World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(Review Article)

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Unconventional stationary phases: Nanomaterials, nanoparticles and the future of liquid chromatography

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World Journal of Advanced Research and Reviews, 2023, 18(02), 492–501

Publication history: Received on 08 March 2023; revised on 09 May 2023; accepted on 11 May 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.18.2.0851

Abstract

This review article discusses the impact of nanostructured stationary phases on liquid chromatography and separation science. These materials have revolutionized chromatography by enabling unprecedented levels of sensitivity, resolution, and applicability. Nanoporous silica, graphenic, monolithic, and nanoparticle-based phases continue to push the boundaries of biomolecular analysis, molecular diagnostics, and traceability testing. Nanostructured phases have made early detection of diseases, comprehensive profiling of proteomes, enhanced food origin traceability, and sensitive environmental monitoring possible. They facilitate isolation and analysis of biomacromolecules, extracellular vesicles, viruses, and trace constituents with high specificity and sensitivity even from minimal sample volumes. Furthermore, nanostructured phases are enabling integrated techniques, sensing capabilities, and responsive microdomains for advanced detection, purification, and separation of analytes. Continued progress in nanomaterial design, surface engineering, and micro-nanofabrication will lead to more sophisticated nano-LC approaches with translation across healthcare, food safety, materials analysis, and global sustainability. The review concludes that nanostructured stationary phases represent a pivotal frontier in chromatography and analytical sciences with tremendous potential to transform molecular diagnosis, precision medicine, origin traceability, and monitoring of health, food, and environment quality. Nano-LC promises to make comprehensive and minimally invasive molecular-level understanding more feasible, accessible, and impactful. These materials are an enabling technology with immense and far-reaching possibilities that will likely shape developments in analytical sciences and their use for years to come.

Keywords: Liquid Chromatography; Nanoparticles; Silica Gel; Proteomics; Molecular diagnostics

1. Introduction

Liquid chromatography (LC) relies on stationary phases with tailored characteristics for effective separation of analytes. Silica has traditionally been the most popular stationary phase material, but various inorganic and organic stationary phases have since been developed to suit diverse analyses [1].

In recent years, nanomaterials have emerged as promising candidates for stationary phases, with their unique properties enabling new levels of performance. Nanoporous silica, zirconia, titania, graphene and other nanomaterials are able to provide ultra-high surface areas, nanoscale confinement effects and facile surface modifications for superior sensitivity, resolution and applicability [2].

Nanoporous silica phases contain a network of nanopores that drastically increase solute retention and saturation capacity. Nanoparticle-coated and monolithic nanomaterials exhibit versatile and optimized characteristics based on their composition, nanostructuring and degree of hydrophobicity/hydrophilicity. Nanoporous graphene phases offer

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an exceptional combination of high surface area, conductivity and biocompatibility for emerging areas like proteomics, metabolomics and biomaterial sensing [3, 4].

Nanomaterial stationary phases are rapidly advancing liquid chromatography to achieve faster, more sensitive and high-resolution separations even for highly complex mixtures. From biosamples to trace contaminants, these innovative "nanophases" are enabling new possibilities in analysis, discovery and precision medicine. Continued progress in nanomaterial design, surface tailoring and integrated applications will ensure that nanoscale confinement and tailored nanoenvironments remain central to future breakthroughs in LC methodology and applications [5].

Nanomaterial stationary phases represent the frontier of liquid chromatography methodology, with nanoscale porosity, nanoparticles and advanced engineering of phase characteristics set to transform separation science and its use in fields like biomedicine, food/environment testing, and materials science. This overview explores the current and emerging possibilities of these transformative stationary phases.

2. Types of Nanoporous stationary phases

Nanoporous stationary phases exploit nanoscale pore structures to maximize surface area and achieve enhanced sensitivity, solute capacity and chromatographic performance. Porous silica, zirconia, activated carbon and graphenic materials have been employed for nanostructuring the pores in these phases [6]. Different kinds of nanostructured stationary phases and their characteristics and applications are shown in Table 1.

