**REVIEW ARTICLE**

**Evaluating Analytical Greenness: A Review of Sustainable Chemistry Advancements in Pharmaceutical Analysis**

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**ABSTRACT**

Sample preparation based on extraction techniques plays a crucial role in the analytical process, as it ensures accurate and reliable analysis of analytes by eliminating matrix interferences. However, traditional sample preparations, which heavily rely on hazardous chemical solvents, are thought to be the time-consuming and labor-intensive aspect of analysis. According to the principles of green analytical chemistry, using sustainable green solvents in sample preparation microextraction procedures greatly aids in the advancement of green analytical approaches. These sustainable green solvents can be adapted as potential extractants for particular microextraction jobs by utilizing their solventation qualities and greenness merits. This will enable an effective and environmentally responsible sample preparation process before instrumental analysis. In this study, we offer a succinct overview of current developments ell-known sustainable.

Key Words: Green Analysis

**INTRODUCTION**

Sampling, sample preparation, and analysis are the three primary components of a conventional analytical technique. For the majority of analytical procedures, sample preparation that depends on solvent extraction is essential in light of matrix interferences in order to guarantee precise and trustworthy analysis results. The two most popular traditional extraction methods are solid-phase extraction (SPE) and liquid-liquid extraction (LLE), which entail laborious and time-consuming steps as well as significant use of volatile and hazardous organic solvents (acetone, ethyl acetate, methanol, ethanol, propanol, or a combination of these).

**Techniques**

In this sense, sample preparation presents a significant opportunity to use the principles of green analytical chemistry (GAC), which promotes the reduction of extraction processes as well as the substitution of environmentally acceptable solvents for hazardous ones. Methods of microextraction, including solid-phase microextraction

liquid-phase microextraction (LPME) and (SPME), or their variations, have been sought as innovative, promising techniques for sample preparation aimed at automation, simplicity, and downsizing. These methods meet the GAC requirements and are beneficial in that they are inexpensive, use few solvents, consume less energy, and produce less trash. It is typically necessary for the extraction solvents used in microextraction to have particular physicochemical characteristics that may impact the target analytes' extraction performance.
Additionally, the use of new sustainable green solvents in microextraction techniques is a promising trend to achieve a quick, easy, effective, and environmentally friendly sample preparation in a variety of analytical methodologies, given the growing concerns regarding the toxicity and sustainability of solvents. According to the 12 GAC principles, a suitable design and thoughtful solvent selection are necessary.

Ionic liquids (ILs), deep eutectic solvents (DESs), natural deep eutectic solvents (NADESs), amphiphilic solvents, switchable solvents (SSs), sub-/supercritical fluids, and bio-solvents are among the new sustainable green solvents that have gained a lot of attention as extraction solvents over the last 20 years and meet many of these requirements. For an analytical method to be successful, the sample must be prepared for efficient target analyte extraction, separation, and preconcentration from complex matrices. Additionally, the sample must be obtained in an appropriate form and at the right concentration levels for instrumental analysis in order to achieve the required sensitivity. In recent years, a large variety of sensitive analytical techniques have been created in tandem with the development of sustainable green solvents and microextraction methods.

**Methods**
Green analytical chemistry (GAC) aims to minimize the environmental impact of analytical procedures. Here's a breakdown of key techniques and concepts:

Core Principles and Strategies:

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| Category | Techniques/Methods | Key Principles |
| Miniaturization | \* Microextraction (SPME, LPME, DLLME) | \* Reduced sample/solvent volume. |
|  | \* Microfluidics | \* Minimized waste. |
| Solvent Reduction/Substitution | \* Water-based extractions | \* Replacement of hazardous solvents. |
|  | \* Supercritical fluid extraction (SFE) | \* Use of environmentally friendly solvents. |
|  | \* Ionic liquids | \* Deep eutectic solvents (DESs) |
| Direct Analysis | \* In-situ analysis | \* Minimized sample pretreatment. |
|  | \* Direct spectroscopy (FTIR, Raman) | \* Reduced reagent consumption. |
| Alternative Extraction | \* Microwave-assisted extraction (MAE) | \* Reduced energy consumption. |
| Methods | \* Ultrasound-assisted extraction (UAE) | \* Faster extraction times. |
| "Greener" Chromatography | \* HPLC with greener solvents | \* Reduced organic solvent use. |
|  | \* Supercritical fluid chromatography (SFC) | \* Use of CO2 as mobile phase. |
| Assessment Tools | \* NEMI (National Environmental Methods Index) | \* Evaluation of method's environmental impact. |
|  | \* Analytical Eco-Scale | \* Scoring system for "greenness". |
|  | \* AGREE (Analytical GREEnness Metric Approach and Software) | \* Graphical representation of method's greenness. |

**Categorization:**

The techniques are grouped by their primary function within green analytical chemistry.

