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Eco-Friendly Solvents and Excipients in Pharmaceutical Development

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Review

ABSTRACT

The extensive use of conventional organic solvents and synthetic excipients in pharmaceutical formulation and manufacturing has raised concerns related to toxicity, environmental burden, regulatory constraints, and sustainability. Many traditional solvents and excipients exhibit adverse toxicological effects, poor biodegradability, and ecological persistence, thereby limiting their long-term applicability in modern pharmaceutical development. In response, green chemistry principles have increasingly emerged as a systemic framework for designing safer, and more sustainable pharmaceutical processes. Eco-friendly solvents and excipients, encompassing bio-based solvents, green co-solvents, natural and semi-synthetic polymers, biodegradable surfactants, and renewable lipid-based systems, have emerged as alternatives to conventional formulation components.

Excipients play a key role in modulating physicochemical properties, thereby enabling the development of advanced drug delivery systems, including polymeric nanoparticles, lipid nanoparticles, nano emulsions, liposomes, hydrogels, and self-emulsifying drug delivery systems. The incorporation of environmentally preferable excipients into pharmaceutical formulations and manufacturing processes has the potential to improve biocompatibility and reduce environmental impact without compromising formulation performance. Despite notable progress, the widespread implementation of these materials is challenged by limitations in scalability, cost-effectiveness, material availability, physicochemical compatibility with active pharmaceutical ingredients, and regulatory acceptance. This review provides a comprehensive examination of the classification, functional roles, and mechanistic contributions of eco-friendly solvents and excipients in pharmaceutical development. It provides insights on advances in formulation strategies, and industrial applications while addressing key challenges and future research directions. Ultimately, the systematic incorporation of green solvents and excipients is expected to drive the transition toward sustainable pharmaceutical innovation, bridging the gap between environmental responsibility and therapeutic efficacy.

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KEY WORDS: eco-friendly solvents, eco-friendly excipients, green chemistry, sustainability, biocompatibility

INTRODUCTION

The increasing demand for safe, effective, and sustainable pharmaceutical products has driven significant changes in formulations and manufacturing strategies. Traditionally, pharmaceutical development has relied heavily on organic solvents and synthetic excipients to address limitations of a drug's physicochemical and biopharmaceutical properties. However, the increasing use of these conventional materials has raised concerns regarding environmental pollution, toxicity, and long-term sustainability. In response to these challenges, the pharmaceutical industry and research community are extensively focusing on the development and implementation of eco-friendly solvents and excipients that align with green chemistry principles and sustainable development [1]. **Eco-friendly** is a term describing choosing materials that are kinder to the environment compared to their conventional or traditional counterparts. However, this doesn't necessarily mean they are sustainable in the long run. **Sustainability** is a broader concept that includes eco-friendly initiatives but goes beyond them by finding a balance between our social and economic needs and the environment's ability to support us in the future. And unlike environmentally friendly practices, sustainable initiatives aim not only to minimize environmental impacts but also to conserve resources and ensure long-term environmental, social and economic well-being.

Sustainable pharmaceutical development can be guided by the principles of reduce, reuse, recycle, conversion of energy, and the use of renewable resources. Reduction involves minimizing the total quantity of materials used and, particularly, reducing the use of solvents or replacing solvents associated with greater health and environmental concerns. Pharmaceutical process redesign, solvent substitution, process intensification, and solvent-free or low-solvent approaches are examples of this strategy. It also involves the direct reuse of suitable process materials or solvents within manufacturing operations provided product quality and process requirements can be maintained. Recycling involves the recovery, purification, and reuse of solvents from process streams, thereby reducing the demand for new solvents and decreasing waste generation. Energy conservation can be achieved by optimizing reactions and processing conditions, reducing unnecessary heating, cooling, and separation steps, and adopting more energy-efficient manufacturing technologies. In addition, the use of renewable feedstocks, including bio-based solvents and naturally derived pharmaceutical materials, may reduce dependence on finite-derived resources. However, a renewable origin alone does not establish overall sustainability, and the environmental suitability of a material that should also be evaluated in relation to its impact on production, processing, pharmaceutical performance, safety, and the product life-cycle [2].

Need for Sustainable Pharmaceutical Formulations

Environmental impact of conventional solvents and excipients

Conventional organic solvents such as chloroform, dichloromethane, toluene, and acetonitrile, along with synthetic excipients, are widely employed in pharmaceutical processes, including drug synthesis, extraction, purification, and formulation design. Many of these substances are volatile, toxic, non-biodegradable, and pose risks to ecosystems. The accumulation of hazardous chemical waste from pharmaceutical manufacturing further worsens environmental degradation and highlights the need for greener alternatives capable of reducing environmental burden while maintaining the efficacy and quality of therapeutic and formulated products.

Regulatory and safety concerns

In addition to environmental issues, the use of toxic solvents and excipients presents significant safety and regulatory challenges. The U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) provide guidance relevant to the control of residual solvents, impurity control, excipient quality, and patient safety. These guidelines aim to protect human health by controlling residual solvents and ensuring excipient safety. For example, ICH Q3C classifies residual solvents according to toxicity and establishes permitted exposure limits that encourage the replacement or restriction of hazardous solvents in pharmaceutical formulations [3].

Concept of Eco-Friendly Solvents and Excipients

Definition and Classification

Eco-friendly solvents and excipients can be defined as materials that exhibit low toxicity, high biodegradability, and minimal environmental impact, while maintaining functional performance in pharmaceutical formulations[4]. These materials can be broadly classified into several categories, including bio-based

solvents (e.g., ethanol, glycerol, ethyl lactate), green co-solvents, natural and semi-synthetic polymers (e.g., cellulose derivatives, chitosan, alginates), biodegradable surfactants, and renewable lipid-based systems. Their diverse physicochemical properties make them suitable for a wide range of pharmaceutical applications.

Advantages over Conventional Materials

Compared to traditional solvents and excipients, eco-friendly alternatives offer multiple advantages, including improved biocompatibility, reduced toxicity, enhanced biodegradability, and lower environmental burden. In addition, many green excipients exhibit multifunctional properties, such as solubilization, stabilization, and controlled drug release, which contribute to formulation performance. The adoption of eco-friendly materials also may support regulatory compliance and aligns with global sustainability goals, making them attractive candidates for next-generation pharmaceutical formulations [5].

Scope and Objectives of the Review

The growing emphasis on sustainable development in the pharmaceutical industry underscores the importance of eco-friendly solvents and excipients in modern drug formulation. As environmental regulations become more stringent and consumer awareness of environmentally responsible products increases, the demand for green pharmaceutical technologies continues to rise. Moreover, the development of advanced drug delivery systems requires innovative materials that combine safety, efficacy, and sustainability, further highlighting the relevance of eco-friendly formulation components.

Aim of the Review Article

The primary aim of this review is to provide a comprehensive overview of eco-friendly solvents and excipients in pharmaceutical development. The review discusses their classification, physicochemical properties, functional roles, and applications in diverse drug delivery systems, while also addressing current challenges and future perspectives. By integrating recent research advances in the development and pharmaceutical application of eco-friendly solvents and excipients based on green chemistry principles, this review seeks to provide insights into the potential of eco-friendly solvents and excipients as key enablers of sustainable and innovative pharmaceutical formulation strategies.

Sustainable Pharmaceutical Development

Sustainable pharmaceutical development integrates environmental, economic, and social considerations throughout the drug product lifecycle. Given that solvents account for a significant portion of material use and waste in pharmaceutical manufacturing, their replacement with eco-friendly alternatives is pivotal to sustainability. Approaches such as solvent minimization, process intensification, and use of sustainable excipients improve the ecological profile of pharmaceutical products. Metrics including the Environmental Factor (E-factor) and Process Mass Intensity (PMI) enable quantitative assessment of environmental impact, supporting informed formulation design and sustainability assessment [6].

