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Capillary liquid chromatography: A Detailed Review

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ABSTRACT

Capillary Liquid Chromatography (CLC) is an advanced miniaturized form of High-Performance Liquid Chromatography (HPLC) that utilizes narrow-bore capillary columns, typically with internal diameters ranging from 50 to 300 µm. This technique has emerged as a powerful analytical tool for separating and quantifying complex mixtures with high sensitivity, efficiency, and minimal sample consumption. The principle of it is based on the same chromatographic mechanisms as conventional HPLC, but the reduced column dimensions lead to enhanced mass transfer, improved resolution, and reduced solvent usage. It offers several advantages, including high separation efficiency, reduced analysis cost, and compatibility with mass spectrometry, making it highly suitable for proteomics, metabolomics, pharmaceutical analysis, and environmental studies. The instrumentation of CLC comprises a micro-pump or pressure-driven solvent delivery system, a micro-injector for precise sample introduction, a temperature-controlled capillary column, and highly sensitive detectors such as UV, fluorescence, or MS. Compared to traditional HPLC, CLC provides improved performance in terms of speed, reproducibility, and eco-friendliness. Despite its benefits, challenges such as complex system design, difficulty in handling small volumes, Overall, Capillary Liquid Chromatography represents a significant step forward in modern analytical chemistry, combining high efficiency with reduced environmental impact and analytical cost.

KEY WORDS: Capillary liquid chromatography,miniaturized, packed column, open tubular column, HPLC, Solvent delivary system, capillary column, temperature controller, detector.

I. INTRODUCTION

Capillary liquid chromatography (CLC) is defined as Technique that utilized narrow bore column to achieve high sensitivity and peak capacity in the analysis of complex mixture often resulting in increased detection metabolites compared to conventional HPLC methods.It operates in various applications including metabolomic assays. columns with inner diameters below 0.5 mm and flow rates from some few µl/min down to the nl/min range Miniaturization of chromatographic procedures using CLC offers substantial advantages over conventional LC separation methods. Capillary columns show increased separation efficiency, minimal solvent consumption, higher peak concentration at the detector and higher peptide recovery.

Horvart first reported CLC in 1967 The preparation, analytical characteristics and some applications of CLC columns were described in the late 1970s by Scott and Kucera . Hirata and Novotny and Ishii and co-workers . Two main classes of CLC columns were developed: wall-coated open tubular (OTLC) columns and packed columns. Several authors have shown the applicability of OTLC columns, which have been coupled to ESI-MS and APCI However, open tubular columns have considerable practical drawbacks in extended use.

Packed CLC columns consist of metal or fused-silica capillaries filled with chromatographic supports with particle sizes ranging from 1.0 to 50 µm. CLC can be divided into micro (0.8–0.15 mm i.d.) and nano (20–100 µm i.d.) LC depending on the inner diameter of the column. Capillary columns usually show overall performance and efficiency comparable with or better than conventional columns.Jorgenson and colleagues reported 40theoretical plates for resorcinol (k' = 2.7) on a 25 µm i.d. column, 33 cm in length, filled with 5 µm particles.

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Empty Cell	Column diameter	Flow-rate
Conventional		
Wide-bore (preparative)	4.6 mm	3 ml/min
Normal-bore (analytical)	3–4.6 mm	0.5–3 ml/min
Narrow-bore	1–2 mm	0.02–0.3 ml/min
Capillary		
Microbore	0.15–0.8 mm	2–20 µl/min

Table:1 Column diameter with flow rate.

Two main classes of capillary LC columns were developed: wall-coated open tubular (OTLC) columns and packed columns.
Capillary liquid chromatography (CLC or micro-LC) uses very narrow-bore columns (generally 0.1–1.0 mm inner diameter) instead of the conventional 4.6 mm analytical columns. These columns reduce solvent consumption and increase sensitivity, especially for mass spectrometry coupling.

feature	Wall-coated open tubular (WCOT) column	Packed column
Column type	Open tube with stationary phase coated on inner wall .	Column filled with solid support material
Stationary phase	Thin film coated directly on inner wall of the capillary	Coated on solid particles packed inside
Column diameter	Narrow (typically 0.1-0.5 mm ID)	Wider (2-4mmlD)
Length	Longer (up to 60 more	Shorter (1-3m)
Efficiency	High	LowMM

