



# Recent Advances, Applications, and Future Perspectives of Sustainable Green Solvents in Pharmaceutical Analysis

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**Abstract:** This study is devoted to the new breakthroughs and practical applications of sustainable green solvents for pharmaceutical analysis, with special attention to environmental and safety hazards linked to conventional organic solvents such as acetonitrile and methanol. It also includes significant environmentally friendly alternatives, such as bio-based organic solvents like ethanol, ethyl lactate, and dimethyl carbonate, as well as neoteric options such as ionic liquids (ILs), deep eutectic solvents (DESs), and natural deep eutectic solvents (NADESs). These sustainable systems are being progressively employed in analytical separation techniques like liquid chromatography (RP-HPLC and UHPLC) and miniaturized sample preparation methods (e.g., solid-phase and liquid-phase microextractions). Although these solvents are able to assist the analytical performance, concerns related to viscosity, purification, and safety evaluation still deserve further considerations. The article also outlines future directions. Researchers turn to miniaturized and automated procedures, such as microextractions, when sample preparation is unavoidable. The report also considers future directions such as predictable molecule design, multi-solvent systems, and industrial scale-up.

**Keywords:** Green solvents; Green Analytical Chemistry; Deep eutectic solvents; Natural deep eutectic solvents; Green chromatography; Miniaturized extraction.

## 1. Introduction of the Study

Industrial progress and advancements in medicine have substantially improved the life expectancy around the globe, and the chemical burden on the environment has also increased <sup>22</sup>. In this respect, analytical laboratories are important and persistent generators of chemical waste <sup>29</sup>. In the past, the focus of pharmaceutical testing has been on the speed and precision of the analysis, with less attention paid to the environmental challenges <sup>3,22</sup>. This approach is presently undergoing a major change <sup>3</sup>. Analytical choices increasingly impact analytical results, worker safety, laboratory costs, and environmental implications <sup>22</sup>.

### 1.1 Importance of Solvent in Pharmaceutical Analysis

Solvents are important working media for drug testing, quality-control procedures, and clinical monitoring <sup>13,29</sup>. Their value is especially pronounced in sample preparation and chromatographic separation <sup>1,13</sup>. Solvents: Normal laboratory practice requires the use of large quantities of solvents. Solvents are used in sample preparation for the extraction, purification, and concentration of active pharmaceutical ingredients (APIs) and their metabolites from complex biological matrices or final pharmaceutical dosage forms <sup>13,23</sup>. Liquid chromatography employs solvents as mobile phases to carry analytes along the column and to modulate their partitioning, particularly in reversed-phase high-performance liquid chromatography (RP-HPLC) <sup>13</sup>, which is used in analytical separation. These activities are valuable for assessment of drug purity, identification of trace contaminants, stability and degradation investigations, and pharmacokinetic study in clinical samples <sup>13</sup>. In normal laboratory work, one

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requires large amounts of solvents. Large quantities of solvents Normal laboratory practice requires the use of large quantities of solvents. in normal laboratory practice. Therefore, large quantities of solvents are needed for routine laboratory operations<sup>13, 13</sup>.

## 1.2 Problems of Traditional Solvents

Conventional solvents, albeit successful analytically, pose considerable environmental and occupational safety concerns<sup>13</sup>. Traditionally, chromatographic procedures have relied heavily on hazardous, petroleum-derived modifiers, particularly acetonitrile and methanol<sup>13</sup>. Laboratory personnel may be exposed to these chemicals for long periods<sup>1,22</sup>. For instance, acetonitrile is rapidly absorbed and then metabolized to deadly cyanide, which severely inhibits cellular respiration<sup>22</sup>, while methanol is degraded to toxic formaldehyde and formic acid that may cause irreversible damage to the optic nerve<sup>9,22</sup>.

The issue is not so much toxicity but the volume of rubbish created. One HPLC system at 1 mL/min for 24 h a day yields around 1.5 L of toxic waste a day, or about 500 L of hazardous effluent a year<sup>13</sup>. Many chromatographic instruments in pharmaceutical laboratories can run simultaneously and produce thousands of liters of hazardous waste each day<sup>13</sup>. Waste disposal also carries economic costs and environmental hardship<sup>13</sup>. Furthermore, the typical sample-preparation procedures are often performed using volatile organic solvents such as chloroform, hexane, or toluene, which may be discharged to the atmosphere, cause photochemical smog, and potentially leave harmful residues in pharmaceutical products<sup>3,10,22</sup>.

## 1.3 Evolution of Green Analytical Chemistry

To confront these difficulties, the scientific community has been more and more adopting the ideas of Green Analytical Chemistry (GAC)<sup>13,22</sup>. GAC originated from the broader field of green chemistry, which aims to prevent the creation of waste at the stage when methods are being designed, instead of addressing trash after it has been generated<sup>22</sup>. The 12 principles of GAC: Gałuszka, Migaszewski, and Namieśnik proposed the 12 principles of GAC in 2013, which are by Gałuszka, Migaszewski, and Namieśnik (2013) and guide sustainable analytical procedures<sup>29,3,22</sup>.

This paradigm enables investigators to reduce analytical procedures and limit their environmental impact through direct, in situ measurements without the need for sample preparation, reduced sample volumes, and energy consumption<sup>22,29</sup>. Where sample preparation cannot be avoided, researchers are increasingly adopting miniaturized and automated methods, such as microextractions. Researchers are increasingly adopting miniaturized and automated approaches, such as microextractions, when sample preparation is unavoidable. Where sample preparation is unavoidable, researchers focus on miniaturized and automated procedures, e.g., microextractions<sup>1,25</sup>. Researchers are interested in miniaturized and automated approaches, such as microextractions<sup>1,25</sup>. One of the main goals of GAC is to replace old petroleum-based solvents with cleaner and more sustainable media<sup>3</sup>. These are bio-based solvents (ethanol, ethyl lactate, and terpenes), supercritical fluids, and neoteric designer systems such as ionic liquids, deep eutectic solvents, and natural deep eutectic solvents<sup>1,3,10,13</sup>.

