

Green Chromatography: A Comprehensive Review of Eco-Friendly Mobile Phases, Column Technologies, and Sustainability Metrics in Pharmaceutical Quality Control

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Abstract

High-Performance Liquid Chromatography (HPLC) and its ultra-high-performance variant (UHPLC) remain the dominant analytical platforms for identity, assay, related-substance, and stability-indicating testing in pharmaceutical quality control (QC), a position reinforced by both the United States Pharmacopoeia and the European Pharmacopoeia. This dominance carries a significant environmental cost, driven largely by the volume and toxicity of solvents consumed in reversed-phase HPLC (RP-HPLC). This review synthesises the current literature on the transition toward eco-friendly mobile phases and sustainable column technologies within standard pharmaceutical QC workflows. Solvent-substitution strategies—ethanol-water systems, propylene-glycol-modified phases, propylene carbonate, superheated water, and other bio-derived modifiers—are evaluated alongside instrumental and stationary-phase innovations such as sub-2 μm and core-shell particles, monolithic columns, narrow-bore formats, and the resurgence of supercritical Fluid Chromatography (SFC). The review also examines how greenness is now quantified through a rapidly maturing family of metrics—NEMI, the Analytical Eco-Scale, GAPI and its variants (Complex GAPI, MoGAPI), AGREE and AGREEprep, and newer practicality- and carbon-focused tools (BAGI, CaFRI, AGSA, GEMAM) — converging under the broader concept of White Analytical Chemistry, which balances environmental impact against analytical performance and practicality. Regulatory alignment with ICH Q14 and ICH Q2(R2) is discussed, together with an illustrative case comparison and the persistent gap between green mobile-phase chemistry and stationary-phase compatibility. The review concludes that eco-friendly chromatography in pharmaceutical QC is no longer an isolated academic exercise but an increasingly important consideration in analytical method development, and outlines priority areas—robust green-compatible stationary phases, automation-linked greenness scoring, and harmonized regulatory guidance—needed to consolidate this shift into routine practice.

Keywords: Green analytical chemistry; Green chromatography; Eco-friendly mobile phase; RP-HPLC; AGREE; GAPI; BAGI; Supercritical fluid chromatography; Pharmaceutical quality control; Sustainable stationary phases.

INTRODUCTION

High-performance liquid chromatography (HPLC) and UHPLC remain the dominant analytical platforms across the pharmaceutical QC landscape. This dominance comes at an environmental cost: a conventional RP-HPLC assay operated at 1.0–1.5 mL/min for 30–45 minutes consumes approximately 30–67.5 mL of total mobile phase per injection; the organic-solvent fraction depends on mobile-phase composition (Table 2). Across a standard QC batch-release schedule of roughly 20–30 injections, a single instrument can accumulate substantial mobile-phase waste over a working day, and disposal of solvent-containing waste requires appropriate hazardous-waste management. Multiplied across thousands of QC

laboratories worldwide, routine testing therefore carries a substantial cumulative footprint in hazardous waste, occupational exposure, and disposal cost.

Green analytical chemistry (GAC) emerged in the early 2000s as an extension of the twelve principles of green chemistry into the analytical domain, aiming to reduce

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the environmental and health footprint of measurement science without compromising data quality, accuracy, or regulatory compliance. Over the past decade this movement has moved from theoretical discussion to practical implementation in pharmaceutical method development, driven by regulatory signals (notably the lifecycle and enhanced-approach philosophy embedded in ICH Q14 [21]), corporate sustainability commitments, escalating solvent and hazardous-waste disposal costs, and a growing body of peer-reviewed literature showing that greener methods can meet, and sometimes exceed, the performance of conventional approaches.

This review focuses on three interconnected levers of green chromatography in standard pharmaceutical QC: the reformulation of mobile phases toward less hazardous solvent systems; the parallel evolution of column and stationary-phase technologies that make such reformulation practically achievable without sacrificing resolution or robustness; and the maturing ecosystem of greenness-assessment tools that now accompanies method validation reporting. It closes with the regulatory and practical barriers that continue to slow full adoption.

