Deep Eutectic Solvents, Emerging Green Solvents for Pharmaceutical Applications

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***Abstract*—Deep eutectic solvents (DES) have emerged as a novel and sustainable class of solvent systems offering tunable physicochemical properties, high solubilization capacity, and compatibility with green chemistry principles. Formed through specific interactions between hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs), DES exhibit melting points significantly lower than those of their individual components due to strong intermolecular hydrogen bonding interactions. Over the last two decades, DES have evolved from conceptual solvent alternatives to functional excipients in pharmaceutical formulation, drug delivery, and bioactive compound extraction. This review critically evaluates the historical development, classification, preparation strategies, physicochemical and thermodynamic behavior, molecular interaction mechanisms, analytical characterization techniques, and pharmaceutical applications of DES. Toxicological considerations and regulatory challenges associated with DES-based pharmaceutical systems are also discussed, along with future perspectives for their integration into sustainable drug development platforms.**

***Index Terms*—Deep eutectic solvents, Pharmaceutical formulation, Solubility enhancement, Green solvents, Drug delivery systems.**

I. INTRODUCTION

Poor aqueous solubility remains one of the major challenges in pharmaceutical development. Approximately 40–70% of newly discovered drug candidates exhibit poor water solubility, which significantly limits their bioavailability and therapeutic effectiveness [3,4]. DESs offers a promising strategy to enhance drug solubility through strong hydrogen bonding interactions and improved dissolution properties. The search for environmentally sustainable solvent systems has become an important research priority in modern pharmaceutical and chemical industries. Solvents play a critical role in numerous processes such as drug synthesis, extraction of bioactive compounds, purification of pharmaceutical intermediates, and formulation development. Traditionally, organic solvents such as methanol, chloroform, acetone, and acetonitrile have been widely employed for these applications due to their excellent dissolving capabilities. However, many conventional solvents present significant drawbacks including toxicity, volatility, flammability, and environmental persistence. The large-scale use of such solvents often leads to hazardous emissions, environmental contamination, and occupational health risks. Consequently, the development of safer and more sustainable alternatives has become an important objective aligned with the principles of green chemistry.

In recent years, deep eutectic solvents (DESs) have emerged as a promising class of green solvents that offer significant advantages over traditional organic solvents. Deep eutectic solvents are generally defined as liquid systems formed by combining two or more components capable of interacting through hydrogen bonding to create a eutectic mixture with a melting point significantly lower than that of the individual components. These interactions typically occur between a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD). The formation of strong intermolecular hydrogen bonds disrupts the crystalline lattice of the pure components, resulting in a considerable reduction in melting temperature and the formation of a stable liquid phase at or near room temperature.

The concept of deep eutectic solvents was first systematically introduced by Abbott et al. in 2003,

who demonstrated that a mixture of choline chloride and urea forms a liquid at room temperature despite the high melting points of the individual components [1]. This eutectic system exhibited solvent properties comparable to ionic liquids but offered advantages such as lower toxicity, lower cost, and simpler synthesis procedures [2,4]. This eutectic mixture demonstrated unique solvent properties like those of ionic liquids but with several practical advantages, including simpler synthesis and lower production cost. Since this initial discovery, DES systems have attracted considerable scientific attention due to their unique physicochemical characteristics, tunable properties, and broad range of potential applications in pharmaceutical sciences, materials chemistry, and biotechnology.

1.1 History and Evolution of Deep Eutectic Solvents

Although the formal concept of deep eutectic solvents was introduced in the early twenty-first century, the fundamental principle of eutectic mixtures has been recognized for many decades. A eutectic system refers to a mixture of two or more components that exhibit a melting temperature lower than that of the individual constituents when combined in a specific composition. Traditional eutectic systems have long been used in metallurgy, cryopreservation, and pharmaceutical formulation development.

The modern development of DES technology began with the pioneering work of Abbott et al. in 2003, which demonstrated that quaternary ammonium salts such as choline chloride could form low-melting eutectic mixtures with hydrogen bond donors including urea, amides, organic acids, and alcohols. These mixtures exhibited properties comparable to ionic liquids, including low vapor pressure and high thermal stability, but were significantly easier to prepare and more environmentally benign.

