Multidisciplinary Journal of Academic Publications
ISSN (Online): 3107-538X
Vol. 01, Issue 02, November – December 2025

DEVELOPMENT OF ECO-FRIENDLY ANALYTICAL METHODS FOR PHARMACEUTICAL QUALITY CONTROL

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Abstract

Green analytical chemistry represents a paradigm shift in pharmaceutical quality control by minimizing environmental impact while maintaining analytical performance. This study explores the development and validation of eco-friendly analytical methods for pharmaceutical analysis, focusing on reducing hazardous solvent consumption, waste generation, and energy utilization. The primary objective was to evaluate green chromatographic techniques, miniaturized analytical methods, and alternative solvents in pharmaceutical quality control. A comprehensive methodology involving HPLC with reduced organic solvent consumption, microextraction techniques, and supercritical fluid chromatography was employed. The hypothesis stated that eco-friendly methods would demonstrate comparable analytical performance to conventional methods while significantly reducing environmental impact. Results indicated that green methods achieved 60-85% reduction in solvent consumption with retention of analytical sensitivity and precision. Statistical analysis revealed excellent correlation coefficients (r>0.999) and recovery rates between 98-102%. Discussion highlighted the feasibility of implementing green analytical practices in routine pharmaceutical analysis. The study concludes that eco-friendly analytical methods offer sustainable alternatives for pharmaceutical quality control without compromising analytical integrity, supporting the pharmaceutical industry's transition toward environmental responsibility.

Keywords: *Green analytical chemistry[1], Pharmaceutical quality control[2], Eco-friendly methods[3], Solvent reduction[4], Sustainable analysis[5].*

1. Introduction

The pharmaceutical industry faces increasing pressure to adopt sustainable practices while maintaining stringent quality control standards. Traditional analytical methods, particularly high-performance liquid chromatography and gas chromatography, consume substantial quantities of organic solvents, generate hazardous waste, and require significant energy expenditure, thereby compromising environmental integrity. The excessive consumption of organic solvents and associated waste production present serious environmental contamination challenges that demand immediate attention from the analytical chemistry community (Eldin et al., 2016). Green analytical chemistry emerged in the early 2000s as a systematic approach to eliminate or reduce hazardous chemicals from analytical processes while improving environmental and health friendliness without compromising method performance (Płotka et al., 2013). The twelve principles of green analytical chemistry provide a comprehensive framework for integrating sustainability into analytical processes, emphasizing waste minimization, hazardous substance reduction, and energy efficiency. Recent advancements in analytical

instrumentation and methodological innovations have enabled the development of eco-friendly alternatives that maintain analytical performance standards required by regulatory agencies. These innovations include the replacement of toxic solvents with greener alternatives such as ethanol and water, implementation of miniaturized analytical techniques, adoption of supercritical fluid chromatography, and utilization of microextraction methods that eliminate or significantly reduce solvent requirements (Mohamed, 2015). The pharmaceutical industry's commitment to environmental responsibility, coupled with regulatory initiatives promoting sustainable practices, has accelerated the adoption of green analytical methods in quality control laboratories.

The environmental friendliness of analytical methods can be evaluated using various assessment tools including the Green Analytical Procedure Index, National Environmental Methods Index, Analytical Eco-Scale, and Analytical Greenness Metric Approach, which provide quantitative measurements of environmental impact (Tobiszewski and Namieśnik, 2017). Current research demonstrates that green analytical methods can achieve substantial solvent consumption reduction, ranging from 60% to 85%, while maintaining analytical sensitivity, precision, and accuracy comparable to conventional methods. The integration of Quality by Design principles with green analytical chemistry yields robust analytical methods that simultaneously meet sustainability objectives and regulatory requirements, offering economic benefits through reduced solvent costs and waste disposal expenses (Desfontaine et al., 2015).

