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### Review



## Green, Portable and Smart HPLC: Sustainable Workflows, Miniaturised Systems and AI-Driven Chromatography

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	<b>Abstract</b>
Published on: 26 Oct 2025	<p>High-performance liquid chromatography (HPLC) remains an indispensable analytical tool in pharmaceutical, environmental, and biochemical sciences. However, conventional HPLC workflows are increasingly challenged by high solvent consumption, energy demands, and environmental footprints. The paradigm of <i>Green, Portable, and Smart HPLC</i> has emerged as a transformative response aligning analytical chemistry with sustainability and digitalisation goals. The integration of <i>green analytical chemistry (GAC) principles, miniaturised architectures, and artificial intelligence (AI)-driven automation</i> has enabled low-solvent, high-efficiency, and intelligent chromatographic operations. This review comprehensively discusses the transition from traditional solvent-intensive systems to eco-efficient, portable, and digitally integrated chromatographic technologies. It critically examines solvent substitution strategies, environmentally benign stationary phases, micro- and nano-HPLC systems, and AI-enhanced method optimisation. Furthermore, the role of <i>Internet of Things (IoT), cloud analytics, and hybrid HPLC-MS platforms</i> in real-time monitoring and field deployment is explored. The review also analyses current regulatory validation frameworks, economic implications, and the evolving vision toward autonomous, self-learning chromatographic systems. Collectively, these innovations signify a paradigm shift toward sustainable and intelligent HPLC, harmonising analytical excellence with environmental stewardship and operational efficiency.</p>
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 <a href="https://creativecommons.org/licenses/by/4.0/">Creative Commons Attribution 4.0 International License.</a>	<b>Keywords:</b> Green chromatography, miniaturised HPLC, solvent-saving strategies, artificial intelligence, sustainable analytical chemistry

## 1.0 INTRODUCTION

High-performance liquid chromatography (HPLC) has long been the cornerstone of analytical separation sciences due to its unparalleled precision, reproducibility, and versatility across pharmaceutical, environmental, and biochemical domains. Traditional HPLC systems, however, rely heavily on high-pressure pumps and solvent-intensive workflows, typically consuming several litres of acetonitrile or methanol per day [1]. This not only elevates operational costs but also contributes significantly to environmental pollution through volatile organic compound (VOC) emissions and solvent waste. In recent years, the intersection of *sustainability*, *miniaturisation*, and *digital intelligence* has redefined the analytical landscape, giving rise to the concept of *Green, Portable, and Smart HPLC*. This emerging paradigm addresses the urgent need to reduce ecological impact while enhancing analytical performance and accessibility. The analytical community has progressively embraced *Green Analytical Chemistry (GAC)* principles, which prioritise environmental protection without compromising analytical quality [2]. Alongside, the miniaturisation of chromatographic systems through *micro-HPLC* and *nano-HPLC* designs has drastically reduced solvent consumption and sample volume requirements [3]. The integration of *AI*, *machine learning*, and *automation* has further augmented method optimisation, predictive analytics, and real-time fault detection in modern HPLC workflows [4]. These converging advancements mark a fundamental shift from conventional bench-top systems to portable, intelligent platforms capable of on-site, sustainable analysis across industries ranging from pharmaceuticals to food safety.

### 1.1 The Concept of Green Chromatography

The concept of *green chromatography* extends from the broader philosophy of sustainable analytical science, focusing on minimizing the ecological impact of separation techniques. Conventional HPLC employs large quantities of organic solvents chiefly acetonitrile and methanol that pose both environmental and health hazards due to their high volatility and toxicity [5]. According to the *Analytical Eco-Scale* and *Green Analytical Procedure Index (GAPI)* frameworks, solvent consumption and waste generation remain among the most critical contributors to the environmental burden of chromatographic methods [6]. Green chromatography seeks to address these challenges through solvent substitution, reduction of mobile-phase volumes, and adoption of biodegradable or less toxic eluents such as ethanol, ethyl lactate, and propylene carbonate [7]. The incorporation of *energy-efficient components*, including variable-speed pumps and low-dead-volume systems, further reduces the carbon footprint of analytical operations. The evolution of sustainability metrics, such as the *Analytical GREEnness Metric Approach (AGREE)*, provides quantitative tools for assessing environmental performance across the entire HPLC workflow from reagent selection to waste disposal [8]. As industries shift toward carbon neutrality and circular economy models, the alignment of HPLC technologies with GAC principles has become both an ethical and operational imperative.

