



A review: Exploratory analysis of recent advancement in green analytical chemistry application

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ABSTRACT

It is always a concern to ensure personnel and environment safety in the field of chemistry which has caused to development in green analytical chemistry methods. Green chemistry aims to create an eco-friendly environment in laboratories by using various analytical methods/strategies to reduce the use of toxic solvents which are harmful to humans and the environment. It is a way to protect the environment by using green solvents and methods. Green analytical chemistry is a rapid analytical technique that describes the separation, identification, and quantification of an analyte in drugs, environments, and humans. Various green methodologies such as automation, miniaturization, precipitations, and passivation are utilized in the recovery of solvents and reagents. Green analytical chemistry aims to create an eco-friendly environment in the laboratories by using various analytical methods/strategies to reduce the use of toxic solvents which are harmful to the environment/humans as well as to decrease the amount of waste generated. In this review, we explore different green solvents that can replace other toxic solvents used during extraction processes. In this review, the various extraction methods and analytical techniques used to analyze different components have been discussed.

1. Introduction

Green chemistry is an emerging field that is concerned with the concept of process design and yielding products that are sustainable and benign to the environment and humans, it was introduced by Anastas in the year 1999 and works on the 12 principles points [1]. The green chemistry fields provide continuously environment-friendly compounds or develop processes that avoid the use of hazardous organic chemicals (benzene, toluene, VOCs solvents). Optimizing the quality of the result

as well as enhancing environmental friendliness prove to be a major hurdle in the future of green analytical chemistry. The first action taken by chemists for the design of green pharmaceutical products and industrial-scale processes offers enhanced economic development [2]. The use of green raw materials, and avoiding toxic chemicals are needed to be considered by chemical industries and companies for the safety of workers and environments. Further, these steps account for better yields and lesser waste. In green analytical chemistry (GAC), the environmental-friendly analyte in samples is of greatest demand. This is important to improve the quality of the sample. The main problems that come in an environment because of using traditional methods can be minimized by

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the use of the *in-situ* process, automation process, taking a minimum number of samples, minimizing reagent waste production, determination of multi-analyte, direct analysis method, use of safe reagent and miniaturized processes. GAC is environment-friendly, and safer to the analyst achieved by the use of more suitable alternative solvents, avoiding too many steps that will result in a clean, healthy and safe environment [3]. In green analytical chemistry, the strategies are applied to utilizing green methodologies and safe solvents to minimize the hazardous waste [4]. Sometimes, it is very difficult to avoid the use of harmful chemicals, in such cases, a minimum volume of solvents should be used. There must be work for the recovery of solvents and reagents. The best method to reduce sample consumption is by automation, miniaturization, precipitations, and passivation [5]. Automation and miniaturization are considered green analytical methodologies that reduce the sample size and reagent consumption. In green analytical chemistry, the miniaturized techniques are solvents, more sustainable, and minimize the risk of exposure from hazardous solvents to analysts [6]. The National Environmental Methods Index (NEMI) was established to evaluate the greenness of designed analytical methods concerning four criteria *i.e.* use of PBT (persistent, bio-accumulative, and toxic), use of hazardous chemicals, corrosiveness based on *pH* time of the analysis and waste [7]. Pfizer scientists in the practical guide have mentioned a new green solvent for medicinal chemists [8] Titanocene dichloride (Cp_2TiCl) that confirmed the principle of green chemistry with high catalytic activity, high selectivity, low toxicity and environmentally compatible industrial chemical process. The catalysis procedure minimizes waste generation and contributes to the development of a sustainable chemical process [9]. This contributes to developing a suitable process with a high step economy and with a low risk of human health [10]. The most widely used safe transition metal on the earth is titanium which can be converted into Cp_2TiCl , which is eco-friendly and catalyses the haemolytic cleavage of C-O, C-halogen, O-O bonds, and carbonyl compounds [11]. The idea of Green analytical chemistry (GAC)

emerged and focused mainly on environmentally friendly laboratory practices rather than industrial scale. Certain modifications in terms of extraction (solventless extraction), analysis, and miniaturization were required to make the laboratory practice more environment-friendly and increase the quality of the result (Fig. 1). This led to the design of guidelines in the form of 12 principles which are as follows [12]:

- *Use of Direct Analytical technique to avoid sampling preparation.*
- *Keeping the size and quantity of the sample as small as possible.*
- *Performing in-situ analysis.*
- *Carrying out the integration of the analytical process and operations.*
- *Selection of automated and miniature methods.*
- *Minimizing or avoiding unnecessary derivatization.*
- *Avoiding the generation of a large amount of analytical waste.*
- *The method that analyses multiple analytes at a time is preferred.*
- *Minimizing the use of electrical energy.*
- *Selecting the reagents from a renewable source.*
- *Removal and replacement of toxic reagents.*
- *Increasing and ensuring the safety of operators.*

2. Green solvents and sample preparation in analytical chemistry

Sample preparation and analysis are the two major steps in the analytical techniques. In analytical chemistry, sample preparation is considered the most important and time-consuming step [13]. The solvents to be used in sample preparation for analysis should meet the criteria of being as non-toxicity, biodegradability, recyclability, and availability [14]. Various organic solvents (methanol, ethanol, acetonitrile, hexane, etc.) are widely used for sample preparation because of easy availability and economical. Some of these solvents show unwanted residue because of long persistence and may be toxic [15]. So, in recent years, a step to develop environmentally friendly solvents has been given much emphasis (such as ionic liquids). The various green solvents developed are discussed as below sections.

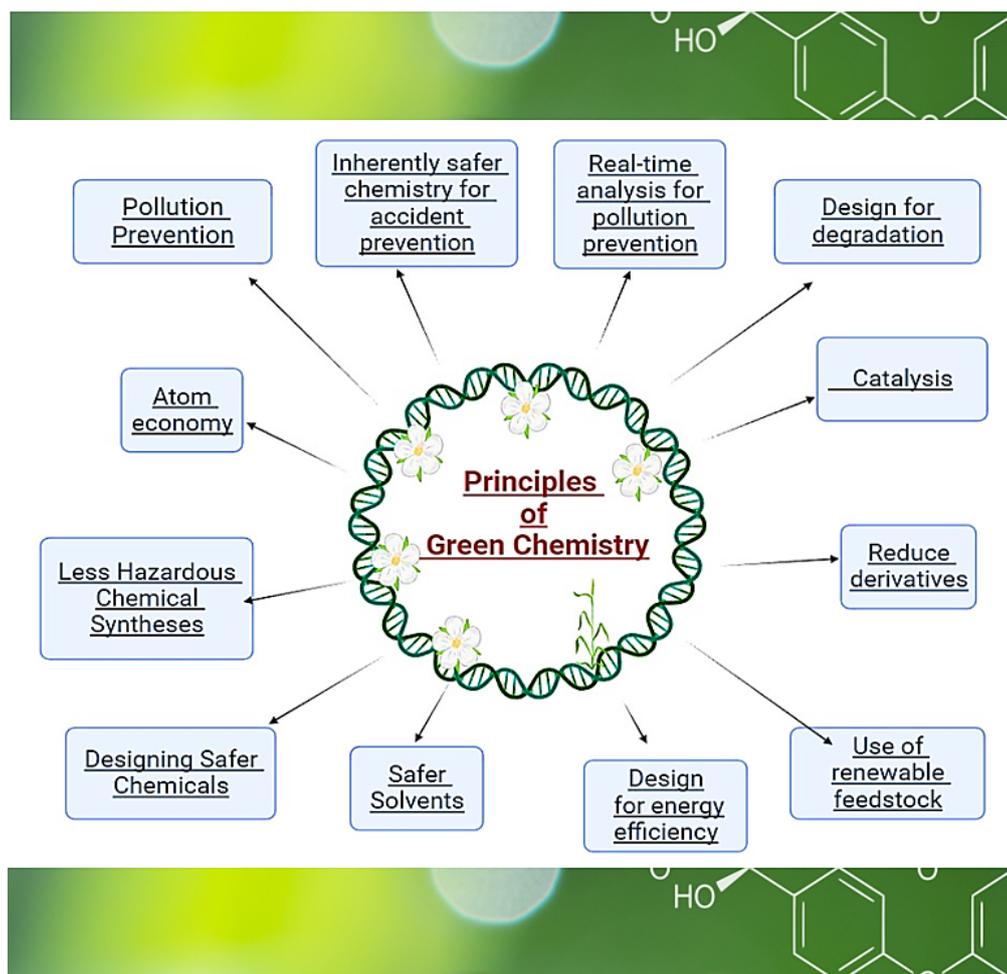


Fig. 1. Principles of using green analytical chemistry in different fields of science

