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REPLACEMENT OF ORGANIC SOLVENTS WITH ENVIRONMENTAL ECO-FRIENDLY SOLVENTS FOR RP-HPLC ANALYSIS

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ABSTRACT: Background: Solvents are major part in chemical industry. Solvents have major impact on cost as well as safety and health issues. Many more organic solvents are considered toxic. Thus the concept of green chemistry is introduced which eliminate or reduce the use of hazardous solvents/chemicals from analytical process for the eco-friendly environment and health without any compromise in Analytical performance. **Aim:** Thus, the green chemistry goals to eliminate the use of hazardous chemicals and to search the non-hazardous solvents. Some of the methods are identified that are eco-friendly which replace the use of harmful organic solvents by use of alternatives such as The EHS method, bio-solvents, solvent less preparation techniques, RP-HPLC and UP-HPLC, Micellar liquid chromatography, Eco-friendly and economic analytical methods using hydrotropic solubilization. **Result and Discussion:** From the results it is identified that Contamination prevention, whether through green chemistry or other means, will be challenging for the environmental pollution.

INTRODUCTION: Solvents are appraised as a significant part of the environmental processes in chemical industry. Solvents also have an influence on cost, safety and health issues. Different organic solvents are used for different purposes such as it may be used in various analytical techniques such as (Gas chromatography, TLC, HPLC, HPTLC, Titrimetry, UV spectrophotometry *etc*.), also used in the extraction of active constituents from herbal powders, in synthesis of organic compounds, in formulation of pharmaceutical dosage form, in identification test of drugs *etc* [1]. A variety of organic solvents have been discovered to be both poisonous and carcinogenic. For example, benzene is carcinogenic, carbon tetrachloride is hazardous and it may cause environmental problems, among other things, and both are included in the class I organic solvents. Solvents can cause "toxicity to the neurological system, harm to the reproductive system, liver and kidney damage, respiratory impairment, cancer, and dermatitis," according to the Occupational Safety and Health Administration (OSHA) [2].

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Classification of Organic Solvents [2]: Class I and II organic solvents are comparatively more toxic than class III organic solvents. We can enhance the solvent power of class III organic solvents by dissolving safe solids in them to replace class II and class I organic solvents.

TABLE 1: CLASSIFICATION OF ORGANIC SOLVENTS

Class I	Class II	Class III
Benzene	Acetonitrile	Acetic acid
Carbon-tetrachloride	Chloroform	Acetone
1,2-Dichloroethane	Pyridine	Anisole
1,2-Dichloroethene	Hexane	Butanol
1,1,1-Trichloroethane	Methanol	Ethanol

Drawbacks of Organic Solvents [1]: Apart from the aforementioned reasons, organic solvents are costlier and their disposal necessitates special treatment once they have been utilised. As a result, the concept of green solvents expresses the goal of reducing the environmental impact of solvent use in chemical production. Examples of green solvents are shown in **Fig. 1.**

TABLE 2: DRAWBACKS OF ORGANIC SOLVENTS

Adverse effects caused by the organic solvents on a single exposure	Effects caused by the organic solvents on long-term exposure
Dermatitis	Chronic renal failure
Headache	Liver damage
Drowsiness	Neurosis
Nausea, Eye Irritation	Mutagenesis disorder

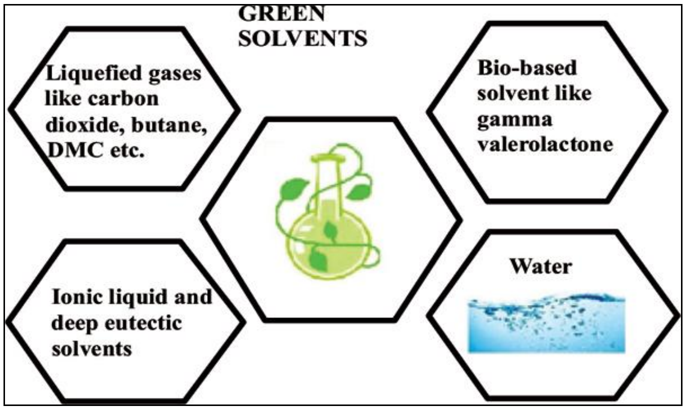


FIG. 1: EXAMPLES OF GREEN SOLVENTS

Green Analytical Chemistry: The concept of green chemistry has its backgrounds in sustainable development. The first activities were initiated by apothecaries for sustainability were focused mostly on industrial-scale processes and products, as clearly put forward in the most widely known characterization of green chemistry which was recommended by Anastas [3].

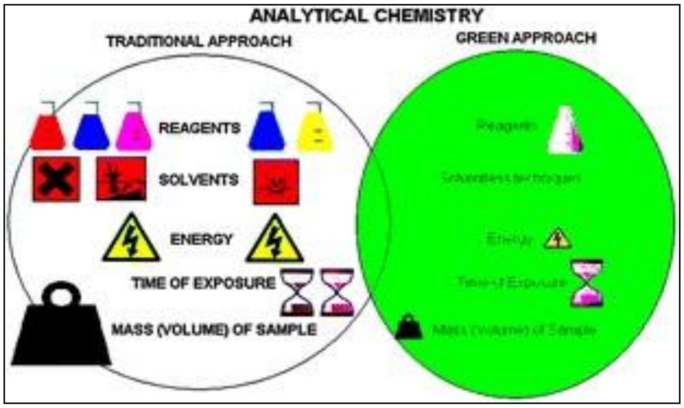


FIG. 2: COMPARISON OF TRADITIONAL APPROACH *VS* GREEN APPROACH

It is appeared from green chemistry in 2000's and it has accomplished the attention of numerous researchers in a wide range. Which states the elimination or reduction of the use of hazardous solvents and/or chemicals from the analytical process for the eco-friendly environmental nature and health without any compromise in an Analytical routine and the comparison of traditional approach *vs* green approach as shown in **Fig. 2.**

Basic Necessities of Green Chemistry: Organic solvents which are employed in wide range in the industrial process which have an vast impact on the economy as well as on the cost of environment. Organic solvents are noted to be combustible as well as poisonous/oncogenic also it may results into pollution.

