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Review Article

Panoramic Review on Novel Liquid Chromatographic Techniques

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ABSTRACT

Objectives - modern liquid Chromatographic techniques have undergone a paradigm shift, driven by Focused on improving separation efficiency, resolution and sensitivity. HPLC, UPLC, UHPLC, HILIC, LC-MS represent-key methodologies", in this evolution.

Methods: Method have advanced with the adoption of UHPLC, UPLC Featuring smaller particle sizes that enables Faster analyses without compromising resolution. Integration with Lc-Ms, HPLC further enhances capabilities by providing simultaneous identification and quantification.

Results: These techniques showcase significant improvements, UHPLC'S UPLC's higher pressure Capabilities contribute to enhanced resolution, While HPLC, HILIC, Lc-Ms extends analytical scope by offering structural information. The Combined Strengths of those techniques have transformative effects across Scientific disciplines.

Conclusion - Modern liquid chromatographic techniques fulfil objectives through techniques fulfil refined methodologies, yielding results marked by improved performance the Continuous evolution of these techniques promised further strides in analytical capabilities

INTRODUCTION

Chromatography is a physicochemical method for separation of complex mixture was discovered at the very beginning of the twentieth century by Russian–Italian botanist M.S. Tswett [1]. In his paper “On the new form of adsorption phenomena and its application in biochemical analysis” presented on March 21, 1903 at the regular meeting of the biology section of the Warsaw Society of Natural Sciences, Tswett gave a very detailed description of the newly discovered phenomena of adsorption-based separation of complex mixtures, which he later called “chromatography” as a transliteration from Greek “color writing”. Serendipitously, the meaning of the Russian word “tsvet” actually means color. Although in all his publications Tswett mentioned that the origin of the name for

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his new method was based on the colorful picture of his first separation of plant pigments[2]. He involuntarily incorporated his own name in the name of the method he invented. The chromatographic method was not appreciated among the scientists at the time of the discovery, as well as after almost 10 years when L. S. Palmer in the United States and C. Dhere in Europe independently published the description of a similar separation processes. In the late 1970's, new methods including reverse phase liquid chromatography allowed for improved Separation between very similar compounds[3]. New techniques improved separation, identification, purification and quantification far above the previous techniques[4]. Liquid chromatography is a separation technique used in analytical chemistry to separate, identify, and quantify components in a mixture. It involves the passage of a liquid sample through a column filled with a stationary phase, where different components interact differently and elute at distinct times. This method is widely employed in various scientific fields, including pharmaceuticals, environmental analysis, and biochemistry[5]. The principle of liquid chromatography involves the separation of components in a mixture based on their differential interaction with a stationary phase and a mobile liquid phase. This technique exploits the equilibrium distribution of components between these phases. The components travel through a column, and their varying affinities for the stationary phase result in distinct elution times[6].

CLASSIFICATION OF LIQUID CHROMATOGRAPHY[7]:

Liquid chromatography can be classified into several types based on the specific principles and modes of separation. Here are some common classifications:

1. *Normal Phase Chromatography (NPC):* Uses a polar stationary phase and a nonpolar mobile phase.
2. *Reverse Phase Chromatography (RPC):* Involves a nonpolar stationary phase and a polar mobile phase.
3. *Ion Exchange Chromatography (IEC):* Separates ions based on their charge.
4. *Size Exclusion Chromatography (SEC):* Separates molecules based on their size.
5. *Affinity Chromatography:* Exploits specific interactions, such as antigen-antibody binding.

NOVEL TYPES OF LIQUID CHROMATOGHRAPHY [8]:

1. HPLC : High performance liquid chromatography
2. HILIC : Hydrophilic interaction liquid chromatography
3. LC-HRMS : Liquid chromatography high resolution mass spectrometry
4. LC-LRMS : Liquid chromatography low resolution mass spectrometry
5. Nano LC: Nano liquid chromatography
6. UPLC : Ultra performance liquid chromatography
7. UHPLC : Ultra high-performance liquid chromatography

I. HIGH PERFORMANCE LIQUID CHROMATOGHAPHY:

High performance liquid chromatography (HPLC) is an important qualitative and quantitative technique, generally used for the estimation of pharmaceutical and biological samples. It is the most versatile, safest, dependable and fastest chromatographic technique for the quality control of drug components[9].