Table 1 Different types of nanostructured stationary phases currently used in liquid chromatography

SN.	Nanostructured Stationary Phase	Characteristics	Applications
1	Nanoporous Silica	Porous structure with high surface area	Separation of small molecules, biomolecules, and peptides
2	Graphene Oxide	High adsorption capacity and selectivity	Separation of aromatic compounds, peptides, and proteins
3	Monolithic	Continuous porous structure with high permeability	Separation of small molecules, peptides, and proteins
4	Nanoparticle-based	High surface area and selectivity	Separation of peptides, proteins, and small molecules
5	Core-shell	Unique surface chemistry and high selectivity	Separation of small molecules, peptides, and proteins

2.1. Silica-based nanoporous hybrid phases

Silica-based nanoporous hybrid phases contain a network of silica Nanopores that provide up to 1000 m^2/g surface area, enabling increased solute retention and saturation. The porous framework also allows for facile mass transfer, resulting in improved sensitivity and less band broadening [7].

2.2. Nanoporous zirconia and titania phases

Nanoporous zirconia and titania phases utilize the high surface area (up to 500 m^2/g) and hydrophilic-hydrophobic switchability of these nanomaterials for enhanced separations of polar and nonpolar compounds. These ceramic nanoporous phases are highly stable and able to withstand harsh mobile phase conditions [8].

2.3. Graphenic Nanoporous phases

Graphenic nanoporous phases, like porous graphene oxide, possess an ultrahigh surface area of up to 2600 m^2/g and exceptional adsorption capacity. They are able to efficiently retain and release biomolecules, facilitating sensitive proteomic analysis and other biomedical applications. Three-dimensional networking of nanopores in these phases provides numerous isolated nano-domains for selective separation of closely related compounds [9]. The unique features of the various nano-based stationary phases are shown in Figure 1.

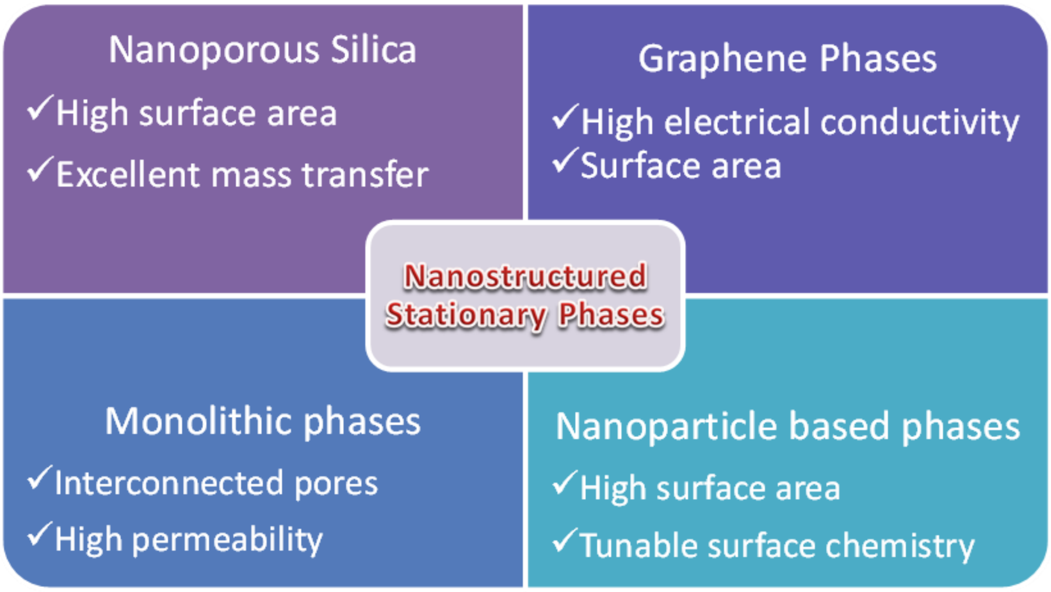

Figure 1 Various nanostructured stationary phases

The array of pore sizes, surface chemistries and structural features possible with nanomaterials enables highly tunable stationary phases with optimized performance for different applications. Nanoporous phases continue to push the boundaries of sensitivity, speed, resolution and applicability of liquid chromatography separations [10].

