REVIEW ARTICLE

Advances in capillary electrophoresis-mass spectrometry for pharmaceutical analysis

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Abstract

Capillary electrophoresis-mass spectrometry (CE-MS) combines the high separation efficiency of capillary electrophoresis with the exceptional sensitivity and specificity of mass spectrometry. CE-MS has gained significant traction in pharmaceutical analysis, offering unique advantages in the analysis of pharmaceuticals, biologics, and their metabolites. Recent technological advancements have enhanced CE-MS applicability, addressing historical challenges in interface design and improving system robustness and sensitivity. Novel capillary coatings and background electrolytes have expanded the range of analyzable compounds. CE-MS is utilized across various stages of drug development and quality control, proving valuable in small-molecule drug analysis, and offering high-resolution separations of structural isomers and chiral compounds. In biopharmaceuticals, CE-MS has emerged as a powerful tool for characterizing complex protein therapeutics, including monoclonal antibodies and biosimilars. The technique provides detailed information on post-translational modifications and higher-order structures, ensuring biologic drug quality and safety. CE-MS has shown potential in metabolomics, contributing to drug metabolism understanding and biomarker discovery. The technique's minimal sample and solvent requirements align with green analytical chemistry principles. Ongoing research focuses on improving sensitivity, throughput, and data analysis capabilities. Integration with other analytical techniques and advancements in bioinformatics tools are enhancing CE-MS applications in pharmaceutical analysis, particularly in the era of personalized medicine and biologics.

Key words: Biomarkers, capillary electrophoresis-mass spectrometry, metabolomics, method development, pharmaceutical analysis

INTRODUCTION

The pharmaceutical industry continually strives to develop innovative analytical techniques that can meet the ever-increasing demands for sensitivity, selectivity, and efficiency in drug analysis. Among the myriad of analytical tools available, capillary electrophoresis-mass spectrometry (CE-MS) has emerged as a powerful and versatile technique, combining the high separation efficiency of capillary electrophoresis with the exceptional sensitivity and specificity of mass spectrometry.[1] This hyphenated technique has gained significant traction in recent years, offering unique advantages in the analysis of pharmaceuticals, biologics, and

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their metabolites.[2] Capillary electrophoresis, first introduced in the early 1980s, has established itself as a robust separation technique based on the differential migration of charged species under the influence of an electric field.[3] The coupling of CE with MS,[4] initially reported in 1987 has undergone remarkable advancements, both in instrumentation and methodologies, positioning itself as an indispensable tool in the pharmaceutical scientist's arsenal.[5]

The pharmaceutical industry faces numerous analytical challenges, including the characterization of complex drug molecules, detection of trace-level impurities, and elucidation of metabolic pathways.[6] Traditional analytical techniques such as high-performance liquid chromatography and gas chromatography coupled with MS have long been the traditional approaches in this field. However, CE-MS offers several unique advantages that complement and, in some cases, surpass these conventional methods.[7] One of the primary strengths of CE-MS lies in its ability to separate and analyze charged species with exceptional efficiency and resolution.[8] This characteristic is particularly valuable in the analysis of ionizable pharmaceuticals, peptides, and proteins, which constitute a significant portion of modern drug candidates.[9] Moreover, the minimal sample and solvent requirements of CE align well with the growing emphasis on green analytical chemistry, making it an environmentally friendly alternative to traditional chromatographic techniques.[10]

Recent years have witnessed significant technological advancements in CE-MS, enhancing its applicability in pharmaceutical analysis. Improvements in interface design have addressed the historical challenges of coupling CE with MS, leading to more robust and sensitive systems.[11] The development of novel capillary coatings and background electrolytes has expanded the range of analytes that can be effectively separated and detected.[12,13] CE-MS is used across various stages of drug development and quality control. It has proven particularly valuable in the analysis of small molecule drugs, offering high-resolution separations of structural isomers and chiral compounds.[14] In the rapidly growing field of biopharmaceuticals, CE-MS has emerged as a powerful tool for characterizing complex protein therapeutics, including monoclonal antibodies and their biosimilars.[15] The technique's ability to provide detailed information on post-translational modifications and higher-order structures has made it indispensable in ensuring the quality and safety of biologic drugs.[16]

Apart from drug analysis, CE-MS has also shown its potential in metabolomics and biomarker discovery.[17] Its capacity to separate and identify a wide range of metabolites in biological matrices has contributed significantly to our understanding of drug metabolism and pharmacokinetics.[18] In addition, the technique has shown promise in the field of personalized medicine, enabling the detection of disease-specific biomarkers and aiding in the development of targeted therapies.[19] The continuous improvements in instrumentation, coupled with innovative methodologies, are pushing the boundaries of what can be achieved in terms of sensitivity, selectivity, and throughput.[20] This review article aims to provide a comprehensive overview of the recent advances in CE-MS for pharmaceutical analysis.

