



ROLE OF GREEN SOLVENTS IN THE PHARMACEUTICAL FIELD

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ABSTRACT

In day-to-day advancement in pharmaceutical formulations, the use of different chemicals increases, increasing the concern about environmental safety. For more than a decade, research has been carried out to reduce environmental pollution through the changes in solvent systems and new technologies have been introduced in solvent repurposing. The introduction of green chemistry which started its studies in using green solvents showed some changes in reducing Pharmaceutical industrial waste. This review article explains the various green solvents and their application in pharmaceutical fields.

Keywords: Green chemistry, Solvent repurposing, green solvents, Pharmaceutical industrial waste, deep eutectic solvent

INTRODUCTION:

A solvent is a substance that dissolves the solutes to form a solution. The solubility of the solute in the solvent depends upon the intermolecular interaction

like Vander Waals force, ionic /dipolar interaction, hydrogen bonding & charge transfer. The solvents have been used as a medium for many chemical reactions [1].

Many factors decide the solubility of solute into the solvent like the strength of intermolecular forces between a pure solute and a solvent. Specifically, 'like dissolves like', which can be explained by an example. A polar substance like sodium chlorides dissolves immediately in the polar solvent like water than a non-polar solvent like pentane, hexane etc. [2].

The role of solvents starts from the synthesis of drugs and ends in determining their purity. The high polarity solvents like amides are used in solubilizing wide samples [3], but the amide-based solvents increase the toxicity. Based on the risk assessment the ICH guidelines Q3C R8 have classified the solvents into three categories (International Council for Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use Impurities: Guideline For Residual Solvents Q3c(R8) 2024)

Category -I: Solvents to be abstained from

These solvents are considered to be human carcinogens. Example: Benzene, carbon tetra chloride, 1,1 Dichloroethane, 1,2 Dichloroethane, 1,1,1 Trichloroethane. The limit of these solvents is 1500ppm.

Category -II: – Solvents to be used minimally

Considering the toxicity level of solvents, their usage should be limited.

Examples: acetonitrile, chlorobenzene, chloroform, cumene, and cyclohexane. These solvents' Permitted Daily Exposure (PDE) is 0.1mg/day.

Category -III: – fewer toxic solvents

Solvents like Acetic acid, Acetone, Anisole, 1-butanol, 2-butanol, Butyl Acetate, DMS, and Heptane should be limited by GMP or other quality-based requirements. The PDE of these kinds of solvents is 50mg/day.

In considering environmental safety Dr. Paul Anastas introduced the theory of Green chemistry. Which is defined as "the design, manufacture, and use of chemical products and processes to limit the usage and creation of hazardous materials" is known as "Green Chemistry." This theory inspired both industrial and academic chemists which resulted in the invention of a new method which is "Benign by Design" and the oath of the green chemist is "Do No Harm" [5].

The merits of green chemistry are, that the product and the process should be more economical, renewable, lower energy costs, and easy to dispose of waste. The greenness idea was first implemented by a German in the Synthetic colour dye industry and they generated the first medicinal chemistry program. It is major in drug synthesis, formulation, and analytical fields. The use of green solvents is the basis for green chemistry since solvents are the major

component of drug synthesis for analysing its purity. Twelve fundamentals of green chemistry were developed by Paul Anastas [6], and the principles been represented in Figure 1.

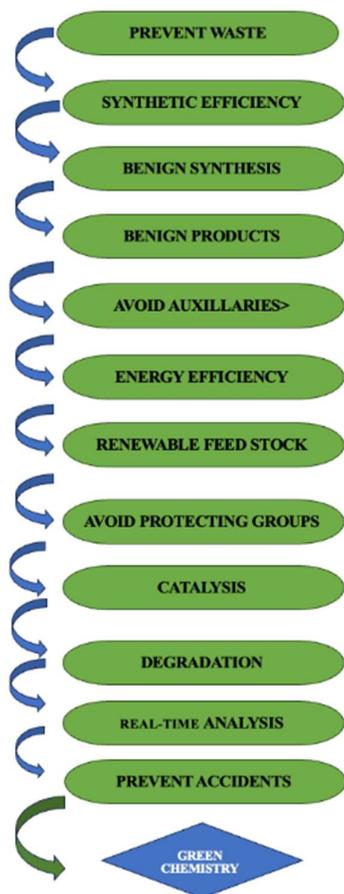


Figure 1: Twelve Principles of Green Chemistry

What does Green Solvents mean?