Life-Cycle Assessment of Excipients and Solvents

Life-cycle assessment (LCA) evaluates the environmental impact of materials from raw material extraction through production, use, and disposal. Application of LCA in pharmaceutical formulation reveals that petrochemical-derived solvents and synthetic excipients often impose higher carbon footprints and greater toxicity compared to bio-based and biodegradable alternatives. For example, solvents like ethyl lactate and glycerol show reduced greenhouse gas emissions and improved biodegradability. Natural polymers and renewable lipid excipients contribute to lower environmental burden due to their renewable origin and degradability. Incorporating LCA data into formulation strategies facilitates selection of environmentally preferable materials and promotes sustainable pharmaceutical innovation [7,8].

GREEN CHEMISTRY PRINCIPLES IN PHARMACEUTICAL FORMULATION

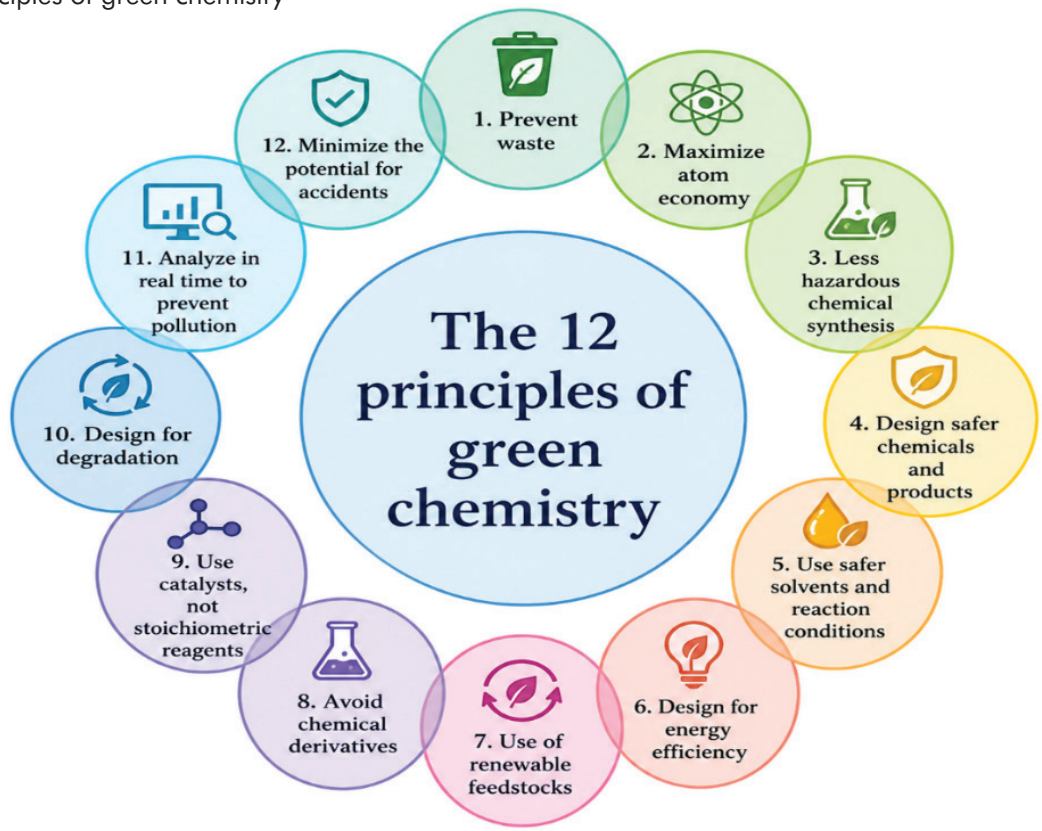
Green chemistry serves as a foundational framework to advance sustainable pharmaceutical formulations by minimizing the environmental footprint while preserving drug efficacy and safety. It promotes the rational design of processes and products that reduce or eliminate hazardous substances, optimize resource use, and enhance overall sustainability. In pharmaceutical sciences, the adoption of green chemistry principles guides the development and selection of eco-friendly solvents, excipients, and manufacturing methods, aligning with both environmental and regulatory expectations.

The twelve principles of green chemistry, formulated by Anastas and Warner (1998) [9] as shown in (Figure 1, Table 1), provide a comprehensive guide for designing safer and more sustainable chemical processes. Relevant principles for phar-

Table 1. Application of Green Chemistry Principles in Pharmaceutical Formulation

Green chemistry principle	Applications in pharmaceutical formulation	Example
Prevention of waste	Minimize solvent use and reduce waste generation	Solvent-free formulations
Atom economy	Maximizing incorporation of raw materials into final product to reduce by-products	High-yield synthesis with minimal side reactions
Less hazardous chemical synthesis	Use of non-toxic reagents and safer synthetic pathways	Replacement of toxic reagents with safer alternatives
Designing safer chemicals	Development of formulations with reduced toxicity and improved safety profile	Use of biocompatible and non-toxic excipients
Safer solvents and auxiliaries	Use low-toxicity, biodegradable solvents	Use of ethanol instead of chloroform
Renewable feedstocks	Use bio-based excipients and polymers	Cellulose derivatives, chitosan
Reduce derivatives	Avoiding unnecessary chemical modifications such as protection/deprotection steps	Direct synthesis without intermediate derivatization
Energy efficiency	Conduct reactions/processes under mild conditions	Room temperature synthesis
Design for degradation	Select biodegradable excipients	Natural polysaccharides
Catalysis	Employ catalytic processes over stoichiometric ones	Enzymatic catalysis
Real-time analysis	Implement process analytical technologies (PAT)	Monitoring solvent use
Inherently safer chemistry for accident prevention	Designing safer processes to minimize risks of chemical hazards	Use of non-flammable and low-reactivity substances

Figure 1. Principles of green chemistry



maceutical formulation include waste prevention, safer chemical design, use of renewable feedstocks, energy efficiency, and design for degradation. Application of these principles encourages the substitution of hazardous organic solvents with greener alternatives such as water, bio-based solvents (e.g., ethanol, ethyl lactate), ionic liquids, and deep eutectic solvents. Likewise, natural and biodegradable polymers, lipid-based excipients, and surfactants support formulation safety and environmental compatibility [10-14]. The implementation of green chemistry in the pharmaceutical sector has also been advanced through industrial collaborations. For example, the IQ Consortium's Green Chemistry Working Group, in collaboration with the ACS Green Chemistry Institute Pharmaceutical Roundtable and academic partners, contributed to the development of the Green Aspiration Level (GAL), its improved innovation Green Aspiration Level (iGAL), and the Green Chemistry Innovation Scorecard as practical tools for evaluating and communicating improvements in the "greenness" of pharmaceutical manufacturing processes [15-17].

ECO-FRIENDLY SOLVENTS IN FORMULATION DEVELOPMENT

Eco-friendly solvents have gained significant attention in pharmaceutical formulation due to their reduced toxicity, biodegradability, and sustainability compared to conventional organic solvents. Their diverse physicochemical properties enable enhanced solubility and stability of active pharmaceutical ingredients (APIs), facilitating the development of advanced drug delivery systems. This section discusses the classification, solubility mechanisms, applications, advantages and limitations of green solvents in pharmaceutical formulation [18].