## 1.4 Objectives and Scope

This review highlights the recent progress in sustainable green solvents in pharmaceutical analysis. Their practical applicability in both miniaturized sample preparation and chromatographic separations is explored<sup>1,13</sup>. We also discuss the performance of bio-based solvents, ionic liquids, and eutectic mixtures, with a focus on the molecular interactions that determine their solvation<sup>1,21</sup>. We then critically discuss practical limitations (viscosity, purification, and toxicity) to identify future study areas in predictable solvent design and automated procedures<sup>3,21</sup>.

## 2. Green Solvents for Pharmaceutical Analysis

The choice of solvent is a crucial aspect in building sustainable processes in pharmaceutical analysis. Conventional analytical processes involve organic media that are volatile, toxic, and produced from petroleum. Therefore, they pose major environmental and occupational hazards<sup>22,15,3</sup>. To minimize these impacts, Green Analytical Chemistry (GAC) promotes the use of environmentally friendly alternatives that reduce the environmental footprints without affecting the analytical performance<sup>13,3,4</sup>. Water, bio-based solvents, ionic liquids, deep eutectic solvents, and supercritical fluids are the main choices. Each has its own set of properties that can be used. Different types of analysis can utilize the unique properties of each solvent. Different types of analysis can utilize the unique properties of each solvent<sup>3,11</sup>.

| Green Solvent Category     | Specific Examples                                                       | Key Applications in Pharmaceutical Analysis                                                                                   | Advantages                                                                    | Limitations & Challenges                                                                                                                                                       |
|----------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Water & Bio-based Solvents | Water, Bioethanol, Ethyl lactate, Glycerol, Terpenes (e.g., D-limonene) | Reversed-phase liquid chromatography (RP-HPLC/UHPLC) modifiers, subcritical water extraction (SWE), phytochemical extractions | Highly abundant, non-toxic, biodegradable, and renewable agricultural sources | High viscosity causing backpressure, chemical instability in acidic/alkaline media, high energy requirements for distillation, and potential for photochemical smog (terpenes) |

| Green Solvent Category                                          | Specific Examples                                                                                  | Key Applications in Pharmaceutical Analysis                                                                                                             | Advantages                                                                                              | Limitations & Challenges                                                                                                 |
|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| <b>Ionic Liquids (ILs) &amp; Deep Eutectic Solvents (DESSs)</b> | Cholinium-based ILs, Type I–V DESs, Natural Deep Eutectic Solvents (NADESs)                        | Mobile-phase additives for blocking silica silanols, extraction solvents in dispersive liquid-liquid microextraction (DLLME), and herbal drug profiling | Excellent solvation power, lower volatility, tunable properties, and improved biodegradability (NADESs) | High synthesis costs, high intrinsic viscosity limiting mass transfer, and scarcity of long-term toxicological data      |
| <b>Supercritical Fluids &amp; Polar Aprotic Alternatives</b>    | Supercritical carbon dioxide ( $\text{CO}_2$ ), Propylene carbonate (PC), Dimethyl carbonate (DMC) | Supercritical fluid extraction (SFE), enhanced fluidity liquid chromatography (EFLC), and replacement of acetonitrile in RP-HPLC                        | Non-toxic, inexpensive, rapid solvent removal via depressurization, and 100% atom economy synthesis     | Low water miscibility, poor mass transfer, and requirement for polar co-modifiers (e.g., ethanol) to solvate polar drugs |

Table 1: Sustainable Green Solvents In Pharmaceutical Analysis

## 2.1 Solvents: water and bio-based solvents

Water is frequently used as one of the safest, most abundant, and cheapest solvents in analytical chemistry<sup>11,17</sup>. Being non-toxic, non-flammable, and entirely biodegradable, it is particularly attractive from the safety perspective<sup>3,11</sup>. One of the major advancements is subcritical water extraction (SWE) or pressured hot water extraction, which makes use of the radical changes in the physicochemical properties of water with increasing temperature under pressure<sup>11</sup>. Normally, water is very polar and has a high dielectric constant, which makes it a poor eluent for relatively nonpolar compounds in reversed-phase high-performance liquid chromatography (RP-HPLC)<sup>13</sup>. The dielectric constant and polarity of water decrease significantly with increasing temperature and pressure, causing them to resemble organic modifiers like methanol<sup>11,3</sup>. This change causes the properties of water to resemble those of organic modifiers, such as methanol<sup>11,3</sup>.

However, in addition to these advantages, water also has certain specific challenges in chromatography. In liquid chromatography, retention loss and peak tailing may occur when traditional C8 or C18 columns are exposed to 100% water mobile phases at ambient temperatures due to “phase collapse” or “phase dewetting”<sup>13</sup>. Generally, using columns with polar end-capping or embedded polar groups generally addresses this problem<sup>13</sup>. by using columns with polar end-capping or embedded polar groups<sup>13</sup>. The large heat capacity of water also means that the downstream distillation and evaporation are particularly energy intensive and should thus be included in a thorough life-cycle assessment<sup>17</sup>.

The target analytes cannot be suitably dissolved in water alone<sup>10,3,4</sup>, so bio-based solvents from natural, renewable agricultural sources have gained growing interest. These bio-solvents can be categorized as cereal/sugar-based, oleo-proteinaceous-based, and wood-based solvents<sup>3</sup>.