PRINCIPLES OF GREEN ANALYTICAL CHEMISTRY

Green analytical chemistry is typically framed around twelve guiding principles, often summarized by the mnemonic SIGNIFICANCE: direct analysis without sample treatment where feasible; minimal sample and reagent quantities; safer solvents and reagents; automation and miniaturization; avoidance of derivatisation where possible; minimisation of waste with appropriate treatment; multi-analyte methods in place of separate

single-analyte procedures; reduced energy consumption; reagents from renewable sources; elimination or substitution of toxic reagents; enhanced operator safety; and preference for green or bio-based solvents. Within chromatography specifically, these principles translate into two dominant, complementary strategies: reducing the intrinsic hazard of the solvents used in the mobile phase, and reducing the absolute volume of solvent consumed per analysis through smaller-format columns, miniaturised instrumentation, and faster separations. Both strategies are explored below.

ECO-FRIENDLY MOBILE PHASES IN PHARMACEUTICAL HPLC

Solvent Substitution: Moving Away from Acetonitrile and Methanol

Acetonitrile and methanol remain the default organic modifiers in reversed-phase separations because of their favourable UV transparency, elution strength, and compatibility with mass-spectrometric detection. Both carry meaningful hazard profiles: acetonitrile is a petrochemical derivative associated with periodic global supply shortages, while methanol is flammable, neurotoxic, and volatile [11]. A substantial body of work has focused on identifying substitute solvents whose polarity, viscosity, UV cut-off, and elution strength closely approximate the traditional modifiers while presenting a more favourable safety and sustainability profile — chiefly ethanol, propylene glycol, propylene carbonate, and, for specific applications, superheated water. Table 1 summarises the physicochemical trade-offs of the main candidates.

Table 1. Comparative physicochemical properties and QC challenges of conventional and green mobile-phase solvents.

Solvent	Viscosity at 25°C (cP)	Elution Strength vs. ACN	Primary QC Challenges
Acetonitrile (ACN)	0.37	Benchmark (1.0)	High toxicity; costly incineration/disposal
Methanol (MeOH)	0.55	Method-dependent	Volatility; higher backpressure than ACN
Ethanol (EtOH)	1.07	Method-dependent	High system backpressure; requires UHPLC or elevated column temperature
Propylene Glycol	≈42 (neat, 25°C)	Lower; used dilute (≈25% v/v)	High neat viscosity; used as a minor aqueous component, not a bulk modifier
Propylene Carbonate	2.50	Moderate	Limited UV window at low wavelengths
Superheated Water	Decreases sharply with temperature	Temperature-dependent	Risk of thermal degradation of analyte/column at 100–200°C

Ethanol-Water Mobile Phase Systems

Ethanol is renewable, comparatively low in toxicity, and readily available from agricultural feedstocks. Method-development work using ethanol-water mobile phases for compounds such as famotidine, paracetamol, and thiocolchicoside has demonstrated regulatory-compliant

assay performance without the resolution or sensitivity losses that might be expected from such a substitution, provided gradient conditions, column chemistry, and detection wavelength are re-optimised around ethanol's distinct UV cut-off and viscosity relative to acetonitrile [11]. The principal practical constraint is ethanol's higher viscosity (1.07 cP at 25°C versus 0.37 cP for ACN), which

raises system backpressure and can necessitate lower flow rates, larger-porosity particles, or elevated column temperature (40–60°C) to remain within instrument pressure limits.

Propylene Glycol and Other Bio-Based Modifiers

Propylene glycol (PG) has recently been demonstrated as a low-toxicity, pharmaceutically familiar mobile-phase modifier suitable for the assay of common analgesic combinations such as acetaminophen and caffeine: a PG-containing aqueous mobile phases have been investigated for acetaminophen analysis; the specific conditions and impurity-separation claims should be checked against the cited experimental study [13]. Although PG is used as a pharmaceutical excipient, analysts and quality units already possess extensive familiarity with its handling and safety profile, lowering the institutional barrier to adoption. The cited work describes a teaching-oriented application; routine industrial QC adoption should not be inferred without further evidence [13].