Table:2 Different between wall coated column and Packed column

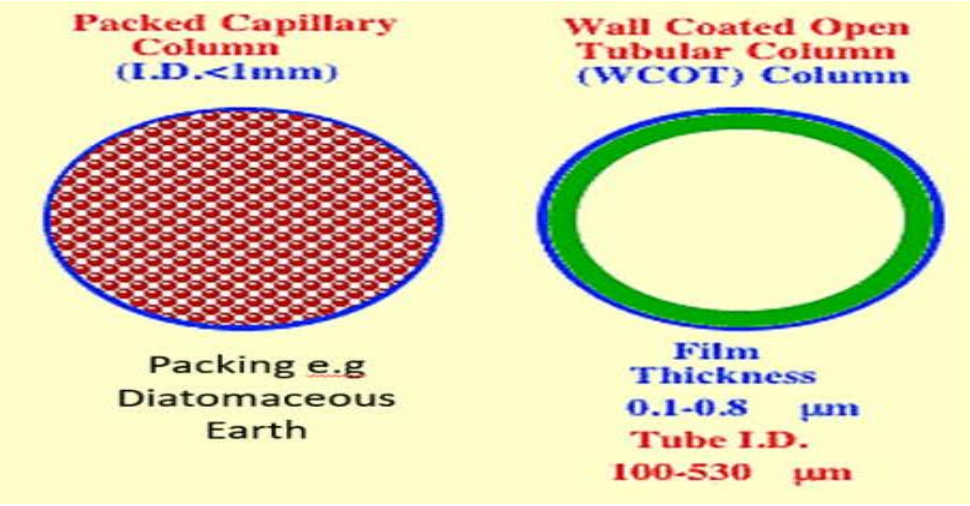

Fig :1 Packed capillary column and wall coated open tubular column.

MINIATURIZATION

Miniaturisation in liquid chromatography refers to the progressive reduction of column internal diameter (I.D.), flow rates, and injection volumes while maintaining or enhancing separation efficiency. Capillary liquid chromatography (CLC) is a direct outcome of this trend, employing columns with I.D. typically in the range of 50–500 µm.

Rationale for Miniaturisation

Sample limitations: Useful for proteomics, metabolomics, and pharmaceutical analysis where only minute sample quantities are available.

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Increased sensitivity: Narrow-bore columns provide improved concentration sensitivity when coupled with mass spectrometry (MS).
Lower solvent consumption: Significant reduction in mobile phase usage, aligning with green chemistry principles.
Enhanced efficiency: Reduced band broadening and better separation performance.
Strategies for MiniaturisationColumn miniaturisation Miniaturised detectors such as Nano-electrospray MS, on-column UV/fluorescence, and microchip-based Sensors Integration with microfluidics Chip-based LC systems with embedded capillaries for highly compact setups. Now, capillary LC, micro-LC, Nano-LC, and chip-based LC packed- and monolithic-bed capillaries have been introduced and commercialized for miniaturized LCs. Manzetal. reported a first 5 × 5 mm silicon chip containing an open-tubular column of 6 µm × 2 µm × 15 cm with conductometric determination Open-tubular columns (OT-LC) with respect to packed columns eliminate the eddy diffusion where are responsible for band broadening in packed columns. Commercially, Agilent developed microfluidic LC chips

The kind of detection system of miniaturized LCs is very important because, at chip-based LC or Capillary LC and Nano LC, the decreased dimension of the channel significantly impacts detector sensitivity. The developed methods are Raman spectroscopy, UV–Vis, NIR spectroscopy, laser- and LED-induced fluorescence spectroscopy, conductivity, amperometry, and potentiometry detection approaches, and X-ray fluorescence spectroscopy. The first portable LC using a multi-wavelength photometric detector was introduced by Baram et al., in 1996 . Glass and plastic materials of microchip absorb the UV radiation and cause the detection difficult. So, quartz and polydimethylsiloxane materials for their optical transparency are good choices. UV–Vis absorption detectors cannot provide high sensitivity, therefore they can be used in projects that higher sensitivity is not a necessity.

