

Advances in Green Analytical Techniques for Impurity Profiling in Pharmaceuticals

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ABSTRACT

This study provides an overview of the green analytical methods in pharmaceutical impurity profiling with focus on regulatory compliance, effectiveness, and environmental impact. We address recent trends in spectroscopic approaches such as Near-Infrared (NIR), Raman spectroscopy, Capillary Electrophoresis (CE), Green Liquid Chromatography (GLC) and Supercritical Fluid Chromatography (SFC). Analyses of the principles of green chemistry are done through avenues including energy efficiency, minimization of wastes generated, as well as the use of safer solvents. The review is based on state-of-the-art sample preparation strategies: miniaturized procedures and SPME. We also address the drawbacks, that is, sensitivity problems and legal restrictions, that halt the wider spread of these techniques. The future perspectives are related to the application of machine learning and artificial intelligence in technique development. This article aims at providing quality control specialists and pharmaceutical researchers with an overview of the latest green analytical techniques, their applications, pitfalls, and promises towards making impurity profiling more sustainable. Using case studies and comparative analysis, we demonstrate how such approaches can be useful in pharmaceutical quality assurance and control.

Keywords: Chromatography, Green Analytical Chemistry, Pharmaceutical Impurity Profiling, Sustainable Methods, Spectroscopy, Sample Preparation, Regulatory Compliance.

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INTRODUCTION

Impurity profiling is the core of pharmaceutical quality control and assurance; it critically underpins drug safety, efficiency, and stability (Jacobson-Kram, 2007). At the same time, the trend for improving analytical methods for impurity analysis towards greener and more sustainable analytical procedures continues to grow as the pharmaceutical industry evolves (Boulder, 2015). In line with international efforts to minimize the environmental impact of chemical processes, "green analytical chemistry" is gaining popularity, and it also responds to rising concerns over the sustainability of conventional analytical methods (Jahani *et al.*, 2023). To maintain or enhance analytical performance, impurity profiling by means of green techniques in analytical chemistry aims at minimizing the consumption of solvents, avoiding waste generation, reducing energy consumption, and lowering the environmental footprint of analytical procedures as a whole and the 12 principles of green chemistry, favouring atom

economy, pollution prevention, and minimal use of highly toxic and hazardous solvents and reaction conditions, provide the basis for these methods (Jain, 2013).

CLASSIFICATION OF IMPURITIES AS PER USP AND ICH

The International Council for Harmonization (ICH) and United States Pharmacopoeia (USP) offer impurity classification schemes for drug products (ICH, 2020). The USP classifies impurities as traditional or organic impurities, whereas the ICH presents a more specific classification: Inorganic impurities (e.g., catalysts, heavy metals), Organic impurities (e.g., process by-products, degradation products), and Residual solvents, classified according to toxicity into Classes 1-3. The major ICH guidelines are Q3A (new drug substances), Q3B (new drug products), Q3C (residual solvents), and Q3D (elemental impurities), outlining identification, qualification, and control specifications (De Camp, 1989). These guidelines provide assurance for drug safety, effectiveness, and regulatory compliance (See Table 1, ICH, 2020).

TYPES OF IMPURITIES AND SOURCES

Impurities can be broadly divided into four types, they are:



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Process related drug substance.

Process related drug product.

Degradation drug substance or drug product and,

Degradation drug product.

GREEN ANALYTICAL TECHNIQUES

Green analytical methods have progressed extensively in pharmaceutical impurity profiling. Green Liquid Chromatography (GLC) reduces the use of solvents and waste through environmentally friendly mobile phases and high-performance columns (Baertschi, 2006). Supercritical Fluid Chromatography (SFC) employs supercritical CO₂, significantly reducing organic solvents while providing selective selectivity. Capillary Electrophoresis (CE) provides excellent efficiency with low solvent and waste generation. Solventless or low-solvent Sample preparation methods minimize further environmental effects. Non-destructive spectroscopic methods such as Raman and Near-Infrared (NIR) spectroscopy now facilitate direct analysis with minimal or no preparation, thus improving sustainability in pharmaceutical analysis (Baertschi, 2006).

