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LETTER TO THE EDITOR

Recent advancement and development of capillary isotachophoresis: A review

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ABSTRACT

Capillary Isotachophoresis (CITP) is an advanced technique that is used for the separation of substances with electrophoretic mobility and their charges. The isotachophoresis electrolyte system is presented, along with how the effective mobilities and molar amounts of the analytes influence the separation and time required to attain the steady state for a certain electrolyte condition. One approach called CITP uses a "moving border." Between the leading and terminating electrolytes is a sample zone where all solutes travel at the same speed in distinct bands. In this article, we have described the different and latest developments of CITP, i.e., isotachophoresis in nanoparticle studies, in the hyphenation technique, in the bioanalytical sector, and in various food tracing elements. Although traditional Isotachophoresis is becoming less popular, isotachophoresis is becoming more used for a variety of samples as a preconcentration approach for CZE analysis.

KEY WORDS: Advance techniques, Analytes, Capillary isotachophoresis

INTRODUCTION

A potent electrophoretic method that enables the separation and preconcentration of substances is isotachophoresis (ITP). In ITP, The electrophoretic mobilities of the co-ions are higher and lower, respectively, depending on the charge of the analyte, than the analytes. The co-ions are arbitrated between the leading electrolytes (LE) and terminating electrolytes (TE). The electrophoretic mobilities of the co-ions are higher and lower, respectively, depending on the charge of the analyte.[1] In this case, To eliminate mass matrix components, collect and condense only the analyte(s) of interest, the structure of an ITP electrolyte method can be deliberately altered, and detect them with high sensitivity as very narrow zones stacked at a sharp moving ITP boundary.[2] The ability to inject specific ionic species from complex samples is a benefit of ITP. The ITP mode is a focus technique that is unaffected by matrices that are very saline and is particularly appropriate for samples with highly saline matrices.[3] This has several features for food analysis involving intricate sample matrices.[4] The crucial aspect of ITP is that each zone's concentration is adjusted to a constant value, regardless of the makeup of the sample, and as a result, the volume (length) of each zone directly relates to the absolute amount of an analyte. The front and back boundaries of the zone of interest must be recognized by the detection technique being employed for quantitation, whereas the instrumentation and operating features are less critical. Since ITP is a straightforward, well-defined approach that is simple to transfer from one laboratory to another, it is a technology that is ideal for accurate and reproducible analyses of routine samples.[5,6] The electrolyte system of ITP mainly consists of a capillary containing two discontinuous electrolytes, which is its most significant characteristic. A steady state is reached after the sample has been injected intermittently and concentrated, revealing a number of intriguing

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characteristics.[7] Ion atmospheres and physicochemical constants, such as acid dissociation constants, absolute mobilities, and complex stability constants, affect the ions mobilities in a real electrolyte solution(effective mobility).[8] ITP self-correcting mechanism allows for the use of lab-on-a-chip technologies to pre-concentrate and separate several analytes simultaneously. Fluorescence dyes and other biological and chemical materials have recently been preconcentrated utilizing ITP and microfluidic channels.[9,10]

Instrumental development efforts concentrated on automating the ITP analysis. It was possible to effectively analyze the conductivity and UV detection signals from the Tachophor device by integrating a code for managing the step-like isotachopherogram with commercial chromatography software. The ITP electrolyte system is composed of two electrolyte solutions: a LE and a TE. When the two electrolyte solutions separate, the sample solution (S) is injected. Both sufficient counter ions with pH-buffering properties and similar-sign leading ions (L) to the sample ions (coion) in the ITP system are included in LE [Figure 1].[11]

In a bioanalytical sector bombarded with capillary ITP-MS, the multifunction medium-alkaline pH cationic electrolyte system for testing and details for the 1st time the ITP working range with electrospray-ionization mass spectrometric (ESI-MS) detection. MS detection offers a quick, ITP stacking, sensitive method with limits of quantification on the sub-nM level for dried blood spots, and direct injection of the aqueous extract.[2] In hyphenation with transient ITP, a simplistic method can be used for monitoring in clinical and biochemical laboratories.[12] Another important application is nanoparticle technology, is demonstrates a label carbon doped with nitrogen Nitrogen-doped carbon dots (NCDs) that enables the capillary transient ITP

