ABSTRACT
Capillary electrophoresis (CE) is a potential analytical and separation technique for wide variety of analytes, ranging from micro to macromolecules of biological or chemical origin belongs to either inorganic or organic class possesses simple or complex molecules. CE technology has been valuable for the comprehensive determination of drug and process related impurities. CE is a family of electrokinetic separation methods performed in capillaries and in micro-fluidic channels rely on a high voltage electric field being applied over a solution which is held in a capillary tube. CE classified according to mode of separation on the basis of differences in charge, size and frictional force, offers fast separations with excellent efficiency. CE is one of favourite analytical tool for assay of pharmaceutical API including determination of drug related impurities, as it provides reliable result in minimum time period; also it offers a high degree of automation and requires minimal sample preparation and. CE possess other versatile applications such as chiral, stoichiometric and bioanalysis of pharmaceutical API. The current review presents basic principles underlying different modes of CE, and their application in analysis of pharmaceutical analysis.

KEYWORDS: Capillary electrophoresis, Pharmaceutical assay, Impurity profiling, Chiral analysis, Bioanalysis.

INTRODUCTION
CE is an alternative to more traditional methods such as gel electrophoresis and liquid chromatography and is employed to detect both high and low affinity molecular interactions, and separation of both charged and non-charged molecules[1]
CE has proved to be an efficient and versatile approach for physicochemical characterization of bioactive molecules and resolution for charged substances such as biomolecules, low molecular weight basic or acidic drugs and ions.[1]

**PRINCIPLE**

Capillary electrophoresis is a physical method of analysis based on the electrophoretic mobility, inside a capillary, of charged analytes dissolved in an electrolyte solution and under the influence of a direct-current electric field. The electrophoretic mobility is dependent upon the charge of the molecule, the viscosity, and the atom’s radius. The rate at which the particle moves is directly proportional to the applied electric field—the greater the field strength, the fast the mobility. In CE, the thin dimensions of the capillaries greatly increased the surface to volume ratio, which eliminated overheating by high voltages.[2]

The electrophoretic mobility of a solute (µep) depends on the characteristics of the solute (electric charge, molecular size and shape) and those of the buffer media in which the migration takes place (type and ionic strength of the electrolyte, pH, viscosity and additives).[2] This electrophoretic mobility called as electrophoresis.

The electrophoretic velocity (νep) of a solute, assuming a spherical shape, is given by the equation (1).[3]

\[
(ν_{ep}) = (µ_{ep}) \times E \quad eq \ (1)
\]

Where, (E) electric intensity

When an electric field is applied through the capillary filled with buffer, a flow of solvent is generated inside the capillary, called electro-osmotic flow. The velocity of the electro-osmotic flow depends on the electro-osmotic mobility (µeo) which in turn depends on the charge density on the capillary internal wall and the buffer characteristics. The electro-osmotic velocity (νeo) is given by the equation (2).[3]

\[
(ν_{eo}) = (µ_{eo}) \times E \quad eq \ (2)
\]

This electrophoretic mobility called as electro-osmosis which refers to the movement of the buffer in the capillary under the influence of the electric field.

The velocity of the solute (ν) is given by equation (3).[3]

\[
(ν) = (ν_{ep}) + (ν_{eo}) \quad eq \ (3)
\]

The electrophoretic mobility and the electro-osmotic mobility may act in the same direction or in opposite directions, depending on the charge of the solute.
CE is now an established technique in several areas of analysis and is capable of detecting millimolar to nanomolar binding interactions and offers the benefits of a powerful and proven technology applied to drug discovery screening on a wide variety of targets such as enzymes, membrane receptor domains, structural proteins, nucleic acid complexes, bioactive peptides, protein-protein interactions and antibodies.

