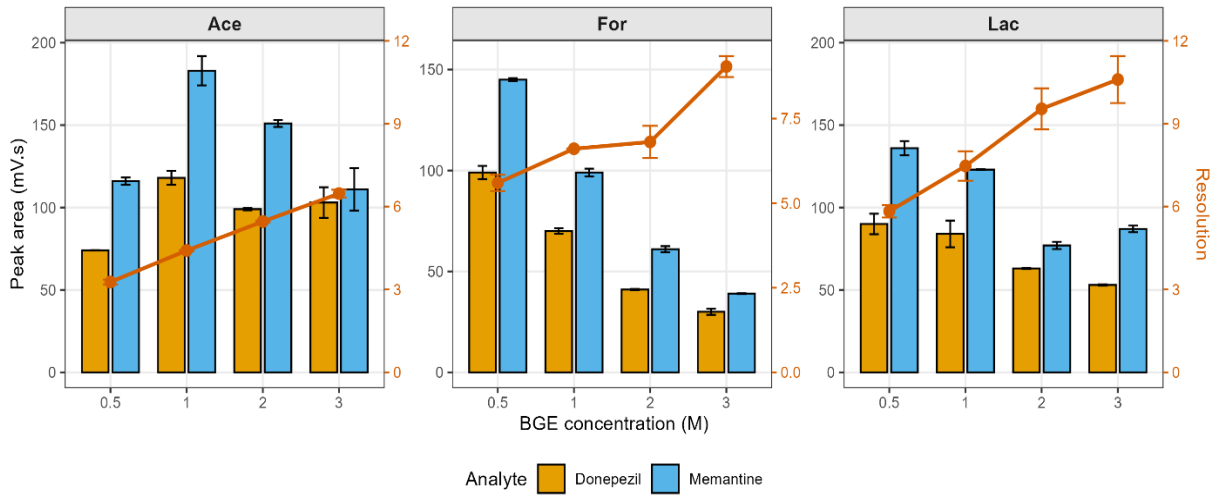

Fig. 3. Changes in peak area and resolution in the analysis of memantine and donepezil with BGEs of different acid types and concentrations. Other analytical conditions as in Fig. 2. Error bars represent the standard deviation of duplicate measurements.

3.2. Results for Method Validation

In this study, the LODs for MEM and DON were 0.59 mg/L and 1.39 mg/L, respectively (Table 1). Compared to HPLC/UPLC or electrochemical methods, the LOD values obtained by CE-C^{4}D are considerably higher. However, these results still demonstrate that CE-C^{4}D is suitable for the intended analysis of major active ingredients in pharmaceuticals.

The linear range was established as 2.00 – 1000 mg/L for MEM and 5.00 – 1000 mg/L for DON, with calibration curves constructed at seven concentration levels between 5.00 and 50.0 mg/L.

The correlation coefficients for the calibration curves were 0.9973 and 0.9994 for MEM and DON, respectively (Table 1). With the established calibration curves, pharmaceutical samples need to be diluted 2 – 5 times before analysis by CE-C^{4}D.

The relative standard deviations (RSD%) for peak areas in the intra-day precision (n = 7) were 2.2% and 5.4% for MEM and DON, respectively. Besides, the *RSDs* for migration time were both 0.7%. For the inter-day reproducibility assessment, the obtained *RSDs* were below 8% for peak area and below 4% for migration time for both analytes. These values indicate that the developed CE-C^{4}D method exhibits good precision. Finally, the recovery efficiencies ranged from 94% to 108% (Table 1).

The validation results demonstrate that the developed CE-C^{4}D method meets the typical requirements for analytical methods in pharmaceutical quality control as per International Council for Harmonisation (ICH) guidelines [17, 18]. The R^2 values for the linearity were greater than 0.99, indicating a strong linear relationship between concentration and peak area. The precision, with *RSD* values for inter-day assessment below the accepted limit of 15%, confirms the reproducibility of the method. Furthermore, the accuracy, with recovery values within the typical range of 80 – 120%, ensures that the developed method provides accurate results for the quantification of MEM and DON in pharmaceutical formulations.

3.3. Application of Developed CE-C^{4}D Method for Pharmaceutical Analysis

The developed CE-C^{4}D method was applied for the quantification of DON in real pharmaceutical samples for Alzheimer's disease treatment. Electropherograms of the standard, pharmaceutical sample, and spiked sample are shown in Fig. 4, and the analytical results are presented in Table 2. The differences between the results obtained by CE-C^{4}D and the label values ranged from -4.7% to 9.2%, indicating no abnormality in the active ingredient content of the tested samples and confirming that CE-C^{4}D is suitable for the analysis of major active ingredients in Alzheimer's disease medications.