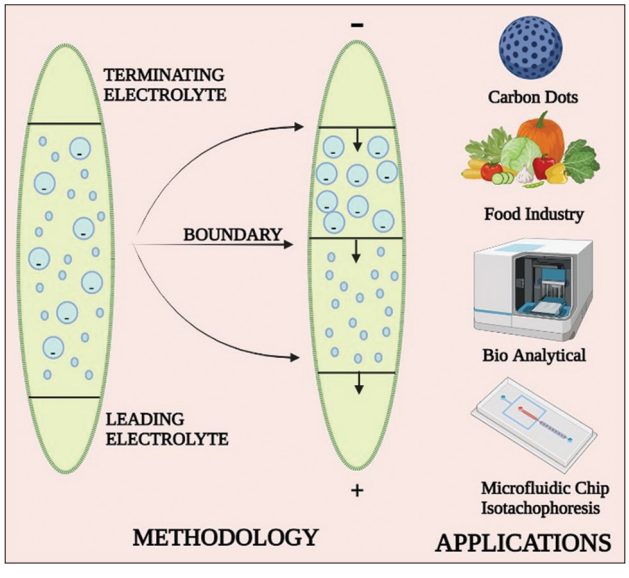

Figure 1: Capillary Isotachophoresis

of different lengths of single-stranded DNA (ssDNA). Attributed to their low toxicity and biocompatibility, carbon dots have recently found extensive use in the disciplines of diagnostics, sensing, and healthcare. To construct biosensors and deliver drugs, there is increased interest in using ssDNA aptamers rather than antibodies. For this reason, it is critical to develop a quick and efficient technique for aptamer separation.[13] In collaboration with capillary ITP-capillary zone electrophoresis (CZE), the dispersion stability of gold nanoparticles (Au NPs) was examined. Depending on the background electrolyte's (BGE) composition, CZE of Au NPs can be carried out dynamic coating beneath circumstances.[1] In the food industry capillary transient ITP, It has been established that tITP-CZE is capable of detecting miniscule amounts of preservatives, sweeteners, antioxidants, and other food additives in beverages even when there is a counter-flow transient ITP work.[3] One another application is during ITP, joule heating, shortest possible assay durations and efforts to scale up the processed sample amounts can be restricted by joule heating in ITP. The tests show a significant temperature increase in the modified trailing electrolyte zone as well as the thermal wave propagating in the ITP channel at a speed equivalent in connection to electromigration.[14] An application on the microfluidic platform with Conventional ITP, a automated optimization of ITP of several analytes using a programmable microfluidic platform (PMP). Buffer selection and repeated ITP procedures were automated by combining a PMP with ITP. A PMP with a two-dimensional microvalve array was created and manufactured using lifting-gate microvalve technology for integration with ITP chips.[10] In microfluidic chip, a miniaturized variant of traditional ITP, known as microchip ITP, has a lower sample and low buffer consumption requirement and produces less waste. Analyte(s) at comparatively high concentrations are present in relatively simple samples for quantitative investigation, micro-ITP with universal conductivity detection is acceptable. The drug is barely processed before the ITP run on a microchip with connected channels and a sample injection channel with 0.9 L volume.[15]

DEVELOPED METHODS OF CAPILLARY ISOTACHOPHORESIS (CITP)

In hyphenated techniques

CITP and ESI-MS detection with medium-alkaline cationic electrolyte

CITP has been employed as a reliable analytical technique. Its unique characteristics, such as its extraordinary capacity for concentration and ability to stack analytes at permanently sharp borders, predetermine its employment for specific tasks.[2] One of its effective application scenarios is trace analysis from samples with complex matrices. Here, the bulk matrix components can be removed, the analyte(s) of

interest can be captured and concentrated, and they can be detected with high sensitivity as very small zones stacked at a sharp-moving ITP boundary. All of this makes ITP an intriguing substitute for conventional separation methods such as high-performance liquid chromatography, which may generally have higher sensitivity but typically call for time-consuming sample pretreatment [Table 1].[16]