Classification of Green Solvents (Figure 2)

Bio-Based Solvents

Bio-based solvents are derived from renewable biomass sources such as plants, microorganisms, or fermentation processes. Common examples include ethanol, ethyl lactate, glycerol, and limonene. These solvents exhibit low toxicity, good biodegradability, and favourable solvating properties, making them suitable alternatives to petrochemical solvents[19]. Ethanol provides a notable example of successful adoption, as bioethanol produced through fermentation is widely used in pharmaceutical extraction, processing, and formulations as a cosolvent and, in some topical systems, as a penetration enhancer. Its use can reduce reliance on more hazardous organic solvents while maintaining effective extraction and solubilization performance. For example, ethanol-containing aqueous systems have been shown to improve the solubility of poorly soluble drugs such as halofantrine, demonstrating their potential as alternatives to conventional cosolvents [20]. However, the overall sustainability of bio-based solvents depends on factors such as feedstock source, production energy requirements, water consumption, and life-cycle environmental impact.

Aqueous Solvents

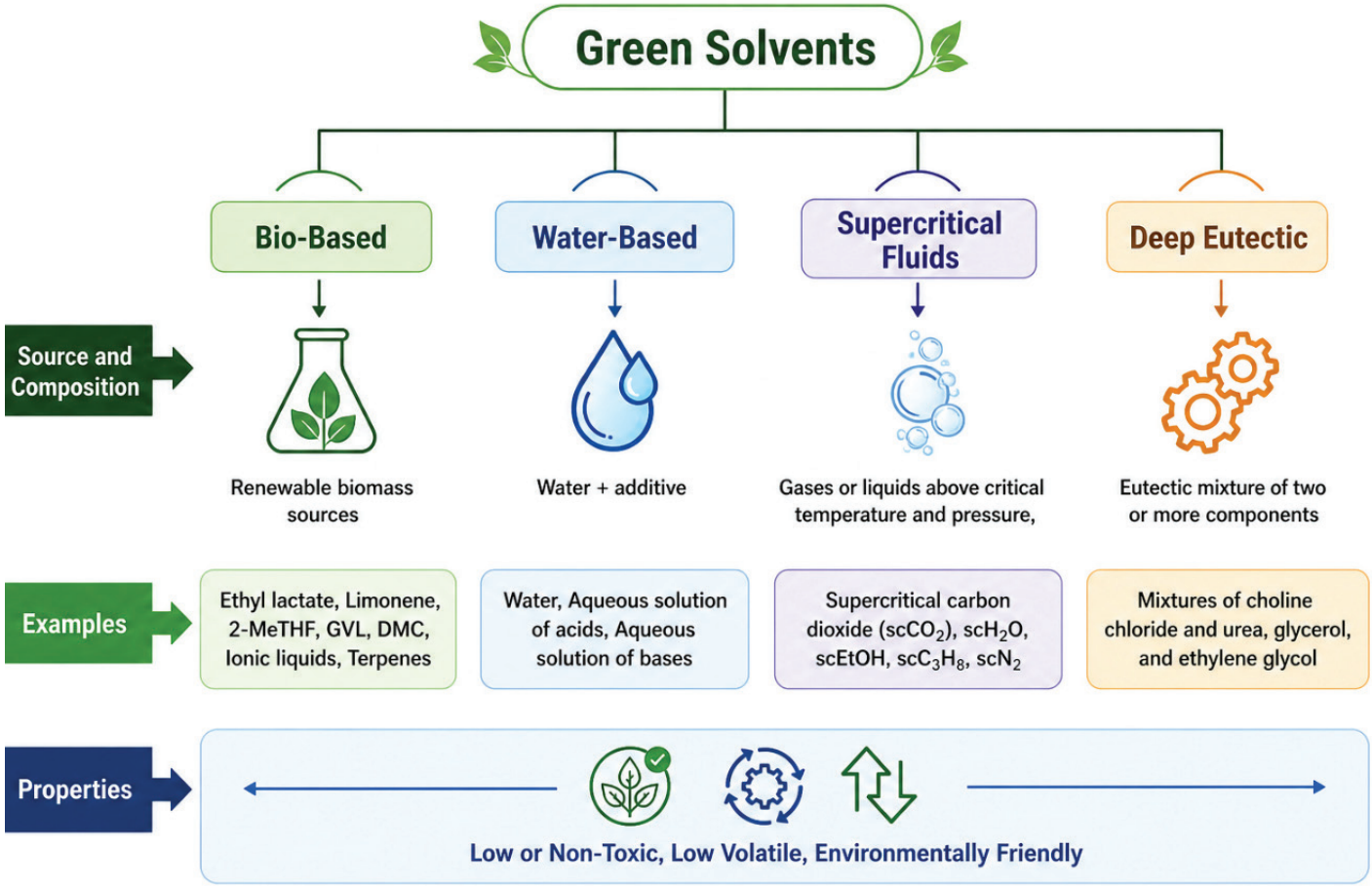
Water remains the most environmentally preferable and widely used solvent in pharmaceutical formulations because of its safety/low toxicity, non-flammability, and abundance [21]. Advances in formulation technology have enabled the use of aqueous systems in nano emulsions, hydrogels, and other dosage forms, leveraging the polarity and biocompatibility of water. However, water use also requires sustainable management, as the production of pharmaceutical-grade water, cleaning operations, and wastewater treatment can be resource and energy intensive. Increasing water scarcity and pharmaceutical contamination of aquatic systems further highlight the need to minimize consumption, improve process efficiency, and promote appropriate water recovery and reuse. Thus, although water is a greener alternative, its overall sustainability should be assessed from a life-cycle and resource-management perspective [22].

Supercritical Fluids

Supercritical carbon dioxide (SC-CO_2) is an attractive alternative to conventional organic solvents because its solvating properties can be tuned by temperature and pressure, and it can be readily removed after processing. For example, supercritical antisolvent (SAS) processing has been used for particle size reduction of poorly water-soluble APIs, modifying API material properties such as reducing crystallinity, and to produce drug-polymer particles, all of which can enhance dissolution and potentially increase bioavailability. However, successful application requires favourable API-solvent-CO_2 phase behaviour, API stability under processing conditions, as well as precise control of pressure, temperature, flow rate, and solvent composition.

Its relatively low polarity, frequent need for cosolvents, reliance on high-pressure equipment, scale-up complexity, and regulatory validation requirements currently challenge pharmaceutical adoption of supercritical fluid processing. Thus, despite its long-established industrial use, particularly in food processing, pharmaceutical and biopharmaceutical applications

Figure 2. Classification of green solvents *(Images generated using Bio render image generator)*



remain relatively limited. Future adoption may increase for advanced particle engineering of high-value APIs, and continuous processing, where reduced solvent residues and precise control of product properties justify the additional cost and complexity [23].

Ionic Liquids

Ionic liquids (ILs) are salts with low-melting points with negligible vapor pressure and tuneable physicochemical properties. Despite extensive research, their pharmaceutical applications remain largely at the preclinical and formulation development stage, with limited clinical translation due to safety, regulatory, and environmental concerns. ILs are particularly useful when conventional approaches cannot adequately overcome poor solubility, polymorphism, or low permeability. A notable example is the conversion of methotrexate into API-ILs, where pairing the drug with selected biocompatible counterions increased its aqueous solubility by up to 5280-fold while retaining antiproliferative activity. However, ILs may be unsuitable when high viscosity, cytotoxicity, poor biodegradability, difficult recovery, or uncertain long-term safety outweigh their formulation benefits. Therefore, rational selection of the cation-anion pair and comprehensive toxicological and environmental evaluation are essential before pharmaceutical adoption [24].