Propylene carbonate offers high thermal stability and low toxicity; when blended with a small proportion of ethanol it provides adequate elution strength for hydrophobic compounds and has been demonstrated as a viable acetonitrile replacement in pharmaceutical RP-HPLC [12].

Ionic Liquids and Deep Eutectic Solvents

Room-temperature ionic liquids and deep eutectic solvents (DES), formed from combinations of hydrogen-bond donors and acceptors such as choline chloride with urea or various polyols, have been explored as mobile-phase additives and, in some cases, as bulk mobile-phase components. Their negligible vapour pressure eliminates volatile organic emission during use, and their tunable polarity allows some control over selectivity unavailable with conventional solvents. Adoption in routine pharmaceutical QC remains limited relative to ethanol- or PG-based systems, largely because of higher viscosity, variable UV-detection compatibility at low wavelengths, and the relative novelty of validated QC methods built around them, but they remain an active area of green mobile-phase research.

Subcritical and Superheated Water Chromatography

Using water as the sole mobile-phase component by raising its temperature (typically 100–200°C under pressure) drastically reduces its dielectric constant, mimicking the polarity of organic solvents such as methanol or acetonitrile [15]. This avoids organic modifiers in the mobile phase and minimises chemical purchase cost, but is not suitable for thermally labile substances or impurities susceptible to hydrolysis at elevated temperature, and requires thermally stable stationary phases and dedicated heating hardware.

Supercritical Fluid Chromatography (SFC)

SFC, which uses carbon dioxide above its critical point as the primary mobile phase — typically modified with a polar co-solvent such as methanol or ethanol — has experienced a marked resurgence in pharmaceutical applications since the 2010s. Because CO₂ is the dominant mobile-phase component, SFC dramatically reduces organic-solvent consumption relative to conventional HPLC, while its low viscosity and high diffusivity enable faster separations with comparable or superior resolution, allowing linear velocities 3- to 5-fold higher than liquid mobile phases without sacrificing resolution [18]. SFC has found particular traction in chiral separations and impurity profiling; head-to-head comparisons against normal-phase liquid chromatography for chiral drugs such as itraconazole show that SFC methods can achieve regulatory-compliant resolution more rapidly and with substantially improved greenness scores [20]. Detector compatibility with variable pressure/temperature conditions and the relative unfamiliarity of SFC instrumentation in many routine QC laboratories remain adoption barriers [19].

GREEN COLUMN TECHNOLOGIES

Reducing solvent waste can also be achieved by altering hardware dimensions and particle architecture to lower flow rate and run duration. Table 2 contrasts a conventional HPLC configuration with a greened UHPLC/core-shell configuration for the same separation.

Sub-2 µm and Superficially Porous (Core-Shell) Particles

Table 2. Representative parameter shift from conventional HPLC to a greened UHPLC/core-shell configuration.

Parameter	Conventional HPLC	Green UHPLC / Core-Shell
Column dimensions	250 mm × 4.6 mm i.d.	50 mm × 2.1 mm i.d.
Particle size	5.0 µm (fully porous)	1.8 µm (sub-2 FPP) or 1.6–2.7 µm (core-shell)
Typical flow rate	1.0–1.5 mL/min	0.2–0.4 mL/min
Typical run time	30–45 min	3–6 min
Total mobile phase per run	30–67.5 mL	0.6–2.4 mL

The shift from fully porous 5 μm particles to sub-2 μm fully porous particles and to superficially porous (core-shell) particles of 1.6–2.7 μm has been one of the most consequential developments in modern liquid chromatography, underpinning the transition from HPLC to UHPLC [16,17]. These particle formats deliver substantially higher chromatographic efficiency per unit column length, allowing shorter columns and faster gradients to achieve resolution equivalent to, or better than, longer columns packed with conventional particles. Core-shell particles in particular achieve efficiency comparable to sub-2 μm fully porous particles at markedly lower operating backpressure — typically 40–50% lower for equivalent efficiency — allowing existing conventional HPLC systems in standard QC labs to run greener, high-efficiency methods without total instrument replacement [16]. The direct green benefit is a proportional reduction in mobile-phase volume and analysis time per sample, which compounds meaningfully across the high sample throughput typical of pharmaceutical QC laboratories.