The most common example of cereal and sugar-based solvents is bioethanol, which is produced by the fermentation of biomass sugars<sup>3</sup>. Ethanol is used as a more environmentally friendly mobile-phase modifier in reversed-phase liquid chromatography instead of hazardous acetonitrile and methanol<sup>13,28</sup>. However, the main disadvantage of ethanol for chromatography is its high viscosity at which results in high backpressure in HPLC systems<sup>13,28</sup>. To avoid the high viscosity, a common way is to do separations at high temperatures which minimizes the viscosity and enhances the mass transfer at the same time<sup>13</sup>. Another solvent is ethyl lactate, which is produced from cereal crops such as corn and soybeans<sup>10</sup>. While ethyl lactate is primarily biodegradable, non-toxic, and appropriate for phytochemical extractions, its use as an HPLC modifier is constrained by its chemical instability in either acidic or alkaline media and high UV cutoff wavelength<sup>10,13</sup>.

Oleo-proteinaceous substances as solvents offer exceptionally stable, non-volatile, and low-cost substitutes to typical chemical reagents with fatty acid esters and glycerol derivatives<sup>3</sup>. The use of glycerol as a lasting reaction medium and as a mobile phase modifier in liquid chromatography is becoming more popular<sup>11,29</sup>.

Terpenes are extracted from trees and fruit peels and used as wood-based solvents<sup>3</sup>. Terpenes such as D-limonene are useful non-polar biosolvent substitutes for the hazardous hexane or toluene<sup>10,3</sup>. However, terpene is not necessarily green; it has a significant propensity to contribute to photochemical smog (tropospheric ozone) due to its volatility in air and relatively high toxicity to aquatic organisms<sup>10,15</sup>.

## 2.2 Ionic Liquids and Deep Eutectic Solvents

Ionic liquids (ILs) are salts of organic bases that are liquid at temperatures below 100°C<sup>1,11</sup>. ILs have also been extensively explored and employed in pharmaceutical analysis as mobile phase additives for blocking silica silanols and preventing the tailing of basic drug peaks<sup>13</sup> or as extraction solvents in dispersive liquid-liquid microextraction (DLLME)<sup>1,16</sup>. But certain popular ILs have high synthesis costs, high viscosity, low biodegradability, and high toxicity to aquatic ecosystems<sup>10,11,26</sup>. Recent investigations have been devoted to the invention of safer biodegradable ILs based on natural metabolites such as cholinium cations<sup>1,17</sup>.

ILs have cost and preparation disadvantages. In an effort to solve these problems, Deep Eutectic Solvents (DES) and Natural Deep Eutectic Solvents (NADES) are attracting more and more attention <sup>1,21</sup>. They are formed by mixing a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD), and the obtained combination shows a considerable melting point depression at their eutectic composition <sup>1,19</sup>. Common HBAs <sup>19</sup> include cholinium chloride, betaine, proline, and glycine, which can be coupled with natural HBDs such as organic acids, sugars, or polyols to generate highly biodegradable NADES <sup>1,11</sup>. Structurally, DES are classified into Type I to Type V <sup>21</sup>. Type V DES is a growing class, which solely contains nonionic components (e.g., coumarin and aromatic organic acids) <sup>8,21</sup>. The relatively high viscosity of DES and NADES is a significant drawback for analytical chemistry. This disadvantage is generally overcome by heating or by the addition of a controlled amount of water (often 28%) as a co-solvent to reduce the density and improve the mass transfer <sup>2,19,21</sup>.

### 2.3 Green Solvents: Supercritical Fluids and Others

#### 2.3.1 Supercritical Fluids

Supercritical fluid extraction (SFE) is an automated technology with advantages in sustainability and is carried out above the critical point of a fluid <sup>3,7</sup>. The most used medium is supercritical carbon dioxide, because of its low critical parameters, which help minimize energy needs <sup>27,3,7</sup>. It is generally inexpensive and non-toxic and can be quickly removed by depressurization to obtain solvent-free extracts <sup>10,3</sup>. The pure fluid is nonpolar; thus, polar medications are usually better solvated by the addition of polar modifiers, e.g., ethanol <sup>3</sup>. These greater levels are called enhanced fluidity liquid chromatography (EFLC) <sup>29</sup>.

Other sustainable organic solvents have been proposed for pharmaceutical chromatography. Propylene carbonate (PC) is a polar aprotic solvent, 100% atom economy synthesis, and biodegradable <sup>24</sup>. It can be utilized as a replacement for hazardous acetonitrile in RP-HPLC in combination with ethanol <sup>7,13</sup>. Mobile phases based on a PC can show similar elution behavior but are constrained by low water miscibility and poor mass transfer, leading to lower optimal flow rates <sup>13</sup>. In addition, dimethyl carbonate (DMC) is a bio-based and highly polar organic solvent <sup>15,28</sup>. DMC and DMC/ethanol mixtures may have a separation efficiency and peak symmetries similar or better than those of common acetonitrile-based mobile phases with the use of appropriate stationary phases <sup>28</sup>.

## 3. Pharmaceutical Applications of Analytical Techniques

The pharmaceutical industry is heading toward a reassessment of its analytical procedures, benchmarking analytical performance against environmental impact <sup>22,29</sup>. Quality control, stability monitoring, and pharmacokinetics are generally chemistry-intensive activities <sup>13</sup>. Two complementary strategies support the development of Green Analytical Chemistry (GAC), including the use of scaled-down systems (resulting in lower resource consumption) and the substitution of hazardous petroleum-based materials with sustainable and non-toxic media <sup>3,29</sup>. The developments in chromatography, spectroscopy, and sample preparation are significant advancements in the field. The next section outlines the developments in chromatography, spectroscopy, and sample preparation. in the next section.