Mala and Gebauer developed a current ITP detection range for medium-alkaline pH analyses using a functional cationic electrolyte system and ESI-MS detection for the 1st time. Despite a wide range of prospective analytes including biogenic amines, alkaloids, or pharmaceuticals, despite the intriguing improvements in sensitivity and specificity that this approach promises, there has not yet been any ITP-MS application that has been recorded for the detection of medium-strong bases. The results are discussed together with suggestions for useful ITP electrolyte systems, a list of appropriate suitable components of volatile ESI-compatible systems, and consideration of system-influencing factors attributes.[2]

Using tandem mass spectrometry and two-dimensional CITP-CZE, serotonin in human urine

In the study of complex samples, strategies for separation in two dimensions (2D) and multiple dimensions provide appealing, potent, and very effective approaches. As a result, these methods can handle a variety of complex jobs in the field of medicine.[17] The 2D separation systems are capable of providing efficient online sample pre-treatment, which is advantageous for increasing selectivity and sensitivity.[18] In contrast to liquid chromatography, capillary electrophoresis (CE) covers a different selectivity and offers a favorable separation efficiency at high speed. In light of this, 2D systems with at least one CE approach are useful analytical tools.[19]

Piestansky *et al*. developed for the ultrasensitive detection of serotonin in actual human urine samples, a technique using tandem mass spectrometry and two-dimensional CITP-CZE was developed and verified. A huge volume of sample was injected, in this case, 10 L, and isotachophoretic preconcentration, the separation was completed under ideal conditions in 12 min (including online sample preparation) and 34 pg mL^{-1} was the detection threshold. This concentration limit denotes the lowest result for serotonin when compared to other previously published separation methods using mass spectrometry detection and applied to urine matrices. This method's high orthogonality, online concentration, and clean-up effects made it simple to obtain other excellent validation parameters such as linearity (coefficient of determination >0.99), inter-day and intra-day precision (relative standard deviations 3.5–12.2%), accuracy (relative errors within 99–109.4%), and recovery (96–102%). We tracked serotonin levels in numerous genuine samples to show the method's applicability. The measured amounts fell between 6.81 and 12.86 ng $mmol^{-1}$ creatinine, adjusted on the creatinine concentrations. This cutting-edge technique is recommended for regular clinical examinations or targeted analyses of serotonin metabolites in urine samples that need to be efficient, dependable, high sample throughput, and inexpensive.[16]

In nano particles studies

Unmodified gold NPs are stabilised and isotachophoresized in CE

Analyzing nano and microparticles has generated a lot of interest in CE. On the one hand, there have been several attempts to use CE for the analysis of biological particles like organelles, viruses, or even whole cells.[20] On the other hand, CE was thoroughly investigated for the characterization of metallic and polymeric NPs. The issue of dispersion stability during CE has been brought up in relation to both biological and synthetic particle electrophoresis.[21]

Dziomba *et al*. developed the dispersion stability of Au NPs by CZE were examined. It was established that depending on the composition of the BGE, CZE of Au NPs can be carried out under dynamic coating conditions. It was determined how the co-ion and counter-ion affected the BGE. It has been demonstrated that the use of somewhat large buffering counter-ions during CZE gives NPs steric stability. Citrate and MOPS were discovered to be favorable for the CZE of Au NPs among the examined co-ions. On the other hand, it has been demonstrated that the zwitter ionic components and multiply charged counter-ions present in BGE facilitate the NPs' aggregation and adsorption to the capillary wall.[1]

Capillary transient isotachophoresis (ctITP) and laser-induced fluorescence (LIF) detection, ssDNA molecules by NCDs