SEPARATION MODES OF CE

Based on the mode of the operation CE separated into following techniques:

1. Capillary zone electrophoresis (CZE)
2. Non aqueous capillary electrophoresis (NAQCE)
3. Capillary gel electrophoresis (CGE)
4. Capillary isoelectric focussing (CIEF)
5. Capillary Isotachophoresis (CITP)
6. Capillary electrokinetic chromatography (CEKC) and capillary electrochromatography (CEC)
7. Micellar electrokinetic chromatography (MEKC)
8. Micro-emulsion electrokinetic chromatography (ME-EKC)
9. Pressurized capillary electrochromatography (PCEC)
10. Affinity capillary electrochromatography (ACE)
11. Microfluidic Capillary electrophoresis (MFCE)

1. Capillary zone electrophoresis

CZE is characterized by the use of open capillaries and relatively low viscosity buffer systems. Analyte molecules move from one end of the capillary to the other according to the vector sum of electrophoresis and electroosmotic mobility. Separation in CZE is based on differences between electrophoretic mobilities which result in different velocities of migration of ionic species in electrophoretic buffer contained buffer.[7]

2. Non Aqueous capillary electrophoresis

NAQCE is similar to other CE techniques in all aspects except the use of non aqueous solvent used. CE can be performed using non-aqueous systems based on such solvents as acetonitrile, methanol, formamide, and dimethyl formamide, to which are added small amounts of anhydrous acid or buffer salts which utilised for hydrophobic analytes. Important factors which influence the choice of organic solvent for given separation are volatility, solubility
parameter, viscosity, dielectric constant, UV transparency. Chiral separations of pharmaceutical racemic amines were achieved by NACE using various cyclodextrins.\[^8\]

Separation of a ten-membered model mixture of aromatic compounds possessing a carboxylic moiety along with other functional groups performed in the pH range 4.5–8.5. non aqueous solvent composition Methanol-acetonitrile (1:1) containing equimolar concentration of sodium acetate and Tris as background electrolyte.\[^9\]

Ceved Demir et al reported an optimised method for separation of metal ions such as Ag, Fe, Cr, Mn, Cd, Co, Pb, Ni, Zn, Cu in solvent acetic acid by using Imidazole as co-ion for indirect detection using UV.\[^10\]

3. **Capillary gel electrophoresis**

CGE performed in a polymeric gel medium. CGE is based on viscous drag, where the capillaries filled with viscous solution or gel separation achieved on the basis of difference in the size. CGE is potentially useful for the separation of large biological molecules such as proteins and DNAs, which have similar electrophoretic migration rates in free solution due to their similar charge-to-mass ratios.\[^3\] CGE separates molecules according to their size in non convective medium. Commonly used separation media include non-crosslinked polymers such as linear polyacrylamide, polyethylene glycol and cellulose derivatives, as well as crosslinked polymers or gels, such as polyacrylamide and agarose.\[^3\] Most commonly used polymer for CGE is polyacrylamide because of its electoneutrality.\[^4\]

4. **Capillary isoelectric focussing (CIEF)**

CIEF is a separation technique based on isoelectric point and it relies on a graduated pH buffer gradient to provide an isoelectric point where the net charge on the molecule is zero. CIEF combines the high resolving power of conventional IEF with the advantages of automation and speed. The separation of charged analytes takes place in a pH gradient created in a capillary by carrier ampholytes under the influence of an electric field. The concentrating effect that occurs during the focusing step, enables components present in small quantities to be detected.\[^14\]

5. **Capillary Isotachophoresis (CITP)**

Isotachophoresis (ITP) is one of the fundamental electrophoretic separation techniques, where charged constituents are separated in an electric Field due to their differences in their
electrophoretic mobilities\[^{15}\]. In CITP, a sample is inserted between a leading electrolyte and a trailing (or terminating) electrolyte without electroosmotic flow. The leading electrolyte has a higher mobility and the trailing electrolyte has a lower mobility than ions in the sample zone. Separation in CITP relies on differences in the velocities of analyte ions within the sample zone. CITP is primarily used as a concentration technique by assembling specific molecules into small focused zones.\[^{16}\]

6. **Capillary electrokinetic chromatography and capillary electrochromatography**

CEKC and CEC are separation technique based on a combination of liquid chromatographic and electrophoretic separation methods. In CEKC, stationary phase is a moving pseudo stationary phase, while it is a fixed stationary phase in capillary column in case of CEC. The first application in the field of CEC was described by Gatschelhofer et al for the enantioseparation of glycyl-dipeptide\[^{12}\]. It can be divided into three parts.\[^{11}\]

I. CEC open-tubular capillary electrochromatography (OT-CEC) in which the stationary phase is immobilized on the inner walls of the capillary

II. CEC with packed columns

III. CEC with monolithic columns.

7. **Micellar electrokinetic chromatography (MEKC)**

In MEKC, the secondary phase is a Micellar dispersed phase in the capillary. The separation principle of MEKC is based on a differential partition between the micelle and the solvent and this principle can be employed with charged or neutral solutes and may involve stationary or mobile micelles. Micellar electrokinetic chromatography (MEKC) is a mode of EKC in which surfactants (micelles) are added to the buffer solution.