### 1.2 Green Analytical Chemistry (GAC) Principles Applied to HPLC

The twelve principles of GAC, as proposed by Anastas and colleagues, serve as a guiding framework for transforming traditional HPLC methods into environmentally benign processes [9]. In practical terms, these principles translate into solvent reduction, renewable reagent utilisation, energy efficiency, waste minimisation, and miniaturisation. Solvent reduction can be achieved through optimised gradient programming, shortened column lengths, and microbore formats that lower mobile-phase demand without compromising resolution [10]. Similarly, the substitution of toxic solvents with greener alternatives such as ethanol, water–ethanol mixtures, or supercritical CO<sub>2</sub> significantly decreases environmental toxicity [11]. Energy efficiency is equally critical. Modern HPLC instruments are now equipped with temperature-controlled microcolumns and smart standby modes that reduce idle energy consumption by up to 40% [12]. Advances in stationary-phase chemistry, including hybrid organic–silica matrices and monolithic materials, have enhanced separation efficiency while enabling operation at lower flow rates [13]. The combined application of GAC principles in HPLC not only reduces solvent use and operational costs but also aligns analytical laboratories with international sustainability standards such as ISO 14001 and UN Sustainable Development Goals (SDGs) [14]. Collectively, these developments represent a paradigm shift toward a cleaner, safer, and more responsible analytical ecosystem.

### 1.3 Solvent-Saving Strategies and Alternative Mobile Phases

Solvent management remains central to the greening of HPLC systems. Recent research has focused on the replacement of acetonitrile once the dominant HPLC solvent with greener alternatives such as ethanol, propylene carbonate, ionic liquids (ILs), and supercritical fluids [15]. Ethanol, for instance, is biodegradable, inexpensive, and less toxic, making it a viable alternative for reversed-phase separations, though it requires temperature optimisation to maintain viscosity and chromatographic efficiency [16]. Propylene carbonate, a non-volatile and non-flammable solvent, has also gained attention due to its compatibility with polar stationary phases and excellent solvating capacity for diverse analytes [17]. Ionic liquids offer unique tunability, functioning as both

solvents and additives that can modulate selectivity through ion-pair interactions [18]. Their negligible vapour pressure and thermal stability make them particularly suitable for green HPLC applications, though concerns regarding recyclability and cost persist [19]. Supercritical fluid chromatography (SFC), often regarded as an extension of green chromatography, employs supercritical CO<sub>2</sub> as a mobile phase drastically reducing solvent waste while achieving rapid separations [20]. Coupled with ethanol-based modifiers, SFC provides high efficiency and eco-friendly performance, especially in pharmaceutical impurity profiling and chiral separations [21]. Collectively, these solvent-saving strategies represent a crucial step toward solvent-free or near-zero-waste chromatographic workflows envisioned in next-generation green laboratories.

#### 1.4 Miniaturised and Portable HPLC Systems

Technological miniaturisation has emerged as a defining feature of modern analytical instrumentation. Micro-HPLC and nano-HPLC systems utilise capillary columns (inner diameters ranging from 50 to 300 µm) and significantly lower flow rates (in the µL/min range), thereby reducing solvent consumption by over 90% compared to conventional systems [22]. These compact systems achieve superior mass sensitivity and are increasingly coupled with mass spectrometry (MS) for proteomic and metabolomic applications [23]. The development of *lab-on-a-chip (LOC)* and *microfluidic HPLC devices* has further extended chromatographic analysis beyond laboratory walls. By integrating microvalves, pumps, and detectors onto a single silicon or polymer substrate, these portable HPLC units enable in-field and point-of-care (POC) analysis with high precision [24]. Recent prototypes of *field-deployable HPLC systems* have demonstrated robust analytical performance in environmental monitoring, forensic testing, and pharmaceutical quality assurance [25]. For instance, portable HPLC units equipped with battery-powered microfluidic pumps and wireless data transmission can perform rapid pesticide or drug assays in remote locations [26]. Furthermore, 3D printing technologies are increasingly utilised to fabricate custom microfluidic channels and column housings, reducing cost and enabling rapid prototyping of novel designs [27]. As a result, miniaturised and portable HPLC systems are transforming chromatography from a centralised laboratory technique into a versatile, accessible, and sustainable analytical modality.