Deep Eutectic Solvents (DES and NaDES)

DES are generated by mixing a hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) in a specific molar ratio, resulting in a liquid with a melting temperature below that of each component alone. Examples of DES include choline chloride: urea (1:2), choline chloride: glycerol (1:2), and choline chloride: lactic acid. Natural deep eutectic solvents (NaDES) may be composed of natural compounds such as choline chloride, sugars, amino acids, organic acids, and polyols. An example of this approach is a choline chloride: glycerol NaDES formulation, which showed an improvement in the solubility of curcumin. At a molar ratio of 1:1, curcumin solubility

was 7.25 mg/g when compared to 0.0006 mg/g in water [25], with improvements in photostability and potential for enhanced gastrointestinal absorption. This approach has potential but selection of DES/NaDES must take into account factors such as the interactions between the API and solvent, molar ratio, viscosity, moisture content, toxicity, and mode of administration because the resulting DES may show high viscosity and altered properties upon dilution [26].

Mechanisms of Solubility Enhancement

Polarity Modification

Green cosolvents may help to increase the dissolution of poorly soluble drugs through alteration of the polarity of the formulation milieu and optimization of drug-cosolvent interactions. Ethanol is a widely investigated bio-based cosolvent and has demonstrated effective solubilization of several poorly water-soluble pharmaceutical compounds. For example, Liu *et al.,* reported that the solubility of Rofecoxib increased progressively with increasing concentrations of ethanol in ethanol-water mixtures. Moreover, ethanol exhibited a higher solubilization capacity for Rofecoxib than glycerol and propylene glycol under the investigated conditions, demonstrating the influence of cosolvent structure and polarity on drug solubilization [27]. Similarly, ethanol-water mixtures have been shown to enhance the solubility of Piroxicam, with an exponential increase in drug solubility as the ethanol concentration increased [28]. Studies involving a broader range of pharmaceutical compounds have also demonstrated that drug solubility in ethanol-water mixtures can deviate from simple linear behaviour, indicating that the magnitude of cosolvent-induced solubilization depends on the physicochemical characteristics of the drug and the composition of the solvent system [29].

Hydrogen Bonding

Jeliński *et al.* demonstrated that natural deep eutectic solvents (NaDES) can effectively improve the solubility and stability of poorly water-soluble drugs through hydrogen bond based solubilization [25]. They reported that the hydrogen bond acceptors (HBA) such as choline chloride are mixed with hydrogen bond donors (HBD) like urea, glycerol, or lactic acid. Application of this principle in pharmaceutical formulations offer benefits because the hydrogen bond network formed can bind the complementary functional group(s) of the API which can weaken drug-drug interactions in the crystalline lattice and increase dissolution and solubility. When exploiting hydrogen bonding in this manner, the selection should be based on functional groups, polarity, ability for hydrogen bonding, chemical stability, and viscosity of the DES system. An example of this approach is the combination of choline chloride and glycerol NaDES that led to an enhancement of curcumin solubility and also prevented photodegradation of the drug. These findings highlight how rational selection of the HBA-HBD system can successfully enhance solubility and chemical stability of an API.

Cosolvency Effect

Cosolvency uses mixtures of water and a water-miscible solvent, such as ethanol–water, to create an intermediate-polarity environment that improves drug–cosolvent interactions and reduces the tendency of poorly water-soluble APIs to remain in the crystalline state [30]. Such systems are useful when the API shows adequate solubility in the cosolvent and the required cosolvent concentration is acceptable for the intended route of administration. However, cosolvency may be unsuitable when high cosolvent concentrations are required or when dilution causes drug precipitation.

Micellar Solubilization

Micellar solubilization employs amphiphilic materials, such as phospholipids, bile salt-derived surfactants, and biodegradable fatty acid- or sugar-based surfactants, which self-assemble in aqueous media above their critical micelle concentration. Their hydrophobic core can incorporate poorly water-soluble APIs, thereby increasing the apparent solubility and, in some cases, protecting the drug from degradation. Selection depends on API lipophilicity, required drug loading, surfactant biocompatibility, route of administration, and formulation stability. However, limited drug loading, dilution-induced micelle disruption, and potential surfactant toxicity may restrict their application [31].

Applications of Drug Delivery Systems

■ ***Self-Micro emulsifying Drug Delivery System and Self-Nanoemulsifying Drug Delivery System (SMEDDS / SNEDDS):*** SMEDDS/SNEDDS can incorporate bio-based oils and relatively sustainable surfactants to improve the oral delivery of poorly water-soluble drugs. For example, lipid systems containing medium-chain triglycerides or oleic acid with phospholipids or non-ionic surfactants can maintain lipophilic APIs in a solubilized state with subsequent formation of a fine emulsion in the GI tract [32]. These systems are particularly suitable for highly lipophilic drugs with good lipid solubility but may be unsuitable if the high surfactant concentrations needed cause toxicity or when the

drug precipitates after dilution and reduces the bioavailability.

■ ***Nanoparticles / Nano Structured Lipid Carriers and Solid Lipid Nanoparticles (NLC / SLN):*** Aqueous or solvent-free processing methods, together with biodegradable lipids such as glyceryl behenate, glyceryl palmitostearate, and medium-chain glycerides, can reduce the use of volatile organic solvents in SLN and NLC preparation.. However, drug–lipid incompatibility, thermal sensitivity, drug expulsion during lipid crystallization, and physical instability can limit their application [33]. These systems are suitable for lipophilic APIs requiring controlled release and improved stability.

■ ***Hydrogels and Emulgel:*** These are aqueous systems based on natural polymers such as chitosan, alginate, and cellulose derivatives, optionally combined with bio-based cosolvents such as glycerol, providing biocompatible matrices for topical and localized drug delivery[34]. They are particularly useful when prolonged residence time and controlled release are required. Polymer–drug compatibility, microbial stability, viscosity, and drug release characteristics must be optimized for successful application. Microbial contamination of aqueous gels is a manageable formulation issue through appropriate use of preservatives, packaging, or sterilization, rather than an inherent limitation of water itself.

■ ***Transdermal and Buccal Systems:*** Bio-based solvents such as ethanol and glycerol, together with phospholipids and lipid excipients, can improve API solubility and facilitate transport across skin or mucosal membranes. These systems are useful for drugs requiring localized or systemic delivery with avoidance of first-pass metabolism. Issues include potential tolerability problems, as excessive ethanol or other penetration enhancers may cause irritation or membrane damage, making concentration and exposure time critical formulation parameters [35].

Advantages and Limitations of Green Solvents and Sustainable Excipients in Pharmaceutical Formulation

■ ***Benefits:*** Green solvents and sustainable excipients can reduce reliance on hazardous volatile solvents while maintaining formulation performance. The major benefits and limitations of these materials in pharmaceutical formulation are summarized in Table 2. For example, water-based lipid nanoparticles can avoid organic solvents, ethanol can replace more hazardous cosolvents in suitable applications, and DES/NaDES systems can improve the solubility and stability of selected poorly soluble APIs. However, environmental benefits should be assessed on a case-by-case and life-cycle basis.