2.1. Conventional green solvents

The solvents are considered a major part of the chemical industry and play a determinant role that impacts the safety, cost, and concerning health issues. Ethanol is a green solvent, less toxic compared to methanol and acetonitrile. Ethanol is one of the most used solvents. In analytical chemistry, especially in HPLC an ethanol/water mixture is being widely used as a replacement for other solvents and is considered a greener alternative to methanol and acetonitrile. e.g. separation of sunscreen molecules and pesticides (triazines) achieved through chromatographic techniques [16]. In another example, ethanol suitably replaces acetonitrile and methanol in HPLC *i.e.* the study of two test mixtures of a series of alkylbenzenes and a mixture of compounds of different classes such as caffeine and *p*-hydroxybenzoic acid [17].

The use of butyl alcohol replacing methanol and acetonitrile was performed for the separation of vitamins. In this study vitamins A, E, K1, and D3 were separated using a modified C-18 column eluted using surfactant sodium dodecyl sulfate (SDS) [18]. Ethyl lactate is a common solvent used in product purification in pharmaceutical, and paint industries because it has low toxicity, low viscosity and is biodegradable [19]. Glycerol (studied as an effective solvent), a major by-product of biodiesel production, is non-volatile, non-toxic, non-flammable, and biodegradable [20]. The solvent 2-methyl tetrahydrofuran (2-methyl THF) is a renewable source and can be used as a substitute for THF and other solvents [21]. It showed a quick and greener approach to LC-MS detection of multiple mycotoxins. The study includes replacement of the solvent acetonitrile

with ethyl acetate for mycotoxin analysis and minimizing solvent consumption. Extraction was promoted with the help of sonication and the addition of sodium sulphate [22]. Shawky *et al* in the year 2018 changed the extraction solvent to a greener one and evaluated the cytotoxic activities of Crinum (Amaryllidaceae) alkaloid. The results showed that the use of natural deep eutectic mixtures (Choline chloride: Fructose, molar ratio 5:2) along with the non-ionic surfactants (Genapol X-80) enhance the biological activities of the extracted

drug [23]. Bi *et al* in the year 2018 developed a novel green and stable dissolving system KOH/urea to successfully dissolve chitosan chains. The KOH-urea bonded with chitosan showed good thermal stability. Thus the solvent mixtures were used for further modifications of the chitosan as carboxymethyl chitosan, *N,N,N*-trimethyl chitosan and hydroxyl butyl chitosan [24]. Table 1 and Table 2 shows solvent selection and solvent replacement adopted by several companies as a green chemistry approach [25].

Table 1. Pfizer solvent selection, solvent solvents and comparing them

No.	Green solvents	Acceptable solvents	Disagreeable solvents
1	Ethyl acetate	Isooctane	Dichloroethane
2	Ethanol	Toluene	Di-isopropyl ether
3	Methyl ethyl ketone	Tetrahydrofuran	Methylpyrrolidinone
4	Water	Cyclohexane	Pentane
5	Acetone	Heptane	Hexane
6	Isopropyl acetate	Acetonitrile	Chloroform
7	Methanol	2-methyltetrahydrofuran	Dimethylformamide
8	t-Butanol	Dimethyl sulfoxide	Dimethyl acetate
9	2-Propanol	Methylcyclohexane	Diethyl ether

Table 2. Replacement of unwanted solvents with alternative solvents with lower toxicity

No.	Unwanted solvents	Alternative
1.	Pentane	Heptane
2.	Hexane	Heptane
3.	Dioxane or Dimethoxyethane	2-MeTHF or tert-butyl methyl ether
4.	Dimethylformamide, Dimethyl acetamide	Acetonitrile
5.	N-methyl pyrrolidinone	Acetonitrile
6.	Dichloromethane (extractions)	EtOAc, MTBE, toluene, 2-MeTHF
7.	Benzene	Toluene
8.	Dichloromethane (chromatography)	EtOAc/heptanes

2.2. Unconventional solvents

2.2.1. Ionic liquids (ILs) and deep eutectic solvents

Ionic liquids (ILs) are organic salts that are liquid at room temperature and have low melting points ($<100^{\circ}\text{C}$). Ionic liquid has low vapour pressure, low combustibility, and higher thermal stability and, can easily dissolve various polar and non-polar compounds [13]. The ionic liquids work as an extraction solvent in dispersive liquid-liquid micro-extraction (D-LLME). Magnetic ionic liquids as extraction solvents can be prepared by incorporating paramagnetic components into the IL structure. The solvent thus prepared can be used in various liquid-phase micro-extraction methods. The ionic liquids can also be employed in single-drop micro-extraction. Ionic liquid-based surfactants as solvents are used in magnetic-assisted extraction methods for the analysis of biological samples [26]. Despite the numerous applications of ILs in sample preparation methods, toxicity profile and poor biodegradability posed a serious problem. Also, the synthesis process of ILs is found to be expensive and time-consuming. So to overcome these problems many research works were carried out which gave rise to a new class of solvents called deep eutectic solvents (DESs) [14]. DESs are synthesized by mixing a hydrogen bond donor and a hydrogen bond acceptor-containing compound whose melting point is lower than the melting point of the individual components. Due to its low cost, low toxicity, and biodegradability nature, CHCl_3 is the preferred choice of organic salt to produce the eutectic mixture with various hydrogen bond donors such as urea, thiourea, glycerol, ethylene glycol etc. The DES thus formed is biodegradable and non-flammable making it easy to store. The synthesis process of DES is easy, no purification is required and environment friendly which makes it a better choice of solvent [14, 15]. DES is safe with low toxicity as a green solvent compared with other solvents [27]. The acid-base produced from fatty gas-based deep eutectic solvents significantly improves extraction efficiency using

the micro-extraction technique. The phenolic compounds were extracted through the micro-extraction technique with the support of N_2 . The fatty acids used in the preparation of deep eutectic solvents have carboxylic acids with long alkyl chains C_8 , C_9 , C_{10} , C_{11} , and C_{12} . Taking the molar concentration ratio and a class of fatty acids into consideration, the effects of DESs can be adjusted or improved. By applying the principle of green chemistry, the separation and extraction of phenolic compounds from a large volume of water samples can be increased. The use of $\text{NH}_3\cdot\text{H}_2\text{O}$ as an emulsifier after reaction with DES forms a cloudy solution and thus increases the efficiency of extraction. The maximum extraction efficiency was achieved $> 91.0\%$. The DESs technique was eco-friendly during the air-assisted liquid-liquid micro-extraction with the good recoveries of phenolic compounds in water samples (87.4% and 106.6%) [28]. Deep eutectic solvents are also used in the desulfurization process *i.e.* for the removal of organic sulphur from liquid fuels. It involves the extraction methods for the removal of organosulfur from fuels based on differences in solubility. The examples of non-toxic deep eutectic solvents identified are acetone, methanol, sulfolane, and nitrogenous solvents. The eco-friendly deep eutectic solvents prepared by using CHCl_3 : Ph (1:4 molar ratio) were selected for the desulfurization of model liquid fuel. It is a new perspective for industry and is beneficial because it is important to recycle the solvents rather than degenerate them. During the desulfurization, solvent utilization was reduced to around 50-60% and desulfurization of fuel was achieved up to 99.99%. Thus this method of desulfurization may be regarded as one of the potential applications for the green industry [29]. Deep eutectic solvents reportedly improve therapeutic efficiency in the evaluation of drug delivery systems [30], used to determine trace constituents of curcumin in nutrition and herbal tea samples [31] and also in the quantification of Aflatoxins (AFs) types in rice samples [32]. Deep eutectic solvents (DESs) are categorized as probable replacements