PRINCIPLE:

The purification takes place in a separation column between a stationary and a mobile phase. The stationary phase is a granular material with very small porous particles in a separation column. The mobile phase, on the other hand, is a solvent or solvent mixture which is forced at high pressure through the separation column. Via a valve with a

connected sample loop, i.e. a small tube or a capillary made of stainless steel, the sample is injected into the mobile phase flow from the pump to the separation column using a syringe. Subsequently, the individual components of the sample migrate through the column at different rates because they are retained to a varying degree by interactions with the stationary phase. After leaving the column, the individual substances are detected by a suitable detector and passed on as a signal to the HPLC software on the computer. At the end of this operation/run, a chromatogram in the HPLC software on the computer is obtained. The chromatogram allows the identification and quantification of the different substances[10].

a. Solvent Reservoir:

Mobile stage substances are contained in a glass reservoir. The versatile stage, or dissolvable, in HPLC is typically a blend of polar and non-polar liquid segments whose particular fixations are changed relying upon the arrangement of the specimen.

b. Pump:

A pump suctions the versatile stage from the dissolvable reservoir and drives it through the framework's column and detector[11].

c. Sample Injector:

An injector for a HPLC framework ought to give infusion of the liquid specimen inside the scope of 0.1–100 mL of volume with high reproducibility and under high weight (up to 4000 psi).

d. Columns:

Columns are generally made of up of stainless steel, are in the vicinity of 50 and 300 mm long and have an inside distance across of in the vicinity of 2 and 5 mm. They are normally loaded with a stationary stage with a molecule size of 3–10 μm. Columns with interior distances across of under 2 mm are regularly alluded to as microbore HPLC columns. In a perfect world the temperature of the portable stage and the column ought to be kept steady amid an examination[12], [13]

e. Detector:

The HPLC indicator, situated toward the finish of the column distinguishes the analytes as they elute from the chromatographic column. Regularly utilized finders are UV spectroscopy, fluorescence, mass-spectrometric and electrochemical indicators.

f. Data Collection Devices:

Signals from the indicator might be gathered on outline recorders or electronic integrators that differ in many-sided quality and in their capacity to process, store and reprocess chromatographic information. The PC coordinates the reaction of the identifier to every part and places it into a chromatograph that is anything but difficult to peruse and decipher.

g. Column Heater:

The LC separation is often largely influenced by the column temperature. In order to obtain repeatable results, it is important to keep the consistent temperature conditions. Also, for some analysis, such as sugar and organic acid, better resolutions can be obtained at elevated temperature (50 to 80°C). It is also important to keep stable temperature to obtain repeatable results even it is analyzed at around room temperature. There are possibilities that small different of temperature causes different separation results. Thus, columns are generally kept inside the column oven (column heater)[14], [15].

APPLICATIONS[16]–[18]:

Environmental Applications

- Detection of phenolic compounds in drinking water.
- Bio-monitoring of pollutants.

Applications in Forensics

- Quantification of drugs in biological samples.
- Identification of steroids in blood, urine, etc.
- Forensic analysis of textile dyes.

- Determination of cocaine and other drugs of abuse in blood, urine, etc.

Applications in Clinical Tests

- Urine analysis, antibiotics analysis in blood.
- Analysis of bilirubin, biliverdin in hepatic disorders.

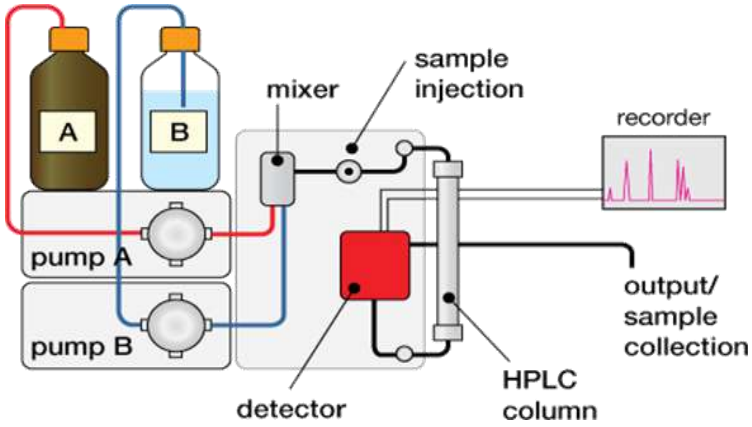

Figure No 1 : HPLC Instrumentation

II. ULTRA PERFORMANCE LIQUID CHROMATOGRAPHY:

Metabolomics is a powerful new technology that allows assessment of global low-molecular weight metabolites in biological systems and holds great potential in biomarker discovery. Analysis of the key metabolites in the body fluids has become an important part of the diagnosis, prognosis, and assessment of therapeutic interventions in clinical application[19].