Thus the prime goal of the green chemistry is to reduce and/or eliminate the use of the chemicals which are more hazardous and to search the solvents that are comparatively safe. The advantages of green chemistry are shown in **Fig. 3.**

FIG. 3: ADVANTAGES OF GREEN CHEMISTRY

Significance of the Green Chemistry:

- Selection of direct analytical technique.
- Never waste energy.
- Avoid derivatization, Increase safety for the operator *etc*.

Ethics of Green Chemistry are as follows [4]:

- Prevention of waste.
- Atom economy.
- Synthesis of less hazardous chemicals.
- Designing safer chemicals.
- Safer solvents and auxiliary.

- Designing for energy efficiency.
- Use of renewable feedstock.
- Reduce derivatives.
- Catalysis.
- Design for degradation.
- Real-time for pollution prevention.
- Safer chemistry for accident prevention.

Based on this, 12 ethics are described above some of the approaches are commonly resolved to achieve greener liquid chromatographic methods. They mainly address the reduction in solvent consumption by causing a decrease in column length, internal diameter and/or column particle size also on the replacement of toxic and hazardous organic solvents such as acetonitrile and methanol with less poisonous and more recyclable alternatives and thereby increasing the importance of recycling in preparative separation technologies on a large scale. The benefits of the green chemistry are shown in **Fig. 4.**

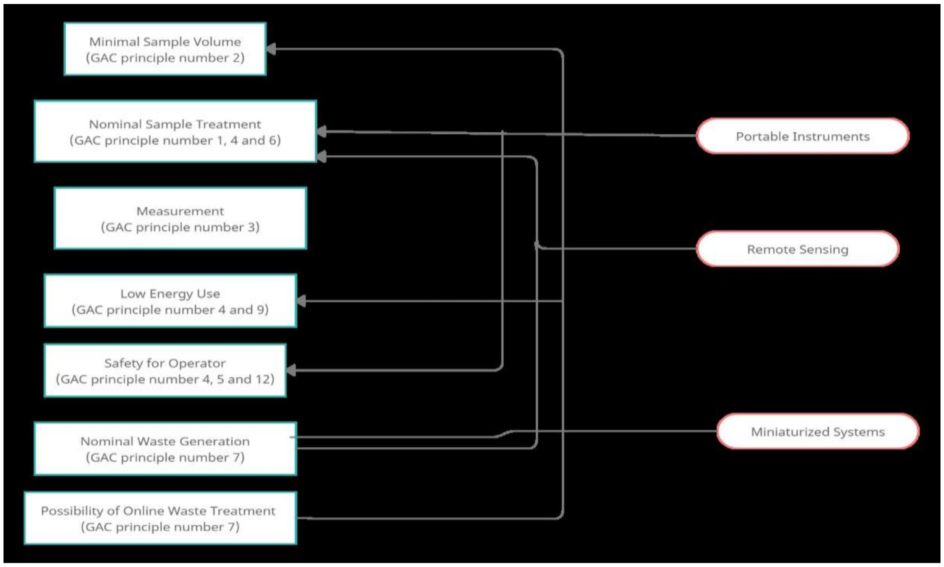


FIG. 4: BENEFITS OF ANALYTICAL CHEMISTRY

Some of the Below Methods are Identified are Green which Replaces the use of Harmful Organic Solvents by use of Alternatives which are Listed in **Fig. 5**:

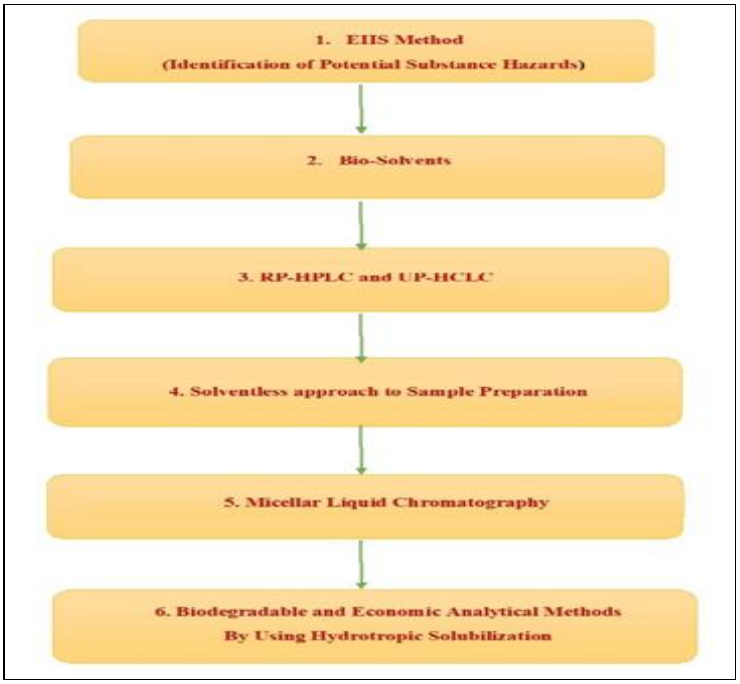


FIG. 5: LIST OF THE METHODS WHICH ARE IDENTIFIED AS GREEN METHODS

The EHS Method: Identification of Potential Substance Hazards: The EHS assessment method is one of the screening methods that identify the chemical substance's possible hazards in the early stage of the chemical process design. In the simple EHS method, 14 substances are evaluated in the 9 effect categories which are indicated in **Table 3.**

TABLE 3: SUBSTANCES ARE CATEGORIZED IN THE FOLLOWING CATEGORIES

Release potential	Chronic toxicity	Reaction / decomposition
Fire/explosion	Persistency	Water hazards
Acute toxicity	Air hazards	Irritation

An index between 0 and 1 was designed for each effect category, which results in an inclusive score between 0 and 9 for each chemical [5].