### 3.1 Green chromatography approaches

Reversed-phase high-performance liquid chromatography (RP-HPLC) is the most common technology used for quality control of active pharmaceutical ingredients (API) for clinical bioanalysis <sup>13</sup>. GAC encourages the use of benign modifiers <sup>3,29</sup> to decrease the use of hazardous acetonitrile and methanol and the waste created by their use <sup>13</sup>.

Ethanol is one of the cheapest and most commonly used organic modifiers due to its low toxicity and biodegradable waste <sup>13</sup>. The relatively high viscosity (1.19 mPa·s) causes a considerable back pressure. The viscosity is regulated by increasing the column temperature (for example, 50 °C), which leads to a drop in viscosity and an increase in mass transfer <sup>13</sup>. Statins (pravastatin, fluvastatin, and atorvastatin) and prednisolone tablets were dissolved in water-ethanol combinations <sup>13</sup>. GAC was used with Quality by Design (QbD) to develop a robust UHPLC method for degradation products of dextromethorphan <sup>13</sup>. Gradient ethanol mobile phases were able to simultaneously separate 16 APIs, including the chromophore-less artemether, despite baseline drift at 200 nm <sup>13</sup>. Capecitabine measurement was performed using plasma and formic acid and ethanol (55:45, v/v) <sup>13,7</sup>.

More green modifiers are opening up chromatographic possibilities. Acetonitrile can be replaced with propylene carbonate (PC) in combination with ethanol or methanol for acidic, neutral, and basic drugs <sup>13</sup>. However, mass transfer is limited by the low miscibility of PC in water and its high viscosity, which necessitates moderate flow rates and extended runs <sup>13</sup>. The PC-ethanol techniques enabled the separation of enalapril and enalaprilat in plasma and voriconazole and tadalafil in formulations. Dimethyl carbonate (DMC) is a novel bio-based modifier. DMC exhibits significant separation efficiency on diphenyl and fluorinated phenyl phases but cannot be used with highly polar medications unless they are pretreated in methanol prior to injection <sup>28</sup>. In mass spectrometry or charged aerosol detection (CAD), high resolution of peptide fingerprinting can be achieved by using acetone instead of acetonitrile <sup>13,29</sup>. Partitioning of indomethacin and olmesartan medoxomil was performed with ethyl acetate <sup>13</sup>.

An alternative is water-only systems. Hot water chromatography under pressure lowers the dielectric constant of water to resemble organic solvents <sup>3</sup>. Standard columns are prone to "phase collapse" with totally aqueous mobile phases at lower temperatures <sup>13</sup>. Paracetamol is determined by means of stationary phases with polar embedding groups (e.g., XTerra RP) or polyethylene glycol (PEG) stationary phases with mobile phases of water-triethylamine <sup>13</sup>.

Micellar Liquid Chromatography (MLC) and Ionic Liquids (ILs) may potentially add to the sustainability of the analytical procedures <sup>13</sup>. MLC employs aqueous solutions of surfactants (e.g., sodium dodecyl sulfate [SDS] or Brij-35) and

tiny quantities of propanol or butanol<sup>13</sup>. MLC permits the injection of complex biological fluids directly without extraction<sup>13</sup>. Oxycams, selective serotonin reuptake inhibitors, and tricyclic antidepressants<sup>13</sup> have proven successful in this respect. Room temperature ionic liquids, such as [BMIM][BF<sub>4</sub>], are employed as mobile phase additions to cap active silica silanols that result in reduced peak tailing for basic drugs<sup>1,13</sup>.

### 3.2 Spectroscopic and Spectrometric Methods

Spectroscopic methods are often considered greener since they consume less energy and produce far less solvent waste than chromatographic methods<sup>7</sup>. In UV–Vis spectroscopy, the substitution of toxic diluents, e.g., methanol, by safe and ecologically friendly solvents has been described<sup>7</sup>.

An inexpensive, non-toxic alternative is buffered water<sup>3</sup>. A pH 7.8 phosphate buffer was used for paracetamol, aceclofenac, and thiocolchicoside, as well as for paracetamol, aceclofenac, and eperisone hydrochloride, resulting in satisfactory recovery and no influence on UV spectra<sup>7</sup>. Also, propylene carbonate is a safe UV diluent<sup>7</sup>. It was effectively used in the assay of chlorthalidone and cildnidipine as a substitute for methanol<sup>7</sup>.

Computational chemometric and spectrophotometric methods solve mixtures with overlapping spectra without solvent-expensive separations<sup>7</sup>. For example, the zero-order spectra and Parent Spectrum Restoration Technique (PSRT) with smart spectrum subtraction were applied to resolve tablet combinations of atenolol, amiloride, and chlortalidone with minimum solvent use<sup>7</sup>. Resolution of fluticasone propionate and azelastine has also been reported<sup>7</sup>.<sup>7</sup> The prospective therapy for COVID-19: a spectrofluorimetric measurement of favipiravir in plasma with a sustained 0.2 M borate buffer. The separation of salicylic acid and mometasone furoate was also performed with minimal cost of operation by capillary zone electrophoresis (CZE) with fused-silica capillaries<sup>7</sup>.

### 3.3 Extraction and Preperation of Green Sample

Sample preparation is often the most resource- and waste-intensive stage of an analytical procedure, accounting for more than 80% of the total analysis time<sup>23</sup>. The GAC stresses the need for downsizing, automation, and the use of non-toxic extraction media<sup>1,23</sup>.

An important example of solventless sample preparation is solid-phase microextraction (SPME)<sup>3,23</sup>. An SPME fiber with a MIP based on acrylic acid has been employed successfully in clinical monitoring for the isolation of the antiviral drug abacavir from urine<sup>23</sup>. Biocompatible fibers based on polyacrylonitrile have permitted direct monitoring of tranexamic acid in plasma and urine of patients with renal failure<sup>23</sup>. In addition, the combination of SPME and TD-ESI/MS has been used for rapid pharmacokinetics evaluation of methylphenidate in plasma<sup>23</sup>.