PRINCIPLE[19]–[22]:

The UPLC is based on the principal of use of stationary phase consisting of particles less than 2 µm. The underlying principles of this evolution are governed by the Van Deemter equation, which is an empirical formula that describes the relationship between, linear (flow rate) and plate height (HETP or column efficiency).

The equation is as follows

$$H = A + B/V + CV$$

Where, A, B and C are constant H= HETP

A = Eddy diffusion

B = Longitudinal diffusion

C = Equilibrium mass transfer V = flow rate

- **Eddy diffusion-**

The mobile phase moves through the column which is packed with stationary phase. Solute molecules will take different paths through the stationary phase at random. This will cause band broadening.

- **Longitudinal diffusion-**

The concentration of analytes is less at the edges of the band than at the centre. Analyte diffuses out from the centre to the edges. This causes band The eddy diffusion A is smallest when the packed column particles are small and uniform. The B term representing longitudinal diffusion or the natural diffusion tendency of molecules diminishes at high flow rates and so this term is divided by B. The C term equilibrium mass transfer is due to kinetic resistance to equilibrium in the separation process and this kinetic resistance is the time lag involved in moving from the gas phase to the packing stationary phase and back again. The greater the flow of gas, more a molecule on the packing tends to lag behind molecules in the mobile phase.

INSTRUMENTATION[23]:

1. Pumping Device[24]:

An ideal pump for UPLC has a capacity of delivering solvent at higher pressure around 15000 psi for the optimum flow rate with maximum efficiency across 15 cm long column packed with 1.7 µm particles.

The two basic classifications are

a) Constant pressure pump

b) Constant flow pump

Constant pressure pump: The constant pressure is used for column packing. Constant flow pump: This type is mostly used in all common UPLC applications.

2. Sample injection[25]:

In UPLC, sample introduction is critical. Conventional injection valves, either automated or manual, are not designed and hardened to work at extreme pressure. To protect the column from extreme pressure fluctuations, the injection process must be relatively pulse-free and the swept volume of the device also needs to be minimal to reduce potential band spreading. A fast injection cycle time is needed to fully capitalize on the speed afforded by UPLC, which in turn requires a high sample capacity. Low volumes injections with minimal carryover are also required to increase sensitivity. There are also direct injection approaches for biological samples.

3. UPLC columns[26]:

In UPLC columns particle size of packing material is approximately 1.7 µm. which increases speed of separation of components. Separation of the components of a sample requires a bonded phase that provides retention and selectivity. The UPLC columns are made up of small particles having size less than 2 µm. The role played by small particle size in UPLC technique has been mentioned below. The particles are bonded in matrix as the bonded stationary phase is required for providing both retention and selectivity. Various types of columns manufactured by ACQUITY are available in the market, which can be used by UPLC technique.

UPLC BEH C18, UPLC BEH C8,UPLC BEH Phenyl columns, UPLC BEH Amide columns, UPLC Shield RP18

APPLICATION:

1. Pharmaceutical Analysis[27]:

- Rapid analysis of drug compounds.
- Higher resolution for complex pharmaceutical mixtures.

2. Proteomics and Biomarker Discovery[28]:

- Improved separation of peptides and proteins.
- Enhanced sensitivity for detecting low-abundance biomarkers.

3. Food and Beverage Analysis[29]:

- Faster analysis of food contaminants and additives.
- Improved detection of food quality parameters.

4. Environmental Monitoring[30]:

- Efficient separation of environmental pollutants.
- Faster analysis of water and soil samples.

5. Clinical Research[31]:

- High-speed separation of biological samples.
- Quantitative analysis of metabolites and biomarkers.

