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Hyphenated Technique - Capillary Electrophoresis-Mass Spectrometry

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ABSTRACT

Capillary electrophoresis –Mass spectrometry is an analytical technique that focused on the analysis of various components. First, the introduction, principle of capillary electrophoresis and mass spectrometry are overviewed. In this section, electrolytes and capillaries used in the capillary electrophoresis, movement of the components along the capillary, and the advantages of interfacing mass spectrometry with capillary electrophoresis is mentioned. The second part is devoted to instrumentation, interfacing CE with MS, electrospray interfacing, and various interface designs such as sheath-flow interface, sheathless interface, nanospray sheath-flow interface, flow through microvial interface, sheath porous emitter nano ESI interface, CE-MALDI-MS. The third part includes various applications such as CE-MS in the analysis of food contaminants, toxins, heparin oligosaccharide & low molecular weight heparin, biopharmaceuticals and the determination of drugs in the biological samples, physiochemical properties of the drug, assay of metabolites by EMMA. We anticipate that CE-MS will play a key role in clinical and biomedical studies for volume or mass –limited biological as well as novel applications involving single cell or subcellular metabolome characterization.

INTRODUCTION

Capillary electrophoresis–mass spectrometry (CE-MS) is an analytical technique having high resolving power and sensitivity. CE-MS combines advantages to provide high separation efficiency and molecular mass information in a single analysis. It requires minimal volume and it can analyze at high speed. Ions are typically formed by electrospray ionization, but they can also be formed by matrix-assisted laser desorption/ionization or other ionization techniques. It has applications in proteomics and quantitative analysis of biomolecules as well as in clinical medicine. CE-MS is applicable for protein and peptides analysis and other biomolecules.

The original interface between capillary zone electrophoresis and mass spectrometry was developed in 1987by Richard D. Smith and co-workers at Pacific Northwest National Laboratory.

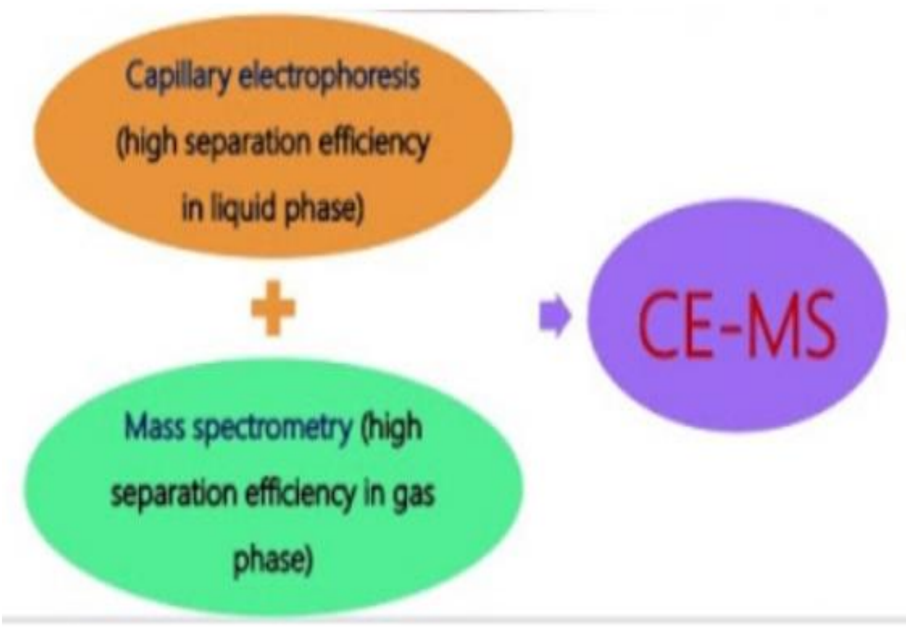


Figure No. 1: Combination of CE-MS

CAPILLARY ELECTROPHORESIS

PRINCIPLE

Capillary electrophoresis is performed in narrow-bore capillaries with atypical inner diameter of 25-75 µm. The separation is based on the different mobilities of charged species in an electric field. The capillary, which is generally between 20-90 cm long, is filled with a

background electrolyte, usually a buffer with a pH that is suitable for the separation of the compounds analysed. A sample is injected into the capillary either electrokinetically using voltage, or hydrodynamically using pressure or vacuum. The capillary ends are then placed in vials containing the electrolyte. When the separation voltage is switched on the compounds starts to migrate. The velocity (ῡ) of the migration is determined not only by the charge (z) and the size of the molecule but also by the electric field strength(E) and the viscosity (K) of the buffer, which is shown in equation 1, where e is the charge of a proton or electron and r is the radius of the solvated ion.

$$\bar{\upsilon}=(z*e*E)/(6\pi r\eta)$$

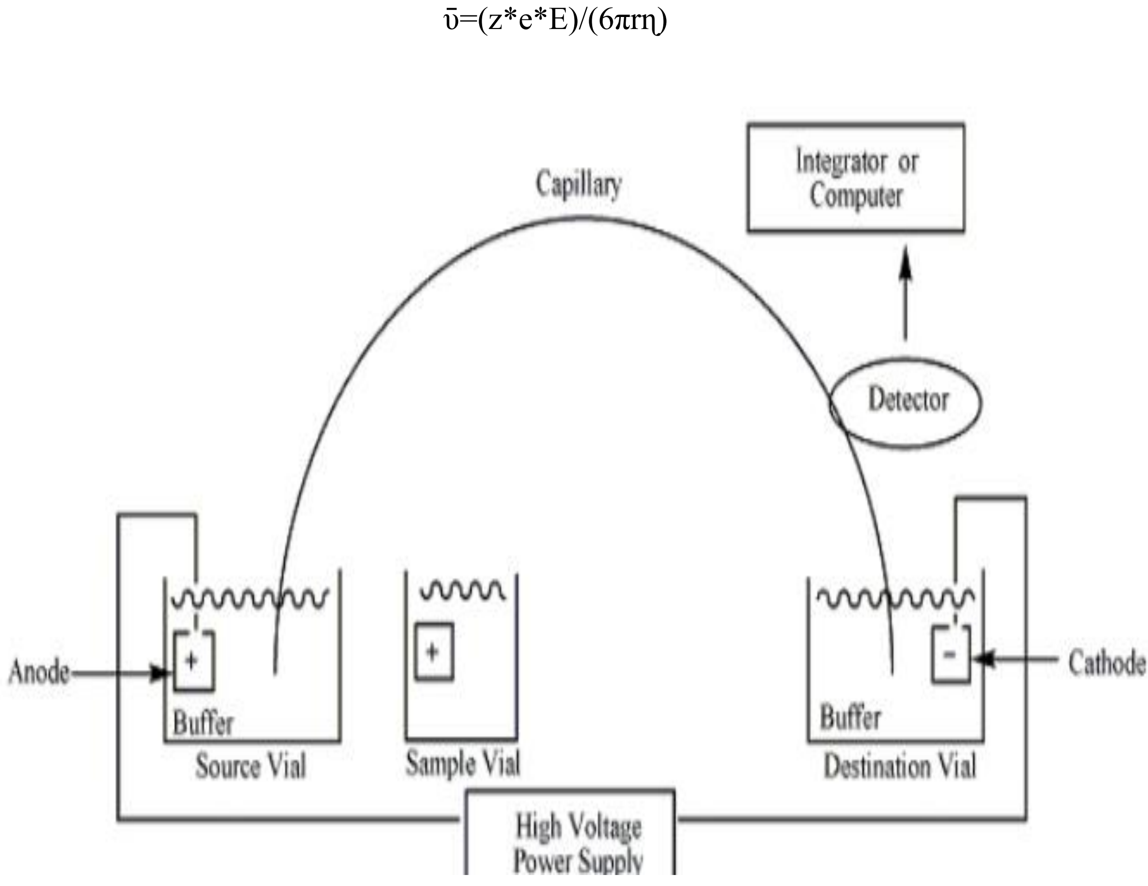


Figure No. 2. Schematic representation of capillary electrophoresis system

ELECTROLYTES

The electrolytes used for the separation must be volatile since involatile salts such as phosphate crystallise during the ionisation process quickly block the CE-capillary and the orifice of the mass spectrometer. The most common electrolytes for use with mass spectrometry are acetic acid, formic acid and ammonium acetate. It is advisable to use as low concentration of the electrolytes as possible without compromising the separation efficiency

since high concentration of the background electrolyte tends to decrease the sensitivity and could also contribute to band broadening due to Joule heating if the current is too high.