COMPARISION BETWEEN CAPILLARY LIQUID CHROMATOGRAPHY AND HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Features	**Capillaryliquid chromatography**	**Highperformance liquid chromatography**
Definition	CLC is a type of LC that use very narrow columns to separate chemical compound.	HPLC is an analytical technique used to separate identify , and quantify components in a mixture by applying high pressure
Columninternal diameter	0.1-1.0	2.1-4.6mm
Column length	Shorter	Typically 100-250
Injection volume	Very small(nL)	Larger (1-100)
Sample consumption	Low	Higher
Injection volume	Very small	Larger
Sample consumpation	Low	Higher
Flow rate	1-100µL	0.2-2.0mL
Solvent consumption	Very low	High
Sensitivity	Higher	Good but not good as capillaryliquid chromatography
Pump requirements	Low-pressure	High pressure
Particle size of column	1.5 -5µm	3-5µm

Table :3 Difference between capillary liquid chromatography and HPLC

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INSTRUMENTATION

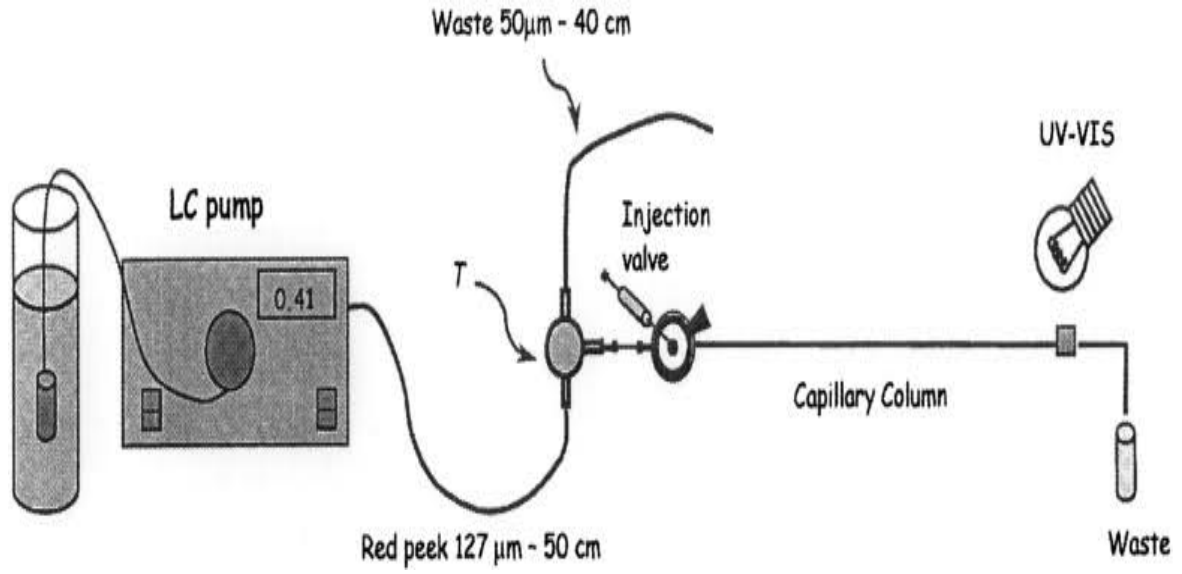

Fig: 2 Instrumention of capillary liquid chromatography.

Components of capillary liquid chromatography instrumentation:

- Solvent delivery system (Pump)
- Sample injector
- Capillary column
- Temperature controller
- Detector
- Data system
- Interface

Solvent Delivary System(pump): The solvent delivery system (or pump system) is one of the most critical components in CLC because it must deliver the mobile phase at extremely low flow rates with high precision.To pump the mobile phase through the capillary column.To maintain constant, pulse-free flow at very low rates (20 nL/min – 10 µL/min).To generate sufficient pressure (up to 400–1000 bar) to overcome column back pressure.To maintain gradient or isocratic conditions accurately.

Types of Solvent Delivery Systems in CLC

1. Syringe Pumps Directly displace solvent using a motor-driven syringe.Provide very stable and precise flow at NL–µL/min.Ideal for Nano-LC applications.