#### 1.5 Advances in Column Design for Green and Portable HPLC

Column design plays a pivotal role in achieving high separation efficiency while maintaining minimal solvent and energy usage. Over the past decade, the emergence of *superficially porous particles (SPPs)*, *short columns*, and *microbore formats* has revolutionised chromatographic performance under green constraints [28]. SPP-based columns, characterised by a solid core and porous shell, offer enhanced mass transfer and reduced backpressure compared to fully porous materials, allowing high-speed separations with lower flow rates [29]. Similarly, short columns (30–50 mm) minimise analysis time and solvent usage, making them ideal for routine quality control under eco-efficient conditions [30]. Hybrid organic–silica stationary phases and polymer-based monoliths have also advanced the field by providing pH stability, tunable selectivity, and compatibility with aqueous or alcohol-based mobile phases [31]. Microfabricated columns integrated with temperature control units further improve efficiency by reducing solvent viscosity and enhancing diffusion kinetics [32]. The development of *fused-core* and *nano-porous monolithic columns* has enabled robust performance even in portable or miniaturised setups where solvent flow and pressure conditions are inherently constrained [33]. Collectively, innovations in column architecture form the technological backbone of green and portable HPLC systems, driving analytical performance alongside sustainability.

**Table 1: Comparative Evaluation of Conventional and Green HPLC Workflows**

Parameter	Conventional HPLC	Green / Sustainable HPLC	Environmental and Operational Impact
<b>Solvent Type</b>	Acetonitrile, Methanol (toxic, volatile)	Ethanol, Propylene Carbonate, Supercritical CO <sub>2</sub> , Water–Ethanol blends	Reduced toxicity, lower VOC emissions
<b>Solvent Consumption</b>	2–5 L/day	<0.5 L/day (micro-/nano-HPLC)	80–90% solvent savings
<b>Column Format</b>	4.6 mm i.d., 150–250 mm length	1.0–2.1 mm microbore, 30–50 mm short columns	Reduced flow rate and waste
<b>Pump System</b>	High-power binary/quaternary	Energy-efficient micro-pumps, gradient-on-demand	Lower energy footprint
<b>Detection Systems</b>	UV, DAD	Miniaturised UV, MS, or hybrid detectors	Enhanced sensitivity with low sample volumes
<b>Waste Management</b>	Centralized collection and disposal	On-chip recycling, solvent recovery modules	Circular solvent use

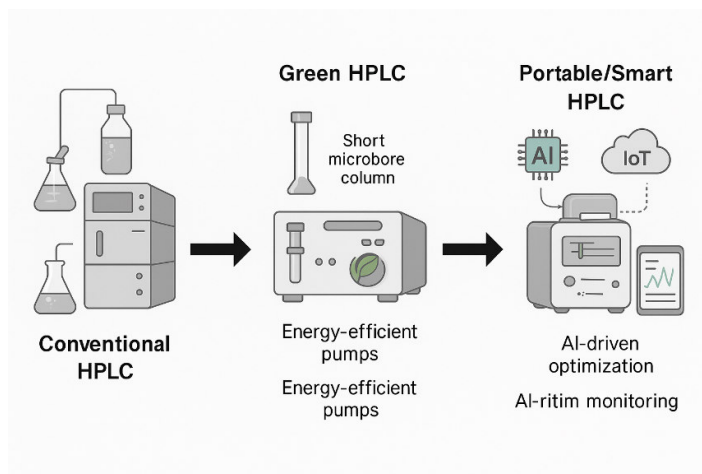
<b>Temperature Control</b>	Fixed oven (high power)	Microcolumn temperature modulation	30–40% lower energy consumption
<b>Automation Level</b>	Manual injection and gradient setup	AI-assisted, automated method optimisation	Faster method development
<b>Footprint</b>	Benchtop (50–70 kg)	Portable (<5 kg, battery powered)	Enables field-deployable operation
<b>Operational Cost</b>	High reagent and energy expenses	Reduced reagent use, lower maintenance	40–60% operational savings