CAPILLARIES

The capillaries used for CE-MS are usually longer than for CE-UV due to the distance between the CE and the mass spectrometer. This may improve the separation but may also make adsorption of analytes to the capillary surface. Additives can be used to decrease the adsorption but will often interfere with the electrospray ionisation. The easiest way of decreasing the adsorption is to derivatise capillaries to make their walls less prone to attracting the analytes. The outer diameter of standard capillary is 375µm used for CE-UV analysis.

Capillaries with outer diameters of 190-220µmcan be used. The advantage of using a thinner capillary is that the electrospray interface can be made smaller by using a narrower spraying capillary to deliver the sheath flow. Not all CE instruments are capable of using the thinner capillaries but usually, the problems can be overcome by minor alterations.

DETECTION OF COMPOUNDS

The compounds are detected when they reach the end of the capillary. The most common method of detection is UV, which is done while the compounds still are in the capillary by creating a detection window by removing a few millimetres of the polyimide coating. Other methods of detection include fluorescence, electrochemical and mass spectrometric ionisation techniques.

UV ABSORPTION

UV absorption is the most common detection mode in CE. It is a universal principle that uses fused-silica capillaries & aqueous buffers allows detection wavelength below 200nm. The use of low wavelengths offers a significant gain in sensitivity and wide applicability. The detector volume is very small, which means that broad broadening is prevented.

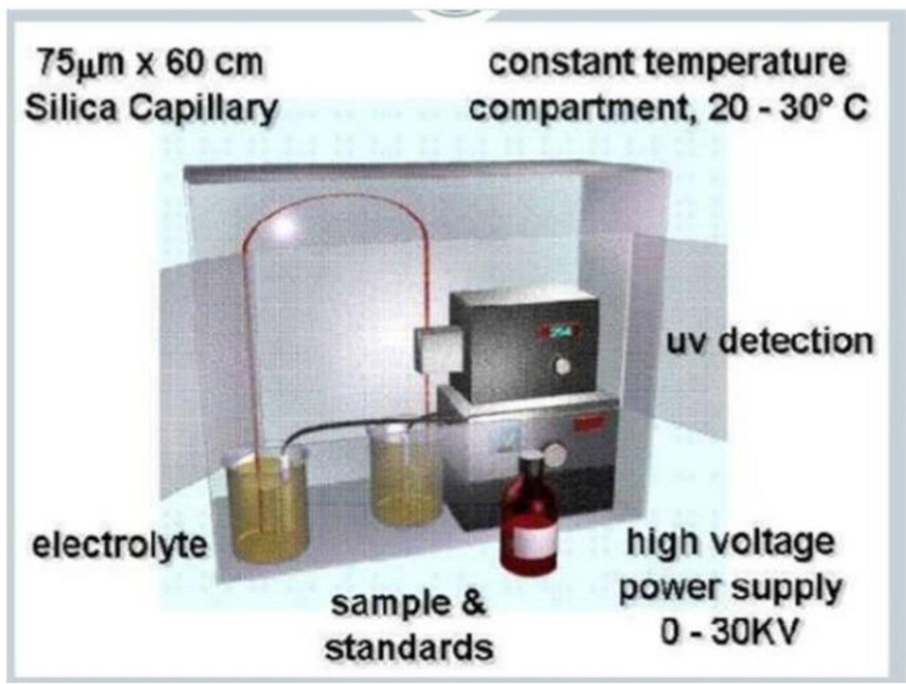


Figure No. 3: UV detector used in CE

FLUORESCENCE

Fluorescence is very sensitive especially if laser is used as excitation source. Excitation light should be focused on a very small detection volume. Furthermore, analyte emission should be effectively collected from the same volume. The inner and outer surface, which refract the excitation and emission light, cause scatter, which in turn can induce significant background noise. The fluorescence is emitted in all directions and only a small part is collected. Because of its small sample requirement, CE with laser-induced fluorescence is an excellent tool for single-cell analysis.

MOVEMENTS OF COMPONENTS ALONG THE CAPILLARY

Movements of component along the capillary by 2 interactions:

- ELECTROPHORETIC MOBILITY
- ELECTROOSMOTIC FLOW

ELECTROPHORETIC MOBILITY

Migration of charged particles in a stationary medium under the influence of an applied electric field. The positive ions move towards the negative charged cathode. Electrophoretic mobility is given by the equation.

$$\mu_{ep} = v_{ep}/ I$$

Where E- Electric field

v-Electrophoretic velocity

$$\mu_{ep} = q/6\pi\eta r_{st}$$

q- charge

η-viscosity of the solution

r_{st} – stokes radius of the ion

ELECTROOSMOTIC FLOW

The interior wall of capillary contains charged sites that are created by the ionization of silanol groups on the fused silica. The positive component interact with the negatively charged inert surface in the capillary. The EOF along with electrophoretic mobility results in effective separation of components. Movement of separation buffer through the silica capillary as a result of existence of a zeta potential at the solvent/silica interface.

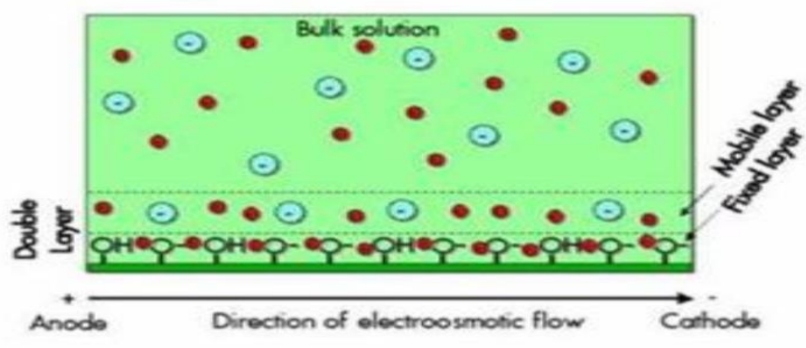
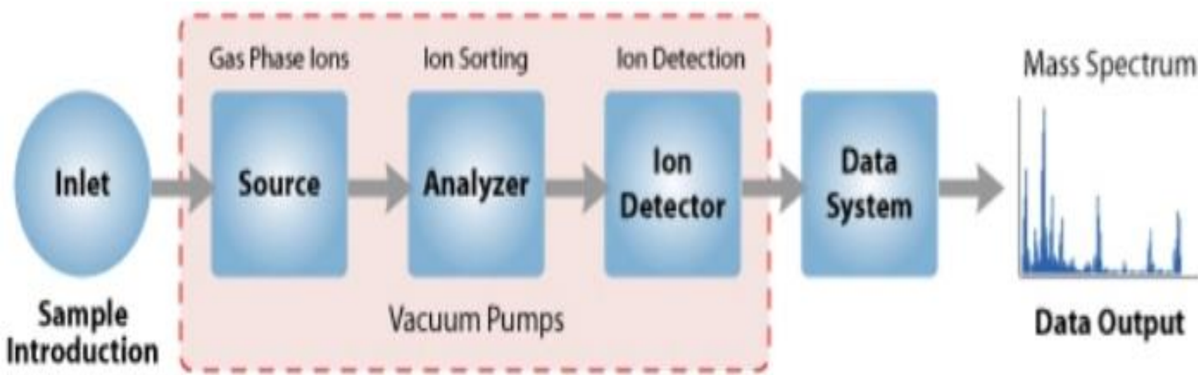