Limitation: Limited solvent volume, need frequent refilling.

2. Split-Flow Systems

Use a conventional HPLC pump (delivering mL/min) flow splitter.Majority of the flow is diverted to waste, and a controlled fraction goes into the capillary column.

Limitation: Flow splitting must be highly accurate; risk of instability at very low flow.

3. Nano-Pumps / Micro-Pumps (Specialized CLC Pumps)

Designed specifically for capillary/Nano-LC.Can deliver continuous, pulse-free Nanoliter flows without splitting.Allow precise gradient formation.More expensive but highly reliable.

Sample injector: The sample injector is the component that introduces a very small, precise volume of sample into the mobile phase stream without disturbing the flow. In CLC, injection is more challenging than in conventional HPLC because of tiny column diameters (10–300 µm) and very low flow rates (nL–µL/min). Introduce sample into the mobile phase with high precision.Avoid sample band broadening and backflow.Handle extremely small sample volumes (as low as nL to µL).Maintain system pressure and prevent leaks.

Challenges in CLC Injection.Conventional HPLC injectors (5–20 µL loops) are unsuitable.Dead volume must be minimized (even nanoliters of extra volume cause peak distortion).Reproducibility is difficult at such small volumes.

Types of Sample Injectors in CLC

1. Nano-Valve Injector (Micro-Injection Valve)

Miniaturized version of HPLC rotary valve.Uses very small sample loops (20 nL – 1 µL).Allows

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reproducible injections under high pressure.Widely used for routine CLC analysis.Sample is directly deposited at the head of the capillary column using pressure or vacuum.Eliminates dead volume.Provides excellent reproducibility but requires skillful handling.
2. Electrokinetic Injection:Sample is introduced by applying a voltage difference (electroosmotic flow).Common in Nano-LC coupled with capillary electrophoresis or MS.Useful for trace-level analysis and proteomics.
Capillary column: Capillary columns are the central component of capillary liquid chromatography. They are miniaturized chromatographic columns with very small internal diameters, typically ranging from 10 µm to 500 µm, much smaller than conventional HPLC columns (4.6 mm i.d.). Structure of Capillary Columns Made of fused silica (similar to capillary GC columns), stainless steel, or polymeric materials. Dimensions:Inner diameter (i.d.): 10–500 µm (common: 50–200 µm)

Types of Capillary Columns
Capillary LC columns can be broadly classified into:
1. Packed Capillary ColumnsFilled with small particles (1.5–5 µm) of stationary phase (e.g., silica, reversed- Provide high surface area → higher sample loading capacity.Used for complex mixtures, proteomics, pharmaceutical analysis.
2.Open-Tubular (OT) Capillary ColumnsHollow tubes with the inner wall coated by a thin stationary phase film.
Types:Wall-coated OT: Stationary phase coated on capillary wall. Porous-layer OT: Porous layer (e.g., silica) deposited on the wall.
Advantage: High efficiency (due to low resistance to mass transfer).
Limitation: Very low sample capacity.
3. Monolithic Capillary Columns:Instead of packed particles, they have a continuous porous rod inside the Made of polymeric or silica-based monoliths.
Advantage: High permeability (low back pressure), fast separation, high reproducibility.
Temperature controller:
capillary liquid chromatography (CLC), columns have very small internal diameters (10–300 µm). Because of this miniaturization.The flow rates are extremely low (nanoliters to microliters per minute).Small variations in temperature can significantly influence solvent viscosity, analyte diffusivity, and separation efficiency.Therefore, a temperature controller is essential for maintaining stable chromatographic conditions.
Components of Temperature Controller in CLC.
1. Column Oven / Chamber:A small, insulated chamber where the capillary column is placed.Provides uniform heating along the entire column.
2. Heating System:Often uses resistive heating coils or Peltier devices.Some designs use liquid baths or air circulation for more uniform heating.
3. Temperature Sensor:Typically a thermocouple or thermistor is placed near or on the column.Monitors real-time temperature to avoid fluctuations.
4. Controller Unit (Electronics): A microprocessor-based system that adjusts the heating element based on sensor feedback.Maintains a constant set temperature or allows programmed gradients.
Types of Temperature Control in CLC
1. Isothermal Control:Column maintained at a single fixed Temperature, common for routine separations.
2. Temperature Gradient Control: Temperature is gradually increased during the run useful for separating compounds with wide polarity ranges.
3. On-Column Heating (Resistive Heating): Current is passed directly through the capillary column wall,Provides.
Detector:
High sensitivity – must detect analytes present in picogram to nanogram amounts.Low internal volume (nanoliter scale) – prevents band broadening and maintains resolution. Fast response time – to detect very sharp and narrow peaks. Compatibility with micro/nano-flow rates. Non-destructive (in some cases) – useful if coupling with another technique (e.g., MS).
Types of Detectors in CLC
1. UV-Visible Absorbance Detectors:Most common in CLC due to universality and simplicity.Uses a capillary flow cell with very small path lengths (~75–100 µm ID).Can be fixed-wavelength (e.g., 254 nm for aromatic compounds) or diode-array detectors (DAD) for spectral data.Advantages: Non-destructive, widely applicable, high linearity.
Limitations: Sensitivity limited for compounds with weak chromophores; short path length reduces absorbance signal.
2. Fluorescence Detectors:Based on the natural or induced fluorescence of analytes.Uses laser-induced fluorescence (LIF) for very high sensitivity (down to femtomole levels).
Advantages: Extremely sensitive, selective.
Limitations: Only works for naturally fluorescent compounds or those derivatized with fluorescent tags.
3. Electrochemical Detectors (ECD): Detect analytes by oxidation or reduction at an electrode surface.Often used for biomolecules,