PRINCIPLES OF CE-MS

CE-MS combines the high-resolution separation capabilities of capillary electrophoresis with the sensitive and specific detection offered by mass spectrometry.[21]

The fundamental principle of CE is based on the differential migration of charged analytes in a narrow-bore capillary under the influence of an applied electric field.[22]

In CE, separation occurs due to differences in the electrophoretic mobility of ions, which is determined by their charge-to-size ratio.[23] The electroosmotic flow (EOF), generated by the applied electric field, plays a crucial role in the overall migration of analytes.[24] The EOF can be manipulated by altering the capillary surface chemistry or adjusting the buffer composition, allowing for the optimization of separation parameters.[25]

The coupling of CE to MS presents unique challenges due to the low flow rates in CE and the need for a stable electrical connection.[26] Various interfaces have been developed to address these issues, with the most common being electrospray ionization (ESI).[20] In ESI-CE-MS, the CE effluent is sprayed into fine droplets, which undergo desolvation to produce gas-phase ions for mass analysis.[27] One of the key advantages of CE-MS is its ability to analyze a wide range of compounds, from small molecules to large biomolecules, with minimal sample preparation.[2] The high separation efficiency of CE, combined with the mass-to-charge ratio information provided by MS, enables the resolution and identification of complex mixtures with high specificity.[28]

INSTRUMENTATION AND TECHNICAL ADVANCEMENTS

Recent years have witnessed significant advancements in CE-MS instrumentation [Figure 2] , enhancing its applicability in pharmaceutical analysis.[29] These improvements have focused on increasing sensitivity, improving robustness, and expanding the range of analyzable compounds.

Interface design

The development of more efficient interfaces has been a major focus of CE-MS research. The sheathless interface, which eliminates the need for a sheath liquid, has gained popularity due to its improved sensitivity and reduced ion

suppression.[30] Porous tip interfaces have shown promise in enhancing ionization efficiency and stability.[31] In addition, novel multi-segment injection techniques have been introduced to improve sample loading capacity.[32]

Capillary technology

Advancements in capillary technology have significantly improved separation performance. The introduction of porous layer open tubular columns has enhanced the separation of small molecules.[33] Monolithic columns, offering high permeability and surface area, have shown excellent performance in the analysis of large biomolecules.[34] Surface-modified capillaries with various coatings have been developed to minimize analyte adsorption and control EOF.[24]

Mass analyzers

The integration of CE with high-resolution mass analyzers has greatly expanded the technique's capabilities. Time-of-flight (TOF) and Orbitrap analyzers provide high mass accuracy and resolution, enabling precise molecular formula determination and structural elucidation.[35] Ion mobility spectrometry coupled with CE-MS adds an additional dimension of separation based on molecular shape, enhancing the analysis of complex mixtures.[36]

Microfluidic devices

The miniaturization of CE-MS systems through microfluidic devices has gained attention. These chip-based platforms offer advantages such as reduced sample and reagent consumption, faster analysis times, and the potential for integration of multiple analytical steps.[37] Microfluidic CE-MS has shown particular promise in high-throughput screening applications.[2]

Data processing and analysis

Advances in data processing algorithms and software have significantly improved the interpretation of CE-MS data. Machine learning approaches have been applied to automate peak identification and quantification.[38] In addition, the development of comprehensive databases and spectral libraries has facilitated the identification of unknown compounds in complex samples.[39]

Sample preparation

The integration of online sample preparation techniques with CE-MS has streamlined analytical workflows. Solid-phase extraction (SPE) coupled directly to CE-MS has been demonstrated for the analysis of trace-level analytes in complex matrices.[17] In-capillary derivatization techniques have also been developed to enhance the detection of specific analyte classes.[40]