Green solvents which are otherwise named as eco-friendly solvents can be obtained by processing the agricultural waste. They have been developed as a substitute for petrochemical solvents. The desirable traits of green solvents are low toxicity, non-mutagenic, available at low cost, easily usable and repurposed. Some of

the examples for bio-solvents are ethyl lactate which is the ester of lactic acid which is obtained from corn [7]. Similarly, furfuraldehyde which is a precursor for acetone and methyl ethyl ketone is obtained from oat-hull which is a byproduct in the manufacture of animal feed. This solvent is used to solubilize the resins [8]. The concept of fermentation also helps in the production of bio-solvents like ethanol which is obtained by fermentation of sugar. The recent research is much focused on solvent repurposing and the use of neoteric solvents or non-conventional solvents for extracting the API.

Solvent Repurposing:

The theory of green chemistry is not only limited to the use of green solvents it is also extended to solvent waste reduction or solvent recovery. Isopropanol (IPA) is a conventional chemical used as a primary pharmaceutical and chemical industry solvent. Abundants of waste are generated during the different stages of drug production. These cause many toxic effects on the soil, human beings, plants, and animals. To control this environmental pollution solvent recovery techniques have been introduced. The waste IPA can be recovered and repurposed by using CO₂ switchable Deep Eutectic solvents (DES) [9]. Another example of a repurposing chemical is N-butyl stannic acid which is easily available, recyclable and reusable and

used as a catalyst in the synthesis of amide which is the key chemical in the synthesis of some of the active Pharmaceutical ingredients like paracetamol, valsartan, atorvastatin, captopril etc. [10].

Neoteric Solvents:

Neoteric solvents are the alternatives for the common organic solvents with the properties of sustainability, easily degradable, non-toxic in nature, economical and help in minimizing waste. Based on their chemical properties they are classified as supercritical CO₂, ionic liquids, bio-renewable solvents, Eutectic Mixtures [11], Supramolecular solvents [12] & surfactants [13]. These solvents have flexible physical properties which helps us to select them for many chemical reactions. The active pharmaceutical ingredients from plants can be effectively extracted using neoteric solvents [14]. The types of neoteric solvents are given in **Figure 2**.

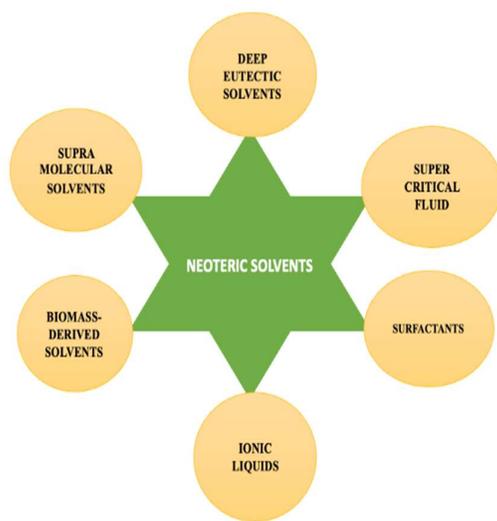


Figure 2: Various types of Neoteric solvents

Supercritical Fluids (SCF)