MEKC is different in that it uses an ionic Micellar solution instead of the simple buffer salt solution used in CZE. The micellar solution generally has a higher conductivity and hence causes a higher current than the simple buffer does in CZE. MEKC can separate both ionic and neutral substances while CZE typically separates only ionic substances.

Thus MEKC has a great advantage over CZE for the separation of mixtures containing both ionic and neutral compounds. However, in MEKC the size of the sample molecules is limited to molecular weights of less than 5000, whereas CZE has virtually no limitation in molecular size. The separation principle of MEKC is based on the differential partition of the solute between the micelle and water; CZE is based on the differential electrophoretic mobility.\[^{17}\]
8. **Micro emulsion electrokinetic chromatography (MEEKC)**

Micro emulsion Electrokinetic chromatography is a family of electrophoresis separation techniques which include electrophoresis and chromatography. The separation is based on a combination of electrophoresis and interactions of the analytes with additives such as surfactants that form a dispersed secondary phase moving at a different velocity, also called a pseudo stationary phase or separation carrier \(^{[18]}\). A microemulsion containing ionic surfactant allows chromatographic separation to be obtained as solutes can partition between the charged oil droplets and the aqueous buffer phase.

High-pH buffers such as borate and phosphate are generally used in MEEKC. These buffers generate a high electroosmotic flow (EOF) when the voltage is applied across the capillary filled with the buffer. Surfactant-coated oil droplets are negatively charged and, therefore, attempt to migrate towards the anode (away from the detector) when the voltage is applied. However, the EOF is sufficiently strong to eventually sweep the oil droplets through the detector to the cathode. If a solute is ionized then it will electrophoretically migrate according to its size and number of charges when the voltage is applied. Repulsion from negatively charged droplets will occur if the solute is also negatively charged. Conversely if the solute is positively charged it may have ion-pair type interaction with the negatively charged droplets. The migration time obtained in MEEKC for ionized solutes reflects a combination of both the electrophoretic and chromatographic behavior of the solute ions \(^{[19]}\).

9. **Pressurized capillary electrochromatography (pCEC)**

Pressurized capillary electrochromatography (pCEC) is a separation technology in which the retention mechanism is based on both chromatographic partition and electrophoresis. pCEC successfully makes use of columns with small particles of 1.5μm, and dramatically enhanced the efficiency, speed, peak capacity, reproducibility and sensitivity, compared to traditional HPLC and CE. CEC technology is widely applied in various fields, including pharmaceutical sciences \(^{[20, 21]}\). pCEC has several advantages over HPLC\(^{[22,23]}\):

I. high separation efficiency and resolution using a column packed with extremely small particles

II. high selectivity with a double separation mechanism

III. high speed with driven force of both pressure and electroosmotic flow

IV. quantitative sample injection with rotary type valve, and
V. gradient solvent elution with binary solvent delivery. It has been widely applied in various fields, including pharmaceuticals.

10. Affinity capillary electrochromatography (ACE)
Affinity CE (ACE) is a versatile analytical technique to study a variety of bimolecular noncovalent interactions and in determining binding and dissociation constants of formed complexes. The technique uses the resolving power of CE to distinguish between free and bound forms of a receptor as a function of the concentration of free ligand.