■ ***Toxicity and Environmental concerns:*** The term "green" does not necessarily mean non-toxic. For example, experimental studies have demonstrated that the cytotoxicity of certain ionic liquids increases with increasing alkyl-chain length of the cation, which has been attributed to enhanced interaction with, and disruption of, the biological membranes [36]. In addition, the negligible vapour pressure of ionic liquids does not eliminate potential environmental concerns, as their persistence, biodegradability, and environmental fate can vary considerably depending on their chemical structure. Similarly, the safety and environmental profile of deep eutectic solvents and natural deep eutectic solvents depend on the identity and toxicity of their individual components, composition, concentration, and exposure conditions. experimental studies have shown that the toxicity and cytotoxicity of DES can differ from those of their individual components and vary according to the structure and composition of the DES [37]. Therefore, toxicity, biodegradability, ecotoxicity, environmental fate, and life-cycle impacts should be systematically evaluated before pharmaceutical adoption. Consequently, a solvent should not be considered environmentally preferable solely

Table 2. Pros and cons of using eco-Friendly Solvents in Pharmaceutical Formulation

Solvent type	Example	Key benefits	Limitations /challenges
Aqueous solvents	Water	Non-toxic, abundant, biodegradable	Microbial contamination risk
Bio-based solvents	Ethanol, ethyl lactate, glycerol	Renewable, low toxicity, good solvency	Sometimes limited solubility range
Supercritical fluids	Supercritical CO_2	Tuneable solvency, non-toxic, no residue	High-pressure equipment required
Ionic liquids (ILs)	Imidazolium, pyridinium salts	Low vapor pressure, tuneable polarity	Potential toxicity, high cost
Deep eutectic solvents / (DES/NaDES)	Choline chloride-base mixtures	Biodegradable, low toxicity, easy synthesis	Limited industrial-scale data

on the basis of low volatility, renewable origin, or ease of preparation; its overall toxicological and environmental profile should be considered when assessing its suitability as a green pharmaceutical solvent [38].

■ ***Formulation and Stability Challenges:*** Green solvents may alter drug solubility, crystallinity, and chemical stability. For example, water may promote hydrolysis or microbial growth, whereas DES systems may undergo substantial viscosity and structural changes following water uptake [39]. These potential challenges should be carefully evaluated to determine whether appropriate mitigation strategies are necessary to prevent or overcome formulation and stability issues.

■ ***Cost and Scalability:*** Scalability depends on the specific system. For instance, water is inexpensive but pharmaceutical-grade water production is resource- and energy-intensive. SC-CO_2 minimizes residual solvents but requires expensive high-pressure equipment; DES may use inexpensive components but high viscosity can complicate mixing and processing; and ionic liquids may require costly synthesis and purification. Consequently, industrial adoption of a particular approach should be based on whether the environmental and formulation advantages outweigh manufacturing cost, process complexity, and regulatory requirements [40,41].

ECO-FRIENDLY EXCIPIENTS IN PHARMACEUTICAL FORMULATIONS

An excipient may contribute towards sustainable pharmaceutical development if its source, process of manufacturing, toxicity, biodegradability, and life cycle characteristics are environmentally favourable [42]. Examples of existing materials include cellulose derivatives, chitosan, alginates, gelatin, natural phospholipids, biodegradable lipids, and selected plant or microbial-derived surfactants. The environmental benefits of each material should be analysed on a case-by-case basis. Some examples are provided in the following sections:

Natural and Bio-Derived Polymers

Natural polymers constitute a significant class of eco-friendly excipients widely employed as binders, stabilizers, gelling agents, and controlled-release matrices in pharmaceutical formulations. Their biodegradability, low toxicity, and biocompatibility make them attractive for diverse drug delivery systems [43].

■ ***Chitosan:*** Chitosan is an eco-friendly biodegradable cationic polysaccharide prepared from chitin, which possesses mucoadhesive, film-forming and antimicrobial properties. Chitosan-based materials have been used in wound dressings such as HemCon and have been studied as mucoadhesive carriers for nasal, buccal and nanoparticle drug delivery systems. Properties of these materials are dependent on molecular weight, degree of deacetylation, and pH dependent solubility [44].

■ ***Alginate:*** Sodium alginate is extracted primarily from brown seaweeds and forms an ionically crosslinked hydrogel with calcium. Gaviscon contains sodium alginate, which forms a gastric raft and reduces reflux. Calcium alginate matrices have been extensively investigated for drug release and wound healing. The properties of these materials depend upon gel strength, viscosity, composition and crosslinking conditions.

■ ***Gelatin:*** Gelatin is a product of partial hydrolysis of collagen, which is used in hard and soft pharmaceutical capsules such as Advil Liqui-Gels. The film-forming and biodegradability characteristics of gelatin make it an effective encapsulating agent with the potential downsides of moisture sensitivity and it being an animal-derived material [45].

■ ***Cellulose Derivatives:*** HPMC and sodium carboxymethylcellulose (NaCMC) are two of the most widely used plant-based pharmaceutical excipients. HPMC serves as a binder and hydrophilic matrix forming material in extended-release tablets while NaCMC acts as a viscosity increasing and suspending agent. Industrial applicability of these materials makes sustainability improvement of these materials important. Sustainability assessment of these materials should include evaluating the environmental impact of the derivatization and purification process [46]. Methods of enhancing sustainability include responsible forestry, non- wood/agricultural biomass, solvent recycling, reduction in chemical and energy use, and improved derivatization processes.

■ ***Plant-Based Gums and Polysaccharides:*** Guar gum, xanthan gum and acacia are renewable polysaccharides that provide thickening, stabilization, and controlled release characteristics to pharmaceutical formulations. The established functionality, biocompatibility, and renewable origin make them valuable natural alternatives or complementary excipients to conventional synthetic polymers used in pharmaceutical formulation and drug-delivery systems [47].

Biocompatible Surfactants and Emulsifiers

Biocompatible surfactants derived from natural sources have gained popularity as safe and biodegradable alternatives to synthetic surfactants in emulsions, micelles, and nanoparticulate systems.

■ ***Phosphatidylcholine from Soya beans and Natural Phospholipids:*** Soy phosphatidylcholine and egg phospholipids serve as emulsifiers and bilayer forming agents in liposomes and lipid nanoparticles. Their importance in drug development

is exemplified by their use in liposomal Amphotericin B and Doxil (liposomal doxorubicin). Quality control is needed because of variability in source [48].

■ ***Sugar-Derived Surfactants:*** Sucrose esters (such as sucrose stearate and sucrose laurate) and alkyl polyglucosides are biodegradable surfactants that can be used for the emulsification and solubilization of substances. The use of sucrose esters for solubilizing and delivering poorly soluble drugs such as cyclosporine has been studied. They are selected based on HLB value, API lipophilicity, concentration, and route of administration [49].

■ ***Biosurfactants:*** Rhamnolipids, sophorolipids, and Surfactin are bacterial amphiphilic molecules capable of emulsification and solubilization. Their biodegradability and biological activity make them promising alternative excipients, but their use in pharmaceuticals remains limited due to production costs, purity and batch-consistency issues, incomplete toxicity data, and regulatory challenges [50].

Lipid and Oil Excipients with sustainability considerations

Lipids and oils derived from renewable natural sources are integral to various drug delivery platforms, offering biocompatibility, biodegradability, and enhanced drug solubilization.

■ ***Natural Waxes and Fatty Acids:*** Beeswax, carnauba wax, stearic acid, and oleic acid play important matrix forming and structural roles in topicals and lipid nanoparticle systems. The sustainability of these compounds is tied to appropriate sourcing and processing [51].

■ ***Vegetable Oils:*** Castor, sunflower, coconut, and various other vegetable oils can serve as solubilizers and lipid components in nano emulsions, SEDDS/SNEDDS, and topical formulations. The suitability of specific vegetable oils depends on API solubility, oxidative stability, and molecular composition [52].