The Life-cycle Assessment (LCA) Method: This method analyzed the emission and resources used over the solvent's whole life cycle. The LCA method examined the use of generic energy related to solvent production and wastewater treatment. The environmental impact of the solvent or the solvent mixture can be calculated using the eco-solvent software tool.

Bio-solvents: Instead of petrochemically derived solvents, one approach to using green solvents in the extraction process is bio-based organic solvents [6].

Following are the application of the bio-based solvents:

a. Ethyl Lactate was used for the determination of total petroleum hydrocarbons as a kind and as a bio-based solvent [8].

b. A chloroform-methanol mixture is widely used for the purification of the membrane proteins, but toxicity and mutagenicity are reported in several cases [9].

c. The determination of fats and oil extraction is carried out by using a by-product of the citrus industry, which is named D-limonene, instead of petroleum solvents such as n-hexane, which are more hazardous. It is also used for water determination (Dean stark) instead of most toxic and petroleum-derived toluene [10, 11].

d. Limonene was successfully used to extract simvastatin, lovastatin, and its hydroxy acid metabolites from human blood plasma. It is also used as an immiscible diluent for a large volume of injection in the RPLC tandem Mass Spectroscopy assay of statins and their related metabolites in human blood plasma [12, 13].

RP-HPLC and UP-HPLC:

RP-HPLC: HPLC is an extensively used analytical procedure for separating and identifying different non-volatile substances from complex mixtures. Recently HPLC has been utilized for many functions, such as in the pharmaceuticals, chemical, and food industries. In all this analysis, such separation, impurity profiling, degradation characterization, and Consumption of organic solvents are quite huge and will cause environmental hazards [7].

Shifting the chromatographic mode from normal phase to reverse phase chromatography was the first step toward greening liquid chromatography [6]. In RP-HPLC, generally, the mobile phase is a blend of water (which also contains additives for the adjustment of ionic strength and pH) and organic solvents such as ethanol, acetonitrile, acetone, methanol, ethyl acetate, or their mixtures or either their mixtures with water. These solvents, especially ethanol, acetone, and ethyl acetate, are preferentially utilized in greenness. Some efforts are made to substitute them with acetonitrile and methanol, which are more toxic. Apart from their notable qualities regarding health safety, these two solvents also contribute to some difficulties and have certain environmental repercussions.

Acetonitrile is explosive, combustible, and even more toxic, although if MeOH is even less noxious as well as more easily decomposable than that of ACN then also MeOH is also ranked as a hazardous solvent only, as there is a greater requirement for its disposal as well as due to its intrinsic toxicity. However, the amount of waste generated by the analyses of RP-HPLC can’t be avoided. Thus the HPLC streams which contain these organic solvents must be disposed of properly as chemical waste only. Thus, it is costly and also adds environmental dumping burden on laboratory [7]. Thus the greening of RP-HPLC methods has received greater interest in the field of analytics, whose aim is to search for new alternative solvents to replace polluting analytical methods with less toxic ones. Thus, the change to the mobile phase from more toxic to less toxic allows the successful separation of neutral, acidic, and basic compounds. Thus, in RP-HPLC, these hazardous organic solvents can be replaced by eco-friendly, less toxic solvents. The output of the traditional RP-HPLC solvents vs. Alternative RP-HPLC solvents is depicted in **Fig. 6.**

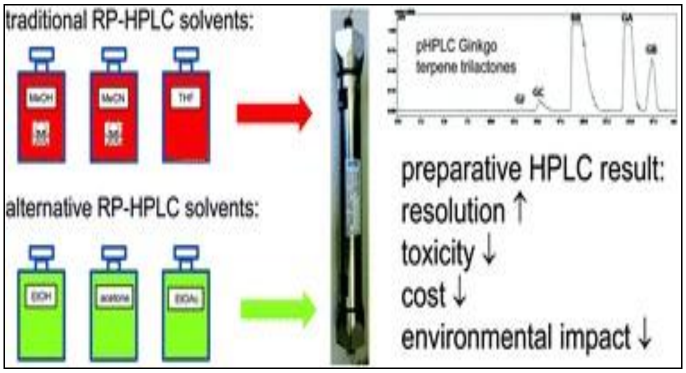


FIG. 6: OUTPUT OF TRADITIONAL RP-HPLC SOLVENTS VS ALTERNATIVE RP-HPLC SOLVENTS

Green organic solvents are selected based on their EHS criterion and LCA.

Apart from this, much attention has been gained to increasing the water content in the mobile phase [6]. To make the RP-HPLC greener, one of the best ways is to use 100% aqueous mobile phase because of the following reasons:

- Water is a universal solvent (which means not threatening to life or health or not malignant.), also readily available, cost-effective, non-toxic, and even non-flammable. Most importantly, it is environmentally friendly without any disposal concerns.

Apart from these properties described above, water cannot absorb UV down to 190nm, so it is possible to detect even weak type of chromophores. For the UV transparent compound analysis, it is more advantageous.

Application of Water-Based Mobile Phase: Eg., the PEG (polyethylene glycol) stationary phase allows the good separation of acidic and basic compounds by use of water containing 0.04% of TEA (triethylamine). Lesser attention is paid to applying greener solvents in normal phase liquid chromatography as the recent trend is to apply reversed-phase systems whenever possible.

UPLC: It is one of the modern techniques which gives a new way for liquid chromatography. UPLC stands for ultra-performance liquid chromatography," which mainly increases the following 3 aspects: Speed, Resolution, and Sensitivity. Particles lesser than 2µm in diameter are only applicable for the UPLC as they result in the good speed, resolution, and sensitivity compared to that HPLC. Nowadays, the industries are mainly focusing on cost-effective methods for the analysis and also give attention to the reduction in the time for the analysis. It comes in an account that UPLC is much more preferable for the good quality of the products nowadays in comparison to that of other analytical methods as in the UPLC the separation and the evaluation of the compounds are carried out under a very high pressure that is up to 100M Pa. No contradiction effect has been noted for the UPLC method in comparison of HPLC.