With their ultra-large surface areas, nanoscale confinement effects and facile surface modification, nanoporous stationary phases represent an exciting frontier in separation science with tremendous potential for biomolecular analysis, precision medicine and other advanced applications. Continued innovation in nanostructuring porous silica, graphenic and other nanomaterials will lead to high-impact developments in nano-LC in the coming years [11].

2.4. Monolithic phases

Three-dimensional nanoporous graphenic materials exhibit an unparalleled combination of high surface area, electrical conductivity and biocompatibility that is ideal for sensing, separation and analysis of biomolecules. Porous graphene oxide (GO) and reduced graphene oxide (rGO) containing a 3D network of nanopores possess specific surface areas of up to 2600 m^2/g, much larger than conventional silica phases [12]. The sensitivity and resolution of nanostructured stationary phases when compared to conventional stationary phases are shown in Figure 2.

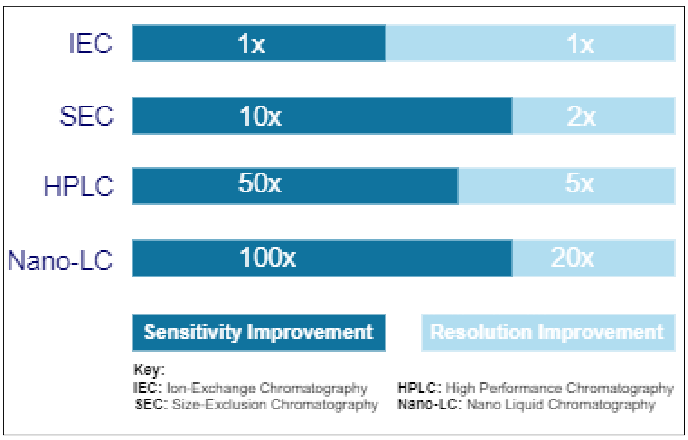

Figure 2 A graph showing the sensitivity and resolution improvements achieved using nano-LC approaches in comparison to traditional liquid chromatography techniques

The huge surface area of nanoporous graphene phases enables exceptional retention of peptides, proteins and other bio-macromolecules for enhanced sensitivity in detection and quantification of these analytes. At the same time, the porous structure allows for facile diffusion of small molecules, resulting in high efficiency and sensitive detection even of trace components. This enables highly sensitive proteomic analyses, early diagnosis of diseases from low-level biomarkers and monitoring of drug responses [13]. The sensitivity, resolution, and applicability of traditional liquid chromatography techniques are compared in Table 2.

Table 2 Sensitivity, resolution, and applicability of traditional liquid chromatography techniques with those of nano-LC approaches

Sl.No.	Technique	Sensitivity (ng)	Resolution (Rs)
01	High-Performance Liquid Chromatography (HPLC)	100	1.5
02	Ultra-High-Performance Liquid Chromatography (UHPLC)	10	2.5
03	Nano-Liquid Chromatography (nano-LC)	1	5

The conductivity and electro-active nature of nanoporous graphenic phases also provides possibilities for direct electrochemical sensing, biosensing, and sensor arrays with high sensitivity, selectivity and real-time measurement ability. These phases can bind biological molecules, enzymes or antibodies on their surface to fabricate selective and responsive biosensors for detection of health-related analytes like glucose, cholesterol, prostate specific antigen, etc. They also show potential as electrochemical electrodes for detection of neurotransmitters, drugs of abuse and other biomolecules [17].

Emerging areas of application include environmental monitoring of contaminants, food testing for additives/pathogens, and analysis of exosomes for noninvasive detection of diseases. Nanoporous graphenic phases continue to enable new sensing opportunities and promote the development of minimally invasive "liquid biopsy" techniques based on detection of circulating biomolecules [18].

With enormous surface areas, superior biocompatibility and intrinsic conductivity, 3D nanoporous graphene promises to revolutionize the field of biosensing, biodetection and molecular diagnostics. While still developing, these innovative phases could make comprehensive health monitoring, precision medicine and prevention of pandemics more feasible through sensitive and controllable analysis of biomolecules. Nanoporous graphenic separators and sensors will likely transform healthcare and global well-being in the years to come [19].