of volatile organic compounds. Li *et al* in the year 2020 synthesized three hydrophobic DESs by mixing trioctylmethyl ammonium chloride as a hydrogen bond acceptor and decanoic acid, ketoprofen and gemfibrozil as hydrogen bond donors. The mixtures were characterized by their melting points, viscosity, density etc. The solvents were used to extract the bisphenol in water contaminants using vortex-assisted liquid-liquid micro extraction and were analyzed with the help of HPLC. The methods developed have a limit of detection (LODs) and (LOQs) in the range of $0.3\text{--}0.5\mu\text{g L}^{-1}$ and $0.06\text{--}0.08\mu\text{g L}^{-1}$ and were used successfully for the determination and extraction of four bisphenol in the food contacted plastic samples [33]. In another study micro-scale extraction of bioactive phenolics from *Vitis vinifera* leaves using microwave-assisted solid-liquid extraction with ionic liquids (ILs) based surfactant was used by Mastellone *et al* in the year 2020. The extracted phenolics were analyzed by HPLC and photodiode array detection [34]. Natural deep eutectic mixtures (NADES) are another class of green solvents. These are different from eutectic mixtures in that they contain natural compounds (sugars, amino acids and organic acids and bases). The solvents with glucose and lactic acid were used by Paradiso *et al* in the year 2019 for the liquid-liquid extraction of selected polyphenols e.g. hydroxytyrosol and its derivatives in olive oil [35]. Another scientist Fraige *et al* used the natural eutectic mixture for the extraction of metabolites in *Byrsonima intermedia* leaves. The mixtures are easy to prepare, non-toxic, inexpensive and are alternative to organic solvents. The natural eutectic mixtures contain five choline chloride-based deep eutectic solvents. The choline chlorides/glycerol considered as best and is having similar efficiency as that of most common solvents. The mixtures was used to extract seven phenolics contents *viz.* digalloyl quinic acid, proanthocyanidin dimer, galloylproanthocyanidin dimer, quercetin-*O*-hexoside, galloyl quercetin hexoside, quercetin-*O*-pentoside, and galloyl quercetin pentoside [36]. Zhang *et al* in the year 2019 also utilized

natural deep eutectic mixtures as both extraction and dilution matrices for the analysis of volatile components in *Ipomoea*-carried sweet (ICS) leaves. He used choline chloride along with glucose in the ratio of 1:1 molar ratio for the extraction of volatile components (2,4-di-*tert*-butylphenol), β -caryophyllene, β -element and others. This makes natural eutectic mixtures work as both extraction and dilution matrix for static headspace gas chromatography-mass spectrometry [37]. Liu *et al* utilize the high viscosity of green deep eutectic solvents (choline chloride) for the extraction of polyphenols in palm samples. Choline chloride-oxalic acid-water *i.e.* Deep eutectic mixtures: H_2O in the ratio of 1:0.1 to 1:50 were used for the extraction of target compounds (polyphenols, protocatechuic acid, catechins, epicatechins and caffeic acid). Thus proper mixtures of deep eutectic mixture with water work as efficient extraction solvents for bioactive compounds [38]. Also, the green eutectic solvents, zinc chloride and acetamide in different molar ratios in non-ionic surfactant (Triton X-114) as extraction methods used for the determination of trace vanadium in water as vanadium with ammonium pyrrolidine in complex form [39]. Figure 2 shows conventional analytical chemistry vs green analytical chemistry approaches.

2.3. Reuse of solvents

Solvents are not reused in pharmaceutical chemistry because of the concern for contaminants. However ionic liquids (ILs) are good alternatives to organic solvents because of their good solvent properties for both organic and inorganic materials and low volatility. They are a group of salts that are liquid at room temperature and thermally robust (stable up to 260°C), which makes them reusable and suitable to work in high temperatures. The physical-chemical properties of ILs can easily be tuned by design, as it is influenced by their cationic and anionic species for extraction and removal of pollutant application in air or water samples [40, 41]. Figure 3 shows the green analytical chemistry based on IL approaches.

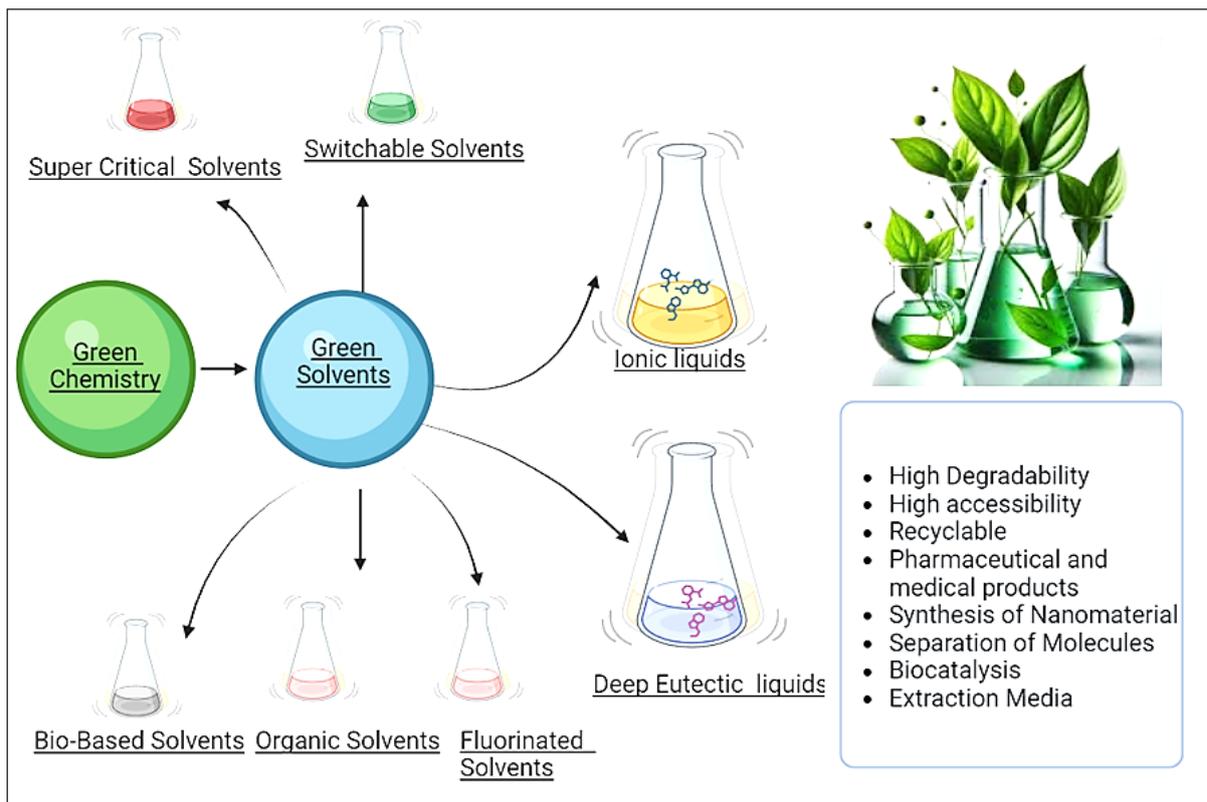


Fig. 2. Green analytical chemistry approaches based on green solvents[39]