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neurotransmitters, and pharmaceutical compounds.Capillary ECD designs use thin-layer or microelectrodes with low dead volume.
Advantages: High sensitivity, selective for electroactive species.
Limitations: Limited to analytes with redox activity.
4. Mass Spectrometry (MS) Detectors:Most powerful and widely used in modern CLC.Coupling is usually via nanoelectrospray ionization (nano-ESI) to match very low flow rates.Provides both qualitative (structural) and quantitative information.
Advantages: Universal detection, high sensitivity, molecular weight + structural data.
Limitations: Expensive, requires careful interface design.
5. Refractive Index (RI) Detectors:Measure changes in refractive index between eluent and analyte.Less common in CLC because sensitivity is poor at very low volumes.Mainly used when analytes lack chromophores.
6. Conductivity Detectors:Useful in ion chromatography or ionic analytes.Detect changes in the electrical conductivity of the mobile phase due to analyte elution.Modified micro-cells are used for CLC.
7. Other Specialized Detectors:Evaporative Light Scattering Detector (ELSD): Detects non-volatile analytes after mobile phase evaporation.Chemiluminescence Detectors: Extremely sensitive for analytes undergoing light-emitting reactions.Capacitively Coupled Contactless Conductivity Detection (C4D): Non-invasive, often used in CE/CLC hybrid systems.

Data system:

Direct connection using a micro flow cell.Must have very small cell volume (nL–µL) to avoid band broadening.
1. LC–Electrochemical Detector Interfaces:Effluent flows directly over an electrode surface requires precise alignment to ensure efficient detection.
2. LC–Mass Spectrometry Interfaces (most important):Electrospray Ionization (ESI) – Most common; effluent is sprayed through a fine tip with high voltage, forming charged droplets that enter MS.Atmospheric Pressure Chemical Ionization (APCI) – Used for less polar analytes; requires nebulization and corona discharge.Nano-ESI (nanoelectrospray) – Specially designed for CLC because it can handle very low flow rates (nL/min) with high sensitivity.