Since the initial reports in 1992 documenting the use of CE to study receptor ligand interactions ACE has been successfully used to examine a wide array of interactions including protein-drug, protein-DNA, peptide-carbohydrate, peptide-peptide, DNA dye, carbohydrate-drug, and antigen-antibody.\(^{[24]}\)

Affinity capillary electrophoresis (ACE) is an electrophoretic mode that takes advantage of the specific interactions of receptors, antibodies, or ligands with the analyte. In contrast to other CE modes, ACE is not dedicated to general analysis, but rather is focused on measuring molecular interactions of the solute with specific receptors.\(^{[25]}\)

11. Microfluidic Capillary electrophoresis (MF-CE)
In practice, microfluidic systems are based on the principles of CE. A universal conductivity detector was presented that allowed detection of charged species down to the μM level. Additionally, powder blasting was presented as a novel technique for direct etching of microfluidic networks. Micro fluidic system consists of an electrospray interface to a mass spectrometer was integrated with a capillary electrophoresis channel, an injector and a protein digestion bed on a monolithic substrate. This chip provided a convenient platform for automated sample processing in proteomics applications.\(^{[26]}\)

The design of most microfabricated electrophoresis systems is relatively simple, consisting of the following fundamental elements: (1) a sample injection zone, (2) an electrophoresis separation channel, and (3) a system for detection of the migrating analytes.\(^{[27]}\)

APPLICATION
CE analyses are usually very fast, use little sample and reagents, and cost much less than chromatography or conventional electrophoresis. Although modern CE is still in its teenage years, it has demonstrated tremendous potential for a wide range of applications, from
smaller biomolecules that includes wide variety of analytes, ranging from micro to macromolecules of biological or chemical origin belongs to either inorganic or organic class possesses simple or complex molecules. Apart from these above mentioned generalised applications CE and its specialized derivatized techniques possess analytical applicability for following:

**Assay of pharmaceutical API**

For pharmaceutical analysis, assay of drug substance and formulated products is a very important and regulated activity. Analytical methods must be validated to strict standards to show that they are robust, accurate, repeatable, and suitable for their purpose.

Advantages of implementing CE methods in place of HPLC for assay of pharmaceuticals:

I. Its relatively small level of solvent consumption for analysis (milliliters compared to the liters of mobile phase used in an HPLC run).

II. Sample pretreatment requirements are often reduced compared to HPLC, as the CE capillary can be washed with NaOH between injections and many interfering components do not migrate, as they are neutral.

III. The ability to quantify a range of sample types using a single set of CE conditions is another strong feature, as this can considerably reduce analysis and system set-up times.

<table>
<thead>
<tr>
<th>No</th>
<th>Validated Pharmaceutical assay by Capillary Electrophoresis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Determination of indinavir sulfate, a protease inhibitor used in HIV therapy in capsule formulations</td>
<td>[28]</td>
</tr>
<tr>
<td>2</td>
<td>Method for assay of raloxifene, an estrogen agonist in bone</td>
<td>[29]</td>
</tr>
<tr>
<td>3</td>
<td>Assay and identification of ragaglitazar, a diabetic therapy, and its counter-ion arginine, chiral purity of ragaglitazar and purity of ragaglitazar in Active Pharmaceutical Ingredients and low dose tablets</td>
<td>[30]</td>
</tr>
<tr>
<td>4</td>
<td>Determination of pravastatin, a cholesterol reducing agent, in tablet formulation</td>
<td>[31]</td>
</tr>
<tr>
<td>5</td>
<td>Determination of the anti-fungal ketoconazole in tablets and creams</td>
<td>[32]</td>
</tr>
</tbody>
</table>

**Chiral application of CE in pharmaceutical analysis**

Chiral CE is a valuable tool for chiral analysis since most pharmaceutical entities are chiral and each Enantiomers expresses distinct pharmacological activity and toxicity. Chiral separation is, therefore, necessary in pharmaceutical analysis to obtain the safe and desirable
enantiomer. CE is popular for chiral drug separation due to its high resolution, simplicity, and speed, chiral drug separation due to its high resolution, simplicity, and speed.