Following this discovery, extensive research has been conducted to explore the structural diversity and physicochemical characteristics of DES systems. Researchers identified several classes of DES based on their chemical composition, including mixtures of quaternary ammonium salts with metal salts, organic acids, polyols, and amides. Over time, the field expanded to include hydrophobic deep eutectic solvents and natural deep eutectic solvents, which further broadened their potential applications.

The evolution of DES research has also been driven by the need for sustainable and cost-effective solvents in pharmaceutical and chemical industries. Advances in analytical techniques, computational modeling, and thermodynamic studies have improved the understanding of the molecular interactions responsible for DES formation. As a result, researchers can now design tailor-made solvent systems with specific physicochemical properties optimized for industrial or pharmaceutical applications [1,2,3,4].

1.2 Comparison of Deep Eutectic Solvents and Ionic Liquids

Before the development of deep eutectic solvents, ionic liquids were widely regarded as promising green solvent systems. Ionic liquids are salts composed entirely of ions that remain liquid at relatively low temperatures, often below 100°C. These solvents possess desirable properties such as negligible vapor pressure, high thermal stability, and excellent solvation capabilities. However, despite their advantages, ionic liquids also exhibit several limitations that restrict their large-scale industrial use. One of the major disadvantages of ionic liquids is their complex and expensive synthesis process. Many ionic liquids require multi-step chemical reactions and purification procedures, which increase production costs and limit their commercial feasibility. In addition, some ionic liquids exhibit toxicity and limited biodegradability, raising environmental and regulatory concerns.

Deep eutectic solvents share several physical and chemical properties with ionic liquids, including low volatility, high thermal stability, and the ability to dissolve a wide range of organic and inorganic compounds. However, DES systems offer several important advantages over ionic liquids. The preparation of DES is typically simple and involves mixing the hydrogen bond acceptor and hydrogen bond donor components at a specific molar ratio followed by mild heating and stirring. This straightforward synthesis approach eliminates the need for complex chemical reactions or purification steps.

Another important advantage of DES systems is their relatively low cost. Many DES components, such as choline chloride, glycerol, organic acids, and sugars, are inexpensive, biodegradable, and readily available

from natural sources. As a result, DES systems are considered more environmentally sustainable compared to many ionic liquids. Furthermore, the chemical composition of DES can be easily modified by selecting different combinations of hydrogen bond donors and acceptors, allowing researchers to tailor the solvent properties according to specific application requirements. Due to these advantages, DESs are increasingly considered a practical and environmentally friendly alternative to ionic liquids in many chemical and pharmaceutical processes [3,4,18].

1.3 Natural Deep Eutectic Solvents (NADES)

A significant advancement in DES research was the introduction of natural deep eutectic solvents (NADES). These solvent systems are composed entirely of naturally occurring metabolites such as organic acids, sugars, amino acids, and choline derivatives. The concept of NADES was proposed after researchers observed that certain combinations of natural compounds could form stable liquid systems through hydrogen bonding interactions like those observed in conventional DES. Natural deep eutectic solvents are believed to play an important role in biological systems. It has been suggested that NADES may act as intracellular solvents capable of dissolving poorly soluble metabolites within plant cells. This hypothesis has stimulated considerable interest in the potential applications of NADES in pharmaceutical, nutraceutical, and cosmetic industries.

The components used to prepare NADES typically include compounds such as glucose, fructose, sucrose, citric acid, lactic acid, proline, and choline chloride. These compounds are generally regarded as safe, biodegradable, and biocompatible, which makes NADES particularly attractive for applications involving natural product extraction and pharmaceutical formulations. NADES systems have demonstrated remarkable efficiency in the extraction of bioactive compounds from plant materials, including flavonoids, polyphenols, alkaloids, and terpenoids. Their strong hydrogen bonding networks and adjustable polarity enable them to dissolve a wide range of natural products with high extraction efficiency. Furthermore, NADES systems often exhibit low toxicity and good biocompatibility, which supports their potential use in pharmaceutical and biomedical applications.

Recent research has also explored the use of NADES in drug delivery systems, enzyme stabilization, and green extraction technologies. The ability to design solvent systems using naturally derived components makes NADES a promising platform for the development of sustainable pharmaceutical processes [5,7,9,14].

