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REVIEW ARTICLE

Capillary electrophoresis: Recent advancements and applications of micellar electrokinetic capillary chromatography

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ABSTRACT

The article discusses capillary electrophoresis (CE) as an advanced technique used for the separation and detection of various pharmaceutical drugs. CE involves the application of high voltages across buffer-filled capillaries to produce separation based on various separation theories, including capillary zone electrophoresis (CZE), micellar electrokinetic capillary chromatography (MEKC), capillary gel electrophoresis, and capillary isoelectric focusing. While traditional CZE is not suitable for the separation of neutral substances, MEKC was developed by Shigeru Terabe in the early 1990s to expand the use of CE to neutral analytes that cannot be separated using straightforward free solution CE. MEKC employs an ionic micellar solution that interacts with the analytes through partitioning processes like a chromatographic technique. To create a pseudostationary phase, a surfactant such as sodium dodecyl sulfate (SDS) is added to the buffer solution at a concentration higher than its critical micellar concentration. The anionic SDS micelles are electrostatically drawn towards the anode, while the electro-osmotic flow carries the bulk solution toward the negative electrode due to the negative charge on the inside surface of the silica capillaries. When a neutral analyte is introduced into the micellar solution, a portion is integrated into the micelle, while the remaining fraction of the analyte migrates with the electroosmotic velocity. Separation depends on the individual partitioning equilibrium of the various analytes between the micellar and the aqueous phase. The bigger percentage of analyte dispersed inside the micelle, the slower it will travel. This article provides an in-depth understanding of the separation principle and the mechanism involved in MEKC, highlighting its usefulness in separating neutral analytes that cannot be separated using traditional CZE.

KEY WORDS: Micellar electrokinetic capillary chromatography, Micelle, Nanotechnology, Surfactants

INTRODUCTION

An important advancement over conventional electrophoretic methods is capillary electrophoresis (CE), which involves applying high voltages across buffer-filled capillaries to produce separation in fused-silica capillaries. CE is a group of separation methods based on various separation theories, including capillary zone electrophoresis (CZE) (based on the variations in the electrophoretic mobilities of the analytes), micellar electrokinetic capillary chromatography (MEKC), capillary gel electrophoresis (CGE), and capillary isoelectric focusing (CIEF) (separation of zwitterion compounds) (separation of analytes in a capillary filled with

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a chromatographic stationary phase).[1] Pharmaceutical analysis is made possible by a variety of CE methods. Each of these approaches will offer distinct benefits for the separation and detection of various pharmaceutical drugs, depending on the complexity of the sample, the makeup of its components, the intended application, and the characteristics of the analytes.[2] Pharmaceutically relevant chemicals are often+ electrophoretically neutral, and it is commonly necessary to separate substances with extremely similar structural and physicochemical characteristics. The traditional CZE technique is unsuitable for separating neutral substances since it relies on variations in the electrophoretic mobilities of the analytes, which migrate toward the detector at the same rate as the electro-osmotic flow (EOF).[3] Shigeru Terabe founded the electrophoretic method known as MEKC in the early 1990s to expand the use of CE to neutral analytes that cannot be separated using straightforward free solution CE. The fact that the same equipment is utilized for MEKC and CZE illustrates the process's flexibility and adaptability. MEKC employs an ionic micellar solution as opposed to a straightforward buffer salt solution, which is how it differs from CZE.[4] While CZE normally only separates ionic chemicals, MEKC may be used to separate both ionic and neutral substances. Because of this, MEKC has a significant advantage over CZE when it comes to separating mixtures that contain both ionic and neutral analytes. While CZE is based on variations in the analytes' electrophoretic mobility, MEKC's separation concept is based on the differential partition of the analytes between micelles and water.[5]