Monolithic Columns

Silica- or polymer-based monolithic columns, characterised by a continuous bed of interconnected macropores and mesopores rather than packed particles, permit operation at substantially higher flow rates for a given backpressure than particle-packed columns. This allows faster separations without the pressure penalty associated with sub-2 μm particles, and can be leveraged either for faster throughput or for operation with higher-viscosity green solvents such as ethanol, partially offsetting the backpressure disadvantage discussed in Section 3.2.

Narrow-Bore and Micro-Bore Column Formats

Reducing column internal diameter from the conventional 4.6 mm to narrow-bore (2.1 mm) or micro-bore (1 mm or below) formats reduces mobile-phase consumption roughly in proportion to the square of the diameter ratio, independent of particle chemistry. Scaling a method from a

4.6 mm i.d. column to a 2.1 mm i.d. column decreases flow rate from approximately 1.0 mL/min to roughly 0.21 mL/min, reducing solvent use by approximately 79% per run while maintaining identical linear velocity. This is among the most direct and broadly applicable greening levers available to a QC laboratory, since narrow-bore columns are widely available as drop-in replacements for many validated method platforms, subject to re-verification of system dwell volume and detector cell compatibility.

Miniaturisation, Microfluidics, and Emerging Formats

Beyond conventional column-format changes, miniaturised liquid chromatography, microfluidic chip-based separation platforms, and two-dimensional liquid chromatography (2D-LC) are being explored as further extensions of the same principle, achieving the resolution required for complex pharmaceutical matrices while operating at nanoliter-to-microliter mobile-phase volumes. These formats remain more common in research and biopharmaceutical characterisation than in routine small-molecule QC at present, but represent a plausible trajectory for further volume reduction as instrumentation matures and cost barriers fall. A persistent theme in the column-technology literature is that stationary-phase greening has not always kept pace with mobile-phase greening: continued development of phases explicitly engineered for compatibility with high-ethanol or other green mobile-phase systems remains a priority.

Assessing Greenness: Metrics and Assessment Tools

A defining feature of the current phase of GAC is the shift from qualitative claims of “eco-friendliness” to quantitative, standardised, and reproducible greenness scoring, sometimes reported alongside conventional validation parameters (specificity, linearity, accuracy, precision, robustness) in pharmaceutical method papers. Table 3 summarises the tools discussed below.

Table 3. Comparative summary of green analytical chemistry metrics and assessment tools.

Tool	Year	Scope / Output	Notes
NEMI	Early 2000s (verify original publication)	Flag-based screen (PBT, hazard, corrosivity, waste)	Simple pass/fail flags; not granular enough for fine comparisons
Analytical Eco-Scale	2012	Penalty-point score (100 – penalties)	Quick numeric score; limited step-by-step resolution
GAPI	2018 [2]	5-pentagram pictogram, whole workflow	Covers sample collection through determination; widely adopted
Complex GAPI	2021 [3]	GAPI + pre-analysis process fields	Adds upstream reagent/material manufacturing impact

AGREE	2020 [1]	12-segment circular pictogram, 0–1 score	Single-number, software-automated; widely used in RP-HPLC studies
AGREEprep	2022 [5]	0–1 score for sample preparation only	Companion to AGREE focused on the prep step
MoGAPI	2024 [4]	GAPI + Eco-Scale hybrid, single total score	Adds a comparable numeric score to GAPI's pictogram
BAGI	2023 [6]	Practicality score (throughput, instrumentation, ease)	Complements greenness tools; core of “White Analytical Chemistry”
CaFRI	2025 [7]	Carbon-footprint reduction index	Focused specifically on laboratory carbon footprint
AGSA	2025 [8]	Star-area graphical score, 12 GAC principles	Visual area-based alternative to AGREE's circular format
GEMAM	2025 [9]	0–10 score across 12 GAC + 10 sample-prep factors	Broadest single-metric scope proposed to date