IMPORTANCE OF IMPURITY PROFILING IN PHARMACEUTICALS

Impurity profiling plays a crucial role in pharmaceutical quality control because it provides assurance for safety, efficacy, and stability of drug products (Almalki, 2024).

- **Safety:** Identification of impurities is necessary because some have been found to be carcinogenic or genotoxic. The find of N-nitrosamines in sartan drugs called for large recalls, highlighting end-to-end impurity profiling.
- **Efficacy:** Impurities can interfere with drug action or change pharmacokinetics. Others may even augment therapeutic effects; hence careful characterization is necessary.
- **Stability:** Impurities may jeopardize shelf life and induce degradation, impacting both safety and efficacy. Profiling anticipates and enhances the product's stability (Periat *et al.*, 2013).

Regulatory Guidelines

The US-FDA has adopted the regulations developed based on the guidance by ICH (FDA, 2020). The ICH guideline on impurities in pharmaceuticals was developed through collaboration of regulators and representatives of industry from the EU, Japan, and the United States (De Camp, 1989). This has contributed to ensuring different regions do have reliable requirements for the data to be presented to the various regulatory bodies. The guidelines also help the field investigators and FDA reviewers in the uniform interpretation and application of regulations, as

well as the sponsors of NDA and ANDA regarding the type of information to be submitted along with the applications.

Analytical Chemistry

Analytical chemistry forms the foundation of pharmaceutical quality control, confirming drug safety, efficacy, and stability by determining, separating, and quantifying components (Tabani *et al.*, 2018). Focus on impurity profiling is particularly important since even trace impurities may drastically modify a drug's therapeutic profile or lead to toxicity (Almalki, 2024; Periat *et al.*, 2013). Regulatory organizations such as the FDA and EMA impose rigid impurity control, creating the need for more sophisticated techniques. Green analytical chemistry has arisen due to environmental issues and advancements in technology, with the goal of minimizing environmental footprint without affecting analytical performance, as well as enhancing the efficiency of impurity profiling (Periat *et al.*, 2013).

Application to Analytical Chemistry

Green chemistry principles are extensively incorporated into analytical chemistry. Green sample preparation techniques are Molecularly Imprinted Polymers (MIPs) for solid-phase extraction and liquid-liquid microextraction based on ionic liquid or deep eutectic solvents (Wang *et al.*, 2025). Chromatographic methods have embraced green practices: GC employs green stationary phases, SFC utilizes CO₂, and UHPLC uses ethanol or water as mobile phases. Miniaturization and automation with lab-on-a-chip devices and microfluidic systems further enhance sustainability (Kumar *et al.*, 2014). Spectroscopic techniques also adopt green approaches, including NMR with cryoprobe, FTIR with reflectance modes, and Raman with LED or laser sources (Kumar *et al.*, 2014).

GREEN CHROMATOGRAPHIC TECHNIQUES

Green Liquid Chromatography (GLC)

Green liquid chromatography has the objectives of achieving at least comparable analytical performance compared with conventional HPLC methods while reducing the negative environmental consequences. The most significant areas of focus are using fewer hazardous chemicals, creating less waste, and consuming less of a solvent (Nakov *et al.*, 2023).

Use of a green mobile phase

Reducing solvent consumption

a) **Acetonitrile Replaced with Ethanol or Methanol:** Ethanol-water mixtures were found to work as efficient eco-friendly substitutes to acetonitrile for separation of enantiomers, achieving lower environmental influence with minimal differences in resolution only through slight modifications in gradients (Nakov *et al.*, 2023).

b) Aqueous Mobile Phases: Aqueous HPLC methods are free of organic solvents, as illustrated in the determination of water-soluble vitamins in dietary supplements, providing lower cost, easier design, and lower environmental impact (Nakov *et al.*, 2023).

c) Ionic Liquids as Green Solvents: Ionic liquids as additives to the mobile phase improve peak quality and minimize organic solvent consumption in simple pharmaceutical separation (Nakov *et al.*, 2023).