These technological advancements have collectively contributed to the increased adoption of CE-MS in pharmaceutical analysis. The improved sensitivity, selectivity, and efficiency offered by modern CE-MS systems have enabled the analysis of increasingly complex pharmaceutical samples, from small molecule drugs to large biopharmaceuticals.[35]

SAMPLE PREPARATION TECHNIQUES

Sample preparation is a critical step in CE-MS analysis, significantly influencing the quality and reliability of results. For pharmaceutical samples, the primary goals of sample preparation are to remove interfering matrix components, concentrate analytes of interest, and ensure compatibility with the CE-MS system.[41]

Liquid-liquid extraction and SPE remain popular techniques for sample clean-up and pre-concentration. Recent advancements include the development of novel sorbent materials for SPE, such as molecularly imprinted polymers (MIPs) and magnetic nanoparticles, offering improved selectivity and extraction efficiency.[42] Microextraction techniques have gained traction due to their minimal solvent usage and potential for automation. Single-drop microextraction and dispersive liquid-liquid microextraction have been successfully applied to the extraction of pharmaceuticals from complex matrices.[43] For biological samples, protein precipitation and ultrafiltration are commonly employed to remove high molecular weight interferents. Dialysis and electromembrane extraction have shown promise for the selective extraction of ionizable analytes.[44]

APPLICATIONS IN PHARMACEUTICAL ANALYSIS

Small molecule drug analysis

CE-MS has proven to be a powerful tool for the analysis of small molecule drugs, offering high-resolution separations and accurate mass measurements. The technique excels in the analysis of ionizable compounds, making it particularly suitable for many pharmaceutical entities.[14] Chiral separations are a key application area, with CE-MS demonstrating superior performance in resolving enantiomers compared to traditional chromatographic methods. The use of cyclodextrins and other chiral selectors in the background electrolyte enables efficient enantioseparation.[45] CE-MS has also been applied to stability testing and forced degradation studies of small molecule drugs. The high separation efficiency allows for the resolution of closely

related degradation products, while MS provides structural information for their identification.[46]

Biopharmaceutical analysis

The analysis of biopharmaceuticals, including proteins, peptides, and oligonucleotides, has become a major application area for CE-MS. The technique offers several advantages over traditional methods, including high resolution, minimal sample consumption, and the ability to maintain native protein conformations.[35] For monoclonal antibodies (mAbs), CE-MS has been used to characterize charge variants, glycoforms, and other post-translational modifications. Capillary zone electrophoresis (CZE) coupled with high-resolution MS has enabled the detailed characterization of mAb heterogeneity.[47]

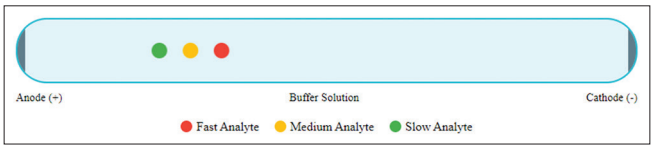

Figure 1: Capillary electrophoresis analyte separation

In the analysis of therapeutic peptides, CE-MS has demonstrated excellent performance in separating and identifying closely related impurities and degradation products [Figure 1]. The technique has been successfully applied to the quality control of synthetic peptides and the characterization of complex peptide mixtures.[47]

Impurity profiling and quality control

CE-MS plays a crucial role in impurity profiling and quality control of pharmaceutical products.[48] The high separation efficiency of CE, combined with the specificity of MS detection, allows for the identification and quantification of trace-level impurities.[49] In the analysis of genotoxic impurities, CE-MS has shown superior sensitivity compared to conventional methods. The technique has been successfully applied to the detection of alkyl sulfonates, alkyl halides, and