Microextraction by Packed Sorbent (MEPS) and Fabric Phase Sorptive Extraction (FPSE)<sup>23,25</sup> are significant improvements over GAC. MEPS uses small sample sizes (10–229 µL) and highly reusable sorbents (up to 80 times in plasma)<sup>23</sup> to extract fluoroquinolones (ciprofloxacin and levofloxacin) from sputum and drugs of addiction (cocaine and amphetamines) from oral fluids<sup>23</sup>. MIPs (MIMEPS) might be determined together with trans,trans-muconic acid<sup>23</sup>. FPSE employs flexible cotton substrates with sol-gel polymer phases for the workflow and for the resolution of benzodiazepines in blood serum<sup>23</sup>.

More environmental benefits are possible with DLLME and new solvents<sup>3</sup>.<sup>22</sup> Lab-in-syringe platforms for online extraction and HPLC detection of fluoroquinolones automated with low-viscosity terpene-and-acid-based DES systems, L-proline:lactic acid (1:2), were more effective than standard methanol extractions in the extraction of active chemicals such as chlorogenic acid and ferulic acid from herbs<sup>21</sup>. The ultrasound-assisted matrix solid-phase dispersion (UA-MSPD) using a betaine and acetic acid (Bet-AA) mixture for solid plant materials led to a rapid extraction within 6 min<sup>19</sup>.

In addition, the solid phase extraction has been improved by using the advanced green membranes and biopolymer sorbents<sup>25</sup>. Agarose gels operate as green membranes for electro membrane extraction (EME)<sup>25</sup>. The liquid acceptor phases (such as HCl or 1-octanol) can be supported on the agarose membranes in an electric field for the removal of polar basic drugs, amino acids, and hypothalamic peptides from body fluids before the chromatographic determination<sup>25</sup>. Alginate-magnetite composites combined with a MIL-101(Cr)-NH<sub>2</sub> metal–organic framework were also successfully used for the collection of polar chlorophenoxy acid herbicides<sup>25</sup>.

## 4. Applications in Pharmaceutical Quality Control

The use of the principles of Green Analytical Chemistry (GAC) in pharmaceutical quality control is an important step to reduce the environmental footprint of the industrial testing laboratories<sup>4</sup>. Quality control labs are among the most intensive sources of hazardous solvent waste, doing thousands of assays a day<sup>8</sup>. The use of sustainable green solvents in regular analyses would help to maintain the important testing activities, such as active ingredient quantification, impurity profiling, shelf-life monitoring, and clinical bioanalysis, highly efficient while safeguarding human health and the environment<sup>3,6</sup>.

### 4.1 Assay and Quantification of Drugs

Currently, ethanol is the most chosen green organic modifier to replace harmful petroleum-derived solvents such as acetonitrile and methanol in reversed-phase liquid chromatography (RP-HPLC) research<sup>4,6</sup>. Analysts have developed and verified robust ethanol-based mobile phases for the measurement of a wide range of commercial active pharmaceutical ingredients (APIs)<sup>4</sup>. For example, prednisolone tablets are routinely measured in an ethanol-water mixture, and the column is operated at 50 °C to reduce solvent viscosity and control backpressure<sup>4</sup>. Also, ternary combinations of phenylephrine, paracetamol, and guaifenesin and multiple statins (pravastatin, fluvastatin, and atorvastatin) are quantified with high precision and peak symmetry using ethanol-modified mobile phases<sup>4</sup>. Even troublesome lyophilized powders such as daptomycin or topical formulations such as permethrin creams have been successfully adapted to ethanol-modified chromatography without

loss of analytical performance <sup>4</sup>.

Besides ethanol, several sustainable organic solvents are opening up new avenues for green tests <sup>4</sup>. The biodegradable, polar aprotic options include propylene carbonate (PC) and dimethyl carbonate (DMC) <sup>4,28</sup>. The PC-ethanol mixture was successful in quantifying the thermodynamic partitioning of the dosage forms of voriconazole, tadalafil, and diltiazem with equal results to known approaches <sup>4</sup>. In contrast, DMC-ethanol combinations exhibited good separation efficiency of polar and nonpolar medicines <sup>28</sup>. Spectroscopic methods using safe diluents such as pH 7.8 phosphate buffers without methanol may satisfactorily measure combinations of paracetamol–aceclofenac <sup>7</sup>. Cilnidipine and chlorthalidone were diluted with propylene carbonate, which is a non-toxic UV diluent <sup>7</sup>.

### 4.2 Analysis of impurities and degradation products

High-resolution analytical methods are important for impurity profiling and degradation monitoring because they can distinguish trace contaminants from the parent API <sup>7</sup>. These analyses: Powerful solvent gradient techniques typically handle these analyses <sup>8</sup>. Powerful solvent gradient techniques are used to conduct these analyses <sup>8</sup>. However, green solvents and modern chromatographic optimization technologies have demonstrated a considerable ability to tackle complex impurity patterns <sup>12</sup>.

Of note, the gradient UHPLC analysis was established for dextromethorphan and its pollutants <sup>4</sup>. Green solvents, quality by design (QbD), and response surface methodologies were used to develop a robust “design space” that allowed baseline resolution of the parent drug and all degradants with a gradient ethanol-ammonium formate system <sup>4</sup>. In a similar manner, gradient ethanol mobile phases were able to separate 16 different active medicinal compounds, including artemether, which has no chromophore, indicating that green mobile phases can provide unique selectivity compared to conventional acetonitrile systems <sup>4</sup>.