6. Polymer and Chemical Analysis[32]:

- Improved resolution for polymer characterization.
- Faster analysis of chemical compounds.

7. Forensic Science[33]:

- Rapid analysis of drugs and toxic compounds.
- Enhanced separation for complex forensic samples.

8. Bioanalysis and Pharmacokinetics[34]:

- Faster analysis of biofluids for drug metabolism studies.
- Higher sensitivity for pharmacokinetic studies.

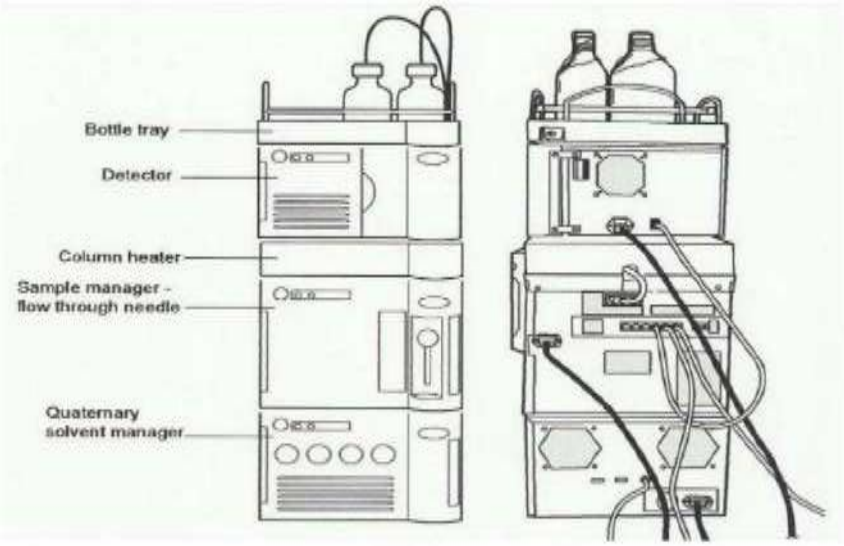

Figure no 2: UPLC Instrument

III. ULTRA HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY :

Ultra-high Performance Liquid Chromatography (UHPLC) offers an advancement of HPLC which is based on the principal of use of stationary phase consisting of particles less than 2µm. By using smaller particles, speed of analysis, peak capacity can be extended to new limits and the sample can be analyzed in a shorter period of time. The UHPLC technique is a new approach in the chromatographic separations and has been successfully employed for fast, high-resolution separations with required sensitivity. This review provides the brief introduction and applications of UHPLC in the pharmaceutical analysis[35], [36].

PRINCIPLE:

Ultra-high-performance liquid-chromatography (UHPLC) covers liquid chromatography separations implementing columns enclose particles smaller than the 2.5–5 µm sizes typically used in high-performance liquid chromatography (HPLC). UHPLC work on the same assumption as that of HPLC and of which governing principle is that, as column packing particle size decrease, efficiency and thus resolution accretion. Separations using column contain smaller particles display enhance efficiency per unit time, but the efficiency cannot minimize at superior mobile phase flow rates or linear velocities. After attribute, slighter particles, rapidity, and to new limits peak resolution can be absolute [37].

INSTRUMENTATION:

Ultra-high-performance liquid chromatography (UHPLC) encompasses LC separations using columns containing particles smaller than the 2.5–5-µm sizes typically used in HPLC. The benefit of using columns containing smaller particles (typically sub-2 µm) is greater efficiency per unit time[38].Ultrahigh-pressure liquid chromatography (UHPLC) instruments from different manufacturers and instruments with different configurations can produce significant variations in chromatographic separation. The variety in instrument configuration increases the complexity of the method development process, which now requires a more thorough evaluation of the effect of instrument variations on the method. The studies presented here determined the typical inter instrument variations in dwell volume, extra column dispersion, and mixing efficiency as measured by mobile-phase compositional accuracy. Additionally, the dwell volume and extra column dispersion were independently and systematically varied to evaluate the resulting impact on resolution for a small-molecule test mixture during gradient elution. To account for

these inter instrument variations, dwell volume and wash-out volume method translation and adjustment techniques were evaluated[39], [40].