Separation principle

MEKC is based on the addition of a micellar "pseudo stationary" phase to the buffer solution, which interacts with the analytes through partitioning processes exactly like a chromatographic technique would. A surfactant that has been added to the buffer solution at a concentration higher than its critical micellar concentration (CMC) makes up the "pseudo stationary" phase CMC.[6] EOF functions as a chromatographic "mobile phase" in this system. The "plug-like" flow profile of the EOF is practically perfect from a "chromatographic point of view" since it reduces band broadening, which can happen during the separation process. The most often used surfactant is sodium dodecyl sulfate (SDS), an anionic surfactant. The anionic SDS micelles are electrostatically drawn toward the anode.[7] The EOF carries the bulk solution toward the negative electrode due to the negative charge on the inside surface of the silica capillaries. However, the EOF is generally greater than the electrophoretic migration of the micelles and hence, the micelles will migrate likewise toward the negative electrode with a delayed velocity. When a neutral analyte is introduced into the micellar solution, a portion is integrated into the micelle, while the remaining fraction of the analyte migrates with the electroosmotic velocity. Consequently, micelles lower selectively the migration of neutral solutes, they contact with (through partitioning mechanism), which otherwise would move with the same velocity as the EOF.[8] The separation depends on the individual partitioning equilibrium of the various analytes between the micellar and the aqueous phase. The bigger percentage of analyte dispersed inside the micelle, the slower it will travel. As a result, compared to analytes that are mainly dispersed in the bulk solution, those that have a stronger affinity for the micelles migrate at a slower rate. The usual migration order in SDS micelles will be anions, neutral analytes, then cations, which is the exact reverse of the ECZ migration order. Due to the micelle's electrostatic repulsions, anions will primarily stay in the bulk solution; neutral molecules will only be separated because of their hydrophobicity; and cations will migrate last because of the high electrostatic attraction. Even though strong hydrophobic interactions between analytes and micelles can outweigh repulsions and attractions, this assumption regarding the migration order might occasionally be helpful. The analytes' electrophoretic mobilities can also change the migration order. Analytes that are strongly retained by the micelle will have slower migration times, whereas those that interact with the micelle just a little will have migration times that are near the EOF (t_0). Very hydrophobic chemicals may be entirely incorporated within the micelle and will travel with the micelle's pace (mc). While Sudan III, a dye, is completely incorporated into the micelle and may be utilized as a micellar marker, methanol is not retained by the micelles and migrates with to as a marker for the EOF.[9] The ability to do separations without an EOF is a recent development in MEKC. Low pH levels or coated capillaries can be used to accomplish this. This could be especially helpful when separating acidic analytes since they would not interact with the negatively charged SDS micelle because they ionize at high pH levels. By absorption on the capillary wall surface through a process involving electrostatic interaction between the positively charged ammonium moieties and the negatively charged Si-O- groups when the EOF is reversed, cationic surfactants can be utilized in MEKC to reverse the charge on the capillary wall.[10]

Surfactants

Surfactants are compounds with detergent-like qualities made of a hydrophilic head group that is water soluble and a hydrophobic hydrocarbon chain group that is water insoluble. Although there are many surfactants on the market, only a small number of them are often utilized in MEKC separations as mentioned in Table 1. The micellar solution must be homogenous, UV transparent, and have a low viscosity for the surfactants suited for MEKC to form micelles in the buffer solution. There are four major classes of surfactants: Anionic, cationic, zwitterionic, and non-ionic.[11]

Sweeping-MEKC

In sweeping-MEKC, the sample is prepared in absence of a pseudo stationary phase (PSP) where conductivity is lower, equal, or higher to the background solution (BGS) which has PSP. The analytes are carried up and accumulated with the help of PSP which penetrates the sample zone when voltage is applied through the partitioning and interaction of analytes in the sample zone and PSP in the background. The narrowing of the analyte zone happens in the sweeping procedure and the enrichment efficiency is mostly measured by the retention factor of the analyte. That process is highly efficient, simple, and with no need for additional instrumentation, sweeping-MEKC has become an effective technique to analyze the same in various matrices.[12-14]