- The basic principle behind the UPLC is the same as that of HPLC, but there are some differences, such as the design of the particle size in the column packaging material, which was found to be 2µm less than HPLC [14].

To Improve the Efficiency of UPLC following Points are to be employed:

- By using high temperature, the mobile phase's viscosity is reduced, thereby allowing lows higher flow rate. Thus ultimately, back pressure is reduced.
- Use of monolith columns makes the UPLC technique discrete from the HPLC technique.

The ideal of the Van Deemter equation can't be completed without smaller particles than those traditionally utilized in HPLC. The Van Deemter equation is influenced by particle size; therefore, the scientist specializing in the planning and development of sub-2 µm particles may be a significant challenge.

Compared to HPLC UPLC's main advantage is as follows:

- It has good efficiency.
- Faster analysis is possible in UPLC as compared to that HPLC.

Both advantages are possible because of the smaller particle size. Thus, the van diameter equation reveals that efficiency increases by utilizing the smaller particles, leading to a rise in the back pressure.

At the same time, many HPLC systems can be used only up to 400 bars. Thus, to increase the analysis without the loss of efficiency, short columns packed with the particles of 2-micrometer size in these systems.

By above two parameters, UPLC analysis improves in the following:

- It Produced a Chromatogram with resolved peaks, it resulted in Fast analysis and Sensitive analysis. Thus, using smaller particles in UPLC reduces solvent composition and also reduces.

But the design and development of sub-2µm particles is a significant challenge. Whereas higher efficiency of nonporous 1.5-µm particles is available, they bear week loading capacity and retention because of the low surface area.

Silica-based particles have better mechanical strength, but it also has several disadvantages, which are as follows: limited pH range, and tailing of basic analytes. The polymeric columns can solve the limitation of PH, but they also have the following disadvantages: limited loading capacities and poor mechanical strength.

In 2000s, Waters introduced XTerra®, first-generation hybrid chemistry. XTerra® columns can operate over an extensive pH range. They are formed using a classical sol-gel synthesis that introduces carbon in the form of methyl group [14].

Advantages of UPLC:

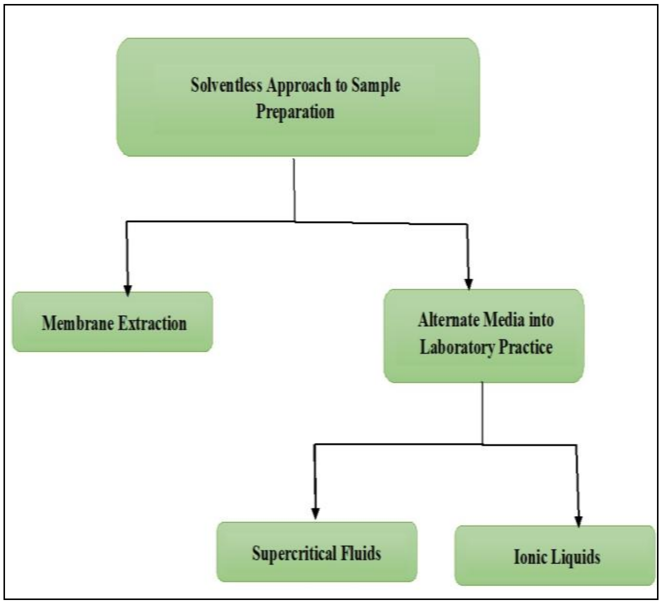
- It offers a good selectivity, sensitivity, and dynamic range of LC analysis.
- In the chromatogram, resolved peaks are developed.
- Uses of the smaller size of particle for packing of stationary phase make analysis fast.
- Time and cost are both decreased and utilization of solvents is less.

Disadvantages of UPLC:

- Life of columns.
- During analysis, high pressure is produced because of the particle size. An increase in pressure decreases the life of the columns. More maintenance is needed because of the increase in the pressure and also decreases the life of the columns.

Thus, the second strategy for reducing risks related to liquid chromatographic separations is the miniaturization of columns dimensions so that less mobile phase is required. Combining both approaches to reduce the amount of mobile phase and its environmental impact should bring the most desired outcome [6].

Solventless Approach to Sample Preparation: Classification of the Solventless Techniques are Depicted in Fig. 7:



Membrane Extraction: The use of various membrane materials in various configurations to extract various analytes in gas and water matrix has become popular in recent years. Although, the low polarity of the membrane limits the number of target compounds and makes the process unsuitable for analysis of polar components. Synthetic membranes can, however, be made of a variety of chemicals and may exhibit different properties.

- Microporous membranes,

- Homogeneous membranes,
- Ion-exchange membranes, and
- Asymmetrical membranes.

For separating the components of the liquid and gaseous mixtures, porous and non-porous membranes are employed, which are semi-permeable. These recent membranes were evolved jointly by chemical engineers, scientists, and polymer technologists.

They do not have ‘‘pores’’ in common recognization; their selectivity is based following:

- On differences in the solubility and.
- Diffusion properties of the various components in a mixture.

Separation is also based on the material it allows to pass through. For e.g., a polymer or liquid membrane material [15].

This process can be classified into three phases:

1. Adsorption of molecules on the outer surface of the membrane;

2. Dissolution of the adsorbed molecules and diffusion through the membrane material;

3. Desorption or evaporation of the molecules on the other side of the membrane to the receiving medium (carrier gas, absorbing solution, solid sorbent).

In the membrane-based process, separation occurs due to the difference in the transport rates of chemical molecules across the interface. The movement of the chemical species through the membranes is a non-equilibrium process in which flow can be related to the force that generated it. These forces are mainly because of differences in concentration, pressure, and electrical potential.