2.5. Other nanoparticle based stationary phases used in liquid chromatography

Nanoparticles of metals (gold, silver), metal oxides (titania, zirconia), magnetic (iron oxide) and semiconductor materials (quantum dots) have been employed as modifiers to tailor the characteristics of stationary phases for improved separations and sensing [20, 21]. These nanoparticles exhibit properties like catalysis, magnetism, fluorescence that can enhance selectivity, sensitivity and resolution of analyses.

Gold nanoparticles (AuNPs) provide catalytic sites to facilitate chemical conversion or sensing of reactive analytes on the stationary phase surface. AuNP-modified phases show potential for detection of biomolecules involved in diseases, pollutants in environment testing, and trace contamination in food analysis with high sensitivity. Silver nanoparticles exhibit antibacterial activity and have been coupled to stationary phases for rapid removal of pathogens [22].

Magnetic iron oxide nanoparticles allow for magnetic separation, pre-concentration and detection of analytes using magnetic fields. Magnetic stationary phases enable highly sensitive detection of biomolecules, nucleic acids, hormones and drugs in complex matrices like blood, serum, urine, etc. They also provide possibilities of on-line extraction and cleanup using magnetic trapping to achieve superior selectivity and detection limits [23].

Semiconductor quantum dots possess unique optical properties that can be tuned based on their size and composition for development of phases with specific sensing capabilities. Quantum dot-modified stationary phases enable highly sensitive and selective fluorometric/colorimetric detection of pharmaceuticals, toxins, food additives, pathogens, etc. Multiplexing the detection of various analytes is feasible using a combination of quantum dots with different emission wavelengths [24].

Nanoparticle-templated stationary phases have been created by self-assembly or layer-by-layer deposition of nanoparticles on phase surfaces to achieve sophisticated characteristics, responsive microdomains, and high surface area with efficient mass transfer. These versatile phases show promise for applications like drug screening, proteomic profiling, metabolomic analyses and biomedical diagnostics with enhanced resolution and detection of analyte subsets [25].

Continued advancement in engineering nanoparticles with improved biocompatibility, catalytic activity, magnetic properties and sensing functionalities will lead to greater sophistication of nanoparticle-based stationary phases [26]. Their ability to enable highly optimized, responsive and multifaceted detection and separation will likely drive progress in molecular detection, precision medicine and health monitoring through minimally invasive means [27]. Nanoparticle modifiers thus represent crucial enabling technology for next-generation bioanalysis and diagnostics [28].

3. Applications

Nanostructured stationary phases have revolutionized proteomics, enabling discovery of biomarkers, monitoring of disease progression, and development of precision medicine. Nanoporous silica and graphenic phases can isolate, concentrate and detect proteomic analytes with ultrahigh sensitivity from minimally invasive biosamples like serum, plasma, urine, etc. This has made early detection of cancers, monitoring of treatment efficacy, and diagnosis/prognosis of mental health conditions possible using low-abundance protein biomarkers [29].

Nano-LC is crucial for comprehensive profiling of the plasma proteome to identify novel disease biomarkers and gain insights into pathophysiological mechanisms. It facilitates detection of biomarkers even at attomolar concentration levels from limited sample volumes. Sensitive proteomic analyses now enable monitoring of disease relapse, response to therapy, and toxicity due to drug treatments. Nanoporous stationary phases thus promote progress in personalized and precision medicine through proteomic applications [30].

Nanophases are also enabling enhanced origin traceability, quality/authenticity testing and detection of food adulterants. They can isolate, retain and detect subtle compositional differences in food products based on origin, variety, processing technique, additive use, etc [31]. This helps ensure food safety, protect geographical indicators, and combat food fraud. Nano-LC based approaches using nanoporous silica or monolithic stationary phases have achieved ppb-level detection of contaminants, adulterants and trace constituents in food, beverages, herbs and spices [32].