Supercritical fluids (SCF) are highly compressed fluid that combines the properties of both liquids & gases. They are created by increasing temperature and pressure beyond a substance's critical point. An example of SCFCO₂ is a most versatile green solvent because of its properties, non-toxic nature, chemically inert and low-cost nature. The scCO₂ can penetrate the solid substrate and remove the desired product or impurities [15]. SCF's properties help solubilise the poorly soluble Active Pharmaceutical Ingredients (API). The strong solubilizing nature helps in the application of many pharmaceutical formulations like controlled drug delivery systems, powder processing etc. [16]. The frequently used SCF solvents are carbon dioxide, water, ethane, ethene, and propane. However, considering the fundamentals of green chemistry, SCFCO₂ is preferred in the pharmaceutical industry. some limitations have been found in SCFCO₂ in solubilizing some solutes according to added cosolvents to increase the solubility. Cosolvents like methanol, propanol, and butanol are preferred [17]. In recent years, SCF has played a major role in novel drug formulations like TDDS, CDDS etc. The formulation of nanoparticles improves the adsorption of low-aqueous solubility drugs in GIT. Super Critical Fluid has been used in

the preparation of polymeric nanoparticles which improves the particle size [18].

Ionic Liquids:

Ionic Liquids are the combinations of anion and cation with a melting point below 100°C. The advantage of Ionic Liquids is their flexible properties. Depending upon the solubility property of the poorly soluble compound the Ionic Liquids can be prepared. Hence, the Ionic Liquids were named designer liquids [19]. Ethyl ammonium nitrate was the first Ionic Liquid discovered by Paul Walden [20]. An ionic liquid has one cation & one anion. Usually, the anions are small and cations are bulky alkyl groups. Based on the structure they are classified as imidazole, pyridine, pyrrolidine, quaternary ammonium salt, pyrrolidinium, and quinolinium. The first-generation ionic liquids are used in electroplating, the second-generation ionic liquids are aqueous stable and synthesised from cation & anion, depending upon the requirement of physical properties like viscosity, vapour pressure, solubility, melting point the ratio of cation & anion will be changed. The new technology has been implemented in the third generation, where the natural sources of cations and anions synthesise ionic liquid [21]. The application of ionic liquids has been extended in formulating transdermal drug delivery system [22]. The Ionic Liquid is not limited

to formulations, this idea has been extended in drug analysis using liquid chromatography and capillary electrophoresis [23].

Surfactants:

Surfactants are surface-active agents with long hydrocarbons. It helps in solubilising the aqueous poorly soluble Active Pharmaceutical Ingredients. This solubilisation is possible because of the micelle formation at Critical Micellar Concentration (CMC). They also act as catalysts in many reactions. They are of three types: cationic surfactant, anionic surfactant and non-ionic surfactant. Recent studies explain the nature of surfactants and their applications in formulating and analysing the drug. In drug analysis, it has been replaced with organic solvent in spectroscopic determinations. The sample's polarity differs from the organic solvents, changing the sample's absorption [24]. Researchers have submitted many articles in extracting the phytochemicals from natural sources using surfactants [25]. The addition of surfactants can change the chemical properties of individual neoteric solvents [26].

Eutectic mixtures:

Eutectic Mixtures are solvents that have similar properties to ionic liquids. They are obtained from a eutectic mixture of Lewis acid and bases. This mixture contains different species of cation & anionic

compounds. This is the major difference between the ILs which contain only one type of cation & anionic compounds [27]. The presence of different ionic species makes the solvents extract micro-level samples from sources. For example, Niclosamide is an anti-helminthic and anti-viral drug extracted using deep eutectic solvent from pharmaceutical & wastewater and analysed using chromatographic techniques [28].

Bio-renewable solvents:

The above discussion on green solvents is based on the physio-chemical properties of the solvents which can be preferred for extraction, sample preparation, formulation and analytical purposes. Other than these solvents the researchers studied solvents obtained from biomass and some researchers have studied the alteration of toxic solvents. Ethanol is a bio-renewable solvent produced from various sources like sugarcane, corn, non-edible feedstock and agricultural waste like rice straw, giant cane & wheat straw [29]. Derivatives of alcohol like furfuryl alcohol and glycerol were produced from different biological sources. The research has been extended to many classes of organic compounds like esters, ketone, alkanes & aromatics, and ethers. Currently, a ketone derivative solvent, marketed as Cyrene, is a more sustainable and eco-friendly solvent used as a mobile phase in High-performance Liquid Chromatography (HPLC) [30].