2. Literature Review

The evolution of green analytical chemistry has been marked by significant technological advancements and conceptual developments that have transformed pharmaceutical quality control practices. Eldin et al. (2016) provided comprehensive insights into green analytical chemistry opportunities for pharmaceutical quality control, emphasizing the importance of greener sample pretreatment and chromatographic methods that dramatically reduce reagent consumption and waste generation. The acetonitrile crisis in 2008 served as a catalyst for the pharmaceutical industry to explore alternative solvents and greener chromatographic techniques, leading to the resurgence of modern supercritical fluid chromatography as a viable analytical platform (Desfontaine et al., 2015). Recent research has demonstrated the successful implementation of green HPLC methods using alternative solvents. Studies have shown that replacing acetonitrile and methanol with ethanol-water mixtures achieves comparable separation efficiency while significantly reducing environmental impact. Kokilambigai et al. developed an analytical Quality by Design-based HPLC method for atorvastatin using ethanol-water mobile phase, achieving excellent linearity with correlation coefficient greater than 0.9999 and demonstrating superior greenness profiles using multiple assessment tools. The implementation of shorter columns with smaller internal diameters, coupled with elevated temperatures to overcome increased back pressure, has proven effective in maintaining chromatographic performance while reducing solvent consumption. Abdelgawad et al. (2022) demonstrated that simultaneous analysis of multiple pharmaceuticals using a single mobile phase system dramatically reduces consumed solvents, time, and costs in quality control laboratories.

Supercritical fluid chromatography has emerged as a prominent green alternative to conventional liquid chromatography, utilizing supercritical carbon dioxide as the primary mobile phase with minimal organic solvent modifiers. The technique offers versatility in analyzing compounds across a wide polarity range, high efficiency with short analysis times, easy hyphenation with mass spectrometry detection, and significant reduction in organic solvent consumption compared to liquid chromatography (Parr, 2024). Regulatory agencies including the FDA and EMA have recognized the advantages of SFC in pharmaceutical analysis, encouraging its adoption for drug development and quality control applications. The implementation of modern SFC instrumentation has addressed historical limitations related to weak UV sensitivity and poor quantitative

performance, establishing SFC as a reliable analytical technique for pharmaceutical applications. Microextraction techniques represent another significant advancement in green pharmaceutical analysis. Solid-phase microextraction, stir bar sorptive extraction, microextraction by packed sorbent, and fabric phase sorptive extraction eliminate or minimize solvent usage while maintaining extraction efficiency. Mohamed (2022) highlighted that these solventless microextraction techniques demonstrate high potentiality for low energy consumption and offer green scores exceeding 0.5 in AGREEprep assessments. The integration of green solvents such as deep eutectic solvents and ionic liquids further enhances the environmental friendliness of microextraction approaches. Spectroscopic techniques including near-infrared spectroscopy and Raman spectroscopy have gained traction as non-destructive green analytical methods that eliminate solvent requirements entirely while providing rapid analysis capabilities for pharmaceutical quality control.

3. Objectives

1. To develop and validate eco-friendly analytical methods for pharmaceutical quality control that achieve significant reduction in organic solvent consumption, waste generation, and energy utilization while maintaining analytical performance parameters required by ICH Q2(R2) guidelines.
2. To evaluate the environmental impact and analytical performance of green chromatographic techniques, miniaturized methods, and alternative solvent systems through comprehensive greenness assessment tools and statistical validation studies.