Applications

Various advantages like an advantage in forensic, biochemical, agriculture, nanotechnology, separation, quantification of illicit drugs, extraction, and environment are the basic applications in MEKC given in Figure 1, but the other recent application includes separation and determination of phenylenediamines and aminophenols by MEKC were done by Wang and Huang where they have analyzed o-aminophenol with the help of LC and MEKC but there were no any successful results for LC has been seen but it was easily quantified successfully by MEKC.[15] Electrochemical detection was done with help of MEKC to determine antioxidants in cosmetics by Guan *et al*., where they separated analytes within 13 min at a separation voltage of 18 KV in a 20 mmol/L containing 25 mmol/L SDS.[16] Phenolic antioxidants in edible oils were analyzed with the help of MEKC by Delgado-Zamarren˜ *et al*. where they did solid-phase and liquid-liquid extraction to find out the best sample treatment before injection into the electrophoretic system. They found that butylated hydroxyanisole, butylated hydroxy-toluene, and dodecyl gallate were evaluated at the level permitted in European Union.[17] Triazoles were identified by Li *et al.* with the help of MEKC from fruit peel. According to the study it was seen that, after the 10th-day treatment of fungicide on fruits, Triazole fungicide was higher than the recommended maximum residue limits in fruit peel.[18] MEKC was applied for the discrimination of red lipsticks by Gładysz *et al*., Mixture of eight dyes and MEKC optimized the separation method. The best separation was accomplished using a buffer at pH 9. The discrimination power achieved, that is, 0.998 was high and confirmed that it has great potential in forensic investigations.[19] Determination of fipronil and fipronil-sulfone in eggs by Aparicio-Muriana *et al*., with the help of MEKC, was done in 2017.[20]

Advancement in micellar electrokinetic chromatography

In recent years, researchers have made significant advancements in micellar electrokinetic chromatography

Table 1: Surfactants classes and their properties

Surfactant	Molecular weight (g/mol)	Appearance	Type	CMC
SDS	288.5	White powder	Anionic	8.1×10^{-3}
STS	316.43	White, waxy solid	Anionic	2.1×10^{-3}
Sodium cholate	430.55	White powder	Anionic	$13\text{-}15\times10^{-3}$
CTAB	364.45	White to off white	Cationic	0.92×10^{-3}
Dodecyl trimethyl ammonium bromide	302.34	White to yellow	Cationic	15×10^{-3}
Briz – 35	1225	Colorless viscous liquid	Nonionic	0.1×10^{-3}
Sulfobetaine	364	White solid	Zwitterionic	3.3×10^{-3}

CMC: Critical micellar concentration, SDS: Sodium dodecyl sulphate, STS: Sodium tetradecyl sulphate, CTAB: Cetyltrimethylammonium bromide

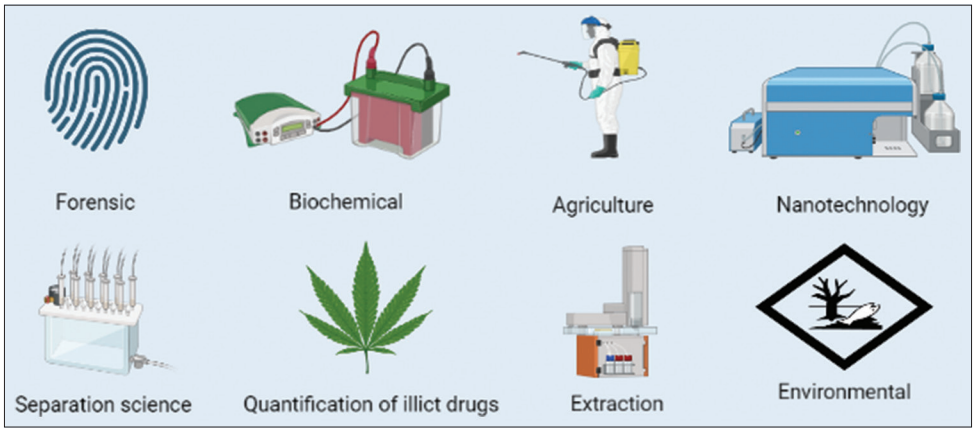

Figure 1: Application of micellar electrokinetic capillary chromatography

(MEKC). These advancements include the use of novel surfactants, such as Gemini surfactants, which have been found to provide higher separation efficiency and selectivity than traditional surfactants like SDS and cetyltrimethylammonium bromide. Incorporating nanoparticles into the MEKC buffer has also been explored, as they can provide additional separation mechanisms and enhance separation efficiency through interactions with analytes. Coating the inner surface of the capillary with a thin layer of a polymer or surfactant is another technique used to improve separation efficiency and reproducibility by preventing the adsorption of analytes onto the capillary wall and minimizing EOF.[21] In addition, MEKC has been successfully used for chiral separations by adding chiral selectors to the buffer, and coupling with mass spectrometry (MS) allows for sensitive and selective detection of analytes, making MEKC a valuable technique in analytical chemistry. Some other advanced techniques used are further explained.