■ ***Biodegradable Lipids:*** Glyceryl behenate (Compritol 888 ATO), glyceryl palmitostearate (Precirol ATO 5), and medium-chain triglycerides are proven lipid excipients in the creation of SLN, NLC, and oral lipid-based formulations [53]. Lipid nanoparticles have potential for the delivery of nucleic acids, indicating that biodegradable lipids can support technologies beyond conventional solubilization. Key considerations include: drug–lipid compatibility, polymorphism, oxidation, loading capacity, and physical stability [54].

Functional Roles of key Sustainable Excipients

■ ***Stabilizers:*** Lecithin/phosphatidylcholine provides stabilization to lipid dispersions and liposomes, while HPMC helps improve suspension stability due to increased viscosity.

■ ***Gelling agents:*** Alginate, chitosan, and xanthan gum provide hydration-based polymer networks for topical, mucosal, and controlled-release dosage forms.

■ ***Release modifiers:*** HPMC is an important hydrophilic matrix-forming agent used in extended-release tablets, while chitosan and alginate control release through swelling, diffusion, and/or erosion.

■ ***Bio adhesive agents:*** Chitosan and carbomers provide mucosal adhesion properties through electrostatic and hydrogen-bonding interactions and are therefore useful in buccal, nasal, ocular, and topical dosage forms [55-57].

Pharmaceutical Applications and Translation of Sustainable Excipients

Bio-based and biodegradable excipients have been employed in various delivery platforms, including lipid-based systems, liposomes, polymeric nanoparticles, hydrogels, and self-emulsifying systems. Examples of well-known pharmaceutical uses include phospholipid based liposomes made from phospholipids, modified release systems containing HPMC, gastroretentive systems containing alginates, and lipid based delivery systems incorporating glyceryl behenate and glyceryl palmitostearate [58]. In these applications, sustainable excipients can enhance various formulation properties such as solubilization, physical stability, controlled release, and biological residence. Their broader pharmaceutical transition depends on reproducibility, regulatory acceptability, scalability and demonstrated clinical utility. More advanced applications of bio-based and biodegradable excipients, such as nanoparticle mediated delivery across or to the blood-brain barrier, show considerable potential but remain largely at the research preclinical stages [59].

CASE STUDIES: SUSTAINABLE EXCIPIENTS APPLICATIONS

■ ***Antifungal Drugs (Clotrimazole, Posaconazole):*** Clotrimazole and posaconazole are examples of poorly water-soluble antifungal drugs where lipid-based and nanoparticle drug delivery systems could offer improved apparent solubility and drug delivery profiles. For example, SLN/NLC systems based on biodegradable lipids, such as glyceryl behenate, glyceryl palmitostearate, or medium-chain triglycerides can provide controlled release and improved drug incorporation while potentially reducing the use of volatile organic solvents when aqueous preparation methods are employed [60]. The environmental sustainability of such systems would there-

fore depend on the combined use of biodegradable lipid carriers, aqueous processing, and reduced organic-solvent consumption, and should ideally be demonstrated through life-cycle assessment.

■ ***Poorly Soluble Drugs (BCS Class II/IV):*** Lipid-based carriers like SMEDDS/SNEDDS and SLN/NLC can promote the dissolution and bioavailability of poorly soluble APIs because they maintain the API in a dissolved or dispersed state. Sustainable natural lipids and phospholipids can replace or reduce the dependence on non-sustainable materials in these formulations; however, the choice of the more environmentally friendly excipients should consider drug–lipid compatibility, drug solubility in the lipid phase, surfactant concentration, physical stability, digestion, and formulation performance in the gastrointestinal trac**t.**.

■ ***Herbal Drug Formulations:*** Natural polymers, phospholipids, and biodegradable lipids have the potential to improve the solubility, stability, and bioavailability of insoluble phytochemicals such as curcumin. In particular, lipid and phospholipid-based nanoparticles are capable of dispersing and protecting curcumin, while natural excipients could lead to reduced use of environmentally non-biodegradable synthetic chemicals. Ultimately the environmental benefit is not determined by its natural origin; rather, its overall life-cycle profile, including sourcing, processing, energy consumption, biodegradability, toxicity, and end-of-life characteristics, should be considered.

EVALUATION AND CHARACTERIZATION TECHNIQUES FOR SUSTAINABLE EXCIPIENTS AND THEIR FORMULATIONS

Rigorous evaluation is required to establish the suitability of sustainable excipients for pharmaceutical use. Physicochemical properties, functional performance, safety, stability, and environmental assessments should be considered to determine whether an excipient provides genuine sustainability benefits without compromising product quality, therapeutic efficacy, or patient safety.

Physicochemical Characterization

■ ***Spectroscopic Methods:*** Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and ultraviolet-visible (UV-Vis) spectroscopy are employed to identify excipient functional groups, chemical structure, and drug-excipient interactions[61].

■ ***Thermal Analysis:*** Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) assess thermal stability, melting behaviour, and degradation profiles which are important for process optimization and stability prediction.

■ ***Particle Size and Morphology:*** Dynamic light scattering (DLS), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) characterize particle size distribution and morphology of nanoparticulate systems, which can influence drug release, stability and bioavailability .

Solubility and Partition Coefficient:

Determination of solubility parameters and log P values aid in understanding drug-excipient compatibility and predicting formulation performance [62].

Considerations in the Characterization of Biopharmaceutical Formulations

With biopharmaceuticals such as monoclonal antibodies, recombinant proteins, peptides, and nucleic acid-based drugs, characterization needs to take into consideration structural integrity, aggregation, purity, biological activity, and product-related impurities as the choice of excipients and processing procedures may affect these attributes. ICH Q6B recommends that the characterization of biotechnology-derived products should include physicochemical, biological, immunochemical, purity, and impurity characterizations. The use of sustainable excipients in biopharmaceutical formulations should therefore consider not only the environmental profile but also their capacity to maintain protein structure, minimize aggregation and adsorption, and preserve biological activity [63].

Stability Studies for Excipients

Stability testing evaluates the physical, chemical, and microbiological integrity of formulations under various environmental conditions:

■ ***Accelerated Stability Testing:*** Accelerated stability studies are conducted under elevated temperature and humidity conditions, such as 40°C/75% relative humidity (RH), to assess degradation rates and support shelf-life estimation according to relevant ICH guidance [64]

■ ***Photostability testing:*** Photostability testing evaluates the influence of light exposure on formulation stability, especially for photosensitive drugs and excipients, and is commonly according to ICH Q1B. (WHO guidelines) [65].

■ ***Microbial stability testing:*** Microbial stability testing evaluates the susceptibility of aqueous or biodegradable formulations to microbial contamination during storage and use, particularly when natural polymers or water-rich systems are used [66].

■ ***Biopharmaceutical Stability:*** For protein and other biopharmaceutical products, stability assessment should include aggregation, fragmentation, oxidation, deamidation, changes in higher-order structure, and loss of biological activity in addition to conventional physical and chemical stability. Excipient selection is particularly important because appropriate stabilizers, buffers, surfactants, and cryoprotectants can reduce protein aggregation, interfacial stress, and adsorption during manufacturing, storage, and administration. Therefore, a sustainable excipient should not be considered advantageous if an improved environmental profile is achieved at the expense of protein stability, potency, or product quality [67].

Toxicity and Biocompatibility Evaluation of Excipients

■ ***Safety assessment:*** Safety assessment is essential because an environmentally preferable origin does not automatically guarantee biological compatibility. A comprehensive toxicological evaluation should be conducted to determine an appropriate safety profile and appropriate exposure limits of the excipient. Important preliminary safety evaluations include the following:

■ **In Vitro** ***Cytotoxicity:*** Cytotoxicity assays, including 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, Lactate dehydrogenase release assay (LDH), and cell viability tests using relevant cell lines help to evaluate cytotoxicity and potential irritancy [68].