Fig. 3. Tree of green analytical chemistry approaches [40,41]

3. Methods: Different techniques in green analytical chemistry

3.1. Infra-red spectroscopy

The infrared range of its three regions; middle infrared region (MIR), near-infrared region (NIR) and Raman spectroscopy are the main vibrational techniques employed for the direct analysis of samples. IR spectroscopy detects vibrations when there is a change in electrical dipole moment in compounds, whereas Raman spectroscopy is a measurement of the electrical polarizability of excited molecules induced by the electric field. In biomedical research, infrared spectroscopy is a rapid, accurate, and sensitive technique mainly for the detection of illness. In research, IR can be used in cancer detection and provides a green analytical approach in clinical oncology and cancer research. Different sampling modes can be used in NIR for various applications. Different modes of measurement in the instruments are transmittance, diffuse transmittance, transmittance and diffuse reflectance. Among these diffuse reflectance and diffuse transmittance are the two most used measurement modes. Diffuse reflectance measurements are performed in the range from 1100 to 2500 nm with a sample thickness of 1 cm, whereas diffuse transmittance is performed in the range of 800-1100 nm using a sample thickness of 1-2 cm. Due to its reliability, accuracy, and non-destructive nature, the NIR technique is considered the most widely used on/in-line process for checking the physical and chemical parameters [42]. Filter instruments used in the NIR range are considered rapid techniques and fulfill the criteria of robustness, compactness and reduced cost. There are three types of NIR on-line analyzers: remote sensors, bypass analyzers, and fibre optic probes [42]. The first on-line NIR sensor was based on a sensing head remote approximately 200 mm at an angle of 60° from the horizontal of the flow sample. Their advantages rely on the low cost of instrumentation and easy installation. It is sensitive to atmospheric humidity, interference from ambient light variation and dust build-up on the optical surface. IR can be used in the food

industry for moisture determination on powders, bread [43], control of protein in flour [44] and meat composition analysis [45]. NIR by-pass samplers were first developed to measure the protein content of flour and are still the most popular application of the NIR feedback control system. In this method, the sample is placed against the optics window for each measurement cycle. The samples were taken directly from the flour stream either from the positive pressure blow line or gravity-fed spouting [46]. Fibre-optic probes have the widest range of applications as on-line analysis. Laboratory NIR analyzer platforms have been modified, enclosed in process-hardened housing, and used extensively for material identifications in the pharmaceutical [47] and nutraceutical industries [48]. Mazivila *et al* in the year 2019 developed FT-IR methods to study polymorph I and II of pharmaceuticals co-crystals of lamivudine and theophylline. With the combined effect of FT-IR and multivariate curve resolution with alternating least-squares (MCR-ALS), it was able to monitor in line synthesis of co-crystal. Also this method allows understanding the mechanism of synthesis through identification of intermediates. The spectral shows clear strong overlapping and quantification concludes for the existence of final products as co-crystals [49]. Weldegebreal *et al* demonstrate new fast and cost-effective analytical methods for the determination of caffeine in green coffee beans using FT-IR and fluorescence spectrophotometry. Caffeine was also determined in the NIR range using dimethyl formamide (DMF) as the solution. The caffeine content in green coffee beans comes out to be 1.50 ± 0.14 (% w/w) using FTIR-ATR in the NIR range and 1.50 ± 0.05 (%w/w) using fluorescence spectroscopy [50].

3.2. Raman spectroscopy

In Raman spectroscopy, a μm -size of samples can be analyzed by using a microscope, and no sample pre-treatment is required. This makes the process less tedious than other spectroscopy method [51]. Raman spectroscopy is a non-destructive technique that provides rapid analysis of untreated samples.

Raman spectroscopy is useful for acquiring inorganic and organic vibrational structure information. This technique is another alternative to analyzing the samples directly over the glass or plastic packages. Raman spectroscopy is efficiently used in the solid state to identify the graphene layers by the Raman spectroscopy. In the Forensic and pharmaceutical field, Raman spectroscopy is applied to analyze the entire sample. Cocaine, heroin, and various other phenethylamine moieties are quantified and identified accurately and rapidly by Raman spectroscopy. The other use of Raman spectroscopy is the identification and analysis of pigments used in antique paintings [52], and glass which may in the future help to restore ancient artifacts [53]. This technique was applied by Legner *et al* in the year 2019 for the real-time analysis of the alcohol fermentation. The conversion of sucrose was performed by yeast cells immobilized in alginate beads. This Raman technique provides faster and robust quantitative spectroscopy for ethanol, glycerol, and sugar content. The Raman spectroscopy is coupled with NMR for resolved signals and higher specificity. This provides the quantitative monitoring of the different reactants [54]. Molnar *et al* in the year 2019 used Raman spectroscopy for food authentication. The technique is green as it requires a minimum sample preparation step. The authors use this for the honey sample preparation (honey diluted to water 1:1w/v) to get reproducible spectra and avoid the formation of crystallization and fluorescence [55].

Raman spectroscopy offers some advantages over NIR spectroscopy. The Raman spectroscopy gives a simple optical configuration that is efficiently interfaced for on-line quantification. Raman spectroscopies are used for quality control (QC) analysis for a wide range of liquid samples filled in glass (clear or amber) or plastic containers. Raman spectroscopy has been selected for the static analysis of ethanol content of spirits whiskey, vodka, and sugary alcoholic drinks in 200 ml (flat) and 700 ml (round) glass bottles. The technique is restricted to the analysis of clear glass bottles because coloured bottles exhibited strong

fluorescence. The quantitative *in situ* analysis of povidone present in eyewash solutions in low-density polyethylene (LDPE) bottles was also made possible by Raman spectroscopy. For on-line and in-line applications of Raman spectroscopy, the spectrometer is incorporated into the sampling location using conventional optical fibre cables [56], enabling remote sampling at tens or even hundreds of meters from the spectrometer. The advantage of Raman spectroscopy is that it is used for both qualitative and quantitative analysis of materials kept inside containers of polymeric bottles, and blisters. Raman spectroscopy has been used to detect liquid explosives within bottles/plastic packaging [57] and illegal drugs dissolved in beverages [58]. It can also be used to find out the active ingredients in pharmaceuticals inside plastic bottles [59], amber vials [60] or capsules [61]. The methods for the quantitative determination of ethanol contents in beverages inside glass bottles by Raman [62] are another application. This implies that bonds that connect two identical or practically identical parts of a molecule can be more active in Raman than in IR, thus providing complementary spectral information, *i.e.* O–H stretching vibration is very strong in IR but very weak in Raman.

Similarly, IR also holds certain advantages over Raman spectroscopy. The important one is cost-effectiveness. It is much cheaper than Raman as it uses high powered laser source to get sensitive results. The high power of the laser may cause heating and destroy the sample. Raman spectroscopy is fewer sensitive technique except surface-enhanced Raman spectroscopy than IR when used alone. NIR can sample large areas and has better penetrability than Raman spectroscopy. Both Raman and IR spectroscopy have advantages over each other but to get more sensitive results it is better to use both techniques together. In many studies, Raman was used for the characterization of nano adsorbents which were used for the extraction of pollutants from water samples. Faghihi *et al* showed that Mn ions were extracted in human blood/serum samples by AMTZ@MWCNTs adsorbent. They showed that Raman of AMTZ@

MWCNTs has two main peak shifts (D band: 1305 cm^{-1}) and another peak at (G band: 1581 cm^{-1}), which confirms the structure of MWCNTs. Raman peaks of MWCNTs with G and D bands confirm the carbon structures. Also, the low height of peaks at 243, 513, 705, and 2612 cm^{-1} were observed by MWCNTs Raman. The ratio of the IG/ID bands showed the sample's graphitization and the quality of the tubes in MWCNTs. Also, Mohammadi et al used bismuth oxide/ titanium oxide nanoparticles functionalized nanographene oxide ($\text{Bi}_2\text{O}_3/\text{TiO}_2@$ NGO) and IL-NGO for the removal of HCHO and toluene from the air, respectively. IR of $\text{Bi}_2\text{O}_3/\text{TiO}_2@$ NGO and IL-GO showed functionalized IL and $\text{Bi}_2\text{O}_3/\text{TiO}_2$ on NGO [63, 64].