a) Ultra-High Performance Liquid Chromatography (UHPLC): UHPLC has revolutionized pharmaceutical analysis through an immense reduction of analysis times and solvent usage (Krishnaiah *et al.*, 2010). Thus, when impurity profile of a complex pharmaceutical mixture was compared for the above two techniques, HPLC and UHPLC, it was found that UHPLC could realize 80% reduction in solvent usage while still achieving a similar or higher degree of separation efficiency.

b) Narrow-bore columns: Narrow-bore columns with an inner diameter of ≤ 2.1 mm in diameter have been used increasingly in green LC (Krishnaiah *et al.*, 2010). Analysis of pharmaceutical contaminants employing 1.0 mm in diameter columns has been found to require up to a 90% decrease in mobile phase consumption as against conventional 4.6 mm in diameter columns without compromising the chromatographic performance.

Elevated temperature liquid chromatography

By substantially reducing mobile phase viscosity, high column temperatures can be attained that allow for faster separations and/or longer columns or smaller particles without excessive backpressure (Edge *et al.*, 2006). Organic solvent waste is minimized by using only aqueous mobile phases for molecules that typically require a substantial organic component; indeed, there is a study on the identification of pharmaceutical contaminants at elevated temperatures, up to 80°C.

Green sample preparation techniques

Green LC encompasses not only the innovations in the chromatographic method but also the sample preparation approach, which is environmentally friendly (Edge *et al.*, 2006). Pharmaceutical compounds have been well extracted from matrices of high complexity using Solid-Phase Micro Extraction (SPME) and Microwave-Assisted Extraction (MAE), which significantly minimizes the volume of the solvent applied in the sample preparation step (Yabré *et al.*, 2018).

Method Optimisation for Greenness

For evaluating and developing more environmentally sustainable LC procedures, numerous technologies have been developed. The HPLC-EAT, which quantitatively measures the impact of an environmental method, evaluates waste creation, energy consumption, and solvent consumption (Shah *et al.*, 2022).

Focused on the promotion of even more environmentally friendly procedures, this tool has thus widely been used for the optimization of LC methods applied in pharmaceutical analysis (Mohamed *et al.*, 2017).

Supercritical Fluid Chromatography (SFC)

Supercritical Fluid Chromatography (SFC) is a green, efficient alternative to traditional gas and liquid chromatography (Grand-Guillaume *et al.*, 2012). With supercritical CO₂ used as the mobile phase, SFC takes advantage of the strengths of both GC and LC to provide faster analysis, reduced solvent consumption, and enhanced resolution (Khater, 2013). It is particularly useful in pharmaceutical impurity profiling, especially in chiral separations where conventional techniques would fail. SFC has been used effectively to examine impurities in pharmaceuticals such as atorvastatin and sildenafil, demonstrating its worth in Active Pharmaceutical Ingredient (API) impurity analysis (Khater, 2013).

Capillary Electrophoresis (CE)

Capillary Electrophoresis (CE) is among the most important pharmaceutical impurity profiling techniques (Cai, 1995). In contrast to conventional techniques such as liquid chromatography, CE provides high-resolution separation according to analytes' charge-to-mass ratios in an electric field (Kok *et al.*, 1998). CE is especially useful in separating complex mixtures and similar structures. The low-pressure conditions and low energy requirements of CE make it a cost-effective and environmentally friendly technique. Its low solvent usage and minimal environmental impact conform to the tenets of green analytical chemistry, providing an efficient and sustainable pharmaceutical impurity analysis tool with good performance and selectivity.

SPECTROSCOPIC METHODS

Near-Infrared Spectroscopy (NIR)

By determining the quantity of near-infrared light that is absorbed by a sample, valuable information can be gained. For instance, when a sample is subjected to near-infrared radiation, part of it is absorbed and the remaining portion is reflected or transmitted (Pan *et al.*, 2008). By quantifying the amount of radiation absorbed per wavelength, a spectrum can be created, telling us about the sample's composition. NIR (Near-Infrared) spectroscopy is a quick, non-destructive technique with little to no preparation needed for samples. NIR spectroscopy relies upon molecular overtone and combination modes of vibration (Chieng *et al.*, 2009).