Chiral CE can be performed by indirect or direct methods. In the former method, racemic mixtures react with chiral reagents to give diastereoisomers with different physical and chemical properties; therefore they can be separated from each other. For the direct method, chiral selectors are added into the background electrolytes to stereoselectively interact with each enantiomer. The direct method is favorable to the indirect method due to its simplicity and the availability of a variety of chiral selectors. Cyclodextrin (CD), chiral crown ether, and acyclic carbohydrate are chiral selectors, which form inclusion complexes with enantiomers.[48]

Table 2: Chiral analysis by CE

<table>
<thead>
<tr>
<th>No</th>
<th>Chiral analysis</th>
<th>Chiral selector</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amlodipine in serum sample</td>
<td>HP-beta–CD</td>
<td>[34]</td>
</tr>
<tr>
<td>2</td>
<td>Timolol in Raw material</td>
<td>ketopinic acid</td>
<td>[35]</td>
</tr>
<tr>
<td>3</td>
<td>Oxprenolol Pharmaceutical formulation</td>
<td>HAS</td>
<td>[36]</td>
</tr>
<tr>
<td>4</td>
<td>Dopa enantiomers used to treat parkinsons disease</td>
<td>18 C6H4</td>
<td>[37]</td>
</tr>
<tr>
<td>5</td>
<td>Enantioseparation of methotrexate disease</td>
<td>HP-beta–CD</td>
<td>[38]</td>
</tr>
</tbody>
</table>

Stoichiometric determination

Typically, acidic drugs are prepared as their sodium or potassium salts, whereas basic drugs may be produced as chloride, sulfate, succinate, or maleate salts. CE has been employed to determine a range of inorganic and organic ionic impurities present in drug substance batches. Limits of detection of <0.1 % w/w were reported. The method allowed the determination drug substances to be conducted on both water-soluble and water-insoluble drug. Analytical-grade inorganic materials such as NaCl are employed as standards to generate a response factor for the ion concerned. Sample weights are adjusted to give an equivalent concentration of the ion being analyzed.[39].

Determination of drug related impurity

The use of capillary electrophoresis (CE) to determine drug-related impurities is becoming established within industrial pharmaceutical analysis laboratories. Increasingly CE is being viewed as an alternative for, and complement to, high-performance liquid chromatography (HPLC). CE has been employed to wide range of drugs to determine drug related impurities. The three main separation mechanisms employed are low pH (for analysis of basic drugs),
high pH (for analysis of acidic drugs) and Micellar electrokinetic capillary chromatography (for the analysis of neutral and/or charged compounds).[40]

i) Low pH determination: Basic drug impurities can be separated at pH 2.0–4.0, and a low-pH electrolyte is often employed in analysis of basic drugs and their related impurities. Sabbah S and Scribagk developed and validated CE assay for ranitidine (Zantac) and potential related substances in bulk drug and pharmaceutical preparations with the ionic strength and pH of the electrolyte shown to be the most critical parameters affecting selectivity.[56]. The CE assay gave detection limits of: diamine (0.03% a/a), oxime (0.04%, a/a), Bis (0.1% a/a), nitroacetamide (0.24% a/a), and a number of unknown peaks, which were not resolved by either TLC or HPLC.[41]

ii) High pH determinations: High-pH buffers, such as phosphate and borate, are employed in the analysis of acidic components. At high pH, the acidic components migrate against the EOF, maximizing mobility differences. Fabre H. et al used High-pH borate buffer at pH 9.2 in CE for the determination of homotaurine (HT), a doubly charged anion at this pH, as an impurity in calcium acamprosate by capillary zone electrophoresis (140). The method was validated and detection limits of between 0.01 and 0.15% homotaurine with respect to drug substance were reported.[42]

iii) Micellar electrokinetic chromatography (MECC): This approach would be adopted when dealing with uncharged solutes or mixtures of charged and neutral species. This approach may also be considered when simple mobility differences prove insufficient in free-solution CE. The selectivity can be manipulated in a similar fashion as with those parameters employed in reverse phase HPLC, and these include addition of cyclodextrin, ion-pair reagents, and organic solvents. Additional selectivity manipulation can be achieved by varying the type and concentration of surfactant or employing combinations of surfactants. Water-insoluble compounds are generally analysed using MECC. Samples can be prepared in 100% organic solvents, but this can produce problems of out-gassing when employing extended injection times.[55] M. Swartz performed separation of a range of salicylamide impurities using an MECC method employing sodium dodecyl sulfate (SDS). A detection wavelength of 214 nm allowed detection of trace impurities at the 0.01% level.[43]
Bioanalysis of pharmaceuticals