Figure No. 4: Direction of Electroosmotic flow

MASS SPECTROMETRY

PRINCIPLE

A mass spectrometer consists of five basic parts. The first part is a sample system where the sample can be introduced into the mass spectrometer for ionisation. This takes place in the ion-source where a beam of charged particles characteristic for the sample is created. The ion beam is then separated into its components according to their mass-to-charge ratio in the analyser and the ions detected by a detector, which is mostly of the electron multiplier type. The fifth essential component is a high vacuum system since the whole process after the creation of the ion beam to the detection takes place under increasingly higher vacuum, in the order of 10^{-4}-10^{-7} mbar.



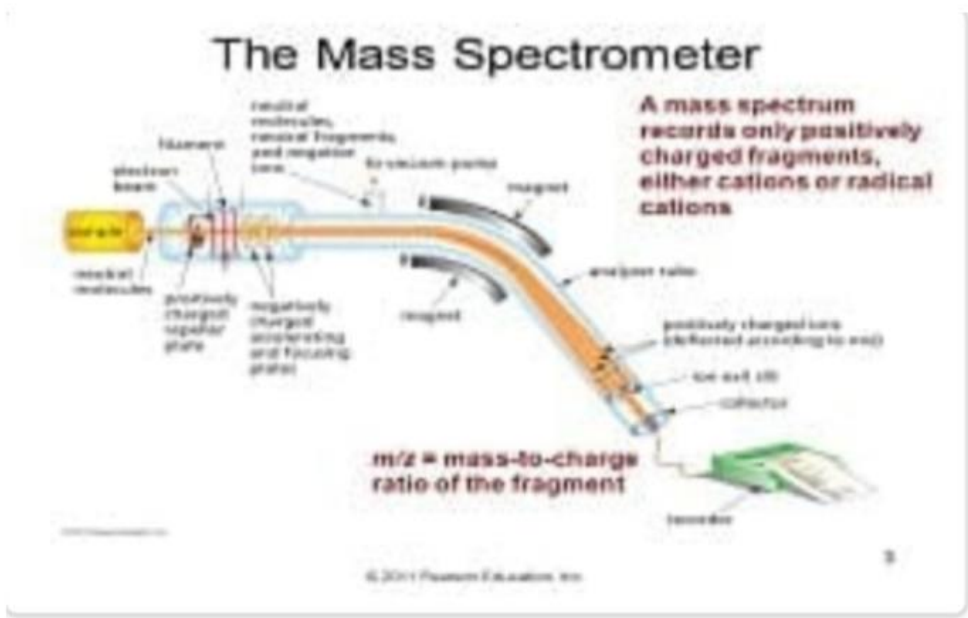


Figure No.5. Schematic representation of Mass Spectrometry and mass spectrometer

ADVANTAGES OF INTERFACING MASS SPECTROMETRY WITH CAPILLARY ELECTROPHORESIS:

Mass spectrometry is attractive for detection in CE as efficient separation is coupled with sensitivity and selective detection of small and large molecules. MS and MS/MS can be used for the identification of compounds. The compounds that coelute in CE may easily be distinguished in MS.

INSTRUMENTATION

An ideal CE instrument for use with mass spectrometry should be able to cope with different detection techniques and be comparatively compact and should be able to be controlled without using a computer if desired. The first thing to find out before attempting to connect your CE to an MS is to see how safe your CE is. The power supply must be able to apply a potential on one of its electrodes without the need for a current being registered at the other. This means that the detection end of the capillary can be taken out of the outlet vial and connected to a CE-MS electrospray interface. The next step is to try to get the detection end of the capillary out of the instrument while keeping the length of it as short as possible. Sometimes it might be necessary to drill a hole in one of the panels of the instrument. If the capillary can go through the UV detector on the way out of the instrument without drastically increasing the capillary length. To minimise band broadening it is recommended to have the level of the buffer surface at the same height as the outlet of the capillary in the electrospray interface to avoid siphoning.

INTERFACING CE WITH MS

Capillary electrophoresis is a separation technique which uses high electric field to produce electroosmotic flow for separation of ions. Analytes migrate from one end of capillary to other based on their charge, viscosity and size. Higher the electric field, greater is the mobility. Mass spectrometry is an analytical technique that identifies chemical species depending on their mass-to-charge ratio. During the process, an ion source will convert molecules coming from CE to ions that can then be manipulated using electric and magnetic field. The separated ions are then measured using a detector. The separation and detection of analytes can be improved with better interface. CE has been coupled to MS using various ionization techniques like FAB, ESI, MALDI, and DESI. The most commonly used ionization technique is ESI.

The most useful and common ionization techniques for CE-MS coupling are ESI and MALDI. Both are soft ionization techniques and so well usable for the analysis of proteins/peptides. Both can be used as online as well as offline coupling. Online coupling by ESI is the preferred method; however, offline coupling of CE to MALDI has a lot of interest due to some advantages, such as higher tolerance of salts, greater sensitivity to some compounds, versatility of separation modes and buffer choice.

ELECTROSPRAY IONIZATION INTERFACING

Electrospray is the most widely used ionisation technique when performing CE-MS or LC-MS. The formation of ions from the liquid to the gas-phase is achieved by applying an electric field over the liquid phase to create charged droplets. These droplets are rapidly reduced in size by evaporation and disintegration due to the increasing charge density, & will eventually form gas phase ions. The electrospray technique is capable of producing multiply charged ions which has revolutionised the analysis of larger compounds, such as peptides and proteins, using mass spectrometry. Different types of interface system exist for CE/ESI-MS.

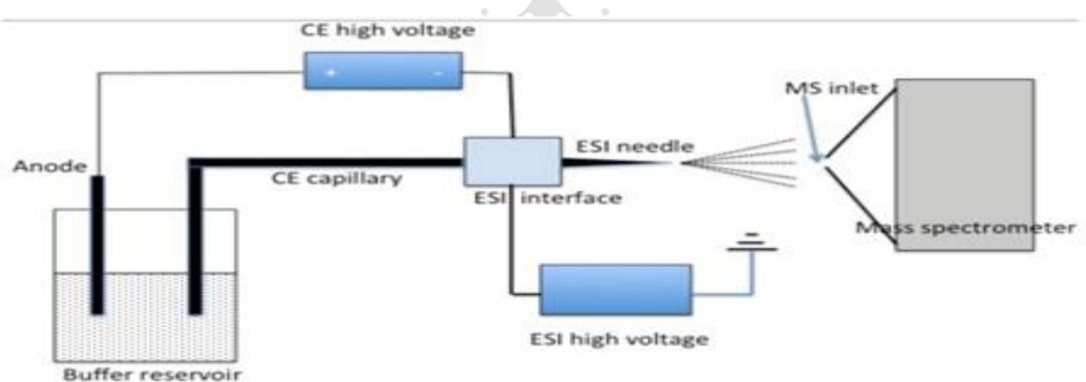


Figure No. 6: CE Interface with MS

INTERFACE DESIGN

CE can be coupled to MS with sheath flow (or) sheathless ESI interfaces. These two types of interface differ in whether or not sheath liquid is applied and establishment of electrical contact. Currently, sheath flow interfaces are most widely used than sheathless interfaces.