Proper membrane equipment can be used directly by contacting a gas or liquid sample with a suitable polymer (such as silicone, rubber, or Teflon) membrane. In contrast, the other side of the membrane is blown through a suitable gas stream. The gas mixture produced in this way is transferred directly to the measuring metal. Solid or liquid samples can be analyzed indirectly when the gas phase above the sample is in contact with the membrane. Membrane extraction can be done using suitable tubes made of less impervious material [16].

Alternative Media in Laboratory Practice:

Supercritical Fluids: Supercritical fluids are increasingly gaining more attention as environmentally acceptable for replacing hazardous organic solvents in chemical reactions and material processing [3]. **Table 4** depicted the Green’’ media that can be used in analytical laboratories [17]:

TABLE 4: GREEN’’ MEDIA WHICH CAN BE USED IN ANALYTICAL LABORATORIES ARE AS FOLLOWS [17]

Medium	Area of utilization
Supercritical fluid	Extraction agent Mobile phase in chromatography
Ionic liquid	Extraction agent Reaction medium
Super-heated water	Extraction agent Mobile phase in gas chromatography

Out of the many prospective supercritical fluids, supercritical carbon dioxide ($scCO_2$) and supercritical water (scH_2O) are the most likely to be applicable for green chemistry, particularly the former.

Properties of the supercritical fluids are as follows:

- It is non-flammable, readily accessible and very cheap.
- Its critical parameters (Tk = 31.1 1C; Pk = 7.38 MPa) are easily feasible
- As the CO_2 has a low heat of evaporation, thus by the use of energy can be saved.
- $ScCO_2$ can dissolve non-polar compounds and some of the polar compounds (e.g., methanol, acetone) at an efficiency comparable to that of halogenated solvents [17].

Apart from their advantages, methods that employed supercritical fluids are rarely used because they are scientifically more difficult: the extraction parameters have to be controlled with accuracy as the solubility of compounds in a supercritical fluid is very perceptive to the changes of pressure and temperature [18]. The generated CO_2 is purified, compressed, and cooled to the liquid state at 20 bar pressure and -20°C temperature and stored or transported in insulated bulk containers for the reutilization in many liquid and supercritical CO_2 processes. Phase diagram of CO_2 are shown in **Fig. 7.** The density of supercritical CO_2 can be changed extremely by the deliberate changes in the pressure or temperature around the critical point. Significant changes in condensed phases are produced by the combination of low viscosity and high diffusivity. Also, supercritical CO_2 influences the properties of components with which it is to be mixed. For example, supercritical CO_2 can dissolve many non-polar compounds beyond the limits of its vapor pressure. Also, a significant amount of supercritical CO_2 can dissolve into condensed phases, significantly decreasing the surface tension and viscosity of the condensed phases making the processing of viscous materials much easier. Table 5 indicates the physical properties of SCF.

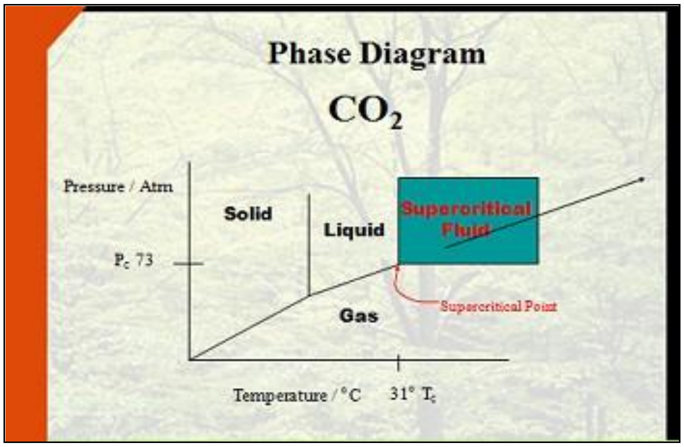


FIG. 7: PHASE DIAGRAM OF CO_2

TABLE 5: PHYSICAL PROPERTIES OF GAS, SCF AND LIQUID

Phase	Density (g/cm^3)	Diffusion (cm^2/s)	Viscosity (g/cm. s)
Gas at 1atm, 21°C	10^{-3}	10^{-1}	10^{-4}
Supercritical fluid	0.3 to 0.8	10^{-3} to 10^{-4}	10^{-4}to10^{-3}
Liquid	1	$<10^{-5}$	10^{-2}

Thus, the judicious use of the CO_2 technology may result in products (and processes) that areas cleaner, cheap, and of good quality [18].

Ionic Liquids: Ionic liquids (ILs) are also sometimes known as room-temperature ionic liquids (RTILs) because they are liquid at room temperature and are made completely of ions, most prominently by organic cations, but they can also contain inorganic or organic anions [19, 20, 21]. Ionic liquids are normally referred to as "designer" solvents [22]. They are low-melting-point salts (below 100 degrees Celsius). Ionic liquids were originally considered only as solvents for organic synthesis, but in recent years they have achieved great success as green solvents for analytical chemistry in industrial sectors.

In reality, they have a variety of beneficial qualities, including the following:

- It is highly miscible with water and organic solvents has excellent thermal stability but also is non-flammable.
- Ionic liquids seem to have an insignificant vapour pressure (low volatility); hence they cannot pollute the environment with volatile pollutants [23, 24].
- There is a 300 °C difference between the boiling and melting points.

  Although their environmentally beneficial aspect has recently been called into doubt, aquatic toxicity is a source of concern for ILs' environmental safety [25].

ILs have also been employed in the following Chromatographic Methods:

- Gas chromatography (GC),
- Capillary electrophoresis (CE) and
- Liquid chromatography (LC).