Raman Spectroscopy

It is a non-destructive analytical technique that maintains sample integrity, a key requirement for pharmaceutical quality control,

and minimizes waste by enabling repeat analysis (Yogurtcu *et al.*, 2024). It demands minimal sample preparation, reducing chemical usage and exposure hazards. Raman spectroscopy can examine liquids, solids, and intricate matrices in their original state, including aqueous samples owing to the weak Raman scattering of water (Li, 2014). Handheld Raman instruments permit *in situ* analysis, minimizing the transportation of samples and energy consumption (Räsänen *et al.*, 2003). Second to minutes of fast data acquisition also improve process efficiency and reduce waste generated from batch failures.

Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR is a non-destructive method, enabling recovery of samples for use in subsequent analysis, particularly useful for rare or expensive materials (Shah *et al.*, 2011). Very low sample preparation—usually no more than dissolution—minimizes waste and the use of chemicals. Solid-state NMR methods, such as Magic Angle Spinning (MAS), make it possible to analyze solid samples without solvents (Mistry *et al.*, 1997). This greatly reduces chemical use and waste. Furthermore, the NMR deuterated solvents can be recovered and reused multiple times, meaning they have fewer environmental implications as well as saving on operational expenditures (Gathungu *et al.*, 2020; Kuballa *et al.*, 2013).

MINIATURIZATION AND MICROFLUIDIC DEVICES

Microextraction Techniques

Miniaturized extraction methods significantly reduce solvent usage:

1. Solid-Phase Micro Extraction (SPME).
2. Liquid-Phase Micro Extraction (LPME).
3. Single-Drop Micro Extraction (SDME).

These techniques offer solvent-free or low-solvent alternatives to traditional liquid-liquid extraction methods.

Microextraction Techniques in Green Analytical Chemistry

Principles of green analytical chemistry correlate well with those microextraction techniques which are miniaturized sample preparation procedures used with a resultant reduction in usage of a solvent. These methods have the advantage of requiring less sample and solvent, producing less waste, and often yielding higher sensitivity. Here three key approaches for micro-extraction summarized:

Solid-Phase Microextraction (SPME)

It integrates sample introduction, extraction, concentration, and sampling into one procedure (M.W.J. van Hout *et al.*, 2003). SPME adsorbs analytes from a headspace matrix or sample onto a fibre coated with an extracting phase. The analytes are subsequently desorbed for analysis. Because it is free from solvents, reusable fibre, and of low waste, SPME finds extensive application in the analysis of volatile and semi-volatile analytes in bio matrices, environmental samples, and food (Alpendurada, 2000).

Liquid-Phase Microextraction (LPME)

LPME encourages green chemistry principles by reducing conventional liquid-liquid extraction to only microliters of organic solvent. LPME entails extracting analytes from aqueous samples into trace amounts of organic solvent, which may be trapped inside a hollow fibre, suspended in the form of a droplet, or sustained by a liquid membrane (A Gjeldstad *et al.*, 2012). Due to its large enrichment factors and significantly lower solvent usage, LPME is particularly beneficial for environmental and pharmaceutical research in organic compounds (Spietelun *et al.*, 2014).

Single-Drop Microextraction (SDME)

Single-Drop Microextraction (SDME) applies a microliter-scale drop of a solvent for effective extraction, which supports direct connection with analytical tools and reduces solvent consumption (Tang *et al.*, 2018). Due to its ease of use and green nature, it is

Table 1: Lists Various Regulatory Requirements Concerning Impurities.

Guidelines	Depiction
Q1A	Ich guidelines “stability testing of new drug substances and products”.
Q3A	Ich guidelines “Impurity in New Drug Substances”.
Q3B	Ich guidelines “Impurities in New Drug Products”.
Q3C	Ich guidelines “Impurities: Guidelines for residual solvents”.
US-FDA	“NDAs- Impurities in New Drug Substances”.
US-FDA	“ANDAs- Impurities in New Drug Substances”.
Australian regulatory guideline	Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia.

an essential green approach in pharmaceuticals, environmental science, and food science analysis (Purgat *et al.*, 2021).