SHEATH-FLOW INTERFACES

The typical configuration of sheath-flow interface is the coaxial sheath-flow interface shown in the figure which was first developed by Smith et al. This configuration uses a triple tube

system in with CE separation capillary is surrounded by a tube of a larger diameter through which the sheath liquid flows. The electrical contact for the CE terminal voltage is applied to the conductive sheath liquid in the outer tube. The sheath liquid then meets and mixes with the effluent that exits capillary. A sheath gas is also commonly used as a part of this configuration and is applied through the outermost tube. Its role is to facilitate a more advantageous spray formation for ESI although sensitivity can be reduced due to dilution by the sheath liquid.

Sheath liquid both helps to stabilize the electrospray that are more typical for CE. The composition of the ESI spray can be made to be more MS compatible due to the modification CE of effluent by the sheath liquid. Liquid junction interfaces may be defined as a separate type of interface different from sheets flow interface by the location at which the shield liquid and CE separation liquid meat and mix.

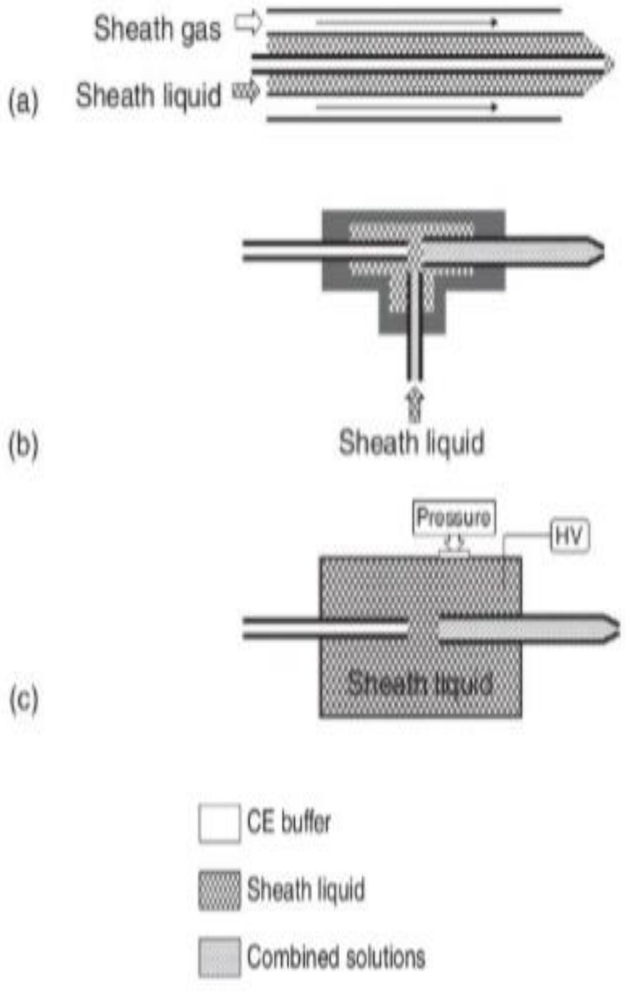


Figure No. 7: Common sheath-flow interface arrangements

(i) Coaxial sheath-flow interface with sheath gas

(ii) Liquid junction interface

(iii) Pressurized liquid junction interface

FLOW THROUGHMICROVIAL INTERFACE:

The Chen group developed a flow through microvial interface. This interface uses of flow through microvial to combine the flow of sample from the CE and modifier liquid which adjust like the BGE composition from CE to maintain a stable spray and increases ionization efficiency. The needle has an asymmetrical tip which causes the electric field to focus at the sharpest point of the metal electrode. At the inner tip of the needle, there is a space formed by the inside wall of the needle and the capillary from the CE called the flow through microvial, which acts as a cathodic electrode and the outlet vial for the CE. This is where the CE sample effluent and the chemical modified liquid meat and mix. This interface typically operates of flow rate of 100-400nl min^{-1}. This interface notably being used in the development of clEF-ESI-MS and in the analysis of N -linked glycans.

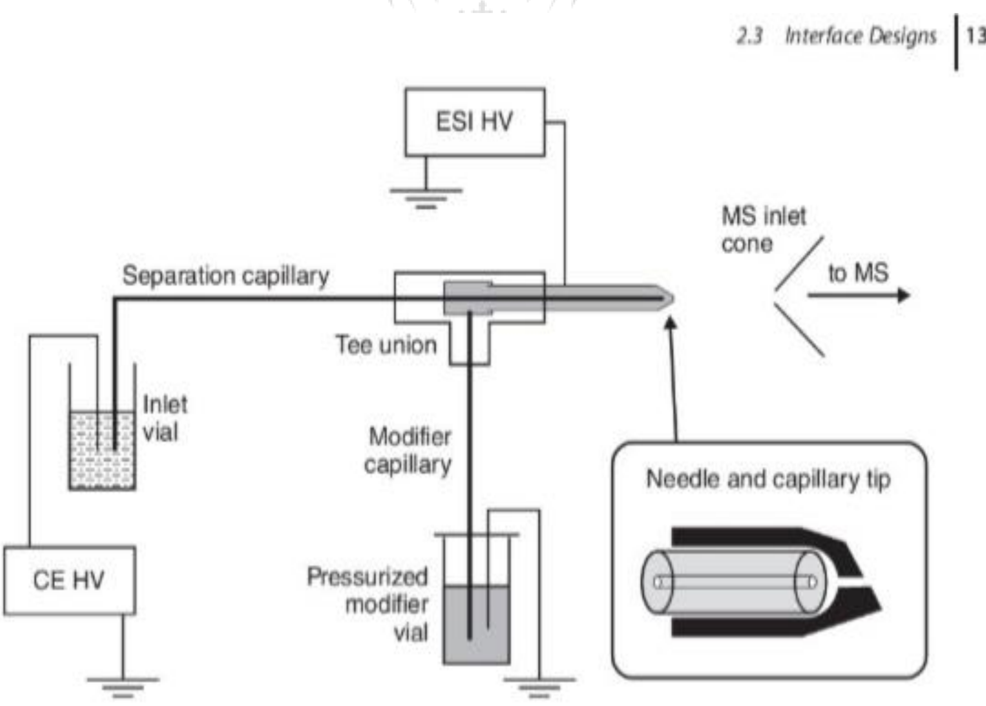


Figure No. 8: Schematic illustration of flow-through microvial interface apparatus

NANOSPRAY SHEATH-FLOW INTERFACE:

Nanospray ionization operates at the flow rate of 1 -1000nl min^{-1} to generate a stable cone into the MS, although currently nanospray ionization typically refers to electrospray generated at low nl min^{-1} flow rates. Nano spray ionization interfaces can be sheath flow (or) sheathless interfaces. The low flow rate of nanospray ESI mean that a reduced MS signal is produced but this is balance by the increase ionization efficiency.