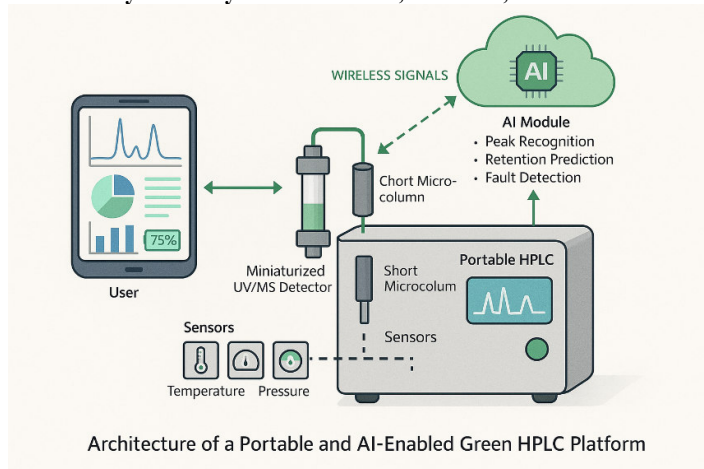
This comparative table highlights the transition from solvent- and energy-intensive HPLC systems to eco-efficient, miniaturised, and automated setups. The implementation of green solvents, short columns, and intelligent control systems substantially reduces the ecological and economic footprint of modern analytical laboratories.

**Table 2: Alternative Green Solvents and Additives for Sustainable HPLC**

Solvent / Additive	Chemical Class	Polarity Index	Boiling Point (°C)	Green Attributes	Typical Applications
Ethanol	Alcohol	5.2	78	Renewable, low toxicity, biodegradable	Reverse-phase separations, pharmaceuticals
Propylene Carbonate	Cyclic carbonate	4.9	240	Non-flammable, low vapour pressure	Polar compound analysis
Ethyl Lactate	Ester	4.3	154	Biodegradable, bio-based	Food and natural product analysis
Supercritical CO <sub>2</sub>	Supercritical fluid	—	31 (critical point)	Solvent-free recovery, recyclable	Chiral separations, drug impurity profiling
Ionic Liquids (e.g., [BMIM][BF <sub>4</sub> ])	Salt (liquid phase)	Variable	>200	Non-volatile, tunable polarity	Ion-pair chromatography, green additives
Water–Ethanol Mixtures	Mixed protic solvent	Variable	78–100	Safe, inexpensive	General purpose HPLC, green gradient systems

Green solvents are chosen based on renewability, toxicity, biodegradability, and energy efficiency. Their selection depends on analyte polarity, detection method, and column compatibility. Ethanol and ethyl lactate have become viable replacements for acetonitrile, while supercritical CO<sub>2</sub> and ionic liquids represent frontier technologies in sustainable chromatographic separations.



**Fig 1: Evolutionary Pathway Toward Green, Portable, and Smart HPLC Systems****Fig 2: Architecture of a Portable and AI-Enabled Green HPLC Platform**

### 1.6 Integration of AI, Machine Learning, and Automation in HPLC

Artificial intelligence (AI) and machine learning (ML) have become powerful tools for enhancing chromatographic performance, automating method development, and ensuring data integrity in analytical workflows. Traditional HPLC method optimisation involves trial-and-error processes that are both time-consuming and resource-intensive. AI-based algorithms, particularly supervised learning models and artificial neural networks (ANNs), have enabled predictive modelling of chromatographic parameters such as retention time, resolution, and peak asymmetry with remarkable precision [34]. ML-driven approaches like random forests, support vector machines (SVMs), and gradient boosting can analyse historical datasets to identify optimal gradient compositions, flow rates, and column chemistries with minimal solvent consumption [35]. Automation of data processing through computer vision and deep learning enhances peak detection, baseline correction, and deconvolution, thus minimising manual intervention [36]. Reinforcement learning models, which continuously adapt based on analytical feedback, are now being developed for autonomous chromatographic control [37]. Additionally, AI has facilitated fault detection and predictive maintenance by analysing sensor data in real-time, reducing downtime and increasing system reliability [38]. Cloud-integrated AI frameworks are also capable of simultaneously analysing large-scale datasets from multiple instruments, allowing standardised method validation across laboratories [39]. Collectively, these developments signify the transition from reactive to predictive and adaptive chromatography ushering in a new era of smart analytical science.