ADVANTAGES:

1. High Efficiency and Resolution: Smaller internal diameter columns (typically <1 mm) allow for better separation of complex mixtures due to reduced band broadening.
2. Reduced Solvent Consumption: Capillary LC uses much less mobile phase compared to conventional HPLC, making it more environmentally friendly and cost-effective.
3. Enhanced Sensitivity: Due to lower flow rates and smaller sample dilution, Capillary LC achieves better detection sensitivity, especially when coupled with mass spectrometry.
4. Improved Sample Economy: Requires only nano liter to microliter sample volumes, ideal for limited or precious biological samples
5. High sensitivity – Due to very small column diameters and reduced sample dilution, CLC provides higher detection sensitivity compared to conventional HPLC.
6. Low sample volume requirement – Only nanoliters to microliters of sample are needed, making it ideal for precious or limited samples.
7. Reduced solvent consumption – Uses significantly less mobile phase (up to 100–1000 times less than HPLC), lowering cost and waste.
8. Improved separation efficiency – Narrow-bore capillaries provide better mass transfer and higher plate numbers, enhancing resolution.
9. Compatibility with mass spectrometry (MS) – Small flow rates are well suited for electrospray ionization (ESI-MS), giving better sensitivity and less ion suppression
10. Cost-effective operation – Lower mobile phase and sample consumption reduce overall operational cost.
11. co-friendly (Green Chemistry) – Minimal solvent usage decreases environmental impact and disposal issues
12. improved reproducibility – Stable temperature control and minimized dead volumes improve reproducibility of results.
13. Ability to analyze complex biological samples – Particularly useful for proteomics, metabolomics, and pharmaceutical research requiring high sensitivity.
14. Better temperature control – Narrow columns allow precise heating/cooling, improving reproducibility and efficiency.
15. Scalability to nano-LC and micro-LC – CLC serves as a bridge between HPLC and nano-LC, adaptable for different analytical needs.

DISADVANTAGES:

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1. complex instrumentation – Requires specialized pumps, injectors, and detectors adapted for very low flow rates.
2. High cost – Equipment and capillary columns are more expensive than conventional HPLC.
3. Fragility of columns – Capillary columns are delicate and easily breakable.
4. Lower sample capacity – Can handle only very small sample volumes (nL–µL), which limits preparative applications.
5. Challenging sample injection – Accurate injection of nanoliter volumes is technically difficult.
6. Detector sensitivity limitations – At very low flow rates, not all detectors are compatible or sensitive enough.
7. Method development difficulties – Optimization of separation conditions is more time-consuming.
8. Limited robustness – More prone to clogging due to narrow bore size.
9. Maintenance issues – Requires high-quality solvents and extensive care to avoid blockages.
10. Limited commercial availability – Not as widely available as conventional HPLC systems.
11.Training requirement – Requires skilled operators to handle micro-volume systems.
12. Compatibility issues – Some traditional detectors (e.g., UV detectors with larger flow cells) are less effective.
13. Temperature control sensitivity – Since volumes are very small, minor temperature fluctuations can affect results.
14. Unsuitable for high-load separations – Cannot be used effectively for preparative-scale chromatography.
15. Time-consuming maintenance – Clogging or leaks in nano fittings are difficult to troubleshoot.

APPLICATION:

1.Proteomics – Separation and identification of peptides and proteins.
2. Genomics – Analysis of nucleotides, DNA fragments, and oligonucleotides.
3. Metabolomics – Profiling of small biomolecules and metabolites.
4. Pharmaceutical analysis – Quantification of drugs and impurities.
5. Biopharmaceuticals – Analysis of monoclonal antibodies, recombinant proteins, and peptides.
6. Clinical diagnostics – Detection of biomarkers in biological fluids
7.Environmental analysis – Monitoring pollutants, pesticides, and toxins in water/soil.
8. Food and beverage analysis – Determination of vitamins, additives, preservatives, and contaminants.
9. Forensic science – Identification of drugs of abuse and toxic substances in body fluids.
10. Natural product analysis – Isolation and characterization of plant extracts and secondary metabolites.
11. Pharmacokinetics – Studying drug absorption, distribution, metabolism, and excretion (ADME).
12. Quality control – Purity testing of pharmaceutical and chemical products.
13. Nanomaterials research – Characterization of nanoparticles and nanocarriers.
14. Chiral separations – Analysis of enantiomers in pharmaceuticals.
15. Biotechnology research – Studying biomolecular interactions and structural analysis.