The determination of pharmaceuticals in biological fluids is essential for purpose of therapeutic drug monitoring, forensic and clinical toxicology and pharmacological research. The important concern for this analysis is sample clean up and pre-concentration of sample, may arise due to the complexity of biological matrices and small quantities of analytes. Generally biological samples consist of many components, such as macromolecules of proteins, lipids, carbohydrates and small molecules of different nature, which may prohibit the performance of the capillary or can interact with analytes. The pharmaceutical contents have been investigated in the variety of matrixes as shown in table given below:

Table3: bioanalysis of pharmaceuticals

<table>
<thead>
<tr>
<th>No</th>
<th>Analyte</th>
<th>Sample matrix</th>
<th>LOD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Salbutamol</td>
<td>Urine</td>
<td>1-5 μg/mL</td>
<td>[44]</td>
</tr>
<tr>
<td>2</td>
<td>Lactic acid</td>
<td>Blood</td>
<td>Trace amount</td>
<td>[45]</td>
</tr>
<tr>
<td>3</td>
<td>Amphetamine and its metabolites</td>
<td>Urine</td>
<td>1-5 μg/mL</td>
<td>[45]</td>
</tr>
<tr>
<td>4</td>
<td>Racemorphan enantiomer determination</td>
<td>Urine</td>
<td>1-5 μg/mL</td>
<td>[46]</td>
</tr>
<tr>
<td>5</td>
<td>R,S-mirtzepine, and R,S-desmethylmirtazepine</td>
<td>Human plasma</td>
<td>0.2 μg/mL</td>
<td>[47]</td>
</tr>
</tbody>
</table>

The development of high speed technology in CE, which allow separations on the millisecond time scale, which have opened new areas of application such as real time chemical monitoring and detection of short-lived species (protein conformers or non-covalent complexes), rapid multi-dimensional separations and high throughput assays for clinical laboratories.

Physicochemical profiling of analytes

Zhong jiang Jia reported utility of CE as a excellent tool for physic-chemical profiling of analytes, physicochemical properties of pharmaceuticals such as acid dissociation constant (pKa), octanol-waterpartition coefficient (logP\(_{o/w}\)), protein binding constant, inclusion complex constant with cyclodextrin (CD), and self association are determined with this which possess importance in drug design, candidate selection, and drug delivery.

Log P determination

I. Gluck S. et al reported method for log p value determination of Neutral pharmaceuticals and steroids in a medium 0.05M phosphate buffer, pH 7.0 (pH 9.0 for steroids)–80mM SC, 100mM SDS or 100mM CTAB surfactant (MEKC).\[49\]
II. Yang S. reported a log P determination method for 24 acidic and basic pharmaceuticals by using Heptane-butanol-SDS borate, pH 12.0.\cite{50}

III. Ishihama Y. determined log p values of Anionic pharmaceuticals by using Heptane-butanol-SDS borate, pH 7.0.\cite{51}

\textbf{pKa determination}

I. Wan H. Et al performed Rapid pKa screening of 26 acidic, basic and multivalent pharmaceuticals pH range 2.5–11.0 in a medium having electrolytes of 0.05M ionic strength composed of 0.5M phosphate and 1M acetate buffers mixed to obtain required pH PACE at 25 mbar “short-end” injection.\cite{52}

II. Ornskov E. determined Pka of labile drug compounds in a medium of PH range 2.0-12.0 electrolytes of 0.05M ionic strength composed of 1M phosphate, 0.1M borate and 1M acetate buffers mixed and adjusted with phosphoric acid, acetic acid and NaOH to obtain required pH “short-end” injection.\cite{53}

\textbf{CONCLUSION}

CE Being a potential analytical technique it separates cationic, anionic and neutral species by applying voltage across buffer filled capillaries. CE Offers an advantage of minimal organic consumption, fast analysis time, and high degree of resolution. CE is employed in quality control of pharmaceuticals, biopharmaceuticals. CE has been increasingly employed for the separation of pharmaceutical agents and drugs; pharmaceutical analysis, assay of active pharmaceutical ingredients, chiral drug separation, detection of impurities in drugs, analysis of metal and non-metal ions, carbohydrates and their derivatives, proteins, DNA, and assessment of potency and stability of drugs. Moreover, CE technique is widely accepted by regulatory authorities.

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