This helps to illustrate the diverse strategies involved.

**Key Principles**:

This column highlights the main environmental benefits associated with each technique.

**Assessment tools:**

These tools are very important for the development and usage of green analytical techniques, because they provide ways to measure the "Greenness" of the analytical process.

**Green Analytical Procedure (Step-by-Step)**

1. **Sample Preparation:**
	1. Accurately weigh a small portion (e.g., 5-10 mg) of powdered tablet.
	2. Place the sample in a microcentrifuge tube.
	3. Add a minimal volume of ethanol (e.g., 50-100 µL) to the tube.
	4. Vortex or sonicate the mixture for a few minutes to ensure complete extraction.
	5. Centrifuge the mixture to separate the extract.
2. **Analysis:**
	1. Fill the capillary electrophoresis (CE) vial with the supernatant.
	2. Perform MEKC analysis using appropriate buffer conditions and voltage.
	3. Detect and quantify the paracetamol peak using UV or fluorescence detection.

(MEKC stands for Micellar Electrokinetic Chromatography, a separation technique in analytical chemistry that extends capillary electrophoresis by using micelles to separate neutral and charged analytes. )

1. To assess the "greenness" of analytical procedures, you can utilize tools like the *National Environmental Method Index (NEMI), Analytical Eco-Scale Assessment (ESA), Green Analytical Procedure Index (GAPI), and Analytical Greenness Metric (AGREE).*



**Green analysis plays a crucial role in the pharmaceutical sector by promoting environmentally sustainable practices. Here's a breakdown of its key applications:**

*1. Reduction of Hazardous Solvents and Reagents*:

Solvent Substitution:Replacing toxic organic solvents with safer alternatives like water, ethanol, supercritical fluids (like CO2), or ionic liquids.

Minimization of Reagent Use:Developing analytical methods that require smaller amounts of reagents.

*2. Waste Minimization:*

Microanalysis:Using techniques that require smaller sample sizes, reducing waste generation.

On-line Analysis:Implementing real-time monitoring to minimize waste from off-line testing.

Recycling and Recovery:Developing methods for recovering and reusing solvents and reagents.

*3. Energy Efficiency:*

Optimizing Analytical Techniques:Employing techniques that require less energy, such as microwave-assisted extraction or ultrasound-assisted extraction.

Performing Reactions at Ambient Conditions:Designing analytical methods that can be carried out at room temperature and pressure.

*4. Green Chromatographic Techniques:*

Alternative Mobile Phases:Using environmentally friendly mobile phases in chromatography, such as water or supercritical CO2.

Miniaturization of Chromatography:Using micro- and nano-chromatography techniques to reduce solvent consumption.

*5. Green Spectroscopic Techniques:*

Non-invasive Techniques:Utilizing spectroscopic methods like UV-Visible, FTIR, and NIR spectroscopy, which minimize the need for hazardous reagents.

*6. Implementation in Pharmaceutical Synthesis:*

Biocatalysis:Using enzymes as catalysts to carry out reactions in a more environmentally friendly manner.

Continuous Flow Chemistry:

Implementing continuous flow processes to minimize waste and increase efficiency.

Utilizing renewable feedstocks:Using raw materials that are derived from renewable resourses.

1. *Quality Control and Analysis*:

Development of Green Analytical Methods:Creating analytical methods for quality control that adhere to green chemistry principles.In-process Monitoring:Implementing in process monitoring to reduce the amount of waste created from off line testing.

8.*Applications of sustainable green solvents in microextraction* for MS Analysis

Utilizing environmentally friendly, sustainable solvents in microextraction for MS analysis
A sample inlet, an ion source, a mass analyzer, and a detector are the four primary parts of a mass spectrometer. Ion sources, mass analyzers, and detectors have essentially stayed the same in terms of design, but their performance capabilities have steadily increased, leading to a lower limit of quantitation and quicker analysis times. In contrast to alternative spectroscopic devices, such as Raman, fluorescence, UV-visible, near-IR, and nuclear magnetic resonance spectrometers,

**CONCLUSION:**
The advancement of analytical techniques has been significantly influenced by the principles of **Green Analytical Chemistry (GAC)**, which emphasizes the reduction of environmental impact through sustainable practices. Traditional sample preparation methods like Solid-Phase Extraction (SPE) and Liquid-Liquid Extraction (LLE) are effective but often involve the use of hazardous solvents and labor-intensive procedures. In contrast, modern approaches such as microextraction techniques, solvent substitution, and the use of green solvents (e.g., ionic liquids, deep eutectic solvents) offer promising alternatives that align with environmental sustainability goals.