In the disciplines of chemical biology, biochemistry, and molecular biology, the separation of ssDNA is crucial. Slab gel electrophoresis has long been the preferred technique for separating DNA of various sizes.[22] The low resolution, lengthy analysis times, low sensitivity, and gel deformation under high applied voltage are just a few of the method's drawbacks. Compared to slab gel, CE has various benefits.[23] Features including tiny sample volume and LIF detection, quick analysis times, high resolution, and high sensitivity are possible. In particular, this work employs a discontinuous buffer system with ctITP as the CE-based separation mode.[24]

Roy and Colyer reported a novel method for using NCDs to separate ssDNA into different lengths using electrokinetics. Carbon dots have lately been discovered to exhibit minimal toxicity and biocompatibility, which is extensively used in the fields of diagnostics, sensing, and healthcare. As the

Table 1: Developments of capillary isotachophoresis

Isotachophoresis development	Applications
In hyphenated techniques	● Capillary isotachophoresis and electrospray-ionization mass spectrometric detection with medium-alkaline cationic electrolyte ● Using tandem mass spectrometry and two-dimensional capillary isotachophoresis-capillary zone electrophoresis, serotonin in human urine
In nano particles studies	● Unmodified gold nanoparticles are stabilised and isotachophoresized in capillary electrophoresis ● Capillary transient isotachophoresis and laser-induced fluorescence detection, ssDNA molecules by nitrogen-doped carbon dots
Some other Development	● Utilizing Counterflow Transient Isotachophoresis, Capillary Zone Electrophoresis was used to determine the presence of five trace food additives ● Optical and infrared thermal imaging of isotachophoresis simultaneously ● Determining the levels of sotalol and metoprolol in samples of human urine, hyphenation of field-amplified sample injection

usage of ssDNA aptamers rather than anti-bodies in the sectors of biosensors and creation and drug administration, it is vital to build a quick and efficient way to separate aptamers. In this study, FAM-labeled ssDNA samples were separated utilizing NCDs as buffer additives in CE-based method, with lengths ranging from 32 to 100 bases and resolutions varying from 1.30 to 1.77. We specifically used the ctITP technique with LIF detection, with the addition of 30 g/mL NCDs to both the separation and sample buffers. These NPs were made from a combination of citric acid and ethylenediamine using a straightforward hydrothermal technique. On its own, the NCDs are highly luminous and photostable. They had no impact on the DNA sample's fluorescence emission that was FAM-labeled because they were part of the background electrolyte.[13]

Some other development

Utilizing counter-flow transient ITP, CZE was used to determine the presence of five trace food additives

Food additives are included in foods to perform certain technological tasks, such as coloring, sweetening, or preserving the food product. It can be divided into many groups, such as preservatives, colorants, and sweeteners, based on their qualities.[25] A number of issues, such as the limit being exceeded and the breadth of its usage, have emerged with the quick development of food additive applications. Artificial synthetic hues include amaranth, Allura crimson, and sunset yellow. They are extensively utilized in beverages because they are more stable and affordable. However, when used in excess, they can have negative health consequences on people, including hyperactivity, chromosomal damage, thyroid tumors, respiratory issues, allergies, and abdominal pain.[26,27]

Feng *et al*., developed technology for universal online sample preconcentration is called transient isotachophoresis (tITP). It effectively increases the sensitivity of CE by using at the first stage of the CE analysis, ITP is used to concentrate electrically charged analytes. In this study, counter-electroosmotic flow tITP was established as a method for the CZE analysis of beverage samples to determine the presence 5 traces of food additives, including sunset yellow, sorbic acid, allura red, benzoic acid and amaranth. In-depth research has been done on the variables that influence the system's preconcentration impact, including the kind of TE used and when it was injected, the ITP's preconcentration time, and the injection time for the sample. The counterflow-tITP mechanism was initially investigated. Five food additives sensitivity was increased by 11.9, 11.5, 13.04, 10.05, and 15.3 times under ideal circumstances. Their limits of detection (LODs, S/N = 3) were 0.15, 0.10, 0.38, 0.33, and 0.11 g/mL, and their calibration graph linearity (r 0.9992) and peak area RSDs (6.9%) were both good. Five food additives had recoveries ranging from 92.0 to 100.8% in samples of flavored beverages, with RSDs between 1.38% and 2.95%. This approach is straightforward, quick, and accurate. It has been used to successfully separate and find minute amounts of food additives in orange juice, cocktails, and carbonated drinks. It has been established that tITP-CZE is capable of detecting minute amounts of additives in beverages even when there is a counterflow.[3]