II. CONCLUSION

Capillary liquid chromatography is a power full and efficient analytical technique that continues to gain importance in modern laboratorie,especially where high sensitivity and minimal sample uses are critical . Integration with advanced detection system further extends its utility in research and industrial

Is a highly valuable and evolving techniques in modern analytical science.Its combination of high efficiency , low sample requriment , and compatibility with advanced detection systems ensures its continued relevance and growth in both research and industrial application.

Capillary Liquid Chromatography (CLC) is an advanced miniaturized form of conventional HPLC that operates with extremely narrow-bore columns and very low flow rates. It has emerged as a powerful analytical technique due to its high separation efficiency, low sample and solvent consumption, and excellent sensitivity. Because of these unique advantages, CLC is particularly useful for analyzing complex biological samples such as peptides, proteins, nucleic acids, and metabolites in the fields of proteomics, genomics, and metabolomics.

Despite its benefits, CLC also presents challenges, including high instrumentation costs, technical complexity, fragile capillary columns, and limited sample loading capacity. These limitations restrict its use mainly to research and specialized laboratories rather than routine analysis.

Nevertheless, CLC has gained wide acceptance in pharmaceutical analysis, clinical diagnostics, environmental monitoring, food testing, forensic science, and biotechnology, making it a versatile and reliable technique. Continuous advancements in miniaturized detectors, automated sample handling, and microfabrication technologies

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are expected to overcome current limitations and further expand its applications.

CLC represents the future direction of liquid chromatography, offering enhanced performance with reduced resource requirements. With ongoing innovations, it is likely to become an indispensable tool in analytical science, particularly where high sensitivity, selectivity, and minimal sample consumption are required.

REPORT

Chromatography is one of the most important analytical techniques used for separating, identifying, and quantifying chemical compounds. Among various types, High-Performance Liquid Chromatography (HPLC) has long been a standard method for liquid-phase separation. However, continuous demand for higher sensitivity, lower sample consumption, and miniaturization led to the development of Capillary Liquid Chromatography (CLC) a modified and miniaturized form of HPLC. Both techniques are based on the same fundamental principle, but CLC uses extremely narrow capillary columns and smaller sample volumes, offering greater efficiency and eco-friendliness.

The principle of both HPLC and CLC is the differential migration of analytes between a stationary phase and a mobile phase. Each compound in a mixture interacts differently with the stationary phase based on its polarity, charge, or molecular size. This difference causes compounds to elute at different times (called retention times), allowing separation.

While HPLC typically operates with larger flow rates and column diameters (4.6 mm), CLC uses very narrow columns (below 0.5 mm) and extremely low flow rates (in nanoliters or microliters per minute). The reduced column size in CLC increases separation efficiency and reduces solvent usage.

Both techniques share the same fundamental components — solvent delivery system, injector, column, detector, and data system — but differ in design and scale.

Solvent Delivery System

In HPLC, pumps deliver the mobile phase at flow rates of 0.5–2 mL/min. In CLC, miniaturized micro-pumps are used, with flow rates in the nanoliter to microliter range, enabling lower solvent consumption and high precision.

Sample Injector

HPLC injectors typically introduce 10–100 µL of sample, while CLC injectors handle much smaller volumes (as low as nanoliters). This allows analysis of very limited or expensive samples.The HPLC column has a larger internal diameter (around 4.6 mm) and length of 15–25 cm. In contrast, CLC uses fused-silica capillary columns with diameters between 75–500 µm and lengths from 10–50 cm. The narrow internal diameter provides high efficiency.

Detector:Both systems may use UV-Visible, fluorescence, or mass spectrometric detectors. CLC is more often coupled with mass spectrometry (CLC-MS) due to its compatibility with small sample volumes and high sensitivity.

Data System:The data acquisition system in both techniques records chromatograms and analyzes results. However, CLC requires more sensitive electronics due to smaller signal intensities.The working of CLC and HPLC is similar in concept. In both methods, the mobile phase carries the sample through the stationary phase inside the column. The compounds interact with the stationary phase and separate according to their affinity. In CLC, because of the small column diameter and high surface-to-volume ratio, heat dissipation is more efficient and band broadening is minimized. As a result, peak shapes are sharper and separation resolution is higher compared to HPLC.

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