Ionic Liquids in Thin Liquid Chromatography: The imidazolium classes of tetrafluoroborate ILs were assessed as a mobile phase modifier for the study of numerous basic compounds on an octadecyl bound-silica stationary phase, including 1-Ethyl-3-methylimidazoliumtetrafluoroateborate [EMIM] [BF4], [HxMIM] [BF4] and [Hx-HpOMIM] [BF4]. The retention of the studied compounds is unaffected by TEA, DMOA, or ammonia. The most efficient suppressor of attractive interactions between acidic free silanols present on the stationary phase surface and assessed basic pharmaceuticals was discovered to be ILs, which resulted in a significant decrease in retention, improved selectivity, and improved spot shape. The effects of the additives under investigation on chromatographic data are compared. Using IL as a mobile phase modifier in normal-phase TLC systems is also advantageous.[22]

Advantages of IL's-

- High thermal robustness.
- They show thermal stability in the range of -40°C to 200°C, substantially wider than other solvents such as water, ammonium, and methanol.

Drawbacksof Il's-

- The fact that ILs have a much higher viscosity than ACN is one of the key drawbacks of utilising them as solvents in liquid chromatography.
- A completely different scenario emerges when ionic liquids are added to aqueous organic mobile phases in tiny portions (2-60 mM). In such small amounts, ionic liquids lose their unique properties and transform into salts.
- In consequence, ILs are a significant risk to the aquatic ecosystem. Due to the presence of salts, colour, or odour, maintaining high purity ionic liquids can be difficult [27].

Application: Ionic liquids are notably useful in investigating basic chemicals on reversed-phase columns made of silica, where silanol interactions are ordinarily a disadvantage.

Ionic liquids are widely used to reduce silanol interactions by including tertiary amines and bivalent cations. The covalent interaction of silanol groups of silica gel with the cation of an ionic liquid is required to modify the stationary phase using ILs. The resulting phases change their attributes to ion-exchanging, allowing inorganic and organic ionic analytes to be distinguished.

Micellar Liquid Chromatography:

Introduction: Micellar liquid chromatography (MLC) is one of the types of liquid chromatographic reversed phase in which the non-polar stationary phase and the aqueous solution of surfactant in the concentration beyond critical micellar concentration (CMC) mobile phase is used [28].

In MLC, retention of analyte depends on three stages which are as follows:

- Stationary phase,
- Bulk solvent and.
- Micellar pseudo-phase.

As a result, compounds are classified according to their different partitioning between the three phases stated above. Surfactants were usually added to the moving phase to produce micelles, but we can also use surfactant-coated stationary phases. Partition commonly occurs between the micellar pseudo-phase and the standing phase of water-soluble compounds by directly transferring analytes [29]. Micellar liquid chromatography has been found to be an attractive alternative to GAC, as it eliminates or minimizes the use of harmful solvents. Indeed, moving phases contain aqueous surfactant solutions and a small amount of organic solvent (approximately less than 15% v v). Additionally, these micellar moving components may contain the following features:

- They are non-flammable and have low toxicity and.
- They do not produce hazardous waste as the biodegradable behaviour of the surfactants used [32].

For example, sodium dodecyl sulfate (SDS) is MLC's most typically used surfactant. SDS is a fatty alcohol sulphate that is aerobically degraded [32–34].

Although, it is frequently important to add organic solvents to the aqueous solutions of micelles to get better separations of Micellar liquid chromatography [32]. Most typically used organic modifiers in MLC are propanol, butanol, and pentanol, which are comparatively less toxic than MeOH or ACN [35]. Apart from this, another benefit of MLC is that it concerns sample treatment. The significant solubilizing capability of micelles permits the direct injection of drugs into the complex matrices (e.g., biological fluids and dosage forms) without any need for sample pre-treatment accept filtration [28]. Furthermore, MLC is agreeable with that of current/recent RP-HPLC instruments. Therefore, it does not require any alteration in the current RP-HPLC instrumentation.

Particularities of the Micellar Mobile Phase: Micelles have two sites such as hydrophobic and electrostatic (for ionic surfactants), for the interaction. In the micelles, three sites of solubilization can be recognized, which are as follows:

- The core (hydrophobic),
- The surface (hydrophilic) and.
- The palisade layer (the region between the surfactant head groups and the core).

Micelle-related solutes are subjected to a microenvironment that differs from that of bulk solvents. While pure micellar mobile phases are infrequently employed in MLC, the vast majority of separations are performed with hybrid micellar mobile phases in a buffered medium containing micelles, surfactant monomers and organic solvent molecules and water.

The organic solvent changes the micelle structure by reducing the polarity of the aqueous solution. The maximum concentration of organic solvent can disrupt the micelle structure. The maximum concentration that can be used is determined by the type of organic solvent and surfactant used [29].

Critical Micellar Concentration: It is the most appropriate surfactant for MLC with a low CMC. When a high CMC is used, it is implicitly running at a high surfactant concentration, which might result in viscous solutions, resulting in high system pressure and unwanted background noise in UV detectors. Selection is often restricted to the surfactant

- The anionic sodium dodecyl sulphate (SDS),
- The cationic cetyltrimethylammonium bromide (CTAB),
- And the non-ionic Brij-35

It's also worth mentioning that the presence of a natural solvent significantly impacts critical micelle concentration (CMC). Several ionic-based surfactants have been utilized in MLC, including 1-hexadecyl-3-butylimidazolium bromide [38, 39, 40].

Krafft Point: For ionic surfactants, the Krafft point is defined as the temperature at which the solubility of a surfactant monomer equals the CMC [41]. Surfactant solubility is slightly lower below the Krafft point temperature, and the solution discovered does not include micelles. To avoid surfactant precipitation, chromatographic operations in MLC must be performed above the Krafft point temperature, which means that the Krafft point must be far below ambient temperature. SDS and CTAB have Krafft points of roughly 15°C and 20–25°C, respectively [42, 43].

Non-ionic surfactants have a specific temperature range; if the temperature exceeds that range, phase separation may occur, referred to as the cloud point [37, 44].