Optical and infrared thermal imaging of ITP simultaneously

Purification of proteins and nucleic acids from complex biological systems materials as well as separate analyses are two frequent uses for the electrophoretic separation and preconcentration method known as ITP.[28] ITP is a technique for regulating and speeding heterogeneous and homogeneous processes, particularly those involving biological species and involving at least one surface-bound molecule. ITP is a topic of ongoing research, application, and invention.[29]

Terzis *et al*., developed test durations and scale-up attempts for the processed sample amounts that can be restricted by joule heating in ITP. ITP systems spatiotemporal temperature field dynamics of Joule heating, despite their importance. Here, we report fresh spatiotemporal measurements. ITP's electromigration field and temperature. We get optical and

thermal images of the ITP process captured simultaneously to do this. To investigate and emphasize the significant effects of buffer-dependent ionic conductivity on the temperature increase that results, we carry out a series of experiments with variable LE concentration and constant current operation. The tests show a significant temperature increase in the modified trailing electrolyte zone as well as the thermal wave propagating in the ITP channel at a speed equivalent to the electromigration front.[14]

Determining the levels of sotalol and metoprolol in samples of human urine, hyphenation of field-amplified sample injection

Both sotalol (Sot) and metoprolol (Met) are adrenergic-blocker medicines, often known as -blockers, which are commonly used to treat a number of disorders including hypertension, angina pectoris, and arrhythmia.[30] They function by preventing adrenaline from acting on the body's receptors, which slows the nerve impulses going to the heart and lessens the job it has to do. Yet, most of them have a very limited therapeutic range and are hazardous. Furthermore, due to their stimulatory effects on the central nervous system and respiration, they are occasionally misused as performance-enhancing substances in humans, which highlights they engage in doping agents.[31]

Xu *et al*., reported two-blockers, sotalol, and metoprolol, were determined simultaneously using a sensitive CE technique combined with field-amplified sample injection and transient ITP. The samples were prepared using simple dissolution in ultrapure water for this dual focusing procedure, and they were then electro-kinetically injected. The both the dominant electrolyte and the background electrolyte were phosphate. It is 80 mM optimal concentration. Glycine was employed as the TE in a total concentration of 25 mM. Within 10 min, under ideal circumstances, sotalol, and metoprolol were successfully separated. With sotalol and metoprolol, respectively, the sensitivity-improving variables ranged between 1031 and 919. In comparison to the conventional approach. Sotalol and metoprolol were found using the suggested method in spiked human urine samples. For sotalol and metoprolol, respectively, UV detection yielded LODs and quantitation of 5 and 12 ng/mL and 10 and 25 ng/mL, respectively. Peak area and migration time had intraday repeatability values that were <2.7 and 1.7%, respectively. The test is an easy-to-use method that can be used in clinical and biochemical laboratories to track the amounts of sotalol and metoprolol.[12]

CONCLUSION

In CITP, the ions in the sample, inserted between a LE and a TE solution encompassing the mobility range of the ions, generate a chain of sharp edges under the influence of a strong electric field neighboring zones traveling between the LE and the TE at the same speed. In this article, we have concluded different parameters of instrumentation in CITP and it also described different development and application like CE-MS technique, food tracing of elements, nanoparticles studies, fluorescence techniques, bio-analytical techniques, and different analytical approaches have been discussed in this articles. This technique is further useful in CE-MS in NMR analysis and also used in plant-related drug studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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