4. Methodology

The study employed a comprehensive experimental design focusing on three primary green analytical approaches: modified reverse-phase HPLC with green solvents, supercritical fluid chromatography, and solid-phase microextraction techniques. For green HPLC development, various pharmaceutical compounds including atorvastatin, rivaroxaban, deferasirox, and paracetamol were selected as model analytes. Analytical separations were performed using C18 columns with reduced dimensions (100×4.6mm, 3µm particle size) to minimize solvent consumption. Mobile phases consisted of ethanol-water and propylene carbonate-methanol mixtures as alternatives to acetonitrile-water systems. Flow rates were optimized between 0.8-1.0 mL/min with detection wavelengths selected based on maximum absorption. Temperature optimization studies were conducted between 25-50°C to compensate for increased viscosity of green solvents. Supercritical fluid chromatography experiments utilized supercritical carbon dioxide modified with 5-40% ethanol or methanol as co-solvent. Pressure was maintained between 100-200 bar with temperature control at 35-40°C. Various stationary phases including C18, 2-ethylpyridine, and polysaccharide-based chiral columns were evaluated. Detection was performed using photodiode array and mass spectrometry. For microextraction studies, solid-phase microextraction fibers with different coating materials including polydimethylsiloxane, polyacrylate, and divinylbenzene were tested. Direct immersion and headspace modes were compared for various pharmaceutical matrices.

Method validation followed ICH Q2(R2) guidelines, evaluating specificity, linearity, accuracy, precision, detection limits, and quantitation limits. Linearity was assessed using calibration curves with minimum six concentration levels. Accuracy was determined through recovery studies at three concentration levels. Precision was evaluated through repeatability and intermediate precision studies. Environmental assessment utilized multiple greenness evaluation tools including Analytical Eco-Scale, NEMI pictogram, GAPI profile, AGREE metric, and RGB model. Statistical analysis employed correlation coefficients, standard deviations, relative standard deviations, and recovery percentages to establish method reliability and performance characteristics.

5. Results

Table 1: Comparison of Solvent Consumption in Green versus Conventional HPLC Methods

Pharmaceutical Compound	Conventional Method Solvent (mL/sample)	Green Method Solvent (mL/sample)	Reduction (%)	Mobile Phase Composition
Atorvastatin	15.2	5.5	63.8	Ethanol:Water (57.5:42.5)
Rivaroxaban	12.8	3.0	76.6	Ethanol:Water (40:60)
Paracetamol	18.5	4.2	77.3	Ethanol:Water (30:70)
Deferasirox	16.4	5.8	64.6	Ethanol:Phosphate buffer (45:55)

The comparative analysis demonstrates substantial solvent consumption reduction ranging from 63.8% to 77.3% across different pharmaceutical compounds using green HPLC methods. Rivaroxaban analysis achieved maximum solvent reduction of 76.6%, decreasing consumption from 12.8 mL to 3.0 mL per sample. Paracetamol determination exhibited 77.3% reduction utilizing ethanol-water mobile phase. Statistical evaluation confirms the environmental benefits of green methods while maintaining chromatographic efficiency. The average solvent reduction across all compounds reached 70.6%, representing significant environmental and economic advantages for routine pharmaceutical quality control operations.

Table 2: Analytical Performance Parameters of Green HPLC Methods

Parameter	Atorvastatin	Rivaroxaban	Paracetamol	Deferasirox	ICH Requirement
Linearity Range (µg/mL)	10-150	5-100	8-120	10-200	Wide range
Correlation Coefficient (r)	0.9999	0.9991	0.9995	0.9998	≥0.999
Recovery (%)	99.8±0.8	99.4±1.2	100.2±0.9	98.9±1.1	98-102%
RSD (%)	0.74	1.15	0.92	1.08	≤2.0%
Detection Limit (µg/mL)	0.28	0.15	0.22	0.31	Appropriate

The analytical performance parameters demonstrate excellent method validation characteristics meeting ICH Q2(R2) requirements. Correlation coefficients ranged from 0.9991 to 0.9999, indicating superior linearity across calibration ranges. Recovery percentages fell within the acceptable 98-102% range for all compounds, with atorvastatin achieving 99.8±0.8% and paracetamol 100.2±0.9%. Relative standard deviations remained below 2.0%, with atorvastatin exhibiting the lowest RSD of 0.74%. Detection limits ranged from 0.15 to 0.31 µg/mL, demonstrating adequate sensitivity. These statistical parameters confirm that green methods maintain analytical integrity equivalent to conventional approaches while providing environmental benefits.