Sweeping-MEKC

Sweeping-MEKC involves preparing the sample in a solution without the addition of a pseudo stationary phase (PSP) and with conductivity that is lower, comparable to, or greater than the conductivity of the BGS, which contains a PSP.[22] When the voltage is provided, the partitioning and interaction of the analytes in the sample zone and PSP in the BGS cause the PSP to penetrate the sample zone and pick up the analytes. During the sweeping process, the analyte zones are reduced, and the retention factor (k) of the analytes largely determines the enrichment efficiency. Online sweeping-MEKC has recently developed into an efficient method to assess trace chemicals in diverse sample matrices because of its many benefits, including high enrichment efficiency, simplicity, and the lack of a requirement for extra apparatus. To identify trace amounts of paliperidone in human plasma, Liu *et al.* used sweeping-MEKC with a high-conductivity sample solution.[23] With a LOD of 10 ng/mL, the method's sensitivity enhancement factor (SEF) was 100 as opposed to the traditional MEKC method's LOD of 10. For the concentration and detection of carbamazepine and clobazam in human urine samples, Chen *et al*. developed a cyclodextrin (CD) aided dispersive liquid-liquid microextraction combined with the sweeping-MEKC technique. The LODs for carbamazepine and clobazam were 0.6 and 0.5 ng/mL, respectively, while the SEFs were 3575 and 4675.[24]

CD in MEKC

CDs have a structure like a truncated cone with a hydrophilic outside and a hydrophobic interior. The many hydroxyl groups on the CD structure may interact with water in aqueous solutions to generate hydrogen bonds, which increases the solubility of CDs in water.[25] The formation of inclusion complexes improved the physicochemical properties of the guest compounds, such as chemical stability and aqueous solubility. The CDs can form inclusion complexes with a wide range of guest compounds by taking up the entire or part of the guest molecule into their hydrophobic cavity through non-covalent interaction.[26] TDs have been widely employed as sorbents in extraction fields and as additives in separation fields because of their unique features. CDs were commonly employed as an additive in BGS for separation in CE, particularly for enantiomer separation. Kodama *et al.* separated the enantiomers of hydroxyeicosatetraenoic acid using MEKC modified with hydroxypropyl-g-CD. Enantiomers were completely resolved, and the stereochemistry of the analytes was satisfactorily assessed. For the simultaneous separation and determination of hirsute and hirsute from Uncaria rhynchophylla and its formulations, Wang *et al*. devised a CD-modified MEKC technique. Within 13 min, hirsute and hirsute were well resolved. Ghiasvand *et al*. generated a micelle to CD stacking-MEKC technology for CE enrichment that has a SEF of 171 for the separation and enrichment of cationic, neutral, and chiral chemicals. However, studies on the use of CD for improving the sensitivity in CE's online concentration approach were still infrequently published.[27,28]

Perfluorinated-micellar electrokinetic chromatography

Ammonium perfluorooctanoate (APFOA) was employed as a surfactant in MEKC research 20 years ago. For the MEKC-ESI/MS analysis of polar chemicals, such as N-methylcarbamate, charged and uncharged phenyl compounds (more or less hydrophobic), pyrene and benzopyrene, benzimidazoles amino acids, and others, it was discovered to be a suitable volatile surfactant. Its usage for FAs separation in MEKC-ESI/MS has not, however, been documented thus far. In addition, the resultant micelles in the background electrolyte (BGE) have not yet been given a physical or chemical description. Ta *et al*., did the separation of unsaturated C18 fatty acids using perfluorinated-micellar electrokinetic chromatography, where APFOA was used as a surfactant for the separation of free unsaturated C18 fatty acids. Regarding several factors (organic solvent, counterion, APFOA concentration, and pH), separation conditions were tuned. A preliminary description of the separation process has been produced as a consequence of the determination of the critical micelle concentration, charge density, and mobility of the micelles.[29]

Comparison between CZE and MEKC

MEKC is an advanced version of CZE, where the charged surfactants are added to the BGE at a concentration higher than their CMC permitting the separation of neutral or charged analytes as a function of their affinity to partition into micelles.[30] MEKC has great resilience to respond to complicated biological and non-biological matrices by extending the use of CE methods for the investigation