3.3. Chromatographic techniques

Capillary zone electrophoresis is an alternative to chromatographic techniques but cannot be used for non-charged molecules. Micro-emulsion electrokinetic chromatography (MEECK) is one of the techniques applied by Felici *et al* in the year 2016 for the analysis of non-charged antiparasitic drugs such as ivermectin (IVM) and moxidectin (MXD).

The technique is environment-friendly, robust, specific, and sensitive techniques for analyzing these macrocyclic lactone drugs. The LOD value of the two drugs IVM and MXD were $3 \times 10^{-3} \mu\text{g L}^{-1}$ and $3.6 \times 10^{-3} \mu\text{g L}^{-1}$ [65].

3.4. Sample Extraction

In the field of natural sources and agri-food industries supercritical fluid extraction (SFE) using CO_2 and pressurized liquid extraction (PLE) are the most widely green analytical techniques used apart from the conventional methods of solid-liquid extraction (SLE). Another scientist Abukhadra *et al* synthesized supported bentonite/chitosan on green fabricated Co_3O_4 and evaluated their adsorption properties for Congo red dyes and Cr (VI) ions. The chemisorption phenomenon exists for the removal of the dye and Cr (VI) and follows a pseudo-second-order model. The adsorption maximum was 303mg g^{-1} and 250mg g^{-1} for Congo red molecules and Cr (VI) metal ions. The bentonite/chitosan@ Co_3O_4 was found to be highly useful in the purification of water and may act as promising adsorbents [66].

Table 3. Various samples were analyzed using SPE based on different cartridges and solvents

Sample	Cartridge	CS	Analyte	Solvent	Instrumental	Ref.
Wine	OASIS/HBL	Methanol/DW	Azolic/fungicides	Methanol	MS-HPLC	[49]
Water	ENVI-18	Acetonitrile	PAHs	Hexane	GC-MS	[50]
Tomatoes	Silica(C_{18})	Methanol/water	P&H	Dichloromethane	HPLC	[51]
Plasma(H)	OASIS/HBL	Methanol	PhCM	Methanol	UPLC/MS/MS	[52]
River	OASIS/HBL	Acetonitrile/DW	**Antibiotic	***ACA	LC-MS	[53]

CS: Conditioning solvent

P&H: Pesticides and Herbicides

PhCM: Phenolic compounds and their metabolites

**Antibiotic: Antibiotic Macrolides

***ACA: Ammonium acetate/acetonitrile (50:50)

3.4.1. Solid-phase extraction

Solid-phase extraction is the most widely used technique for extraction, and cleaning of analyte from environmental, food and drinks [67]. In SPE, the analyte solution to be extracted is loaded into a cartridge containing the sorbent. The impurities and undesired components are then washed away by using suitable solvents whereas the desired component is collected using a suitable solvent [67-71] (Table 3).

3.4.2. Solid-phase micro-extraction (SPME)

The SPME method is identified as a green approach to reduce solvent consumption and waste during the preparation of the sample. SPME has a certain advantage such as it is solvent-free. A small volume of sample is required and is considered highly sensitive. SPME can analyze the non-polar compound in liquid, gas, and solid samples with various instruments with HPLC and GC, etc. In SPME, the coating of a fused silica fibre is done with a stationary phase. Equilibrium between the analyte in the sample and the fibre is attained by exposing the fibre to aqueous or gaseous samples. The analyte can be desorbed from the fibre thermally or by using solvents. The thermal desorption of the sample refrains the use of solvents. Similarly, chemical desorption uses a very low amount of sample (in μL). Thermal desorption and chemical desorption are two greener techniques. In a study conducted by Andrade M.A *et al.* to determine the Ochratoxin A in wine, they utilized the SPME technique for sample preparation as it is necessary for analyte purification and to achieve a lower detection limit of the sample or analyte [72]. Rivellino S. R. *et al.* utilized the SPME technique to detect the extraction artifacts in the analysis of honey volatiles. In this, the honey mixture was heated at 40°C for 30 seconds and was stirred before extraction. A specific amount of honey mixture was then added directly into a vial having a magnetic stirrer in a saturated aqueous solution of sodium chloride [73]. In another study performed by Merola G *et al.*, they combined SPME and GC

for the measurement and determination of various recreational drugs such as ketamine, methadone, amphetamines, cocaine, coca ethylene, and Δ^9 -tetrahydrocannabinol (THC) in hair. The limit range for detection and quantification is from $0.01\text{-}0.12\text{ ng mg}^{-1}$ and $0.02\text{ to }0.37\text{ ng mg}^{-1}$ [74]. Schacker R *et al.* carried out fermentation using *Monascus* fungus and checked the viability of the use of SPME in the extraction of various microbial volatile organic compounds such as ethanol, 2-methyl-propanol, 3-methyl-butanol, 2-methyl-butanol, and 2-phenyl-ethanol. During a fermentation process, the SPME provided greater accuracy when assessing the MVOCs (*in vivo*) [75].

3.4.3. Liquid phase micro extraction

Liquid phase micro-extraction is a simple approach for sample pre-treatment and utilizes a very small amount of solvent. Less than $10\ \mu\text{L}$ of extraction solvent is required to extract analyte from the sample. It can be combined with GC and CE for the detection of the extracted analyte [76]. Liquid phase micro-extraction finds its uses in clinical and forensic science as well as in the analysis of food and drinks. The proper selection of the different forms of liquid-liquid micro-extraction is very important. This was demonstrated by Saraji *et al* in the year 2018 using three solvents chloroform, 1-butyl-3-methylimidazolium tetrafluoroborate, and 1-hexyl-3-methylimidazolium hexafluorophosphate for phenolics, neutral phenolics and amino compounds. Analytes with polar groups give the best results with *in-situ* ionic liquid dispersiveliquid-liquid micro-extraction, whereas neutral hydrocarbon compounds with polar groups use chloroform solvent called traditional dispersive liquid-liquid micro-extraction techniques. Hydrophilic analytes were not suitable to be extracted by any of the liquid-liquid micro-extraction [77]. Liquid phase micro-extraction is of three types.

- i. Hollow Fibre Liquid Phase Microextraction (HF-LPME)
- ii. Dispersive Liquid-Liquid Microextraction

(DLLME)

iii. Single Drop Microextraction (SDME)

3.4.4. Hollow fibre liquid phase micro-extraction (HF-LPME)

In HF-LPME, the hydrophobic pores present in hollow fibre hold the extraction solvent during the extraction process. The hollow fibre is attached to the needle of a micro syringe. Once the extraction process is complete, the extraction solvent containing the analyte is collected and then analyzed using a suitable instrument [78]. In this process, less volume of solvent is consumed during extraction (2-25 μL).