SHEATHLESS INTERFACE:

The electrical contact for sheat less interface is established on near the CE BG directly at the outlet of the capillary. Figure shows examples of different sheathless interface configurations. A potential may be applied to the capillary outlet in the several different ways depending on the design of the interface. Some interface design coat the end of the capillary spring tip with metal while others attach a spray tip to the end of the capillary.

Sheathless interface have the advantage of improved sensitivity due to the lack of dilution by sheath liquid. Disadvantages of the sheath liquid interface tend to be specific to the individual design of the interface.

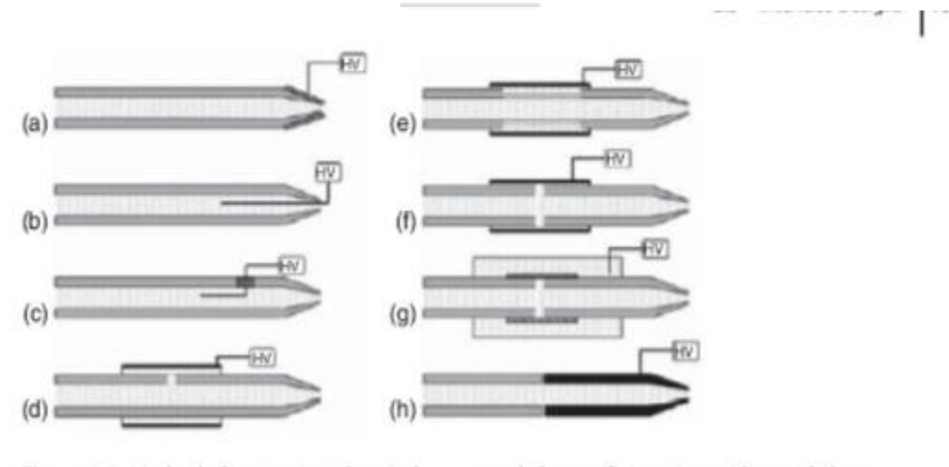


Figure No. 9: Methods for creating electrical contact in sheathless interface

(i) Conductive coating applied to the emitter tip

(ii) Wire inserted at the tip

(iii) Wire inserted through the hole

(iv) Spilt flow interface with a metal sheath

(v) Porous, etched capillary walls in metal sleeve

(vi) Junction with metal sleeve

(vii) Microdialysis junction

(viii) Junction with conductive emitter tip.

SHEATHLESS POROUS EMITTER NANO ESI INTERFACE:

Sheathlees Porous Emitter Nano ESI interface was developed by Wang et.al. one as seen in the figure. This interface uses hydrofluoric acid to etch the end of a piece of capillary making it porous. The difference is that in this interface instead of the end of the separation capillary a separate piece of capillary is made porous. The porous piece of capillary is smaller in diameter than the seperation capillary, so the porous piece of the capillary can be inserted into the separation capillary and glued in place. The connected capillaries are inserting into metal Tube and Porus capillary tip emerges from the end of the metal tube. The metal tube is also filled with BGE and the ESI voltage is applied to the metal tube, allowing an electrical contact with the porous emitter tip. As a sheathless interface, the sample is not diluted and therefore a better sensitivity is possible. So far being used in the studies of cITP and selected reaction monitoring (SRM).

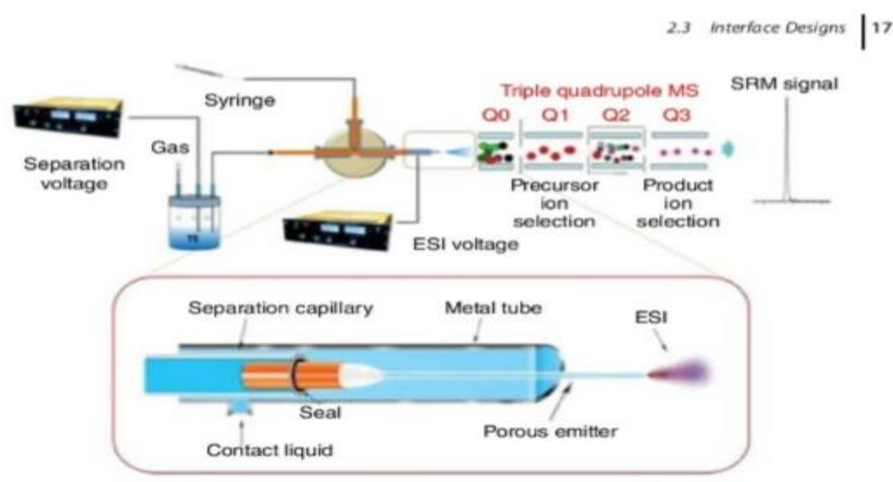


Figure No. 10: Schematic of CZE-nanoESI-QQQ MS setup

CE-MALDI-MS:

The combination of CE and MALDI is realized in an offline regime. This offline arrangement has two main advantages:

(i) better tolerance to salts and

(ii) (ii) Possibility to store samples/analytes. The offline combination also means that it is possible to make independent optimization of CE separation and MS detection.

Off-line coupling of CE to MALDI, the CE effluent could be sprayed or added dropwise on MALDI target plate then dried and analyzed by MS. For online coupling, a moving target with continuous contact to CE capillary end is required. The moving target takes analytes into MS where it is desorbed and ionized. Musyimi et al. developed a new technique where rotating ball was used to transfer CE to MS. The sample from CE is mixed with matrix coming though another capillary. As the ball rotates the sample is dried before it reaches ionization region. This technique has high sensitivity since no makeup fluid is used.

The most important problem with CE-MALDI-MS is to maintain electrical continuity when collecting the CE effluent at the capillary outlet. In this case, methods used in CE-ESI-MS coupling can be adapted for CE-MALDI-MS coupling, such as the coaxial sheath-flow liquid interfaces, liquid-junction, or sheathless interface using a metal-coated capillary. It is also a challenge to collect CE effluent with minimum perturbation to the separation process and maintaining maximum separation efficiency.

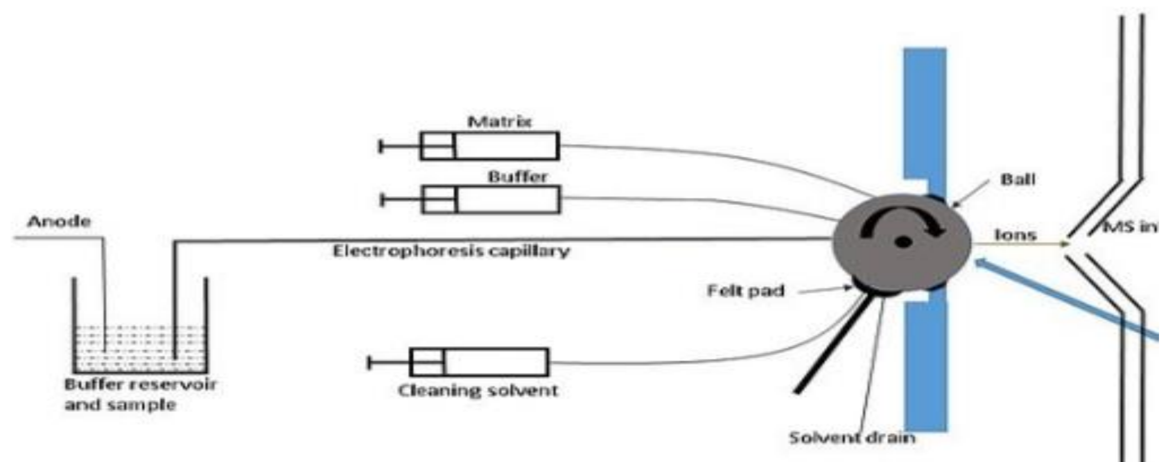


Figure No. 11: Schematic representation of CE-MALDI-MS

APPLICATIONS:

CE-MS has ability to separate analytes in extremely low concentration with high efficiency at high speed. CE-MS has application in bioanalytical, pharmaceuticals, environmental and forensic application. The major application of CE-MS has been for biological studies, mostly for protein and peptide analysis. It is used for routine analysis of pharmaceutical drugs. CE-MS can be used for clinical checkup. Body fluids like blood and urine have been analyzed with CE-MS to identify biomarkers for renal diseases and cancer.