CHALLENGES AND FUTURE PERSPECTIVES

One of the biggest challenges to implementing green analytical techniques for pharmaceutical impurity profiling is obtaining similar sensitivity and selectivity as conventional methods, particularly for trace-level impurities in challenging matrices (Naguib *et al.*, 2018). Regulatory barriers and initial investment expenses are also obstacles to adoption. Nevertheless, advancements in greener mobile phases and stationary phases, miniaturized and automated instrumentation, and AI-optimized processes present potential solutions. Combining green extraction with green chromatography will further increase impurity profiling. In addition, the incorporation of AI and quality by design principles in method development enhances the environmental and analytical advantages, indicating an increasing place for green strategies in pharmaceutical analysis.

RESULTS

The research outlined some progress in green analytical methods used for impurity profiling in drug products. The findings are as follows:

- **Use of solvent-free and green solvent systems:** Methods like Supercritical Fluid Chromatography (SFC) and Microwave-Assisted Extraction (MAE) have dramatically lowered the utilization of toxic organic solvents.
- **Miniaturization of analysis methods:** Microextraction and capillary electrophoresis have facilitated the miniaturization of samples, reducing waste and costs (Zhang *et al.*, 2018).
- **Integration of machine learning and AI:** Analytical platforms augmented with artificial intelligence have shown enhanced speed and accuracy in detecting and characterizing pharmaceutical impurities, particularly at trace levels.
- **Environmental impact:** The use of green methods resulted in a quantifiable decrease in the carbon footprint and environmental load of traditional impurity profiling workflows.
- **Economic factors:** While higher initial investments were made in green technologies, long-term cost benefits were realized in terms of less solvent usage, less energy consumption, and reduced waste disposal costs.

DISCUSSION

Green analytical approaches have appeared over the past decades to address the critical demand for sustainable pharmaceutical quality control. Classic impurity profiling techniques, dependent on hazardous solvents, have been rebuilt based on green chemistry concepts. Solvent-free methods, safer substitutes, and miniaturization have greatly minimized environmental footprint. Spectroscopy, electrophoresis, and chromatography technologies have undergone revolutionary evolution under green concepts. In addition, the combination of artificial intelligence and machine learning has improved sensitivity and accuracy in impurity detection with low resource consumption. Nonetheless, there are challenges. The detection of trace-level impurities in complicated matrices remains challenging, and regulatory standardization is incomplete (Abdelwahab *et al.*, 2023). Economic hindrances, specifically high upfront costs, restrict general application despite long-term advantages. Regulatory bodies are only starting to incorporate green requirements into official guidelines. A single global regulation would be necessary to spur wider application. Generally speaking, although benefits are evident, future studies need to aim at enhancing sensitivity, harmonization of regulations, and cost-effectiveness.

CONCLUSION

Green analytical methods have quickly evolved in pharmaceutical impurity profiling, equating analytical accuracy with sustainability in the environment. New developments in Capillary Electrophoresis (CE), Supercritical Fluid Chromatography (SFC), and Green Liquid Chromatography (GLC) minimize solvent consumption while improving performance. Spectroscopic techniques such as Raman and Near-Infrared (NIR) spectroscopy enable quick, non-destructive analysis without sample preparation. Application of green chemistry principles has resulted in waste minimization, enhanced energy efficiency, and lower environmental footprint. Miniaturization and microfluidic devices also save resources, with unparalleled efficiency. But there are challenges, such as the need for higher sensitivity for the detection of trace impurities and the mitigation of high entry and regulatory costs. In spite of these challenges, green analytical techniques are paving the way for a sustainable future in pharmaceutical quality control, with a persuasive way forward.

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ABBREVIATIONS

NIR: Near-Infrared (spectroscopy); **CE:** Capillary Electrophoresis; **GLC:** Green Liquid Chromatography; **SFC:** Supercritical Fluid Chromatography; **SPME:** Solid-Phase Micro Extraction; **USP:** United States Pharmacopeia; **ICH:** International Council for Harmonisation; **FDA:** Food and Drug Administration; **EMA:** European Medicines Agency; **UHPLC:** Ultra-High Performance Liquid Chromatography; **NDA:** New Drug Application; **ANDA:** Abbreviated New Drug Application; **TGA:** Therapeutic Governance Authority.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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