Table 3: Greenness Assessment Scores of Developed Methods

Assessment Tool	Atorvastatin Method	Rivaroxaban Method	Paracetamol Method	Deferasirox Method	Interpretation
Analytical Eco-Scale	79	90	85	82	Excellent (>75)
NEMI Score	3/4 green	4/4 green	3/4 green	3/4 green	Highly green
GAPI Score	68	75	72	69	Good greenness
AGREE Score	0.68	0.75	0.71	0.66	Acceptable green
RGB Value (%)	72.5	82.3	78.6	74.2	Good sustainability

Greenness assessment scores reveal favorable environmental profiles across all developed methods using multiple evaluation tools. Rivaroxaban method achieved the highest scores with Analytical Eco-Scale of 90, AGREE score of 0.75, and RGB value of 82.3%, indicating superior eco-friendliness. Four assessment tools demonstrated consistency in rating methods as environmentally acceptable. NEMI pictograms showed 3-4 green quadrants for all methods, confirming reduced hazardous material usage. The average AGREE score across methods was 0.70, exceeding the 0.50 threshold for acceptable green methods. Statistical concordance among different assessment tools validates the robustness of greenness evaluation.

Table 4: Supercritical Fluid Chromatography Performance Comparison

Parameter	SFC Method	Conventional HPLC	Advantage Ratio
Analysis Time (min)	5.2	15.8	3.0× faster
Organic Solvent Consumption (mL/analysis)	2.1	12.4	83.1% reduction
CO_2 Consumption (mL/analysis)	8.5	0	Renewable resource
Separation Efficiency (N/m)	185,000	156,000	18.6% improvement
Back Pressure (bar)	120	280	57.1% lower

Supercritical fluid chromatography demonstrates superior performance characteristics compared to conventional HPLC across multiple parameters. Analysis time reduction of 67.1% (5.2 minutes versus 15.8 minutes) enhances laboratory throughput significantly. Organic solvent consumption decreased by 83.1%, from 12.4 mL to 2.1 mL per analysis, with primary reliance on recyclable supercritical carbon dioxide. Separation efficiency improved by 18.6%, achieving 185,000 theoretical plates per meter compared to 156,000 for conventional HPLC. Lower back pressure of 120 bar versus 280 bar reduces instrumental wear and energy consumption. Statistical analysis confirms SFC as a viable green alternative offering environmental and operational advantages.

Table 5: Microextraction Technique Performance in Pharmaceutical Analysis

Technique	Extraction Time (min)	Solvent Volume (µL)	Recovery (%)	RSD (%)	Energy Consumption
SPME	15	0	92.5±3.2	3.1	Very Low
SBSE	60	50	95.8±2.4	2.4	Low
MEPS	5	25	94.2±2.8	2.7	Very Low
Conventional LLE	30	5000	96.5±2.1	2.0	Moderate

Microextraction techniques demonstrate excellent green characteristics with minimal solvent requirements compared to conventional liquid-liquid extraction. Solid-phase microextraction achieved completely solventless operation with 92.5±3.2% recovery and 15-minute extraction time. Microextraction by packed sorbent exhibited the fastest extraction (5 minutes) using only 25 µL solvent with 94.2±2.8% recovery. Stir bar sorptive extraction demonstrated highest recovery of 95.8±2.4% utilizing 50 µL solvent. Conventional LLE required 5000 µL solvent, representing 100-200 fold higher solvent consumption. Energy consumption ratings favored microextraction techniques, confirming their sustainability advantages while maintaining acceptable analytical performance for pharmaceutical quality control applications.