Early Metrics: NEMI and the Analytical Eco-Scale

The National Environmental Methods Index (NEMI) and the Analytical Eco-Scale were among the earliest tools proposed for greenness evaluation, offering relatively simple flag- or penalty-point-based systems that capture major hazard, waste, and energy considerations. While useful for quick screening, both are now less detailed than newer metrics for comparisons involving multiple environmental dimensions.

GAPI and Its Extensions

GAPI, introduced in 2018, evaluates the entire analytical workflow — from sample collection through preparation to final determination — using a pictogram of five linked pentagrams, each colored green, yellow, or red to indicate low, medium, or high environmental impact at that stage [2]. Its comprehensiveness and intuitive visual format have made it one of the most widely applied greenness tools in the pharmaceutical analytical literature. It has since been extended through Complex GAPI, which adds finer granularity for pre-analysis and sample-preparation steps [3], and Modified GAPI (MoGAPI), introduced in 2024 to add a single comparable total score alongside the pictogram [4].

AGREE: The Analytical GREENness Metric

Introduced in 2020, AGREE represents a method as a circular pictogram divided into twelve segments, one for each GAC principle, individually scored on a continuous 0–1 scale and averaged into a single overall greenness score with an accompanying color gradient [1]. Its combination of comprehensiveness, ease of automated calculation via freely available software, and single-number comparability has driven its adoption as a frequently used assessment approach in newer RP-HPLC and UHPLC method-validation

publications. A companion tool, AGREEprep, applies the same logic specifically to the sample-preparation step [5].

BAGI and the White Analytical Chemistry Concept

Because a method can score well on greenness while being impractical for routine use (for example, requiring instrumentation unavailable in most QC laboratories), the Blue Applicability Grade Index (BAGI) was introduced in 2023 as a complementary metric evaluating ten practicality attributes: type of analysis, number of analytes determined simultaneously, sample throughput, reagent and material type, required instrumentation, degree of automation, and related factors [6]. The combined consideration of greenness (AGREE/GAPI), practicality (BAGI), and conventional analytical performance is increasingly discussed under the umbrella term White Analytical Chemistry — a deliberate move away from optimising greenness in isolation toward a balanced method that is simultaneously green, practical, and analytically sound.

Emerging Composite Metrics

More recent tools attempt to combine the twelve GAC principles with additional lifecycle or sample-preparation factors into unified scores. The Carbon Footprint Reduction Index (CaFRI) provides a software-supported estimate of a laboratory's carbon footprint reduction [7]; the Analytical Green Star Area (AGSA) offers a star-area graphical alternative to AGREE's circular pictogram, scored across the same twelve GAC principles [8]; and the Greenness Evaluation Metric for Analytical Methods (GEMAM) combines the twelve GAC principles with ten green sample-preparation factors into a single 0–10 scale [9]. A recent survey catalogued sixteen distinct GAC metrics in circulation [10], and a recurring theme in the comparative literature is the call for a single harmonised

framework that captures energy use, waste type and volume, and reagent hazard without the redundancy of maintaining multiple parallel scoring systems.

REGULATORY AND PHARMACOPOEIAL PERSPECTIVE

ICH Q14 formalises a lifecycle and enhanced-approach philosophy to analytical procedure development that, while not mandating specific green-chemistry criteria, creates a structural opening for sustainability considerations to be documented as part of a method's design space and control strategy [21]. Compendial procedures and allowable adjustments depend on the applicable pharmacopoeia and monograph. Changes outside permitted adjustments may require additional validation and, where applicable,

regulatory approval. ICH Q2(R2) [22] provides principles for demonstrating that a revised analytical procedure is fit for its intended purpose; greenness itself is not a requirement of these guidelines. Table 4 outlines the resulting workflow linking greenness criteria to formal method lifecycle management.