APPLICATIONS OF GREEN SOLVENTS IN VARIOUS FIELDS OF PHARMACEUTICALS

Role of green solvents in drug and chemical synthesis:

In chemical and drug synthesis, selecting the starting material, solvent and catalyst plays a major role. Most of the reactions had been carried out in the aqueous phase. Benzene is a carcinogenic solvent that must be avoided during the synthesis. The method of synthesizing must be selected accordingly, the maximum of the starting material must be converted into a final product with less amount of solvent and a reusable catalyst. In the early days, reactions are believed to be impossible without solvents. Later it was found that many reactions are possible in solids without solvents. Such solvent-free reactions are considered environmentally safe. The percentage yield of the product obtained during solvent-free reactions is higher comparatively with normal methods [31]. For example, polyglycerol Polyricinoleate can be synthesised using *Rhizopus Arrhizus* lipase as a catalyst [32]. Many comparative studies were made between classical methods and solvent-free methods in synthesising chemicals Jasminaldehyde [33], α – hydroxy phosphonates [34], α -amino phosphonates [35], Pyrazolone [36], and pregabalin [37] using different types of organic catalysts or ultraviolet radiations.

The product had been obtained with a satisfactory percentage yield. This shows that solvent-free synthesis of organic compounds is the best technique in green chemistry. Safaei *et al* compared the percentage yield of 4H-Pyran using glycerol and water as solvents. Though water is a natural solvent it can yield only 75% of the product, whereas glycerol can produce 93% [38].

Role of Green Solvent in Pharmaceutical formulations:

An active Pharmaceutical Ingredient (API) is converted into formulations using excipients. Depending upon the requirement of formulation the nature of excipients varies. The excipients play a major role in the formulation since they decide the product's efficacy, safety, applicability & acceptability. In topical formulation, the emulsifiers, emollients, preservatives, gelling agents, humectants, and permeation enhancers can be obtained naturally [39]. The green solvents dimethyl isosorbide and isopropylidene glycerol were used in the preparation of colloidal Lignin Nano Particle (cLNP) which is being used in the formulating eco-friendly sunscreen cream [40] Green solvents like Ionic liquids (ILs) are used in pharmaceutical formulations to obtain the desired biological potential of API. Many researchers investigated the physiochemical nature of Ionic Liquids, enabling the poorly soluble API to give good

therapeutic efficacy. It was found that the Ionic liquids (ILs) mixed with natural or synthetic bioactive substances improved their bioavailability [41]. The bioavailability of poorly soluble drugs was improved when loaded with an Ionic Liquid rutin polymer nanoparticle hybrid system [42]. The studies on green solvents in formulations have been extended to eutectic solvents. The Deep eutectic solvent (DES), remains liquid at room temperature which is consisting of a hydrogen bond acceptor and hydrogen bond donor. They have extensive physical and chemical properties like low vapour pressure, non-inflammability, solvency power for a wide range of solutes and water non-reactivity [43]. Dimethyl sulfoxide (DMSO) is a universal solvent for poorly soluble drugs. Considering the environmental safety, the researchers tried to replace DMSO with DES. Salsalate, a poorly soluble drug is dissolved even in higher concentrations in DES composed of Choline Chloride-Propylene Glycol -water in the ratio of 1:1:1 [44]. Additionally, the application of DES has been extended to dermal and transdermal patches. Further research is proceeded with highly insoluble drugs with DES to enhance their Bioavailability.