Emerging applications include isolation of extracellular vesicles (exosomes), virus particles and other biocolloids for analysis, detection or other applications. Nanostructured stationary phases can effectively concentrate, isolate and purify these nanoscale structures from complex mixtures. They also promote improved final elution and recovery of intact vesicles/virus particles enabling their use in drug delivery, regenerative medicine, diagnostics, and vaccine development. The comparative advantages and disadvantages of nanostructured stationary phases with different types of analytes are shown in Table 3.

Table 3 Comparative advantages and disadvantages of nanostructured stationary phases with different types of analytes

Sl.No.	Analyte Type	Advantages	Disadvantages
01	Biomacromolecules [25]	✓High separation efficiency ✓High resolution ✓Improved sensitivity ✓Reduced sample size required	×Limited availability of stationary phases ×Cost ×Complexity of synthesis ×Potential degradation of stationary phase
02	Extracellular Vesicles [25]	✓Improved selectivity ✓Enhanced detection sensitivity ✓Reduced sample size required	×Limited availability of stationary phases ×Complexity of synthesis ×Potential degradation of stationary phase

03	Viruses [25]	✓High separation efficiency ✓High resolution ✓Improved sensitivity ✓Reduced sample size required	×Limited availability of stationary phases ×Complexity of synthesis ×Potential degradation of stationary phase
04	Trace Constituents [25]	✓High separation efficiency ✓High resolution ✓Improved sensitivity ✓Reduced sample size required	×Limited availability of stationary phases ×Complexity of synthesis ×Potential degradation of stationary phase

Nanostructured stationary phases have revolutionized biomedical analysis, biodetection, and origin traceability testing through applications like proteomics, food testing, extracellular vesicle isolation, and virus purification. Continued progress in nanomaterial design, phase engineering and integrated techniques will lead to more sophisticated nano-LC based approaches and widespread use of these methodologies in healthcare, diagnostics, and monitoring of health, food and environment quality [28, 32]. Nanostructured stationary phases thus represent a pivotal enabling technology for analytical sciences with tremendous potential impact. The various workflows involved in using nanostructured stationary phases in liquid chromatography are shown in Figure 3.

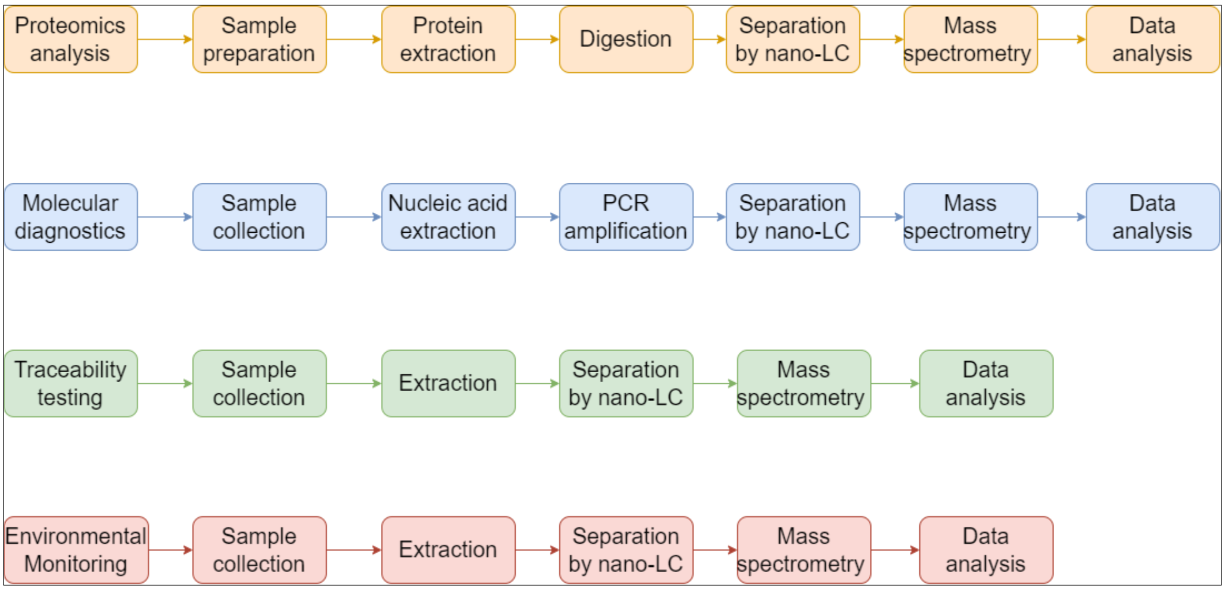

Figure 3 Workflow of a typical experiment using nano-LC approaches for the analysis of proteomics, molecular diagnostics, traceability testing, and environmental monitoring