Green chromatographic techniques have been proven beneficial for the separation of hazardous chemicals in combination formulations <sup>12</sup>. The optimized runs were employed for the analysis of dimenhydrinate and cinnarizine and their synthetic impurities with a reduction in the consumption of the solvent <sup>12</sup>. It successfully isolated the dangerous degradant 4-aminophenol from caffeine and propyphenazone in paracetamol preparations using a stable PEG stationary phase with a totally water-based mobile phase <sup>4</sup>. In addition, green thin layer chromatography (TLC) densitometric methods were validated for measurement of zonisamide and modafinil, where good separation of their degradation products was achieved by using benign non-halogenated mobile phases <sup>7</sup>.

### 4.3 Stability and Dissolution Studies

Continuous analytical monitoring under forced degradation conditions (e.g., acidic, alkaline, oxidative, thermal, and photolytic stress) is necessary for the stability testing of pharmaceuticals because dissolution testing produces enormous volumes of samples <sup>7,12</sup>. Green analytical techniques may substantially decrease the environmental load of these high-frequency processes <sup>12</sup>.

Green dissolution monitoring based on chemometric techniques has been developed <sup>12</sup>. A green dissolution-monitoring method for meloxicam and pridinol combinations was devised, using mathematical algorithms to prevent expensive solvent chromatographic separations <sup>12</sup>.

Micellar liquid chromatography (MLC) has been suggested as a very sustainable alternative in stability studies <sup>4</sup>. Efficient stability-indicating separations may be accomplished using MLC with biodegradable surfactant solutions such as sodium dodecyl sulfate (SDS) or Brij-35 and tiny quantities of organic modifiers such as propanol or butanol <sup>4</sup>. A confirmed stability-indicating MLC method could separate the anti-inflammatory drugs piroxicam, tenoxicam, and lornoxicam in commercial gels and suppositories and allowed the direct injection of these semi-solid matrices without hazardous organic extractions <sup>4</sup>. Likewise, the stability of new anti-HIV prodrugs of zidovudine and lamivudine was tested in simulated stomach and intestinal fluids using green MLC mobile phases <sup>4</sup>. This approach has also been used for stability studies of flavoxate HCl and several cardiovascular drugs <sup>4</sup>. It is shown that micellar eluents are useful for routine shelf life investigations.

### 4.4 Herbal Drug Analysis and Bioanalytical

Bioanalytical work is particularly challenging because of the complexity and protein richness of bodily fluids like plasma and urine <sup>6,23</sup>. Capecitabine was determined in human plasma for clinical bioanalysis by a simple mobile phase of formic acid and ethanol for pharmacokinetic monitoring <sup>4</sup>. Also, a green UHPLC-MS/MS approach was used for the determination of quetiapine in rat plasma <sup>4</sup>. PC-ethanol combinations were used for extraction and testing of enalapril and enalaprilat instead of hazardous acetonitrile at all stages of the workflow <sup>4</sup>. MLC can also be used for biological tests. The anti-HIV medicines abacavir, lamivudine, and raltegravir were directly assessed in human plasma without protein precipitation with a totally aqueous SDS mobile phase <sup>4</sup>.

The advent of natural deep eutectic solvents (NADESs) and green extraction technologies <sup>19,21</sup> has opened new ways for therapeutic screening in the research of herbal and natural goods. Betaine-acrylic acid (Bet-Aa) combined with ultrasound-assisted matrix solid-phase dispersion (UA-MSPD) was used to extract and quantify seven alkaloids and chlorogenic acid from *Coptidis Rhizoma* in six minutes, which was five times faster than the conventional methanol extractions <sup>19</sup>. The DES system of choline chloride/acetamide was applied for the high-efficiency recovery of bioactive flavonoids from the nutritious species *Torreya grandis*, with maintenance and increase of their natural antioxidant activity compared with typical organic macerations <sup>21</sup>. In addition, L-proline/lactic acid NADES have been utilized to extract medicinal phenolic compounds and sesquiterpene lactones from lettuce leaves <sup>21</sup>, and ChCl-citric acid and ChCl-glycerol combinations extracted bioactive terpenoids from citrus leaves <sup>21</sup>. This also emphasizes the considerable flexibility of designer green fluids in profiling complicated natural medicines.

## 5. Analytical Methods for Greenness Assessment

The move to sustainable analytical techniques in pharmaceutical laboratories calls for objective tools that can demonstrate significant advances in environmental sustainability<sup>29</sup>. Regular assessments are required to reliably quantify ecological benefits from replacement of hazardous solvents<sup>29</sup>. In the last two decades, green-assessment metrics have been transformed from simple qualitative checklists into sophisticated quantitative and visual multi-criteria platforms<sup>25</sup>. These measurements allow analysts to analyze the entire process life cycle without mistakenly moving the environmental load to other steps in the workflow through the use of green mobile phases or extraction technologies<sup>28,29</sup>.

### 5.1 Evaluation of the Eco-Scale

The ecological footprint of analytical procedures was evaluated on the basis of the Analytical Eco-Scale, a semiquantitative methodology developed by Gałuszka et al.<sup>13,25</sup>. The system is based on a value of 100 points as a reference for the ideal, fully eco-friendly, and pollution-free process<sup>25,29</sup>. Four operational factors are used to assign the “penalty points” from this baseline value: the quantity and hazards of the chemical reagents employed, the overall energy consumption of the instruments, the risks to the workers’ safety, and the generation and treatment of waste<sup>13,25,29</sup>. If the final score is above 75, the method is considered a special green analysis, whereas a score below 50 is a non-sustainable process<sup>25</sup>.