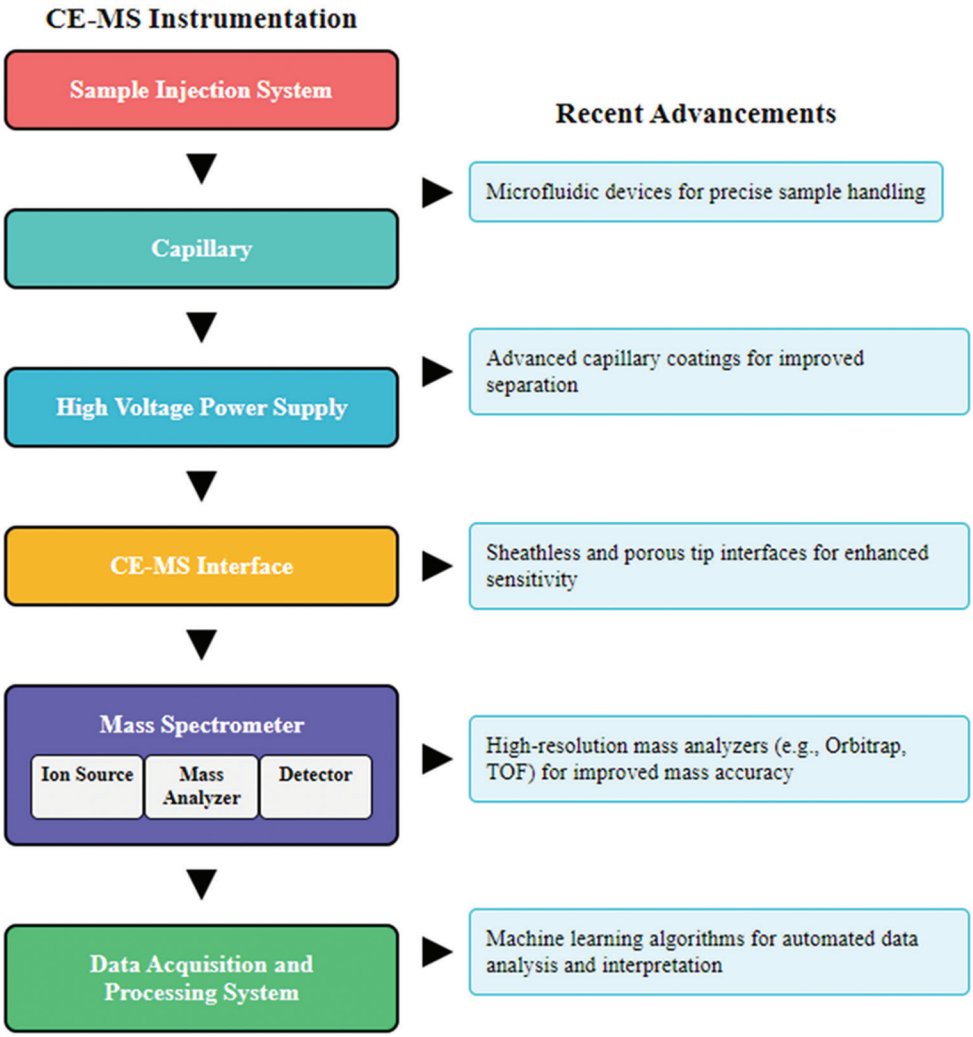

Figure 2: Recent advances in capillary electrophoresis-mass spectrometry instrumentation

Table 1: Applications of CE-MS in pharmaceutical analysis

Application field	Advantages of CE-MS	Example analytes	Typical CE mode
Small molecule drug analysis	High-resolution separations Chiral analysis capabilities- Minimal sample consumption	Drug substances Enantiomers Degradation products	CZE MEKC CD-modified CE*
Biopharmaceutical analysis	Native protein analysis Charge variant separation Glycoform characterization	Monoclonal antibodies Therapeutic proteins Peptides	CZE CGE CZE-ESI-MS*
Impurity profiling and quality control	High sensitivity for trace impurities Separation of charged and neutral species Complementary to LC-MS	Genotoxic impurities Extractables and leachables Process-related impurities	CZE MEKC CD-modified CE*
Metabolomics and biomarker discovery	Analysis of polar and charged metabolites High-throughput capability-complementary to LC-MS	Amino acids Organic acids Nucleotides	CZE MEKC CE-TOF-MS*

*CZE: Capillary zone electrophoresis, MEKC: Micellar electrokinetic chromatography, CD: Cyclodextrin, CGE: Capillary gel electrophoresis, TOF: Time-of-flight, LC-MS: Liquid chromatography-mass spectrometry