■ ***Hemocompatibility and Immunogenicity:*** Hemocompatibility and immunogenicity studies, including haemolysis and immune response evaluations, are important for formulations intended for parenteral, mucosal, or systemic exposure.

■ ***Biodegradability Testing:*** Biodegradability testing according to Organisation for Economic Co-operation and Development (OECD) guidelines can help assess environmental compatibility and safe degradation behaviour [69].

■ ***Biopharmaceutical Safety:*** For biopharmaceuticals, safety evaluation should additionally consider immunogenicity, particularly for therapeutic proteins and monoclonal antibodies. Assessment may include anti-drug antibody (ADA) responses and, where relevant, neutralizing antibody responses because unwanted immune responses can alter pharmacokinetics, reduce efficacy, or cause adverse reactions. The biological origin of an excipient does not inherently ensure low immunogenicity; therefore, its composition, impurities, manufacturing process, and interaction with the biopharmaceutical should be considered during risk assessment.[70]

In Vitro **and** ***In Vivo*** **Studies for assessment of delivery performance for APIs and formulations**

■ **In Vitro** ***Drug Release and Permeation:*** Dissolution apparatus, Franz diffusion cells and Caco-2 cell models can be used to evaluate drug release, permeation and intestinal permeability respectively.

■ **In Vivo** ***Pharmacokinetics (PK):*** Animal studies can assess bioavailability and pharmacokinetic parameters and provide information on absorption, distribution, metabolism, and excretion (ADME) across relevant animal species. Such studies provide important translational data before clinical evaluation.

■ ***Localized Delivery Assessment:*** Specialized models can be used to evaluate mucoadhesion, tissue retention, permeation, and targeting efficiency. Examples include Franz diffusion cells for skin permeation and retention, *ex vivo* mucosal tissue models for residence and adhesion, texture-analyzer methods for measuring mucoadhesive strength, and fluorescence imaging or confocal microscopy for tissue localization and delivery assessment.

■ ***Biopharmaceutical Formulations:*** For biopharmaceutical formulations, *in vitro* and *in vivo* evaluation should additionally confirm preservation of biological activity, pharmacokinetic performance, and, where appropriate, immunogenicity following formulation and storage. Cell-based potency assays and appropriate bioanalytical methods are particularly important because physicochemical integrity alone does not necessarily demonstrate maintenance of therapeutic activity [71].

REGULATORY SAFETY ASSESSMENT

Regulatory safety assessment involves evaluation of formulation quality, residual solvent limits, impurities, stability, excipient safety, and environmental impact. ICH guidelines such as Q1A(R2) for stability, Q1B for photostability, Q3C for residual solvents, and M7 for mutagenic impurities provide standardized frameworks. Pharmacopeial Standards such as USP-NF, European Pharmacopoeia (EP), and Japanese Pharmacopoeia (JP) standards provide quality requirements for established pharmaceutical excipients and formulation components.

For biopharmaceuticals, regulatory assessment additionally emphasizes product specific critical quality attributes, structural integrity, purity, biological activity, aggregation, and immunogenicity. ICH Q6B provides a framework for specifications and analytical characterization of biotechnology-derived and biological products. For therapeutic proteins,

immunogenicity should be evaluated using a risk-based strategy, including assessment of anti-drug antibodies and where appropriate, neutralizing antibodies. Consequently, sustainable excipients need to demonstrate both environmental advantages and adequate control of product quality, stability, potency, and immunogenicity.

Regulatory and Safety Perspectives

The regulatory landscape for pharmaceutical solvents and excipients is designed to ensure patient safety, product efficacy, and environmental protection. For eco-friendly solvents and excipients, adherence to established regulatory guidelines and comprehensive safety evaluations are essential to facilitate their acceptance and commercialization.

Regulatory Guidelines: FDA, EMA, and ICH

Regulatory agencies such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and the International Council for Harmonisation (ICH) provide detailed guidance on the quality, safety, and efficacy of pharmaceutical excipients:

■ ***FDA:*** The FDA evaluates excipient safety as part of drug product development and approval, with consideration of factors such as: intended route of administration, exposure, concentration, and prior use. The FDA maintains the *Inactive Ingredient Database (IID)* which provides information on inactive ingredients used in FDA-approved drug products, including dosage form, route of administration, and maximum potency information [72].

■ ***EMA:*** The EMA requires appropriate quality, safety, and risk assessment of excipients used in medicinal products. European requirements also include compliance with applicable Good Manufacturing Practice (GMP) requirements, while the European Pharmacopoeia (Ph. Eur.) provides quality standards for pharmaceutical substances and excipients [73].

■ ***ICH:*** The ICH harmonizes technical requirements for pharmaceutical development and registration across major regulatory regions. ICH Q3C addresses residual solvents, while ICH Q3A and Q3B address impurities in new drug substances and drug products, respectively, supporting consistent assessment and control of impurity-related risks[74].

Generally Recognized as Safe (GRAS) Status

GRAS is generally used for food ingredients (which includes many excipients) and indicates that a substance is considered safe under specified conditions of use based on scientific evidence or a history of safe use [75]. Some natural solvents and excipients may have GRAS status or a long history of safe use, which can provide supportive safety information during pharmaceutical development. However, GRAS status alone does not constitute approval or authorization for use as a pharmaceutical excipient. Pharmaceutical use requires appropriate regulatory assessment based on the intended route of administration, dose, duration and extent of exposure, formulation, and product-specific safety and quality requirements. The FDA Inactive Ingredient Database (IID) can provide evidence of prior use of an inactive ingredient in approved drug products, but inclusion in the IID does not constitute approval for all pharmaceutical applications [76].

Toxicological Evaluation

Comprehensive toxicological assessments are mandated to establish safety profiles:

■ ***Acute and chronic toxicity:*** Acute and chronic toxicity studies evaluate the immediate and long-term effects, respectively, in relevant biological systems.

■ ***Genotoxicity and carcinogenicity:*** Genotoxicity and carcinogenicity studies assess the potential for DNA damage, genetic alterations and cancer related risk.

■ ***Reproductive and developmental toxicity:*** Reproductive and developmental toxicity studies evaluate potential adverse effects on fertility, embryonic and foetal development, and postnatal development, where applicable.

■ ***Nonclinical safety assessment.*** Nonclinical safety data should be generated and interpreted in accordance with relevant ICH guidance, including ICH M3(R2) and ICH S7A/S7B, where applicable [77].

Environmental Regulations

Sustainability considerations extend beyond patient safety to include manufacturing emissions, waste generation, solvent use and recovery, and end-of-life environmental impact. Environmental regulations aim to reduce pollution, waste, and harmful chemical emissions from pharmaceutical manufacturing. In the European Union, REACH regulates the safe use of chemicals, while the US EPA regulates areas such as hazardous waste, air emissions, and wastewater. Following these regulations, along with using biodegradable materials, recovering solvents, and reducing waste, can improve the environmental sustainability of pharmaceutical manufacturing [78].

CHALLENGES AND LIMITATIONS

Despite the significant benefits of eco-friendly solvents and excipients in pharmaceutical formulations, their widespread adoption faces several challenges and limitations that must be addressed to fully realize their potential in sustainable drug development.