The analytical Eco-Scale is useful for routine laboratory testing, but it has many disadvantages<sup>25</sup>. The scoring approach does not consider early life cycle events such as sample collection, preservation, and transport<sup>25</sup>. Moreover, the outcome is a single number instead of a graphical representation. This makes it challenging to understand the exact environmental restrictions of a procedure and impairs a fast target-oriented optimization<sup>25</sup>. Thus, researchers prefer to combine the Eco-Scale with modern visual profiling tools to achieve a more balanced analysis<sup>29</sup>.

### 5.2 AGREE and GAPI

To overcome these shortcomings, advanced multi-criteria tools have been created for the study of the full analytical process<sup>29</sup>. In 2019, Płotka-Wasyłka<sup>25</sup> presented the Green Analytical Procedure Index (GAPI). The GAPI diagram is made up of five pentagons, which evaluate fifteen distinct elements, from sample collection, preparation, reagents used, and instrumentation to final waste disposal<sup>25,29</sup>. GAPI shows impact using a simple scale of three colors. Green denotes low environmental impact, yellow denotes medium impact, and red denotes major ecological or safety problems<sup>19,25</sup>. This visualization enables rapid identification of procedural “hotspots”<sup>25</sup>.

In 2019, Pena-Pereira et al.<sup>29</sup> proposed the Analytical Greenness Calculator (AGREE), which is a quantitative evaluation based on analytical software. AGREE summarizes 12 principles of green analytical chemistry into one number score from 0 to 1<sup>29</sup>. The result is shown as a circular clock-like sign with the overall sustainability score in the middle and twelve color-coded segments surrounding it, one for each principle<sup>29</sup>. AGREE and GAPI are currently the gold standards for general eco-assessments, but they may have difficulties in distinguishing subtle differences in greenness when comparing complex chromatographic mobile phases under identical conditions, thus indicating the need for specialized comparative algorithms<sup>28</sup>.

### 5.3 Comparison of green analytical methods

In the development of chromatographic methods the sustainability of the solvent may influence the chromatographic performance<sup>28</sup>. For example, reducing the amount of organic modifiers or using safer substitutes may lead to low peak resolution and extended run times<sup>12,28</sup>. To resolve these conflicting objectives, researchers use multicriteria decision analysis (MCDA) approaches, including the TOPSIS algorithm<sup>28</sup>. TOPSIS enables investigators to objectively balance analytical capabilities (peak resolution, symmetry, analysis durations) and chemical safety indices (CHEMS-1, ChlorTox risks) to select the most efficient and sustainable separation system<sup>28</sup>.

Increasingly, researchers adopted White Analytical Chemistry (WAC)<sup>29</sup> to relate ecological markers with test results. The WAC extends the existing green-chemistry concept by integrating the three pillars of sustainable development: environmental safety, analytical quality, and economic productivity<sup>29</sup>. The grading is based on the red-green-blue (RGB) additive color paradigm. The score of a method is calculated based on its validation efficiency (Red), environmental greenness (Green), and cost-effectiveness (Blue)<sup>29</sup>. To be accorded the final classification of a “white” approach<sup>29</sup>, a technique must receive the final designation (66.6% or higher) for all three characteristics. Thus, this balanced multidimensional structure ensures that the green analytical processes are ecologically benign as well as scientifically validated, practicable, and highly viable for commercial pharmaceutical quality control<sup>29</sup>.

## 6. State of the Art and Perspectives

Green analytical chemistry has developed from a simple substitution of solvents to a very comprehensive technical science<sup>3,29</sup>. The increasing convergence of pharmaceutical analysis with sophisticated technologies is a result of the synergy between green chemistry and advanced digitalization, automation, and molecular engineering<sup>16,21,29</sup>. Recent developments are shifting the way laboratories optimize analytical performance and reduce their environmental footprint<sup>22,29</sup>.

### 6.1 AI and Digital Methods for Green Development Methods

A recent major success in the development of a sustainable approach is the integration of digital devices with artificial intelligence<sup>16</sup>. The choice of green solvent was typically based on experimental trial and error<sup>13</sup>. For high-throughput virtual screening of sustainable materials and solvents, computational methods such as density functional theory (DFT), molecular dynamics, and machine learning algorithms can be used before any actual laboratory testing<sup>16</sup>.

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Besides these computational approaches, the quantum chemical modeling using the COnductor-like Screening MOdel for Real Solvents (COSMO-RS) can be used for the prediction of thermodynamic properties, solubility, and phase behavior of complex mixtures based on molecular frameworks only <sup>24</sup>. In parallel, unsupervised chemometric methods, such as principal component analysis (PCA) and cluster analysis, can be applied to classify solvents based on their physical properties, thus allowing for rapid identification of green replacements with similar solvation properties to the hazardous target solvents <sup>12</sup>. The application of improved quantitative structure–activity relationships (QSARs) for the prediction of ecotoxicity and safety features can also enable early screening of risky candidates <sup>30</sup>. Multicriteria decision analysis (MCDA) methods such as TOPSIS have been applied to obtain the optimal compromise in chromatography <sup>28</sup> so as to solve the unavoidable trade-off between separation efficiency and greenness metrics.

### 6.2.1 Miniaturization and Reduction of Solvent

Toxic solvent removal is critical, but the most straightforward way to reduce the impact of solvents is often to avoid them <sup>15,29</sup>. This strategy has inspired a lot of work on the development of tools that minimize solvent consumption and use <sup>29</sup>. The advent of ultra-high-performance liquid chromatography (UHPLC) and nano-LC in liquid chromatography has resulted in a significant decrease in capillary and column dimensions and thus a substantial decrease in mobile phase consumption compared to conventional amounts <sup>1</sup>.