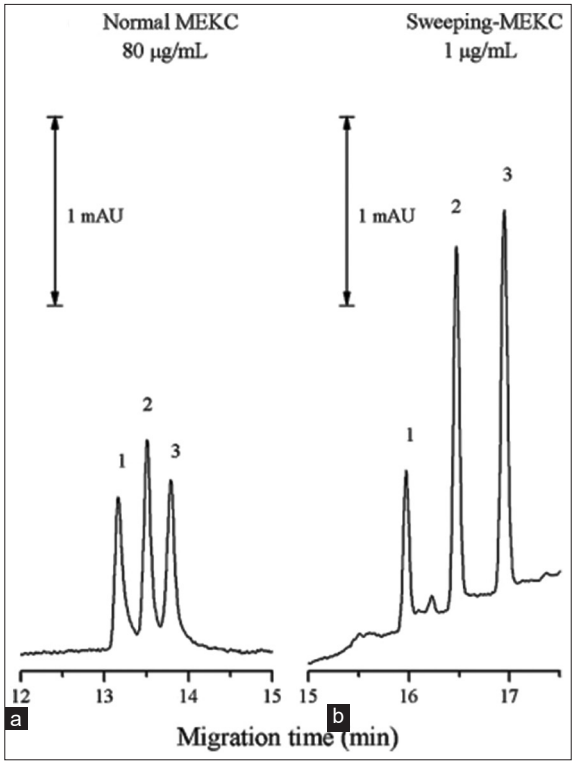

Figure 2: Comparison between the normal MEKC and sweeping-MEKC methods for simultaneous separation of THC and its metabolites [analytical conditions (a): 25 mM citric acid/disodium hydrogen phosphate BGE, 40% methanol, injection 3.45 kPa × 300s, 80 µg/mL sample concentration; (b): 25mM citric acid/disodium hydrogen phosphate BGE, 40% methanol, injection 3.45 kPa × 300s, 1 µg/mL sample concentration. Peaks (1) THC; (2) THC-COOH; (3) THC-OH]. The figure is reproduced with permission from Elsevier

of neutral substances that cannot be separated using the traditional CZE. If we take the example of cannabinoids, for the study of cannabinoids, which co-migrate with the EOF in aqueous CZE and produce unresolved peaks because of their hydrophobic nature and lack of electrophoretic mobility, MEKC is a promising alternative.[31,32]

Comparison between MEKC and sweeping-MEKC

For the simultaneous assessment of THC and its metabolites (11-hydroxy-9-THC-THC-OH, THC-COOH) in urine, Su *et al*. devised a sensitive MEKC method. The authors' use of SPE for sample clean-up, offline preconcentration, as well as online preconcentration based on sweeping, resulted in enhancement factors that were up to 200 times greater than those obtained using conventional MEKC with UV detection. In a univariate mode, the impacts of various sweeping-MEKC analytical parameters on the separation were evaluated. The outcomes of the sweeping-MEKC approach and the regular MEKC method are compared. The BGE with 25 mM citric acid/disodium hydrogen phosphate 75 mM SDS, and 40% (v/v) methanol produced the greatest results when used at pH 2.6. Below the threshold of 50 ng/mL in urine, the LODs varied from 3.87 to 15.2 ng/mL. The approach is less desirable for regular analysis since it took around 80 min to complete the analysis and sample preparation. The great sensitivity of the sweeping MEKC approach allowed for the accurate detection of THC and its metabolites in the urine of suspected THC users.[33] All the data is given below in Figure 2.

CONCLUSION

CE has revolutionized separation science, offering various techniques such as CZE, micellar electrokinetic capillary chromatography (MEKC), CGE, and CIEF that provide unique benefits for the separation and detection of pharmaceutical drugs. MEKC, in particular, is a valuable method for separating neutral substances that cannot be easily separated using free solution CE. This technique employs an ionic micellar solution as a "pseudo stationary" phase, allowing analytes to interact with the solution via partitioning processes, similar to chromatographic techniques. MEKC is a versatile process that utilizes the same equipment as CZE and is based on the differential partition of analytes between micelles and water. MEKC outperforms CZE when separating mixtures containing both ionic and neutral analytes, making it a crucial tool in pharmaceutical analysis.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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