This creates both an opportunity and a limitation: laboratories are free to adopt greener methods where validated equivalence can be shown, but in the absence of a regulatory mandate, the pace of adoption in routine industrial QC continues to lag behind the pace of academic publication. Where method changes alter solvent identity or column internal diameter beyond allowable compendial adjustment limits, the extent of additional validation and any regulatory submission should be determined through a

Table 4. Regulatory workflow integrating green criteria into Analytical Quality by Design (AQbD).

Stage	Key Activities
1. Analytical Target Profile (ATP)	Define target analytes, required accuracy/precision, and green criteria (AGREE/GAPI score) as part of the method's intended purpose (ICH Q14).
2. Method Development via AQbD	Establish a Method Operable Design Region (MODR) using Design of Experiments (DoE); evaluate green solvent selection and column geometry within that design space.
3. Method Validation (ICH Q2(R2))	Confirm specificity, linearity, range, accuracy, precision, and limit of detection/quantitation for the greened procedure.
4. Regulatory Submission & Re-Validation	Manage post-approval changes (e.g., SUPAC) or variation filings; re-validate where solvent identity or column i.d. changes exceed allowable compendial adjustments.

documented, risk-based assessment before implementation [22].

APPLICATIONS IN PHARMACEUTICAL QUALITY CONTROL

Assay and Related-Substance (Impurity) Testing

Ethanol- and propylene-glycol-based RP-HPLC methods have been validated for assay and related-substance determination of both single-drug and multi-drug formulations, generally following ICH Q2(R1)/Q2(R2) validation frameworks for specificity, linearity, accuracy, precision, and robustness, with an added greenness-scoring section reporting AGREE or GAPI outcomes alongside the conventional validation summary [11,13].

Chiral Separations

SFC has demonstrated particular value in chiral quality control. A head-to-head validation of SFC against normal-phase LC for the four stereoisomers of itraconazole showed both methods meeting the USP-recommended resolution of at least 1.5 between adjacent stereoisomer peaks, with SFC achieving separation more rapidly and with a substantially improved analytical-method greenness score [20], positioning SFC as a credible platform for QC

laboratories handling chiral drug substances.

Multi-Analyte and Combination Formulations

"White" HPLC methods explicitly balancing greenness, cost, and analytical performance have been validated for simultaneous multi-component formulations — for example, an eco-friendly stability-indicating method for combined glucosamine, chondroitin, and ascorbic acid in bulk and caplet formulations [14] — demonstrating that eco-conscious method design applies not only to single active pharmaceutical ingredients but also to nutraceutical and multi-ingredient QC contexts where several analytes of differing polarity must be resolved simultaneously.

Illustrative Case Study: Greening a Paracetamol (Acetaminophen) Assay

To illustrate how the strategies in Sections 3–4 combine in practice, Table 5 presents a representative, literature-informed comparison between a conventional ACN-based RP-HPLC assay for paracetamol and a greened equivalent using an ethanol mobile phase on a core-shell column. The figures are illustrative engineering estimates intended to show the magnitude of achievable improvement; they should be confirmed experimentally before being cited as validated method performance.

The comparison illustrates the cumulative effect of switching the organic modifier from acetonitrile to ethanol, which removes the most hazardous waste stream, combined with a shorter core-shell column at elevated temperature, which recovers the throughput and resolution that the higher-viscosity solvent would otherwise cost. The estimated reduction in solvent consumption suggests

a potentially greener procedure; a defensible AGREE score requires a complete method inventory although chromatographic selectivity and method performance would need experimental confirmation.

CHALLENGES AND LIMITATIONS

Table 5. Illustrative comparison of a conventional and a greened RP-HPLC assay for paracetamol.