The sample preparation phase, historically the most inefficient process <sup>23</sup>, is more and more often performed with smaller and solvent-free or low-solvent technology. The solid-phase microextraction (SPME), microextraction in a packed sorbent (MEPS), and fabric-phase sorptive extraction (FPSE) procedures utilize just microliter volumes of green eluents <sup>23</sup>. In the case of highly automated systems such as lab-in-syringe manifolds, the extraction of the sample and injection are performed online directly in the syringe pump, avoiding manual work and energy-consuming centrifugation <sup>22</sup>. Another step in miniaturization is the lab-on-a-chip (LOC) technology that combines sample preparation, separation, and detection on a single microfluidic platform, allowing for portable, high-throughput, and almost waste-free pharmaceutical testing <sup>29</sup>.

### 6.3 Sustainable solvents for the future

The array of sustainable solvents is growing steadily, beyond simple biobased organic liquids <sup>1,9</sup>. NaDESs (Natural Deep Eutectic Solvents) are gaining attention as versatile, biocompatible media composed of abundant natural metabolites such as organic acids, sugars, and choline <sup>9</sup>. Currently, NaDESs are used beyond extraction as therapeutic deep eutectic systems (TDES), where the active pharmaceutical ingredient serves as a eutectic partner to increase drug delivery and stability <sup>9,21</sup>.

Type V deep eutectic solvents, which are hydrophobic systems comprising only nonionic species (e.g., coumarin with aromatic organic acids), are also being investigated for their potential in extraction of polar analytes from aqueous solutions <sup>8</sup>. Switchable-hydrophilicity solvents (SHSs) are another recent development that can undergo phase separation or miscibility changes in response to simple external stimuli such as bubbling CO<sub>2</sub>, thus improving analyte recovery and solvent reusability <sup>29</sup>. “Ephemeral” systems are also being developed as a temporary reaction or extraction medium that can be rapidly disassembled after use, thus simplifying purification <sup>17</sup>.

### 6.4 Obstacles and Prospects

Nevertheless, there are still some critical hurdles to the widespread industrial adoption of green solvents <sup>21</sup>. Deep eutectic mixtures and ionic liquids have high inherent viscosity, which hinders mass transfer and affects flow-based automation <sup>21</sup>. The lack of standardized toxicological and metabolic data is another challenge, making it difficult to evaluate the long-term safety and biodegradability of many designer solvents <sup>21</sup>. This lack of information creates uncertainty about their regulatory status, with agencies debating whether innovative green fluids should be classified as co-solvents, excipients, or active carriers <sup>21</sup>.

The high capital expenditure of new instruments and the changing price of emerging green solvents are further barriers to change <sup>11</sup>. Academics should perform thorough life-cycle assessments (LCAs) for true sustainability. For example, the energy required to distill water can sometimes outweigh the environmental benefits of water over easily recyclable organics <sup>17</sup>. Smart recovery solutions are being developed for efficient recovery and reuse of high-value polar solvents, such as improved multi-stage membrane distillation systems. This approach will allow the development of a circular model for solvent use <sup>14</sup>.

## 7. Conclusion

The shift to greener solvents in pharmaceutical analysis is a key part of integrating modern medicine with responsibility for the environment. Green solvents, such as water, bio-based organic media, ionic liquids (ILs), deep eutectic solvents (DESs), and supercritical fluids, have several essential advantages. One of the most significant advantages is their better environmental, health, and safety profiles. The systems are characterized by minimal flammability, minor volatility (low vapor pressure), and reduced toxicity in comparison with standard petroleum-derived solvents such as acetonitrile and chloroform. Bio-based alternatives (e.g., ethanol and dimethyl carbonate) utilize sustainable agricultural feedstocks. Designer solvents such as NADESs provide excellent solvation power, biodegradability, and ease of synthesis. Moreover, supercritical carbon dioxide and other methods offer high extraction yields and allow for the straightforward, solvent-free recovery of analytes through simple depressurization.

However, there are still some barriers to their widespread use. A major problem with eutectic mixtures, glycerol, and some ILs is their high intrinsic viscosity, which limits mass transfer and leads to high backpressures in chromatographic and automated flow systems. Water is the safest solvent, but it is energy-expensive to distill due to its high specific heat. Conventional chromatographic columns are prone to “phase collapse” when mobile phases are completely aqueous. Some bio-

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based alternatives, such as terpenes (e.g., D-limonene), are hazardous to aquatic habitats and contribute to photochemical haze. In addition, the low vapor pressure of the designer solvents makes it difficult to recover the product and recycle the solvent, as the solvents cannot be separated using the usual evaporation methods.

To overcome these limitations, several practical molecular and engineering solutions are to be applied. High viscosity can be overcome by operating the system at higher temperatures to reduce the intermolecular hydrogen bonding or by adding regulated volumes of water (up to 28-50%) as a co-solvent in an effort to increase the mass transfer. In aqueous chromatography, the analyst can use columns specifically designed to avoid the collapse of the stationary phase, such as those with embedded polar groups or polar end-capping or polyethylene glycol phases.

To avoid toxicity and environmental concerns, researchers are moving toward predictable *in silico* computer-aided design employing density functional theory (DFT), QSAR modeling, and COSMO-RS to test thermodynamic and ecotoxicological features before wet synthesis. This strategy underpins the targeted design of fundamentally benign NADESs and biocompatible ILs based on natural metabolites such as cholinium, amino acids, and organic acids. Other separation protocols are being developed for recycling non-volatile solvents. Macroporous adsorption resins (e.g., HP-19) are used for solid-liquid separation; water is added as an anti-solvent to precipitate target analytes, or stimulus-responsive switchable solvent systems are used. The implementation of these strategies will be critical for the successful establishment of a fully sustainable and circular solvent economy in pharmaceutical testing.

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