The integration of **innovative extraction methods** and **sensitive analytical techniques** not only enhances the accuracy and efficiency of analytical procedures but also reduces the consumption of solvents, energy, and reagents. Tools like the **National Environmental Methods Index (NEMI)** and the **Analytical Eco-Scale** provide quantitative measures to assess the environmental footprint of analytical methods.

In conclusion, adopting green analytical practices is vital for promoting eco-friendly laboratory environments, reducing hazardous waste, and contributing to global sustainability efforts. The continuous development of sustainable methodologies will play a crucial role in advancing analytical chemistry while preserving environmental health.

**Reference**

1. Collier R (2018) A short history of pain management. Can Med Assoc J 190:E26–E27. <https://doi.org/10.1503/cmaj.109-5523>
2. National Library of Medicine (US), Paracetamol, (n.d.).

<https://pubchem.ncbi.nlm.nih.gov/compound/Paracetamol-d3.> Accessed 1 Oct 2023

1. Patel DM, Sardhara BM, Thumbadiya DH, Patel CN (2012) Development and validation of spectrophotometric method for simultaneous estimation of paracetamol and lornoxicam in different dissolution media, Pharm. Methods 3:98–101. <https://doi.org/10.4103/2229-4708.103885>
2. Divya K, Narayana B, Sapnakumari M (2013) Sensitive spectrophotometric determinations of paracetamol and protriptyline HCl using 3-Chloro-7-hydroxy-4- ethyl-2 H -chromen-2-one. ISRN Spectrosc 2013:1–6. <https://doi.org/10.1155/2013/935819>
3. Chandra P (2012) Application of HPLC for the simultaneous determination of ceclofenac, paracetamol and tramadol hydrochloride in pharmaceutical dosage form. Sci Pharm 80:337–351. <https://doi.org/10.3797/scipharm.1108-04>
4. Martel-Pelletier J, Cloutier J-M, Pelletier J-P (1997) Effects of aceclofenac and diclofenac on synovial inflammatory factors in human osteoarthritis. Clin Drug Investig 14:226–232. <https://doi.org/10.2165/00044011-199714030-00011>
5. Legrand E (2004) Aceclofenac in the management of inflammatory pain. Expert Opin Pharmacother 5:1347–1357. <https://doi.org/10.1517/14656566.5.6.1347>
6. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R (2017) Trends in tramadol: pharmacology, metabolism, and misuse. Anesth Analg 124:44–51. <https://doi.org/10.1213/ANE.0000000000001683>
7. Mauger AR, Thomas T, Smith SA, Fennell CRJ (2023) Tramadol is a performance-enhancing drug in highly trained cyclists: a randomized controlled trial. J Appl Physiol 135:467–474. <https://doi.org/10.1152/japplphysiol.00338.2023>
8. Warning tramadol added to the prohibited list, (n.d.). https://www.sportintegrity.gov.au/news/integrity-blog/2023-10/warning-tramadol-added-2024-prohibited-list#::text=Tramadol. misuse is of concern,Tramadol to enhance sports performance. Accessed 3 Jan 2024
9. Lewis KS, Han NH (1997) Tramadol: a new centrally acting analgesic. Am J Heal Pharm 54:643–652. <https://doi.org/10.1093/ajhp/54.6.643>
10. Armenta S, Garrigues S, de la Guardia M (2008) Green analytical chemistry. TrAC Trends Anal Chem 27:497–511. <https://doi.org/10.1016/j.trac.2008.05.003>
11. Kannaiah KP, Chanduluru HK, Obaydo RH, Lotfy HM, Erk N, Krishnan M, El Hamd MA (2023) Application of advanced environmentally benign assessment tools in determining ternary cardiovascular drug combination by RP-HPLC with analytical quality by design: application to stability indicating method evaluation. Sustain Chem Pharm 35:101197. <https://doi.org/10.1016/j.scp.2023.101197>
12. Mihkel Koel, Green chemistry, (n.d.). <https://pubs.rsc.org/en/content/getauthorversionpdf/C5GC02156A>
13. Siddiqui FA, Arayne MS, Sultana N, Qureshi F (2011) Development and validation of stability-indicating HPLC method for the simultaneous determination of paracetamol, tizanidine, and diclofenac in pharmaceuticals and human serum. J AOAC Int 94:150–158