URINARY BIOMARKERS FOR RENAL DISEASES:

CE-MS analysis of urine samples from patients with various types of chronic renal diseases resulted in the establishment of panels that consisted of 20 to 50 urinary polypeptide markers that allowed diagnosis and discrimination of IgA nephropathy, focal-segmental glomerulosclerosis (FSGS), membranous glomerulonephritis MGN),& minimal change disease.

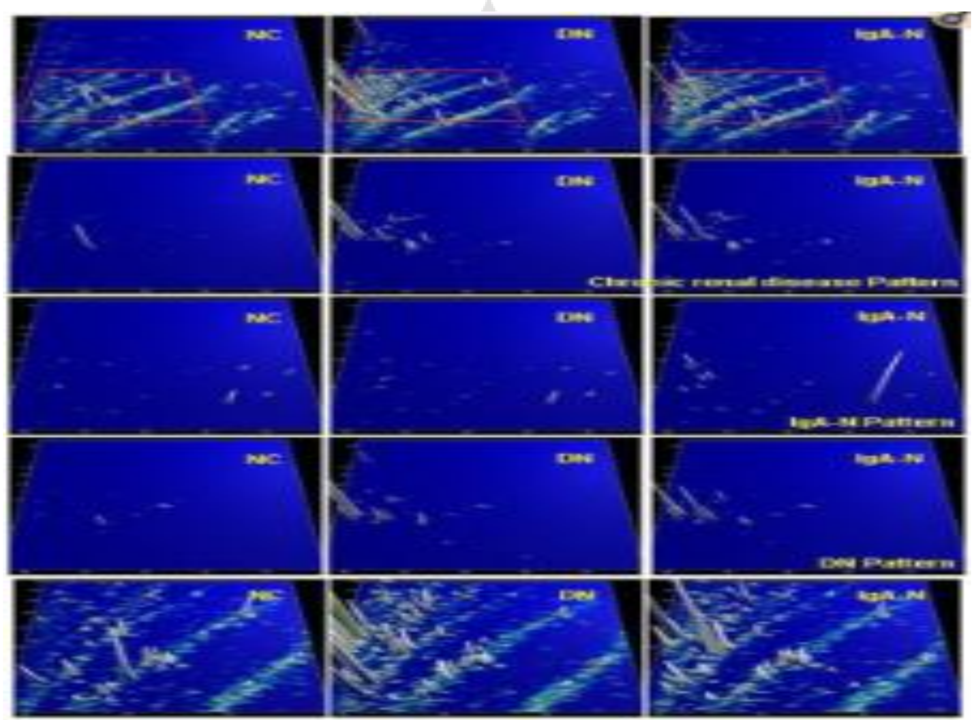


Figure No. 12: Showing distribution of potential biomarkers for different chronic renal diseases

Protein patterns of healthy volunteers (NC), and patients with diabetic nephropathy (DN) and IgA nephropathy (IgA-N), respectively.

URINARY BIOMARKERS FOR UROLOGICAL DISORDERS:

The CE-MS detection and validation of biomarkers of urothelial carcinoma. A bladder cancer-specific biomarker pattern was established by an initial definition in a training set composed of 46 patients with urothelial carcinoma and 33 healthy subjects, and further refinement with CE-MS spectra of 366 urine samples from healthy volunteers and patients with malignant and non-malignant genitourinary diseases. With this two-step biomarker discovery approach, the authors could establish a prediction model composed of 22 urinary peptides. This model correctly classified all urothelial carcinoma patients and all healthy controls. Differentiation between bladder cancer and other malignant and non-malignant diseases (such as renal nephrolithiasis) was accomplished with at least 86% – 100% sensitivity.

CE-MS IN ANALYSIS OF TOXINS:

Toxins and poisons are products of living organisms that often have a polypeptide nature being complex and very unstable molecules. CE- MS method was developed for the identification separation and determination of mushroom toxins namely ibotenic acid, muscimol and muscarine. This CE-MS proved to be useful for the analysis of toxic substances and thus preventing time consuming pretreatment step. In forensic toxicology, a two step approach is used in the analysis of biological and complex nonbiological samples. The first step consist of rapid screening. In case of presumptively positive results it is necessary to perform the analytical step of confirmation.

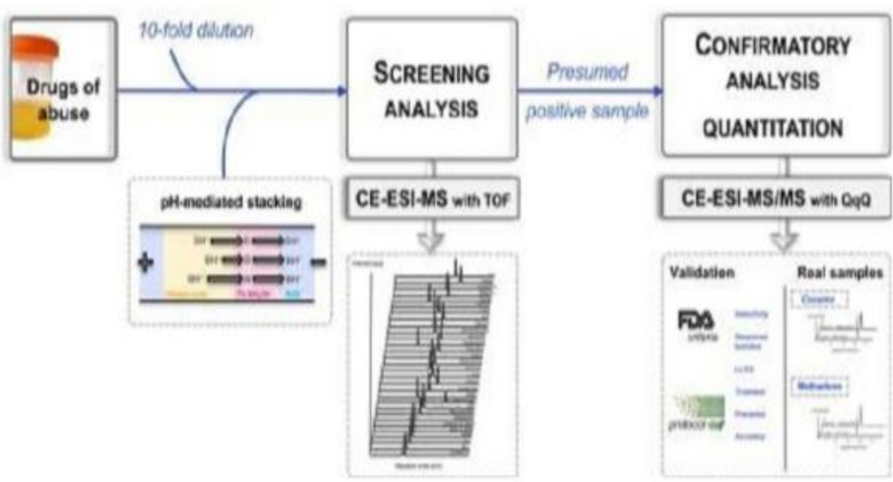


Figure No. 13: Scheme of two step forensic toxicology analysis

CE-MS IN ANALYSIS OF FOOD CONTAMINANTS:

Trace analysis by CE-MS of analytes such as low molecular mass amines, nitroaromatics, alkyl phosphonic acids, azo dyes, antidepressants, and antibiotic drugs, among others, in air, sediment and water samples have been reviewed. The CE-MS analysis of pesticides such as triazolopyrimidine sulphoanilides, different types of antibiotics (sulphonamides, beta-lactones, quinolones and tetracyclines) and other exogenous compounds such as acrylamide and toxic oligopeptides in food samples has also been reviewed.