3.4.5. Dispersive liquid-liquid micro-extraction (DLLME)

In DLLME, the partitioning is between mixtures of extraction solvent-dispersive solvent and the aqueous phase in which the sample is dissolved. The mixture is then added to the sample solvent with the help of a micro syringe, which gives rise to an emulsion-like solution. The formation of cloudy microdroplets partitioned the sample between the extraction phase and the aqueous phase. The solution is centrifuged, breaks the emulsion into two phases and the sediment phase so formed is then collected and analyzed [79]. The technique uses minimum amounts of 1-100 μL of extraction solvents are used. In DLLME most common solvents used are acetonitrile, methanol, ethanol, and acetone whereas, other solvents such as carbon tetrachloride, toluene, hexane, chlorobenzene, 1,1,2,2-tetra chloroethane may also be used. The techniques were used for the determination of Caffeine, alkaloids, amino acids, cinnamic acids, coumarin, curcumin, essential oils, pesticides and many more [80]. Pacheco-Fernández *et al* used ILs-based surfactant water-soluble octyl guanidinium chloride (C8Gu-Cl) of low cytotoxicity to water-insoluble IL micro-droplet by metathesis reaction and extracted personal care products. The methods were used in combination with HPLC and diode array detection. The metathesis used the addition of anion exchange reagent (bis[(trifluoromethyl) sulfonyl] imide-1:1

molar ratio). It gives low detection limits of $0.4\mu\text{g L}^{-1}$ with the use of low volume of IL surfactants [81]. Sheikh *et al* developed novel methods for the determination of cadmium and lead in the ground water samples (tube well and hand pump) by liquid-based vortex-assisted dispersive liquid-liquid micro-extraction. The contents were determined ion the scalp of the children (1-3 years) exposed to contaminated water and domestically treated water. A green chelating agent γ -cysteine (2-amino-3-sulphydrylpropanoic acid) was used to concentrate the Cd and Pb and ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM] [PF₆] used as micro extractant [82]. Fast deep eutectic mixtures were used for the first time for the extraction of phthalates from food beverages by Santana-Mayor *et al*. The technique used is dispersive liquid-liquid micro-extraction. Choline chloride: The phenol mixture shows good results for the extraction of different phthalates and was coupled with HPLC-diode array detection for separation and analysis [83].

3.4.6. Ionic liquids application

Ionic liquids (ILs) as green solvents based on organic cation (R- imidazolium/pyridinium) and organic or inorganic anion (Halogen Cl, Tetrafluoroborate BF₄ and Hexafluorophosphate PF₆) have a critical role for extraction pollutants from different matrixes. ILs are three form, hydrophilic ([R-IM][A⁻]; A = NO₃, Cl, OH), hydrophobic ([R-IM][A⁻]; A = PF₆) and intermediate ([R-IM][A⁻]; A = BF₄), so, they used in various matrixes. A special form of Task-Specific Ionic Liquids (TSILs) such as Trioctylmethylammonium thiosalicylate (TOMATS) was used for extraction of heavy metals, such as mercury in water samples (Fig. 4a). In TSIL, the thioether, urea, or thiourea functionalized on imidazolium cations act as metal ligating moieties, whereas the PF₆⁻ anions provide the desired water immiscibility. Due to the unique physicochemical properties of ionic liquids, they can replace traditional organic solvents in a very efficient manner. These properties involve their good solubility in organic solvents, low

volatility, and most importantly their higher thermostability when compared to the traditional solvents. Due to those highly appreciated properties, a novel method based on dispersive liquid–liquid microextraction was developed for the preconcentration of cadmium in human body fluids and determination by electro thermal atomic absorption spectrometry [84]. It also has been reported that speciation and determination of trace inorganic and organic mercury species in water and caprine blood samples were performed by the mean of Ultrasound assisted-dispersive-ionic liquid-micro-solid phase extraction based on carboxyl-functionalized nanoporous graphene [85]. A method for removing hazardous toluene vapor from the air was developed based on an ionic liquid phase adsorbent. Due to its high toxic effects on the environment, toluene needs to be removed by an efficient and qualified method. Five ionic liquids were pasted on micro glassy balls and used for toluene removal from air by liquid–gas-phase extraction method. Based on the

proposed procedure, toluene vapor was absorbed on ionic liquids (0.2 g, 25 °C) and desorbed from it at 110 °C before being determined by gas chromatography [86,87]. Mercury is another highly toxic element which can be found in the daily used water, so an Ultrasound assisted-dispersive-modification solid-phase extraction using task-specific ionic liquid immobilized on multiwall carbon nanotubes was performed for speciation and determination of mercury in water samples. This method was based on 1-(3-aminopropyl)-3-methylimidazolium hexafluorophosphate (TSIL) immobilized on multiwall carbon nanotubes (MWCNTs@ [Apmim][PF6]) was used for speciation of inorganic/organic mercury (Hg^{2+} , R-Hg or O-Hg) by ultrasound assisted-dispersive modification solid-phase extraction (UAS-DMSPE) which was combined with cold vapour atomic absorption spectrometry (CV-AAS) [88]. The chemical and physical properties of ILs and their potential in many applications caused to use in different fields of science (Fig.4b).

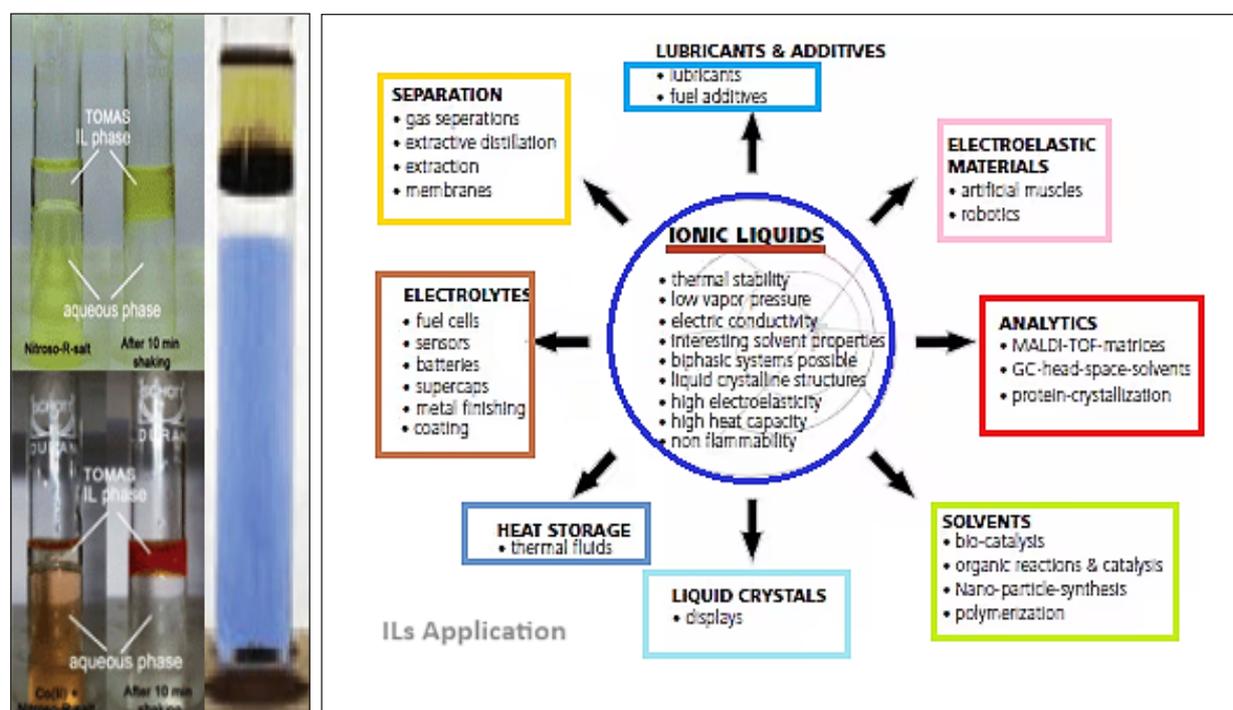


Fig.4. TSIL of TOMATS (left, a), the application of ILs in different fields of science (Right, b)

3.4.7. Single drop micro-extraction (SDME)

A micro drop of extraction solvent (1-10 μL) is used to extract the analyte from the sample. During extraction, the micro drop of the solvent is held over the sample with the help of a micro syringe. The extraction solvent used should have low volatility, and low water solubility, and must be immiscible in water [89]. SDME techniques were used for the determination of essential oils and volatile components [80]. SDME has 3 different modes such as:

3.4.7.1. Direct SDME

To the bulk aqueous sample solution, a micro drop of water-immiscible extraction solvent is directly immersed and stirred during extraction. By this method, both volatile and non-volatile analytes can be extracted [89].