Limited Stability

Bio-derived polymers, lipids and surfactants may undergo hydrolysis, oxidation, microbially mediated degradation, or through structural alterations during their storage period which can affect formulation performance and shelf-life . For instance, chitosan may degrade under improper storage conditions, while lipid-based excipients such as medium-chain triglycerides and phospholipid-based systems are vulnerable to oxidation. Polysorbate 20 and Polysorbate 80, commonly used to stabilize biopharmaceuticals, can also undergo hydrolysis, oxidation, or enzymatic degradation, producing fatty acids and other by-products that may contribute to the formation of visible or sub-visible particles. Polysorbate degradation can occur even during refrigerated storage, although its effect on product quality depends on the formulation. Therefore, selection of sustainable or bio-derived excipients should consider their chemical stability, compatibility, degradation products, and required shelf-life [79,80].

Scalability and Batch-to-Batch variability

Large-scale use of natural excipients can be challenging because their properties may vary depending on the source, species, cultivation, extraction, and processing methods. For example, the molecular weight and degree of deacetylation of chitosan, and the composition and viscosity of alginate, may differ between sources. These variations can affect drug release, rheological properties, and bio adhesion [81]. Similarly, variations in phospholipid composition can influence the stability and performance of liposomal systems [82]. Therefore, controlled sourcing, standardized manufacturing, supplier qualification, and appropriate analytical controls are important for consistent industrial production.

Regulatory Barriers

Regulatory acceptance poses a major obstacle for new, or alternative sustainable versions of existing excipients with stringent requirements for quality, purity, and consistency of manufacture. The FDA provides guidance for evaluating the nonclinical safety of new excipients. In addition, excipients should have appropriate specifications and manufacturing controls to ensure consistent quality, as described in USP General Chapter <1078>. Therefore, regulatory acceptance depends not only on the environmental benefits of an excipient but also on its quality, safety, consistency, and functionality. Regulatory requirements vary between countries and must be met for the intended pharmaceutical market. Detailed regulatory requirements are beyond the scope of this review.

Cost and Availability

Eco-friendly solvents and excipients may be more expensive and less readily available than conventional materials because of limited sources, complex extraction or processing methods, and seasonal variations in supply. These factors can increase production costs and make large-scale manufacturing and cost competitiveness more difficult, limiting their widespread adoption [83].

Standardization Problems

Natural excipients inherently possess variability in chemical composition and physicochemical properties due to differences in botanical origin, harvesting conditions, and processing methods. Therefore, appropriate characterization, standardization, and quality-control measures are essential to ensure consistent formulation performance. [84].

FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

Sustainability is expected to become increasingly important and necessary with applications of eco-friendly excipients ranging from formulation of small molecules through to delivery in advanced therapeutics such as antibodies, vaccines, and gene therapies. In this context, future pharmaceutical development and production should integrate sustainability aspects with formulation functionality, manufacturability, quality, and life cycle assessment rather than considering environmental impact as a separate consideration.

Sustainable excipients and materials

Future research should focus on bio-sourced polymers, phospholipids, biodegradable lipids, and biosurfactants with reliable quality, scalable manufacturing processes, and well-defined environmental impact. For widely used excipients such as cellulose derivatives, considerable gains can be achieved through the use of renewable raw materials, efficient derivatization processes, reduced energy and solvent consumption, and solvent recycling. It is essential to note that "bio-based" or "natural" does not automatically mean sustainable.

Biopharmaceutical and advanced therapies

With the growing significance of monoclonal antibodies, recombinant proteins, vaccines, nucleic-acid-based therapies, and other forms of advanced drugs, there is a growing need for sustainable excipients and processing. Considering the issues previously encountered with polysorbates in certain biologics products, future work should focus on developing excipients with improved stabilizing properties and improved stability, high-quality materials, and processing methods that minimize degradation without sacrificing biological activity [85]. Moreover, sustainability may be achieved through more efficient processing of biopharmaceuticals, including process intensification, continuous manufacturing, improved process integration, and reductions in water, energy, and material consumption. Closed-loop recovery and recycling of process materials can further reduce waste and resource use. However, the sustainability benefits of these approaches should be evaluated using appropriate environmental metrics or life-cycle assessment [86].

AI-Based formulation design

AI and machine learning (ML) methods can accelerate formulation development by predicting drug-excipient compatibility, solubility, stability, and formulation composition before extensive experimental screening. For example, ML models can use molecular descriptors or chemical fingerprints of drugs and excipients to predict whether a drug-excipient pair is likely to be compatible or incompatible [87]. Patel *et al.,* developed the DE-INTERACT model using molecular fingerprints and experimentally validated "its ability to predict predict incompatibilities using DSC, FTIR, HPTLC, and HPLC [88]. More recently, Nguyen *et al.,* developed a stacking-based ML model using molecular descriptors and Mol2vec representations to improve drug-excipient compatibility prediction. AI-based formulation design is also increasingly being combined with Quality by Design (QbD) and high-throughput experimentation to prioritize promising formulations and reduce unnecessary experimental trials. These approaches may reduce material consumption, development time, and formulation waste; however, their reliability depends on data quality, model interpretability, external validation, and experimental confirmation [89].

Sustainable Nano formulations

Future development of sustainable nano formulations will involve the application of biodegradable materials, aqueous or minimal impact processes, and lower amounts of hazardous solvents. Recent developments in sustainable nanomedicines include the use of biological sources for nanoparticle formation, including plant materials, microorganisms, enzymes, and biopolymers [90]. However, the green approach cannot be considered automatically environmentally friendly since nanoparticle toxicity, batch-to-batch variability, energy consumption, purification requirements, and scalability should also be studied.

Individualized and adaptive formulation

If personalized medicine becomes more common in the future, there will be an increased need for adaptable manufacturing methods. Three-dimensional printing technology using polymers and hydrogels offers exciting potential opportunities to produce individualized doses, drug cocktails, and adaptive release profiles, which may help to cut down on the wastage that occurs in conventional manufacturing processes [91].

Commercial Green Manufacturing Processes

Commercial-scale production of sustainable formulation technologies will require scalable processes, reliable supply chain management, process analytical technologies, solvent recovery, and sustainability metrics such as process mass intensity (PMI) and E-Factor. Continuous manufacturing can improve process control, reduce processing time, and decrease material and energy consumption. However, these sustainability benefits should be demonstrated for each manufacturing process and formulation [92-94].

CONCLUSION

The growing global interest in the environmental impact of pharmaceuticals including the materials used, processing conditions and waste management, etc., is driving the shift toward eco-friendly solvents and excipients. Meeting current and future expectations for green chemistry and sustainability requires a more comprehensive approach to drug development and manufacturing. Environmental considerations should be integrated throughout the pharmaceutical product life cycle, from drug discovery and formulation development to manufacturing and market supply, and should include all relevant materials and manufacturing processes. This review provides insights into the diverse classes of green solvents and sustainable excipients that offer safer, biodegradable, and renewable alternatives to conventional materials. These materials have the potential to improve drug solubility, stability, delivery, and formulation performance. Despite challenges related to stability, scalability, batch-to-batch variability, cost, and regulatory

acceptance, advances in green chemistry, nanotechnology, continuous manufacturing, and AI-driven formulation design are expected to support the development of more sustainable pharmaceutical products. Continued integration of green chemistry initiatives and eco-friendly excipients into pharmaceutical development and production is not only essential for minimizing environmental impact but also for ensuring therapeutic efficacy and patient safety. The development of novel green solvents and excipients, together with more sustainable manufacturing processes and their application to next-generation pharmaceutical and biopharmaceutical products, will contribute to sustainability in the pharmaceutical industry for the future. Ultimately, integrating environmental responsibility with pharmaceutical innovation offers exciting potential possibilities for the development of more sustainable, effective, and environmentally responsible healthcare solutions.

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