Table 2: Comparison of CE-MS interfaces

Interface type	Advantages	Limitations	Typical applications
Sheath-flow	Stable operation Easy implementation Compatible with a wide range of BGEs*	Potential sample dilution Lower sensitivity compared to sheathless	Small molecule analysis Peptide mapping Metabolomics
Sheathless	Higher sensitivity Minimal sample dilution Lower flow rates	More complex setup Limited BGE compatibility	Protein characterization Trace analysis Biomarker discovery
Junction-at-the-tip	Good stability Improved sensitivity over sheath-flow Easier implementation than sheathless	Intermediate sensitivity between sheath-flow and sheathless	Biopharmaceutical analysis Impurity profiling Chiral separations

*BGE: Background electrolyte, CE-MS: Capillary electrophoresis-mass spectrometry

other potentially genotoxic compounds at parts-per-million levels.[50] For the analysis of extractables and leachables in pharmaceutical packaging, CE-MS offers the advantage of being able to separate and identify both neutral and charged species. This capability is particularly valuable for comprehensive impurity profiling.[51]

Metabolomics and biomarker discovery

CE-MS has emerged as a powerful tool in metabolomics and biomarker discovery, complementing traditional liquid chromatography–mass spectrometry (LC-MS) approaches. The technique's ability to separate and detect a wide range of polar and charged metabolites makes it particularly suited for comprehensive metabolome analysis.[2] In targeted metabolomics, CE-MS has been applied to the quantification of specific metabolite panels, such as amino acids, organic acids, and nucleotides [Table 1]. The high separation efficiency of CE allows for the resolution of isomeric metabolites that may be challenging to separate by LC.[28] For untargeted metabolomics and biomarker discovery, CE-MS offers the advantage of detecting metabolites across a wide range of molecular weights and physicochemical properties. The technique has been successfully used to identify novel biomarkers in various disease states, including cancer, diabetes, and neurological disorders.[17]

In pharmacometabolomics, CE-MS has been employed to study drug metabolism and to identify potential biomarkers of drug efficacy and toxicity. The ability to analyze both parent drugs and their metabolites in a single run makes CE-MS an attractive option for comprehensive pharmacokinetic studies.[2]

COUPLING STRATEGIES AND INTERFACES

The successful integration of CE with MS relies heavily on effective coupling strategies and interfaces. The primary challenge in CE-MS coupling is maintaining a stable electrical connection for CE while simultaneously providing a suitable ion source for MS [Table 2].[26] ESI remains the most widely used interface for CE-MS. Sheath-flow interfaces, which introduce a coaxial liquid flow around the CE capillary, have been widely adopted due to their stability and ease of implementation. Recent advancements in sheath-flow interfaces include the development of ultra-low flow rate systems, which improve sensitivity by reducing sample

dilution.[52] Sheathless interfaces have gained popularity due to their potential for higher sensitivity. These interfaces directly connect the CE capillary to the MS, eliminating the need for additional liquid flow. Porous tip interfaces, which use a porous section at the capillary outlet to establish electrical contact, have shown promising results in terms of stability and sensitivity.[30] Junction-at-the-tip interfaces represent a hybrid approach, combining elements of both sheath-flow and sheathless designs. These interfaces offer improved stability compared to traditional sheathless designs while maintaining high sensitivity.[53]

DATA ANALYSIS AND INTERPRETATION

The complex nature of CE-MS data necessitates sophisticated data analysis and interpretation strategies. Recent advancements in this area have focused on improving data processing efficiency and enhancing the extraction of meaningful information from large datasets.[38] Peak detection and alignment algorithms have been refined to handle the high-resolution data generated by modern CE-MS systems. Machine learning approaches, including artificial neural networks and support vector machines, have been applied to automate peak identification and quantification.[54] For untargeted analysis, multivariate statistical methods such as principal component analysis and partial least squares discriminant analysis are commonly employed to identify significant features in complex datasets. These techniques have proven particularly valuable in metabolomics and biomarker discovery applications.[55]

The integration of CE-MS data with other omics datasets has become increasingly important in systems biology approaches. Pathway analysis tools and network visualization software have been adapted to incorporate CE-MS data, enabling a more comprehensive understanding of biological systems.[56]

CONCLUSION

CE-MS has emerged as a powerful analytical technique in pharmaceutical analysis, offering unique advantages in terms of separation efficiency, sensitivity, and versatility. Advancements in instrumentation, coupling strategies, and data analysis have significantly expanded the applicability of CE-MS across various stages of drug development and quality control. The technique's ability to analyze a wide range of compounds, from small molecules to large biomolecules, positions it as a valuable complement to traditional chromatographic methods.

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