3.4.7.2. Headspace SDME

In this technique, the extraction solvent is exposed at the headspace above the sample with the help of a syringe. The extraction of volatile and semi-volatile analytes in the sample is carried out. As this extraction technique is time-dependent, an extraction solvent with low volatility is used to reduce any chance of drop evaporation during extraction [90].

3.4.7.3. Liquid-liquid-liquid micro-extraction:

In this mode, a thin layer of organic extraction solvent having a low density is formed over the sample solution. To the layer of extraction solvent, a micro drop of an aqueous solution is immersed. For the extraction to occur by this method, the pH of the sample solution should be maintained in such a way that non-charged analytes are formed [91].

Various samples analyzed using different Liquid-phase micro-extraction techniques are given in Table 4 [92-103].

3.4.8. Supercritical fluid extraction

Several researchers have carried out an experimental and theoretical investigation on the SFE using CO_2 . Many articles have been published on the studies for the SFE. In comparison with different extraction methods available, SFE provides numerous choices of solvents to be used. Supercritical fluid extraction is used for the extraction of non-polar organic compounds but can be used for polar ones also with the aid of modifiers [98]. The technique is robust, fast and highly efficient and has the advantage that it is easily hyphenated with MS for the separation and identification of bioanalytics [104, 105].

Supercritical carbon dioxide is a fluid state of carbon dioxide, green and eco-friendly technology with the capability to extract composition without thermal degradation and oxidation [106].

Table 4. Various samples were analyzed using liquid-phase microextraction techniques (LPME)

Techniques	Sample	Analyte	Solvent (volume)	Instruments	Ref.
HF-LPME	Cucumber	7 pesticides	Chloroform (5 mL)	UHPLCMS/MS	[64]
DLLME	Wine	Ochratoxin A	Chloroform (660 μL)	HPLC-LIFD	[65]
DLLME	Honey	5 Fungicides	Dibromoethane (130 μL)	GC	[66]
HF-LPME	Milk	9 StHor	Methanol (400 μL)	GC-MS	[67]
SME	Urine	CCM	Chloroform (10 μL)	GC-PDHID	[68]
HFMSME	Saliva	CCM	Chloroform (10 μL)	GC-PDHID	[69]

CCM: Cocaine and cocaine metabolites,
StHor: Steroidal Hormones

The advancement of green analytical chemistry minimizes the risk in the first step during sample preparation. The corona-charged aerosol detector considered as universal detector used to analyze a wide range of analytes. The structures of related impurities in risperidone were analyzed by a suitable reverse phase HPLC method using suitable solvents ethanol, acetone, and another modifier. The steps were optimized by experimental designed methodology and better separation occurred by using the simple Derringer's desirability with 3D surface plots. In the case of ethanol, the selected condition of the mobile phase has a flow rate of 0.6 mL min⁻¹, column temperature of 37.5°C and organic modifier content of 20% (v/v) whereas, another method utilizes acetone as the mobile phase with flow rate 0.8 mL min⁻¹, organic modifier content 17% (v/v) and column temperature 37.5°C. Both methods lack waste management principles but are well-validated and selective. Green analytical procedure index pentagrams represent one of the reported methods and are assigned as eco-friendly analytical methods. Ethanol is unsafe or harmful as compared to acetone so acetone is mostly preferred [107]. Supercritical carbon dioxide has many excellent improvements as being non-toxic, harmless, high-quality extraction, and safe in use. The supercritical fluid has a low cost that overcomes the conventional method of extraction. Supercritical fluid extraction CO₂ is an alternative green chemistry solvent, considered eco-friendly with good performance for disposal of impurities in oil-based mud. Extraction is obtained with economic efficiency and is applicable to remove the hydrocarbon contamination from the wastage of oil mud. Supercritical fluids CO₂, propane, and freon are used to treat the wastes in the process of drilling. The increased pressure of extraction reduces the diffusion coefficient and will increase the density of SC-CO₂. The saturated vapour pressure leads to an increase in SC-CO₂ solubility with the increase in temperature. According to this research paper, the disposal of waste in OBM (oil-based mud) result was found

in good agreement with extraction performance of 98% utilizing the pressure 20mpa time for 60 min and temperature of 35°C. Among the many advantages of supercritical CO₂ in the industry for the preparation of polymer material, medicine, and chemical components is that it is recycled after use [108]. Carbon dioxide and modifiers or co-solvents increased the extraction yield of cinnamoyl pyrrolidine amides from dried leaves of *Piper hispidum*. Around 5% methanol was added and reported improvement in the extraction yield of amide components. Polar compounds are extracted with the low polarity of SC-CO₂. The plants which have pharmacological activity like *Panax ginseng*, *Taxusbacata*, *Piper nigrum*, *Acoruscalamus*, *Curcuma longa*, and *Ocimum gratissimum*, are recognized by the eco-friendly supercritical fluid CO₂. The supercritical fluid has a good resolution for bioactive compounds in plants [108]. Cádiz-Gurrea *et al* in the year 2019 used food-grade solvents in the extraction of bioactive from the barks of *Sclerocarya birrea* through green analytical techniques. The author utilizes supercritical fluid extraction (SFE) and pressurized liquid extraction (PLE) to extract flavonoid aglycones [109]. Supercritical fluid chromatography with reversed phase chromatography using modifiers such as MeOH, ACN and MeOH: ACN 50:50 was used for the separation of the chlorophyll pigments by Lefebvre *et al* in the year 2019 [110].

3.4.9. Carbon dots extraction

Carbon dots nowadays are considered under green analytical techniques as C-dots also follow the basic principle of elimination of toxic, expensive, hazardous substances and minimization of time and energy consumption. C-dots are used in sample preparation, imaging, bio sensing, and drug delivery using photovoltaic. The application is because the C-dots are natural, biocompatible, low toxicity and show the phenomenon of photoluminescence. Yuvali *et al* in the year 2019 utilize a first-time magnetic carbon nanodot/graphene oxide hybrid material (Fe₃O₄@C-

nanodot@GO) for solid phase extraction (MSPE) of the drug ibuprofen in human plasma and its determination by MSPE-HPLC-DAD. Graphene oxide (GO) nanodots, C-nanodots and magnetic properties of nano Fe_3O_4 are combined altogether. C-nanodots are prepared from the pasteurized cow milk then a step hydrothermal method was applied for the preparation of Fe_3O_4 @C-nanodot@GO hybrid material. The nanodots were characterized by Fourier transform infrared spectrometry (FT-IR), X-ray diffraction spectrometry (XRD), Raman spectrometry, scanning electron microscopy, vibrating sample magnetometry and energy dispersive X-rays. The limit of detection was found to be (LOD) 8.0 mg L^{-1} [111].

4. Application of green analytical chemistry

In the past, many products such as medicines, dyes, cosmetics, paints, polymers, etc. were manufactured or synthesized using various chemical processes. Along with the beneficial products many undesired and harmful substances are also produced and the reduction or removal of these undesired substances has become a major issue. So the need to introduce a greener alternative has recently gained interest. Green chemistry contributes to the synthesis of products in such a way that it provides less threat to health and the environment.

4.1. Pharmaceutical Field

The synthesis of aspirin was carried out by microwave irradiation and by using a catalyst such as H_2SO_4 , or $\text{MgBr}_3\cdot\text{OEt}_2$, AlCl_3 , and CaCO_3 . The synthesis process was solvent-free and the production of waste products was at a minimum. The process was thus more environments friendly and a greener approach. Celecoxib an anti-inflammatory agent was synthesized by using a green approach during the developmental stage and it was found that the yield increased from 63% to 84% whereas, the waste production decreased by 35%. The obtained product was clean enough

and was purified by washing with more amounts of solvents. The synthetic methods avoided the use of undesirable solvents such as methylene chloride and hexane [112].