### 1.7 Internet-of-Things (IoT) and Cloud-Enabled Chromatography Platforms

The integration of Internet-of-Things (IoT) technologies into chromatographic systems has revolutionised remote control, real-time monitoring, and performance diagnostics. IoT-enabled HPLC instruments employ embedded sensors and wireless communication modules to transmit operational data such as flow rate, temperature, and pressure to cloud-based dashboards [40]. These systems allow remote access and control, facilitating analytical continuity even in decentralised or field-based environments. For instance, IoT-based chromatography networks can automatically alert operators about deviations in column backpressure or pump performance, enabling timely interventions that prevent equipment failure [41]. Cloud connectivity provides additional advantages by centralising chromatographic data for collaborative analysis, quality assurance, and compliance tracking [42]. The convergence of IoT and AI technologies further enhances decision-making through integrated dashboards that display sustainability metrics such as solvent consumption and carbon emissions [43]. Blockchain-based data management frameworks are being explored for secure traceability of analytical data in pharmaceutical quality control [44]. Such digital ecosystems enable laboratories to transition from isolated analytical workstations to interconnected, adaptive networks aligned with Industry 4.0 paradigms. The combination of IoT and AI effectively transforms HPLC into a self-aware analytical entity capable of optimising itself within dynamic laboratory environments.

The evolution of green and portable HPLC systems has facilitated the integration of hybrid analytical platforms that combine chromatographic separation with complementary spectroscopic and mass spectrometric

detection. HPLC–MS coupling remains the gold standard for structural elucidation, impurity profiling, and bioanalytical quantification, but recent innovations have miniaturised these systems for portable deployment [45]. Compact ion-trap and time-of-flight (TOF) mass spectrometers are now being integrated into micro-HPLC units, enabling field-based identification of environmental pollutants, drug residues, and metabolites with high sensitivity [46]. Similarly, coupling portable HPLC with spectroscopic modules such as Fourier-transform infrared (FTIR) and Raman detectors enhances chemical specificity while maintaining eco-friendly operation [47]. These multimodal devices operate with minimal sample preparation, making them ideal for on-site food safety, forensic, and clinical diagnostics [48]. The development of *hyphenated microfluidic devices* which combine separation, detection, and data analytics within a single chip has further pushed the frontier of analytical portability [49]. These hybrid systems exemplify how analytical chemistry is converging toward compact, multi-sensor platforms capable of delivering high-throughput, green, and intelligent diagnostics outside traditional laboratory boundaries.

### 1.9 Application Domains of Green and Smart HPLC

Green and intelligent HPLC systems are increasingly being adopted across multiple domains that require high analytical precision combined with environmental responsibility. In *pharmaceutical analysis*, solvent-free or low-solvent workflows are being employed for quality control of active pharmaceutical ingredients (APIs), stability testing, and bioequivalence studies [50]. Miniaturised systems are particularly advantageous in *clinical diagnostics*, where they enable point-of-care detection of biomarkers and therapeutic drug monitoring using microlitre sample volumes [51]. In *environmental monitoring*, portable HPLC units have facilitated rapid field analysis of heavy metals, pesticides, and emerging contaminants, significantly reducing sample transport and storage issues [52]. The *food and beverage industry* benefits from portable and green HPLC by enabling on-site testing for contaminants, additives, and nutritional components, ensuring faster regulatory compliance [53]. Similarly, *forensic and toxicological applications* exploit miniaturised HPLC–MS systems for in-situ detection of narcotics, explosives, and poisons with real-time data transmission [54]. The capacity to integrate eco-friendly solvents and automated data processing aligns these analytical domains with sustainable practices and global environmental standards, while also improving throughput and decision-making accuracy.

### 1.10 Regulatory Perspectives and Validation of Green HPLC Methods

As HPLC methodologies evolve toward sustainability and automation, regulatory frameworks must adapt to accommodate new operational paradigms. International Council for Harmonisation (ICH) guidelines, particularly ICH Q2(R2) and Q14, emphasise method validation through specificity, precision, linearity, accuracy, and robustness parameters that remain essential for green and miniaturised systems [55]. However, novel solvent systems and portable architectures introduce unique challenges in validation, such as ensuring reproducibility under variable temperature and flow conditions [56]. Agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have begun to acknowledge the role of alternative solvents and microfluidic devices in analytical quality assurance [57]. System suitability testing (SST) has also evolved to incorporate sustainability parameters, such as solvent recovery efficiency and energy consumption per analysis [58]. The *Analytical Quality by Design (AQbD)* framework has proven particularly relevant for green HPLC, as it integrates method robustness, risk assessment, and process analytical technology (PAT) principles for continuous method optimisation [59]. While standardisation remains an ongoing challenge, harmonisation efforts across ASTM, ISO, and USP are expected to formalise sustainability metrics and digital traceability within regulatory validation protocols by the end of the decade [60].