APPLICATION[29], [41]–[43]:

1. Metabonomic studies
2. Peptide mapping
3. Identification of metabolites
4. Detection and identification of Impurities
5. Analysis of natural product and herbal medicine
6. Screening of antibiotics in surface and wastewater
7. Analysia of doping agent
8. Screening of synthetic compound
9. Screening of organic pollutants in water
10. Toxicity studies

Figure no 3: UHPLC Instrument

IV. LIQUID CHROMATOGRAPHY HIGH RESOLUTION MASS SPECTROMETRY:

Liquid Chromatography High-Resolution Mass Spectrometry (LC-HRMS) is a powerful analytical technique that combines the separation capabilities of liquid chromatography with the high-resolution mass measurement capabilities of mass spectrometry[42].

PRINCIPLE :

Principle involves the integration of liquid chromatography and high-resolution mass spectrometry , enabling the accurate separation ,ionization and mass analysis of compound in a sample[44].

WORKING STEPS

1. **Sample Injection and Chromatographic Separation:**

LC-HRMS begins with the injection of the sample into a liquid chromatograph, where it undergoes separation based on its chemical properties. This separation is achieved using a liquid mobile phase, which carries the sample through a stationary phase. Compounds in the sample interact differently with the stationary phase, leading to distinct elution times.

2. **Ionization:**

As the separated compounds exit the chromatographic column, they enter the mass spectrometer for ionization. Common ionization techniques include electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI). These methods convert the analytes into ions, facilitating their entry into the mass spectrometer[44].

3. **Mass Analysis:**

The ionized compounds are then subjected to high-resolution mass analysis. Unlike conventional mass spectrometry, HRMS provides superior mass accuracy and resolution. High- resolution instruments can distinguish between ions with similar mass-to-charge ratios, reducing the likelihood of false positives and increasing the confidence in compound identification[45].

4. Detection and Data Acquisition:

The mass spectrometer detects the ions based on their mass-to-charge ratios. The resulting mass spectra provide information about the elemental composition of the compounds present in the sample. HRMS allows for precise determination of molecular weights, aiding in the identification of unknown compounds[46].

5. Data Interpretation:

The acquired data is processed and interpreted using specialized software. By comparing the experimental data with reference databases and applying advanced algorithms, researchers can identify and quantify the individual components within the sample[47].

APPLICATION:

1. Metabolomics: Identifying and quantifying small molecules in biological samples.
2. Proteomics: Analyzing proteins and peptides for identification and characterization.
3. Environmental Analysis: Detecting and quantifying pollutants or contaminants in water, soil, and air.
4. Pharmaceutical Analysis: Characterizing drug compounds and their metabolites in pharmaceutical research.
5. Food Safety: Identifying and quantifying contaminants or additives In food sample.
6. Forensic Toxicology: Analyzing biological samples for the presence of drugs or toxins.
7. The high resolution of the mass spectrometer provides accurate mass measurements, improving the specificity and reliability of compound identification[48],[49].

Figure No 4: LCHRMS Instrument

V. NANO LIQUID CHROMATOGRAPHY:

Nano liquid chromatography is a kind of microfluidic system used to resolve different pharmaceutical, clinical, biomedical, chiral, metabolic, protein, peptides and enantiomeric compound. It is used to detect compound in nanogram level by using nano liter of solvents hence ensuring low consumption of solvent. Miniaturized separation techniques have emerged as ecofriendly alternatives to available separation methods. Nano-liquid chromatography (nano-LC), microchip devices and nano-capillary electrophoresis are miniaturized techniques that minimize reagent utilization and waste generation. Moreover, high cost of equipment may be some

limitation although nano liquid chromatography is a newer technology ensures opening of new bridge to newer application for industry and laboratories[50], [51].

PRINCIPLE:

The fundamental principle of this advancement is governed by the van Deemter equation, which is an empirical formula that describes the relationship between linear velocity (flow rate) and plate height (HETP or 1/column efficiency).

$$H=A+B/u+Cu$$

Whereas, A is Eddy's diffusion; B is longitudinal diffusion; C is Concentration and u is Linear Velocity.[12, 13] Nanoflow LC chromatographic separations are performed using flow rates in the range of low nano liter per minute, which result in high analytical sensitivity due to the large concentration efficiency afforded by this type of chromatography[52].

INSTRUMENTATION:

Miniaturizing an LC system implies that all system components should be downscaled, including column, Pumps, connecting tubing, connections, injector, and the interface to the detector.