4.2. Diagnosis of Cancer

IR spectroscopy has been recognized as a green tool in the diagnosis of Cancer. It provides a completely greener and environmentally friendly style of analyzing the blood sample as the analysis does not use any kind of chemicals during analysis. Mohammadi *et al* collected blood samples from two different groups and analyzed them by using IR Spectroscopy in the range of 1800 to 900cm^{-1} . Spectra were observed for N-H stretching, amide I and II bands. They also confirmed the shift in the α -helix and β -sheet amide I band in the case of malignant tumours. The results were compared with the current clinical methods and showed 97.6% accuracy [113].

4.3. Application in the detection of heavy metals

Several heavy metals such as arsenic, cadmium, lead, zinc, etc. can be detected in the soil by using portable X-ray fluorescence which provides a rapid, simple and accurate metal analysis. By this method, a large number of heavy metals can be detected with a very low generation of residues and high sensitivity [114].

4.4. Application in Detection of Organic Pollutants

Various organic pollutants such as sulphonamide can be detected in water by using a liquid-liquid-liquid micro extraction technique combined with HPLC (265 nm) (Lin CY *et al.*) [115]. Similarly, acidic pharmaceuticals such as salicylic acid, ibuprofen, diclofenac, etc. can be detected in wastewater by using hollow fibre-based micro-extraction followed by HPLC/MS-MS [80]. Organophosphates and pyrethroid pesticides in water can be detected by SDME coupled with GC-FID [116].

4.5. Application in Analysis of blood sample

Human blood is a very complex bio-fluid containing WBC, RBC, glucose, hormones, minerals, etc. Qualitative and quantitative analysis of blood samples through IR spectroscopy can be done for the diagnosis of various diseases or for determining various blood constituents such as albumin, glycoprotein, fibrinogen, etc. This estimation will help in understanding the disease patterns [117,118]. Figure 5 shows the application of green chemistry in the analysis of blood samples. Also, some methods with ionic liquids or solvent-free based on nanotechnology were used for extraction and determination heavy metals in human blood samples (Fig.5) [119-123].

4.6. Analysis of Particulate Matters

Different microscopic solid or liquid matter suspended in the atmosphere (dust, metals, VOCs) may have some harmful effects on human health. The particles present can be analyzed based on their chemical composition (inorganic and organic). The inorganic particle can be analyzed by colorimetric methods, ion chromatography, and selective ion electrodes (requires sample solubilization) mass spectrometer, atomic absorption spectrometry (AAS), inductively coupled plasma mass spectrometry (ICP-MS), IR Spectroscopy, Raman spectroscopy (sample solubilization not required). Organic particulates

can be analyzed by thermal, optical, and extraction techniques. The analysis of solvent extraction is coupled with GC-MS or HPLC. The solvent during extraction is replaced by supercritical fluid (CO_2) making it a green approach [124-128]. In addition, the pollutants such as metals and VOCs may be determined in water samples by GC-FID, GC-MS, AAS, and ICP-MS [129-132].

4.7. Patent application on green analytical techniques

After the scaling up of analytical techniques from the laboratory scale to the industrial scale, it was necessary to make sure that the technique being used was greener and had no effect on the environment or the analyst. In the recent era, various modifications have been carried out to the analytical technique which has led to the development of various modern analytical techniques which make the detection and analysis of samples easy, rapid, and safe. Many types of research have been carried out for the analysis and extraction of samples using these novel techniques and patents have been filed for it [133-135].

5. Conclusion

Green analytical techniques have a goal to design processes and methods in a way that they produce products that are sustainable and benign to both humans and the environment. The

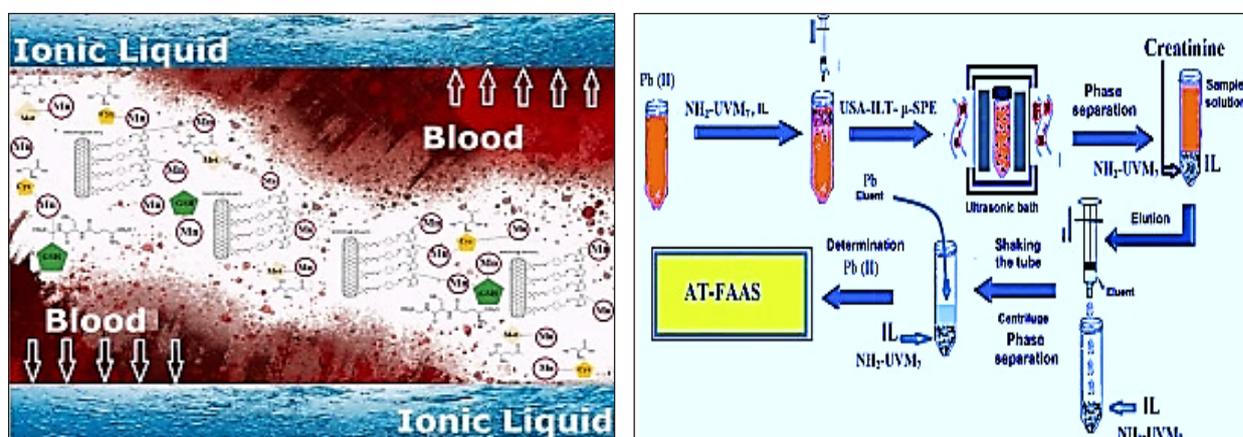


Fig. 5. Use of ILs as green solvents for analytical chemistry in blood samples

greener analytical laboratories can be made after meeting the guidelines or requirements of GAC. Significant efforts have been made in recent years to develop methods for product development using greener techniques. The methods include the use of greener solvents, analytical techniques and different extraction methods. The analytical methods can be described as green by substituting toxic reagents/solvents with green solvents, reducing the use of reagents. The use of greener solvents also increases the safety of the operator. The utilization of newer greener methods for analysis can have an impact on the workplace to perform work quickly. The emphasis of the review is to discuss some greener extraction techniques used by the researchers including micro-extraction techniques and supercritical fluid extraction. Selection of greener solvents and replacement are the two methods adopted to replace hazardous solvents. The development of greener analytical techniques results in a reduction of solvent and minimization of waste production.

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Abbreviation

ACN	Acetonitrile
AF	Aflatoxins
BMIM	1-Butyl -3-methylimidazolium
CE	Capillary Electrophoresis
ChCl	Choline chloride
DES	Deep eutectic solvents
DLLME	Dispersive liquid-liquid phase micro extraction

DMF	Dimethyl formamide
FT-IR-ATR	Fourier transform infrared – attenuated total reflection
GAC	Green analytical chemistry
GC	Gas chromatography
GC- FID	Gas chromatography– flame ionization detector
GO	Graphene oxide
HF-LPME	Hollow fibre liquid phase micro extraction
HPLC	High-performance liquid chromatography
ILs	Ionic liquid
IR	Infrared
IVM	Ivermectin
KOH	Potassium hydroxide
LOD	Limit of detection
MCR-ALS	Multivariate curve resolution – alternating least squares
MEECK	Microemulsion electrokinetic chromatography
MeOH	Methanol
MIR	Middle infrared
MSPE	Magnetic solid phase extraction
MVOC	Microbial volatile organic compounds
MXD	Moxidectin
NADES	Natural deep eutectic mixture
NIR	Near infrared
PLE	Pressurized liquid extraction
SC- CO ₂	Supercritical-carbon dioxide
SDME	Single drop micro extraction
SFE	Supercritical fluid extraction
SPE	Solid phase extraction
SPME	Solid phase micro extraction
XRD	X-ray diffraction spectrometry

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