### 1.11 Economic and Operational Advantages of Sustainable and Portable HPLC

The economic case for adopting green and portable HPLC technologies extends beyond environmental ethics, offering tangible benefits in cost efficiency, resource optimisation, and operational flexibility. Solvent expenditure constitutes up to 40% of operational costs in conventional HPLC laboratories, which can be reduced by over 80% through microbore and solvent-recycling designs [61]. Energy-efficient pumps, compact detectors, and battery-powered modules further lower power consumption, resulting in substantial long-term savings [62]. The smaller instrument footprint also reduces spatial requirements, making such systems ideal for decentralised or resource-limited analytical settings [63]. Operational efficiency is enhanced through automation and AI integration, which minimise human error, improve reproducibility, and reduce the time-to-result [64]. Decentralised analytical capacity also reduces logistical costs associated with sample transport and cold-chain management, particularly in pharmaceutical and environmental applications [65]. The cumulative benefits lower reagent use, reduced maintenance, shorter analysis times, and portable field deployment translate into high return on investment (ROI) and accelerated adoption in both industrial and academic sectors [66].

### 1.12 Limitations, Challenges, and Standardisation Needs

Despite its numerous advantages, the transition toward green and smart HPLC is accompanied by significant technical and infrastructural challenges. Miniaturised systems often exhibit sensitivity to fluctuations

in temperature, pressure, and micro-pump calibration, which may affect reproducibility [67]. The limited availability of compatible green solvents and stationary-phase materials suitable for all analyte classes remains a constraint [68]. Additionally, the development of reliable, miniaturised detectors that maintain adequate sensitivity and signal-to-noise ratio is still ongoing [69]. Another critical limitation lies in the absence of universally accepted *green performance metrics* for HPLC. While tools such as GAPI and AGREE provide environmental scoring frameworks, their integration into regulatory and industrial practice remains limited [70]. The high cost of advanced AI and IoT-enabled systems also restricts their adoption in smaller laboratories. Standardisation efforts must therefore focus on defining *method greenness indices*, *digital traceability standards*, and *cross-platform calibration protocols* to ensure consistency and global interoperability [71]. Addressing these challenges will be essential for scaling sustainable HPLC practices from research prototypes to widespread industrial implementation.

### 1.13 Future Outlook: Toward Autonomous and Self-Learning Chromatography Systems

The future of HPLC lies in full automation, self-optimisation, and zero-waste operation through the convergence of AI, robotics, and sustainable engineering. *Autonomous chromatography systems* capable of learning from experimental outcomes and dynamically adjusting gradient programs are already under development [72]. These systems employ *digital twins* virtual replicas of chromatographic processes that simulate and optimise parameters in silico before real-world application [73]. Integration with robotic sample handling and AI-assisted solvent recycling is expected to create self-sustaining analytical loops that operate with minimal human oversight [74]. By 2030, the vision for *net-zero chromatography* involves instruments constructed from recyclable materials, operating with renewable energy, and utilising solvent-free or water-based eluents [75]. The fusion of 3D printing, microfluidics, and generative design will likely yield customisable column architectures tailored to specific analytes or environmental conditions [76]. Furthermore, integration with cloud-based *laboratory information management systems (LIMS)* and *blockchain authentication* will ensure data transparency, reproducibility, and regulatory compliance. Collectively, these advancements point toward an era of sustainable, intelligent, and autonomous analytical chemistry that harmonises precision with planetary responsibility.

### 1.14 CONCLUSION

Green, portable, and smart HPLC technologies represent the vanguard of analytical evolution, transforming a traditionally resource-intensive discipline into one defined by sustainability, efficiency, and intelligence. By integrating green analytical chemistry principles, solvent-saving innovations, miniaturised architectures, and AI-driven automation, modern HPLC systems achieve superior analytical precision while reducing environmental impact. The adoption of IoT connectivity, hybrid analytical platforms, and cloud-based data ecosystems further extends the reach of chromatography beyond laboratory confines. Regulatory adaptation and standardisation will remain pivotal in mainstreaming these innovations, ensuring quality and compliance. As we progress toward 2030, the synthesis of automation, eco-design, and digital intelligence will yield autonomous, zero-waste chromatographic ecosystems that embody the true essence of sustainable analytical science.

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