ANALYSIS OF HEPARIN OLIGOSACCHARIDES & LOW MOLECULAR WEIGHT HEPARIN:

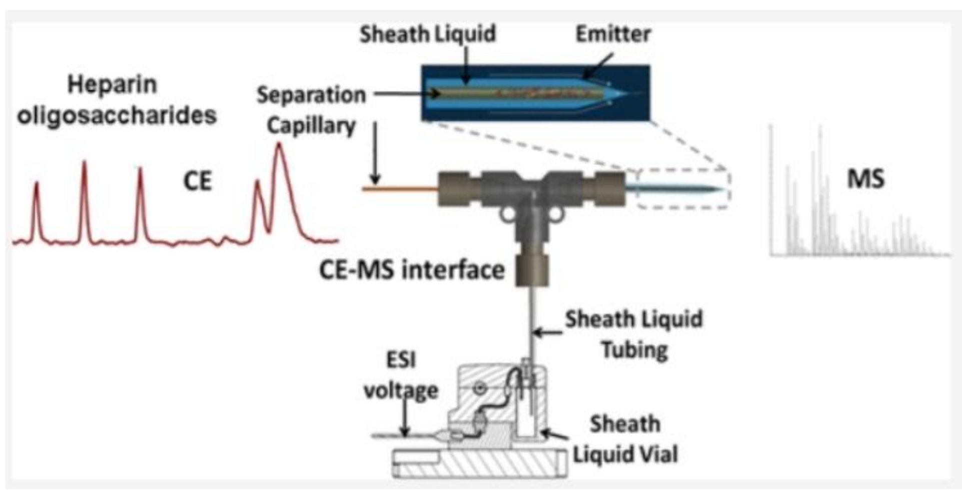


Figure No. 14: Analysis of Heparin oligosaccharide & low molecular weight heparin by CE-MS

Heparins, highly sulfated, linear polysaccharides also known as glycosaminoglycans, are among the most challenging biopolymers to analyze. Hyphenated techniques in conjunction with mass spectrometry (MS) offer rapid analysis of complex glycosaminoglycan mixtures, providing detailed structural and quantitative data. The analysis of glycosaminoglycan oligosaccharides using a novel electrokinetic pump-based capillary electrophoresis (CE)–MS interface. CE separation and electrospray were optimized using a volatile ammonium bicarbonate electrolyte and a methanol–formic acid sheath fluid. The online analyses of highly sulfated heparin oligosaccharides, ranging from disaccharides to low molecular weight heparins, were performed within a 10 min time frame. Disaccharide compositional analysis as well as top-down analysis of low molecular weight heparin was demonstrated. Using normal

polarity CE separation and positive-ion electrospray ionization MS, excellent run-to-run reproducibility and sensitivity could be achieved.

CE-MS IN BIOANALYSIS:

In bioanalysis, two step methodologies is generally used for the determination of the drugs in the biological samples particularly in the forensic toxicology field. First rapid sensitive and genetic screening is performed followed by an independent confirmatory procedure prior to quantitation use of positive results. The combination of the CE with mass spectrometer is practically well adapted to screening due to its relatively high data acquisition rate mass resolution and accuracy location of unknown compounds. In second state CE is hyphenated to highly selective analyser such as triple quadrupole for sensitive and selective quantitation. An example of this two step analytical workflow is presented in the figure for the analysis of the drug abuse in the urine after simple dilution prior to injection in CE MS and he is the pH mediated stacking approach.

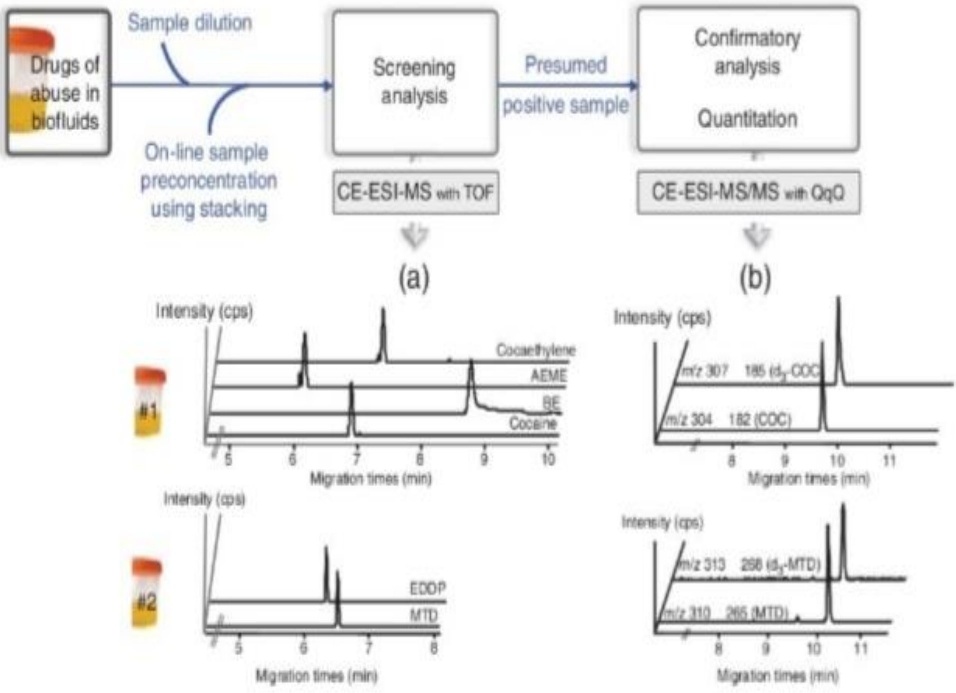


Figure No. 15: CE-MS two-step workflow used in bioanalysis

(i) Screening with CE-TOF/MS

(ii) Quantitation by CE-MS/MSof 2 urine samples containing cocaine and methadone.

CE- MS IN DRUG METABOLISM STUDIES:

Metabolism converts drug into metabolites which are typically more hydrophilic compounds that are eliminated from the body. The biotransformation processes include;

(i) Oxidative (Phase 1) and

(ii) Conjugative (Phase 2) reactions.

The cytochrome P 450 catalyzes the (Phase 1) reactions while (Phase2) reactions are catalyzed analyzed by various enzymes. In most cases, metabolism reduces or elevates drug activities but some metabolites from (Phase1) metabolism may represent higher therapeutic activities or particular toxicity. Determination of the metabolic properties of the NCE (New chemical entity) during the drug Discovery process is therefore essential.

CE based assays are used in the metabolism studies by main 2 strategies:

1) Electrophoretically mediated microanalysis

2) Coupled MS detection for the determination of the parent drug or the metabolites. Thus determination the metabolic properties of NCE can be done.

ELECTROPHORETICALLY MEDIATED MICRO ANALYSIS:

Electrophoretically mediated microanalysis was used to evaluate the potential inhibitory activity of the fruit juices jaboticaba, pitanga toward acetylcholinesterase (AChE) and α-glucosidase, target enzymes in the strategies for the treatment of Alzheimer's disease and diabetes mellitus.

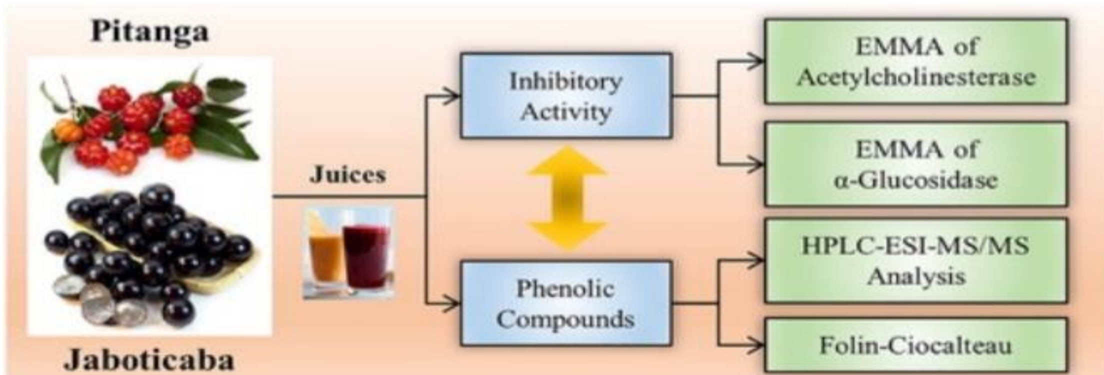


Figure No. 16: EMMA of Enzymes.