Parameter	Conventional Method (ACN-based)	Greened Method (Ethanol / Core-Shell)
Column	250 mm × 4.6 mm, 5 µm C18	100 mm × 3.0 mm, 2.7 µm core-shell C18
Mobile phase	Acetonitrile : phosphate buffer (pH 4.5), 30:70 v/v	Ethanol : acetate buffer (pH 4.5), 22:78 v/v, column at 45°C
Flow rate	1.5 mL/min	0.6 mL/min
Run time	≈10 min	≈4 min
Organic solvent used per injection	4.5 mL ACN (1.5 mL/min × 10 min × 0.30)	0.53 mL ethanol (0.6 mL/min × 4 min × 0.22)
AGREE score	Not calculated; full method inventory needed	Not calculated; full method inventory needed

- Higher viscosity of several green solvents (notably ethanol and ionic liquids) increases system backpressure, sometimes requiring hardware or column-format changes to remain within operating limits.
- Column and stationary-phase chemistries explicitly optimised for compatibility with high-ethanol or other green mobile phases remain less mature and less commercially widespread than conventional acetonitrile/methanol-optimised phases.
- The proliferation of greenness metrics (Table 3) complicates cross-study and cross-laboratory comparison, despite AGREE's emergence as a widely used tool.
- Method revalidation costs and regulatory change-control burden associated with converting an already-approved, validated QC method to a greener alternative can be substantial, slowing adoption in already-marketed products.
- SFC and other emerging green platforms require specialised instrumentation and analyst training not yet universally available in routine QC laboratories, particularly in resource-limited settings.
- Green solvent substitution can shift, rather than eliminate, certain UV-detection or MS-compatibility constraints, requiring re-optimisation of detection wavelength or ionisation conditions.

FUTURE PERSPECTIVES

Several trajectories are likely to shape the next phase of

green chromatography in pharmaceutical QC. Continued development of stationary phases explicitly engineered for compatibility with ethanol-rich and other green mobile phases should narrow the current gap between mobile-phase and column-side greening. Integration of greenness-scoring tools (AGREE, GAPI, BAGI) into method-development and chromatography-data-system software would allow real-time greenness feedback during optimisation rather than retrospective scoring at the validation-reporting stage. Continued resurgence of SFC, supported by improved detector compatibility and growing analyst familiarity, is likely to expand its role beyond chiral separations into broader routine QC. Finally, convergence toward White Analytical Chemistry — jointly optimising greenness, practicality, and analytical performance — is likely to become the dominant reporting framework, superseding the current practice of reporting a standalone greenness score in isolation from cost and feasibility considerations.

CONCLUSION

The shift toward eco-friendly mobile phases and sustainable column technologies in pharmaceutical quality control has progressed from a niche academic pursuit to an increasingly expected component of modern method development. Ethanol- and propylene-glycol-based mobile phases, alongside the resurgence of supercritical fluid chromatography, offer credible, validated alternatives to conventional acetonitrile- and methanol-based RP-HPLC without necessarily compromising the resolution, sensitivity, or robustness required for regulatory acceptance. Parallel advances in column technology —

sub-2 μm and core-shell particles, monolithic formats, and narrower-bore columns — provide the practical means to reduce solvent consumption independent of solvent choice. The maturing ecosystem of greenness-assessment tools, led by AGREE and GAPI and increasingly complemented by practicality-focused metrics such as BAGI, has given the field a shared, quantitative language for reporting and comparing sustainability, gradually consolidating under the broader White Analytical Chemistry framework. Continued progress will depend on closing the remaining gap between green mobile-phase chemistry and compatible stationary-phase technology, and on regulatory and industry mechanisms that make it practically feasible to transition already-validated QC methods toward greener alternatives.

Review approach and scope

This narrative review synthesises selected literature on green mobile phases, column miniaturisation, greenness assessment and regulatory considerations relevant to pharmaceutical quality control. It is not a systematic review or meta-analysis; no exhaustive database search or formal risk-of-bias assessment is claimed. The illustrative method comparison is a calculation-based example rather than original experimental validation.

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