4. Current Trends and Future Perspectives on Nano-LC Phases

Nanostructured stationary phases have changed liquid chromatography, creating new levels of sensitivity, resolution, applicability and integration with other techniques. Nanoporous silica, graphenic, monolithic and nanoparticle-based phases continue to push the boundaries of biomolecular analysis, molecular diagnostics, food/environment testing and traceability. Some key current and emerging trends include:

4.1. Ultrahigh surface area nanoporous phases

Phases with 3000 m2/g surface area and advanced nanopore architectures for ultrasensitive detection of macromolecules, biomacromolecular complexes and molecular assemblies [2, 3].

4.2. Nanoparticle templating

Layer-by-layer assembly of nanoparticles on phases to create hybrid responsive microdomains and enable sensing, separation, purification and catalysis of samples. Integration of plasmonic, magnetic, quantum dot and other nanoparticles [33] for qualitative and quantitative analysis.

4.3. Nanocage and nanocrystal phases

Metal-organic frameworks, porous carbon nanocages, metal/metal oxide nanocrystals and other engineered nanomaterials as stationary phases with optimized pore size/shape, surface functionality and host-guest interactions [34].

4.4. Monoliths

New monolithic stationary phases including organic, hybrid and biomimetic materials for sample preconcentration, high-throughput separation and integrated reaction-separation. Superior permeability, efficiency and ease of column preparation [35].

4.5. Functionalized 2D materials

Advanced functionalization of graphene, MoS2, WS2 and other 2D nanomaterials to develop highly tailorable stationary phases for bioanalysis, molecular recognition, sensing and separation of small molecules to large biomolecules [36].

4.6. Hyphenated techniques

Tighter integration of nano-LC with MS, NMR, ATR-FTIR and other techniques to gain enhanced molecular-level insights, characterization of unknowns, separate isomers, detect trace components and study complex mixtures in a comprehensive manner [37].

4.7. Microfluidic applications

Use of nanostructured stationary phases in microchips, capillaries and other microfluidic systems for high sensitivity and high-throughput analysis, integration of separation with sample preparation/detection, and development of miniaturized analytical devices [28].

Nanostructured stationary phases will continue to facilitate more sensitive, rapid, highly resolving and multifaceted analysis of biomolecules, contaminants, food/origin constituents and clinical samples. Advanced nanomaterials, nanoparticle engineering, monolith design, surface tailoring and integrated micro-nanofabrication techniques will enable progressively more sophisticated nano-LC based approaches with widespread impact. Nanostructured stationary phases thus represent one of the most exciting and impactful frontiers of chromatography and separation science today with tremendous potential for progress in molecular analysis, healthcare, food safety and environmental monitoring.

5. Conclusion

Nanostructured stationary phases have transformed liquid chromatography, enabling high sensitivity, resolution, and applicability. They have facilitated early disease detection, proteome profiling, food traceability, and environmental monitoring. These materials enable the isolation and analysis of biomolecules, viruses, and trace constituents with high specificity and sensitivity. Nano-LC approaches offer advanced detection, purification, and separation of analytes, with potential for healthcare, food safety, materials analysis, and sustainability. Nanostructured stationary phases are a pivotal frontier in analytical sciences, with immense possibilities for precise, preventive, and personalized healthcare.

Compliance with ethical standards

Acknowledgements

The authors would like to express warmest gratitude to Principal, Dr. K. Ravishankar, Aditya College of Pharmacy.

Disclosure of Conflict of interest

Authors declare no conflict of interest.

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