As a result, chromatographic work with these surfactants should be done below this temperature (for example, Brij-35 is around 100°C for aqueous 1–6% solutions, while Triton X–100 is around 64°C).

pH of the Mobile Phase: MLC uses packing materials that are identical to those used in classic RPLC, with a pH range of 2.5–7.5 for conventional columns. On the other hand, the appropriate pH levels are determined by two factors: the type of the analytes and the surfactant used.

Typically, phosphoric or citric acid buffers are used to adjust the pH of the micellar mobile phase [36, 45]. Potassium salts are not suitable for mobile phases containing SDS because potassium dodecyl sulphate has a high Krafft point and precipitates from aqueous solutions at ambient temperature [36].

Organic Solvents: Types and Concentration: The polarity of the analytes must be considered while selecting an organic solvent modifier in MLC. Solvents like 1-propanol, 2-propanol, or acetonitrile provide sufficient short retention periods (below 20 minutes) for polar chemicals. Stronger solvents, such as 1-butanol or 1-pentanol, are required for non-polar molecules or compounds with a higher affinity for the surfactant deposited on the stationary phase [46].

It is important to note that the micelles disaggregate at high organic solvent concentrations, leaving only free surfactant molecules in the mobile phase. The organic solvent contents help micelles maintain their integrity: 15% for propanol and acetonitrile, 10% for butanol, and 6% for pentanol [47]. In comparison to what is required in traditional RPLC, their contents are modest. Minimal organic solvent consumption reduces toxicity while also helping in improving efficiency, a phenomenon that may become known as "green chemistry." Furthermore, stabilizing the organic solvent in the micellar media lowers the possibility of evaporation, allowing micellar mobile phases to be preserved in the laboratory for extended periods with no or little changes in composition [48].

Green Evaluation of MLC: In terms of eco-friendly perspectives, RPLC techniques are distinguished by a large consumption of organic solvents. Evolving a greener process in chromatography is an exception. MLC is detected to be a good alternative to RPLC, which upgrades both economical and eco-friendly aspects. MLC is much greener than RPLC in all steps of the analysis, from sample collection and preparation to separation and final determination.

Sub Micellar Liquid Chromatography: The Novel approach in the MLC depends on the concentration level of surfactant and organic solvent [48].

Low Sub-Micellar Chromatography: The stationary phase in this chromatographic technique is coated with SDS, and so contains a negative charge. The electrostatic attraction allows cationic solutes to interact hydrophobically with the uncovered alkyl-bonded layer or the adsorbed surfactant monomers. Surfactant coating on the stationary phase rises with surfactant concentration in the mobile phase as long as the adsorbed amount of surfactant does not exceed the column's maximum capacity, resulting in significant Rt (retention times). The amount of free surfactant molecules in the mobile phase is negligible under sub-micellar conditions and at low surfactant concentrations. This shows that an ion-exchange retention mechanism is a primary mechanism and that ion-pair creation with the surfactant in the mobile phase is almost non-existent. Adding an organic solvent to the mobile phase enhances the elution strength as a result of the reduced polarity of the mobile phase, and the competition between organic solvent and surfactant molecules for adsorption sites, reducing the amount of surfactant adsorbed on the stationary phase.

High Sub-Micellar Chromatography: The surfactant concentration is at the point where micelles form in water, but the organic solvent level is significant, preventing micelle formation. As a result, the mobile phase solely contains surfactant monomers, dissolved in the hydro-organic medium. The amount of surfactant swept off the alkyl-bonded phase by the organic solvent and the presence of micelles determine the major retention mechanism in this area.

The retention mechanism will be typical of the micellar mode as long as a specific amount of surfactant stays adsorbed and the micelles exist. Micelle disaggregation results in a sub-micellar condition, in which ion-pair interactions with surfactant monomers in the bulk mobile phase replace micelle interactions.

Advantages:

- Micellar mobile phases are cheap as compared to that of hydro-organic mobile phases.
- They enable the direct determination of physiological samples without needing any prior treatment, and they are well equipped with typical RPLC instruments, so no specific preparations are required.

As a result, it has been established that several green chemical principles have been developed in MLC, which will improve both the operator's and the environment's safety.

Application of MLC: However, SDS was used in many of the procedures, and some of the methods additionally used Brij-35 [49, 50], cetyltrimethylammonium bromide (CTAB) [51], or Tween-20 [51].

Hybrid micellar liquid chromatography has been found to use mobile phases that consist of an aqueous surfactant solution and a small volume of organic modifiers, such as n-propanol, n-butanol, and n-pentanol, in a wide range of applications. The feasibility of this method was then thoroughly confirmed by analyzing tablets and biological samples (*i.e.,* plasma and urine samples) from patients treated with selective serotonin reuptake inhibitors without the need for extraction processes (SSIRS). Green MLC analysis of pharmaceuticals using completely aqueous mobile phases is another appealing example [49-52]. As a result, MLC appears to be a viable option for developing green chromatographic procedures for pharmaceutical analysis. In particular, MLC enables the simplicity of sample preparation for complex biological sample analysis. It can also be used with UV, fluorescence, and electrochemical detections.

However, the type and concentration of surfactants and the nature and proportion of organic solvents contribute to slightly challenging chromatographic developments in such procedures. Because of the complexity of the mobile phase, retention mechanisms are frequently difficult to conclude or define.

Biodegradable and Economic Analytical Methods by using Hydrotropic Solubilization [53-54]:

Introduction: Improvement in the aqueous solubility of a weakly water-soluble API in the presence of a large concentration of an agent such as a hydrotropic agent is referred to as hydrotropic solubilization. Newberg was the first to use the term hydrotropic agent (1916).

According to Newberg, a hydrotropic agent is a metallic salt of an organic acid with a high concentration in water that can improve the aqueous solubility of organic molecules that are soluble in water to some extent. Salts that produce an elevation in solubility are said to be "salt in" the solute, while salts that cause a decline in solubility are said to be "salt out [1, 53].