Role of green solvent in drug analysis:

In recent years, environmental safety has been considered in every research step. The emergence of the Greenness topic arose

initially from the field of drug analysis, because of the extensive use of various chemicals in analysing the purity with a minimal sample concentration. The initial step for analysis is sample preparation. The samples are being derivatised based on the method of analysis. In the field of bioanalytical, the sample is extracted from the biological samples and analysed in hyphenated instruments. However advanced research is carried out by analysing the sample without any physical and chemical changes, which is the researchers' main objective. The role of green solvent in green analytical chemistry begins with sample preparation which is the quality-determining step in the analytical procedure. Based on their chemical nature green solvents can be classified into three types: Amphiphilic solvents, Ionic liquids & Deep Eutectic solvents (DES) [45]. Amphiphilic solvents like non-ionic & ionic surfactants, alcohols & carboxylic acids, and natural Deep Eutectic solvents like glucose, lactic acids, and citric acids are used in extracting the sample even at the micro level. However, considering the 12 principles of the Green Analytical Procedure, the solvent-free

extraction method is followed [46, 47]. An analytical procedure's final step is quantifying the sample using different instrumental methods. Then preferring the indirect methods of analysis the direct techniques make the procedure simple and greener. Direct methods like Electro Thermal Atomic Absorption Spectrometry (ETAAS), Inductively coupled mass Spectroscopy (ICP-MS) & Inductively Coupled -Optical Emission Spectrometry (ICP-OES) are used to analyse the sample without any physical or chemical change

USC Environmental Health Safety has given an idea about safer and sustainable solvents and replacements of greener solvents with hazardous solvents based on Pfizer's study in 2008, this is explained in **Table 1 [48]**.

Some solvents like 1,2 Dichloroethane, and carbon tetrachloride have been replaced with dichloromethane (DCM) which is comparatively less hazardous than the former solvent. The summary of various types of green solvents which is used in Pharmaceutical Industries with examples has been mentioned in **Table (2)**.

Table :1 Regular solvents and their replacement

S.no	Solvents	Replacement greener solvent
1.	1,2 Dimethoxy ethane	Tert- butyl methyl ether or 2-MeTHF
2.	1,2 dichloroethane	Dichloromethane
3.	1,4 dioxane	Tert- butyl methyl ether or 2-MeTHF
4.	Benzene	Toluene
5.	Carbon tetrachloride	Dichloromethane
6.	Dichloromethane (for analysis)	Ethyl acetate/alcohol
7.	Diethyl ether	Tert- butyl methyl ether or 2-MeTHF
8.	DMF	Acetonitrile / Cyrene

9.	n-Hexane	Heptane
10.	Pentane	Heptane
11.	Pyridine	Triethylamine
12.	NMP	Acetonitrile / Cyrene

Table: 2 Summary of Green Solvents with Example

S.no	Types of Green solvents	Examples
1.	Super Critical Fluid	Super critical carbondioxide & supercritical water
2.	Ionic liquids (cations)	1-alkyl 3- methyl imidazolium N-alkyl pyridinium N-methyl pyrrolidinium Tetra alkyl ammonium Tetra alkyl phosphonium
	Ionic liquids (anions)	[PF6] ⁻ , [BF4] ⁻ , Cl ⁻ , Br ⁻ , I ⁻
3.	Bio renewable solvents	γ -Valero lactone Dimethyl isosorbide Acetone Cyrene Glycerol 2-methyl tetrahydrofuran 2-propanol Ethanol
4.	Deep Eutectic solvent	Type I: organic salt +metal chloride (eg: choline chloride -ZnCl ₂) Type :2: organic salt +metal chloride hydrate (eg: choline chloride -CoCl ₂) Type III- organic salt + hydrogen bond donor (e.g: Choline chloride -urea) Type IV – hydrogen bond donor + metal chloride (eg. Urea -ZnCl ₂)

CONCLUSION:

The application of various green solvents would allow the discovery of new green technologies in Pharmaceuticals. These reviews can explicit that, neoteric solvents have been considered cost-effective green solvents. Indeed, it can be concluded that, with the fast progress of green chemistry, researchers have been eager to develop a robust analytical method development using green solvents which is a cost-effective method for Pharmaceuticals. In the future, the concept of green chemistry will not only be concerned with environmental safety but will also contribute to the advancement of pharmaceutical research in line with artificial intelligence

(AI) because AI is already a part of the production and analysis of drugs.

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