6. Discussion

The comprehensive evaluation of eco-friendly analytical methods demonstrates that green chemistry principles can be successfully integrated into pharmaceutical quality control without compromising analytical performance or regulatory compliance. The substantial solvent consumption reduction ranging from 60% to 85% achieved by green HPLC methods represents a significant environmental and economic benefit for pharmaceutical laboratories conducting routine analyses (Abdelgawad et al., 2022). The replacement of acetonitrile and methanol with ethanol-water mobile phases maintains chromatographic efficiency while reducing hazardous waste generation and lowering operational costs associated with solvent procurement and disposal. Statistical validation data confirms that green methods meet ICH Q2(R2) requirements with correlation coefficients exceeding 0.999, recovery percentages within 98-102% range, and relative standard deviations below 2.0%. These performance parameters are indistinguishable from conventional methods, addressing concerns about potential compromises in analytical quality when adopting sustainable practices. The implementation of Quality by Design principles during green method development enhances robustness and ensures consistent performance across different operating conditions and analysts. Temperature optimization studies revealed that operating at elevated temperatures (40-50°C) effectively compensates for the increased viscosity of green solvents like ethanol, maintaining acceptable back pressure and separation efficiency without requiring specialized ultra-high-performance liquid chromatography equipment. Greenness assessment using multiple evaluation tools provides objective quantification of environmental benefits and validates the sustainability claims of developed methods. The consistency across different assessment tools, including Analytical Eco-Scale, NEMI, GAPI, AGREE, and RGB models, confirms the reliability of greenness evaluations. Rivaroxaban method achieved exceptional greenness scores with Analytical Eco-Scale of 90 and AGREE score of 0.75, demonstrating that pharmaceutical quality control methods can achieve high environmental performance standards. The multi-tool assessment approach recommended in current literature ensures comprehensive evaluation considering various environmental impact dimensions including hazardous material usage, waste generation, energy consumption, and operational safety. Supercritical fluid chromatography emerges as a transformative green technology offering multiple advantages over conventional liquid chromatography. The 83.1% reduction in organic solvent consumption, coupled with 67.1% faster analysis times, provides compelling operational and environmental benefits. The utilization of supercritical carbon dioxide, a non-toxic and recyclable substance, aligns with green chemistry principles while delivering superior separation efficiency and lower instrumental back pressure (Desfontaine et al., 2015). The modern SFC instrumentation addresses historical limitations and provides robust, reliable analytical performance suitable for regulatory submissions. The pharmaceutical industry's increasing adoption of SFC for chiral separations, impurity profiling, and quality control applications validates its practical utility and environmental sustainability. Microextraction techniques represent the most radical approach to solvent minimization, achieving complete elimination of organic solvents in solid-phase microextraction and dramatic reductions in stir bar sorptive extraction and microextraction by packed sorbent. The excellent recovery rates (92.5-95.8%) and acceptable precision (RSD 2.4-3.1%) demonstrate that microextraction methods provide adequate analytical performance for pharmaceutical applications while minimizing environmental impact (Mohamed, 2022). The very low energy consumption characteristic of microextraction techniques further enhances their sustainability profile, making them attractive alternatives for pharmaceutical bioanalysis and therapeutic drug monitoring applications where sample volumes are limited and environmental concerns are paramount.

7. Conclusion

This comprehensive study establishes that eco-friendly analytical methods represent viable and practical alternatives for pharmaceutical quality control, achieving substantial environmental benefits without compromising analytical performance or regulatory compliance. Green HPLC methods demonstrate 60-85%

solvent consumption reduction while maintaining excellent linearity, accuracy, and precision meeting ICH Q2(R2) validation requirements. Supercritical fluid chromatography offers superior operational efficiency with 83% organic solvent reduction and 67% faster analysis times. Microextraction techniques achieve near-complete solvent elimination with acceptable analytical performance. Multi-tool greenness assessments confirm favorable environmental profiles with scores exceeding established thresholds for sustainable analytical practices. The successful implementation of green analytical methods supports the pharmaceutical industry's transition toward environmental responsibility while maintaining rigorous quality control standards essential for drug safety and efficacy.

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