1. PUMP:

Nano-LC requires a pump system, which gives reproducible nano flow rates and stability during the separation, and permit gradient elution at nano-scale levels. It requires flow rates of 500 nL/min or less.

2. COLUMNS:

The commonly accepted standard internal diameter of nano LC columns is 75 µm. This column format provides a good compromise between sensitivity, load ability, and robustness.

Two types of columns are used in nano LC

1. Packed columns
2. Monolithic columns

Packed columns

The packed columns used in the nano LC columns are made of Polyimide-coated fused silica capillaries.

Monolithic columns

In this type of column, a porous (silica or polymer) structure is formed throughout the column, eliminating the need for frits because the stationary phase is fixed to the column wall.

3. INJECTION:

Typically, the sample is limited, so the injection system should ensure that no sample is lost to waste. Direct injection setups can be used in nano LC setups. The maximum injection volumes for nano columns can be expressed as a function of the column length, plate number, retention factor or some other parameters, and are generally a few nanolitres. Small injected volumes are a major problem in nano-LC, causing loss of detectability, but larger injected volumes produce a band broadening effect, decreasing the efficiency of the separation, especially for poorly retained compounds. Commercial auto-samplers, which usually work at microliter levels, require an instrument adjustment for use in the nanoliter range.

4. DETECTOR:

A nano liquid chromatography detector is an essential component in analytical chemistry. Common types include UV-Vis detectors, fluorescence detectors, and mass spectrometers. These detectors help analyze and quantify separated compounds in nano-scale liquid chromatography, offering high sensitivity and precision. The choice of detector depends on the specific requirements of your analysis[53],[22].

APPLICATION[54], [55]:

1. Phospholipid determination in human urine.
2. Oligosaccharide determination in ovarian tissues.
3. Determination of abused drugs and metabolites in human hair.
4. Separation of sulfonamides.
5. Analysis of phenolic compounds in olive oil.
6. Determination of ricin by Nano-LC/MS

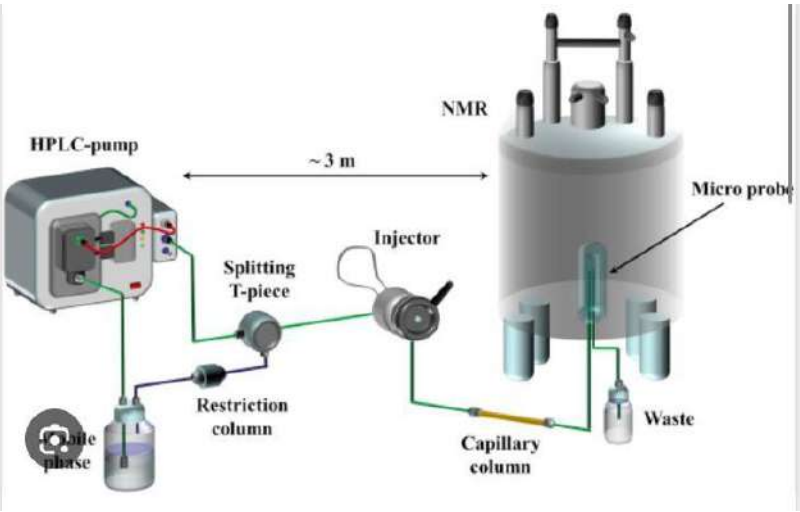

Figure no 5: Nano Liquid Chromatography

CONCLUSION:

In conclusion, modern analytical liquid chromatographic techniques, including HPLC, HILIC, LC-MS, UPLC, and UHPLC, have revolutionized analytical chemistry. High Performance Liquid Chromatography (HPLC) offers robust separation, while Hydrophilic Interaction Liquid Chromatography (HILIC) excels in polar compound analysis. Liquid Chromatography-Mass Spectrometry (LC-MS) combines separation power with precise mass identification. Ultra- Performance Liquid Chromatography (UPLC) enhances speed and resolution, and Ultra-High- Performance Liquid Chromatography (UHPLC) further optimizes efficiency. These techniques collectively empower researchers with versatile tools for diverse applications, from pharmaceuticals to environmental analysis, ensuring accurate and efficient separation and quantification of complex mixtures.

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