Advantages of Hydrotropic Solubilization are as follows:

- It is a novel, cost-effective, safe, efficient, and accurate technique.
- An eco-sustainable approach for analyzing compounds that are weakly water-soluble.

The technique is simple and effective. This approach does not require any chemical alteration of the hydrophobic compounds or the use of organic solvents.

Novel Pharmaceutical Applications of Hydrotropy:

In Titrimetric Analysis: The hydrotropic solubilization method is used to perform titrimetric analysis on a range of inadequately water-soluble drugs.

For example,

1. Using 2.5 M sodium salicylate, aceclofenac bulk medication's aqueous solubility (a poorly water-soluble NSAID) can be increased by 400 times. The current study's major goal is to use this hydrotropic solution to extract the substance from its dosage forms without using any life-threatening organic solvents.
2. Maheshwari invented a unique, reliable, and efficient approach for titrimetric detection of salicylic acid in bulk, a sparingly water-soluble keratolytic medication, using a 2.0 M sodium saccharin solution as a hydrotropic solubilizing agent. Compared to the distilled water's solubility, a 15-fold increase in the aqueous solubility of salicylic acid in 2.0 M sodium saccharin solution was observed. Another application of hydrotropic in the titrimetric analysis is shown in **Table 6.**

TABLE 6: APPLICATION OF HYDROTROPY IN TITRIMETRIC ANALYSIS

S. no.	Drug	Official method (organic solvents employed)	Hydrotropic solution Employed
1	Aceclofenac (bulk drug +tablet)	Methanol (bulk drug, IP method	2.5 M Sodium salicylate
2	Aspirin (tablet)	-	0.5 M Ibuprofen sodium
3	Benzoic acid (bulk drug)	Ethanol (I.P. method)	0.1 M Calcium disodium Edetate
4	Salicylic acid (bulk drug)	Ethanol (I.P. method)	2.0 M Sodium saccharin

In UV Spectrophotometric Analysis:

1. For the UV spectrophotometric analysis of the poorly water-soluble medication ornidazole at 319 nm, Maheshwari used a 10.0 M urea solution, which causes a greater than 10-fold increase in ornidazole solubility in 10.0 M urea solution compared to pure water. This approach does not use any organic solvents and is also environmentally conscious. In the presence of urea, Beer's law was followed in the concentration range of 5-25 g/ml. The presence of urea had no influence on the outcomes. As a result, the proposed method is superior, faster, simpler, more accurate and reliable.

2. He also employed a 2.0 M hydrotropic sodium tartrate solution to solubilize the poorly water-soluble drug cefixime from its fine powder tablet dosage form for spectrophotometric measurement in the UV region. Cefixime has a maximum absorbance of 288 nm and follows Beer's law in concentrations ranging from 5 to 30 g/ml. The results of the study were statistically and by recovery studies validated, and they can be used in routine to examine cefixime pills. In the analysis, the hydrotropic agent and regularly used tablet additives had no effect.

TABLE 7: APPLICATION OF HYDROTROPIC IN UV SPECTROPHOTOMETRIC ANALYSIS

S. no.	Drug	Official method (organic solvents employed)	Hydrotropic solution Employed
1	Atenolol (tablet)	Methanol (IP method)	1 M Metformin hydrochloride
2	Metronidazole (tablet)	-	7.5 M N, N – dimethyl urea
3	Piroxicam (tablet)	-	1.5 M Ibuprofen sodium
4	Tinidazole (tablet)	Methanol(I.P. method)	1.25 M Sodium citrate

In Thin Layer Chromatography: The literature review reveals that a wide range of organic solvents have been used for thin layer chromatographic studies of generally weak water-soluble drugs, which include methanol, chloroform, dimethyl formamide, acetonitrile, benzene, hexane, pyridine, tetralin, methyl cyclo-hexane, methyl butyl ketone, toluene, methylene chloride, chlorobenzene, nitromethane *etc*. Organic solvents have a number of drawbacks, namely toxicity, increased cost and pollution. As a result, in such circumstances, hydrotropic solubilization appears to be a better substitute for these organic solvents. As a result, poorly water-soluble drugs such as atenolol, paracetamol, and ibuprofen were chosen as analogues. TLC was done on these poorly water-soluble pharmaceuticals using hydrotropic sodium benzoate and urea solutions separately in distilled water. This approach eliminates the use of noxious and expensive organic solvents. As a result, the proposed TLC methods are accurate, easy, cost-effective, environmentally sustainable, and convenient.

TABLE 8: APPLICATION OF HYDROTROPY IN THIN LAYER CHROMATOGRAPHY

S. no.	Drug	Official method (organic solvents employed)	R_f value of official methods	Hydrotropic method	R_f value of hydrotropic methods
1	Atenolol	99 vol methanol, 1 vol strong ammonia solution (IP)	0.67	5.0 M urea solution, 1.0 M sodium benzoate solution	0.77 0.63
2	Paracetamol	A mixture of 65 vol of chloroform, 25 vol of acetone and 10 vol of toluene (IP)	0.65	5.0 M urea solution, 0.5 M sodium benzoate solution	0.86 0.68

CONCLUSION: Environmental pollution is a global problem nowadays. So, to remove such issues, we have to shift towards Green chemistry [55]. Developers of analytical procedures frequently claim that the solvents employed in extraction and liquid chromatography separation processes are environmentally friendly, although this claim is not backed up by evidence. Analysts interested in using green solvents should keep up with new developments in green or bio-based solvents in other fields of chemistry. Using solvents derived from renewable sources is one of the developments that will acquire more attraction in analytical sciences. The use of environmentally hazardous, non-polar solvents is being phased out in favour of more environmentally friendly, polar solvents such as esters, ethers, and alcohols. There are just a few solvents that can be treated as green; however, there are many examples of greener solvent alternatives for various analytical techniques. Here, this article discusses different techniques that replace harmful organic solvents and preserve the environment.

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