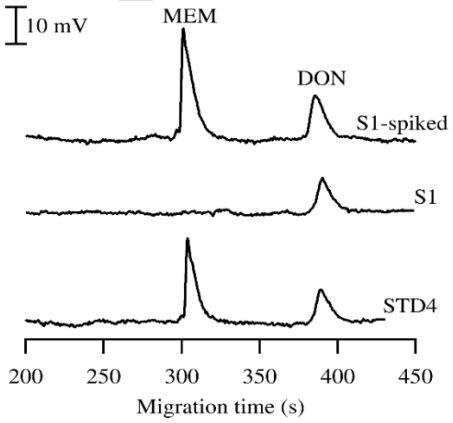

Fig. 4. Electropherograms of standard, pharmaceutical sample, and spiked sample for real Alzheimer's disease medication (sample S1) analyzed by CE-C^{4}D. CE conditions: BGE containing 1.0 M acetic acid. Other analytical conditions as in Fig. 2

Table 1. Validation parameters for simultaneous analysis of memantine and donepezil by CE-C^{4}D

Analyte		**Memantine**	**Donepezil**
Calibration curve		$y = 5.15x + 9.00$	$y = 2.97x + 2.02$
R^2		0.9973	0.9994
Linear range (mg/L)		2.00 – 1000	5.00 – 1000
LOD (mg/L)		0.59	1.39
LOQ (mg/L)		1.97	4.63
Repeatability (n = 7)	RSD^a (%)	2.2	5.4
	RSD^b (%)	0.7	0.7
Reproducibility (n = 5)	RSD^a (%)	7.1	5.2
	RSD^b (%)	1.6	3.2
Recovery (%)		95.5 – 107.2	94.7 – 102.7

y: peak area (mV·s); x: concentration (mg/L); RSD^a: relative standard deviation for peak area; RSD^b: relative standard deviation for migration time

It should be noted that while the CE-C^{4}D method was developed for the simultaneous analysis of both MEM and DON, a commercial pharmaceutical product containing MEM was not available in the local market during this study. However, the successful results of the method validation, particularly the recovery study with spiked samples on the real matrix, demonstrate the suitability and accuracy of the proposed CE-C^{4}D method for the quantification of MEM in pharmaceutical matrices. Future studies will aim to apply the developed method to commercial products containing MEM, as well as combination formulations.

Table 2. Results of donepezil analysis in Alzheimer's disease pharmaceutical samples by CE-C^{4}D

Sample	S1	S2
Concentration measured by CE-C^{4}D (mg/L)	21.8	19.1
Content calculated by CE-C^{4}D (mg/tablet)	5.46	9.53
Labeled content (mg/tablet)	5.00	10.0
Deviation* (%)	9.2	–4.7

Deviation = (Content calculated by CE-C⁴D – Labeled content) / Label content × 100 (%)

4. Conclusion

This study successfully developed a novel analytical procedure based on the CE-C^{4}D method for the simultaneous quantification of MEM and DON in Alzheimer's disease medications. The optimal CE conditions included a BGE of 1.0 M acetic acid, a separation voltage of -22 kV, and siphonic injection at a height of 10 cm for 60 seconds. The CE-C^{4}D method demonstrated good analytical performance, with LOD of 0.59 mg/L for MEM and 1.39 mg/L for DON. The precision was excellent, with intra-day and inter-day *RSDs* for peak area and migration time below 6% and 8%, respectively. The accuracy was confirmed by recovery studies, with recovery rates ranging from 94% to 108% for both analytes. The CE-C^{4}D method was subsequently applied to real pharmaceutical samples, and the results showed that the differences between the content determined by CE-C^{4}D and the labeled value were less than 10%.

CRediT authorship contribution statement

Thanh Dam Nguyen: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology. Manh Huy Nguyen: Software, Investigation, Formal analysis, Data curation. Linh Ngoc Nguyen: Investigation, Validation, Formal analysis, Data curation. Thi Khanh Chi Nguyen: Validation, Formal analysis, Data curation. Hong Anh Duong: Writing – review & editing, Resources, Conceptualization. Hung Viet Pham: Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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