DETERMINATION OF DRUG PHSIOCHEMICAL PROPERTIES:

Measurement of the physicochemical properties of a new chemical entities and an early phase of a drug discovery and development is crucial to reduce attrition rate and represents one of the big challenge for the pharmaceutical industry. The physicochemical properties of NCE in early ADMET (absorption distribution metabolism and elimination toxicity) are assayed. CE and CE-MS essays are particularly involved in the determination of three major physicochemical properties:

Table No. 1: CE-MS in the analysis of physicochemical properties

Acid base properties	(pk_a)
Lipophilicity	(Log p)
Plasma protein binding	(PPB)

ANALYSIS OF BIOPHARMACEUTICALS BY CE-MS:

Biopharmaceuticals have gained increasing attention as a way to improve therapy for diseases biopharmaceuticals characterization have been focused by various CE-MS approaches. CZE-ESI-MS has been used for the analysis of glycosylation of various other proteins. An interseting example of glycoprotein analysis by CZE-ESI-MS is the analysis of vascular endothelial growth factor165. ($VEGF_{165}$).Various CE-MS methods have been developed for the characterization of the (glycosylated) biopharmaceuticals.

Table No. 2: CE-MS in the analysis of biopharmaceuticals.

ANALYTES	BGE	CAPILLARY COATING	MASS ANALYZER	REMARKS
Human chronic gonadotropin	2% Acetic acid (Ph-2.5)	Poly vinly alcohol	FTICR	Glycoform profiling
VEGF 165	60mM Formic acid	Poly-LA 313	TOF	Glycoform profiling
Heamoglobin	75 mM Ammonium formate (Ph-9.5)	No coating	TOF	Determination of oxygen carriers in plasma
Protein -drug conjugates	100m M Acetic acid (pH-3.1)	Polyethyleneimine	TOF	Determination of degree of conjugation.
Erythropoietin	1M Acetic acid	Linear polyacrylamide	TOF	Statistical evaluation of glycoprofiles
Glucagon	1% Pharmalyte	Commercial neutral coating	TOF	CIEF-MALDI-TOF analysis
Protein-linker conjugates	100m M Acetic acid (pH-3.1)	Polyethyleneimine	TOF	Determination of degree of conjugation

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CE-MS IN FOODOMICS:

CE-MS based metabolomics strategies to study cancer cell structures following a foodomics approach Investigations have been carried out given the potential antiproliferative effects of certain food ingredients such as dietary polyphenols or rosemary. Treatment of colon cancer was done from polyphenol rich extracts obtained from Rosemary.

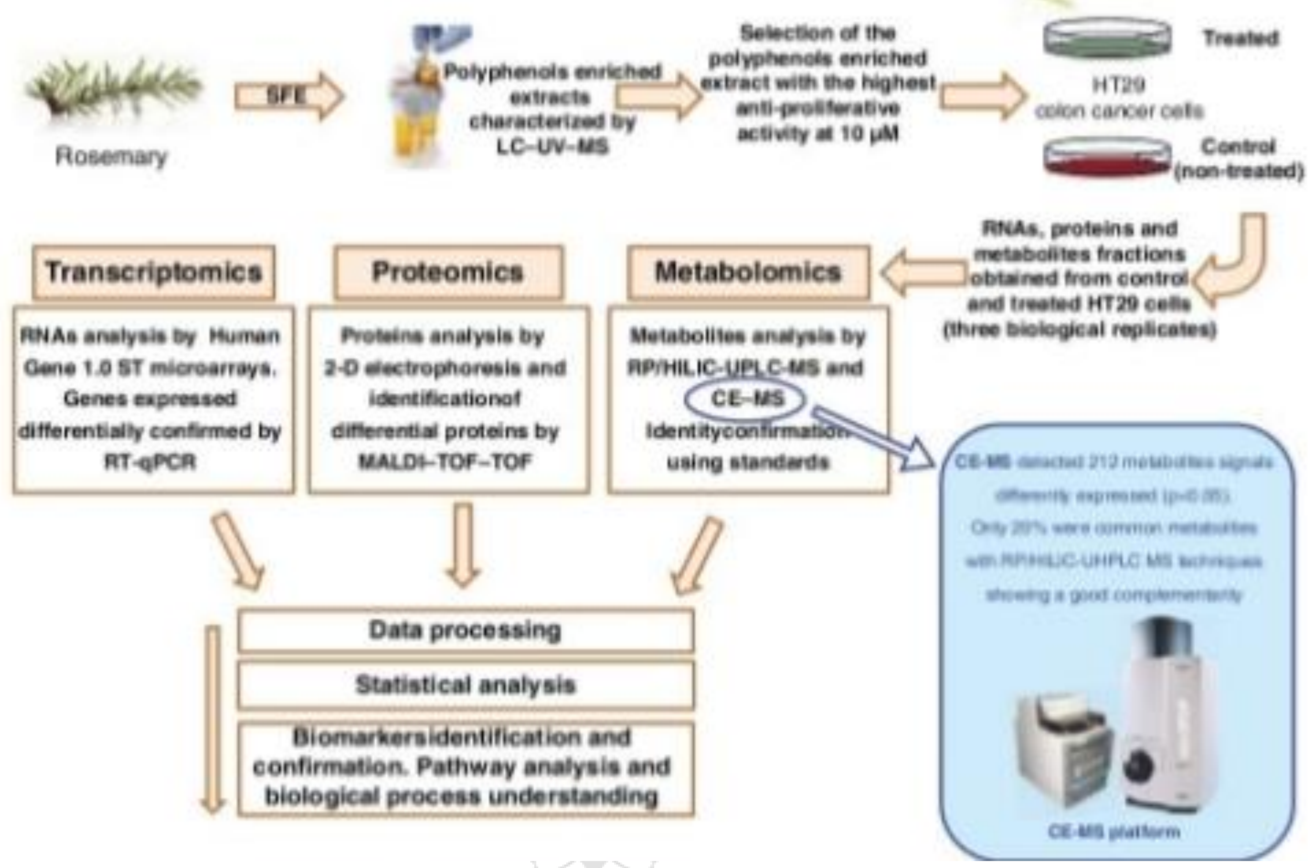

Figure No. 17: CE-MS in foodomics (Global foodomics strategy & contribution of CE-MS on this workflow is highlighted).

HUMAN

CONCLUSION

CE-MS has gained increased attention for various applications, especially with the development of new interface designs to enhance concentration sensitivity. The usefulness of recent low-flow/sheathless interfacing techniques has been clearly demonstrated for improving the concentration sensitivity of CE-MS. CE-MS fulfills the requirements in routine clinical practice. CE-MS is a good alternative for trace analysis in Q.C. (i.e., degradation substances, impurities), for HTS in drug discovery (i.e, physiochemical properties) and for samples at low concentration and/or small volume in bioanalysis. CE-MS is widely used in qualitative analyses. CE-MS coupling can now be easily achieved and implemented in labs as an orthogonal strategy to chromatographic-based assays.

We anticipate that CE-MS will play a key role in those clinical and biomedical studies for volume or mass –limited biological as well as novel applications involving single cell or subcellular metabolome characterization.

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