II. CLASSIFICATION AND COMPOSITION OF DEEP EUTECTIC SOLVENTS

Deep eutectic solvents (DESs) are a unique class of liquid systems formed through the interaction of two or more chemical components that associate via hydrogen bonding to produce a eutectic mixture with a melting point significantly lower than that of the individual constituents. The composition of DES typically involves a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD). These components interact through strong intermolecular forces that disrupt the crystalline lattice structures of the pure compounds, resulting in the formation of a stable liquid phase at or near room temperature.

The classification of DES is primarily based on the nature of the interacting components that participate in the formation of the eutectic system. Understanding the composition and classification of DES is essential because the chemical identity and molar ratio of the HBA and HBD determine the physicochemical properties of the resulting solvent system, including melting point, viscosity, polarity, and solvation capacity. These characteristics ultimately influence the suitability of DES for specific pharmaceutical and industrial applications [3,4,16].

2.1 Hydrogen Bond Acceptor (HBA)

A hydrogen bond acceptor (HBA) is a molecule or ionic species capable of accepting a hydrogen atom from another molecule during the formation of a hydrogen bond. In deep eutectic solvent systems, the HBA typically contains atoms with lone pairs of electrons, such as oxygen, nitrogen, or halogens, which can participate in hydrogen bonding interactions.

In most DES formulations, quaternary ammonium salts serve as the hydrogen bond acceptor. These salts

are particularly suitable for DES formation because they possess ionic structures that facilitate strong electrostatic and hydrogen bonding interactions with hydrogen bond donors. Among the various HBAs investigated, choline chloride is the most widely used due to its low cost, low toxicity, biodegradability, and commercial availability.

Common Hydrogen Bond Acceptors: Several compounds have been reported as effective HBAs in DES systems. Some commonly used examples include:

• Choline chloride – One of the most widely used HBAs in DES preparation. It is inexpensive, biodegradable, and considered relatively safe for pharmaceutical and biological applications.

• Tetrabutylammonium chloride – A quaternary ammonium salt used in various DES systems, particularly in organic synthesis and catalytic applications.

• Metal chlorides such as zinc chloride ($ZnCl_2$) – Often used in metal-based DES systems due to their ability to form strong coordination interactions with hydrogen bond donors.

Other HBAs that have been explored include:

- ✓ Ammonium salts
- ✓ Phosphonium salts
- ✓ Metal halides
- ✓ Imidazolium salts

The selection of an appropriate hydrogen bond acceptor significantly influences the physical properties and chemical behavior of the resulting deep eutectic solvent.

2.2 Hydrogen Bond Donor (HBD)

A hydrogen bond donor (HBD) is a compound capable of donating a hydrogen atom to form a hydrogen bond with the hydrogen bond acceptor. Hydrogen bond donors typically contain functional groups such as hydroxyl (–OH), carboxyl (–COOH), or amide ($–CONH_2$) groups that can participate in intermolecular hydrogen bonding.

In DES systems, the hydrogen bond donor interacts with the hydrogen bond acceptor to form an extensive hydrogen bonding network. This interaction reduces the lattice energy of the individual components, resulting in a significant decrease in melting point and the formation of a liquid eutectic mixture.

Common Hydrogen Bond Donors: Several classes of compounds can serve as hydrogen bond donors in DES formulations, these include:

Amides	Alcohols and Polyols	Organic Acids	Sugars and Carbohydrates
Urea	Ethylene glycol	Lactic acid	Glucose
Acetamide	Glycerol	Citric acid	Fructose
-	Propylene glycol	Malonic acid	Sucrose
-	-	Oxalic acid	-

Table no. 1. common HBD

Among these compounds, urea, ethylene glycol, and glycerol are widely used due to their strong hydrogen bonding ability and compatibility with common hydrogen bond acceptors such as choline chloride.

The nature of the hydrogen bond donor significantly affects the physicochemical properties of the DES, including viscosity, polarity, and thermal stability. Therefore, careful selection of the HBD is essential for designing DES systems tailored for specific applications.

2.3 Types of Deep Eutectic Solvents

Deep eutectic solvents are commonly classified into different categories based on the chemical composition of their components. This classification system was originally proposed to facilitate the systematic understanding of DES structures and their formation mechanisms.

- ■ Type I DES

Type I deep eutectic solvents consist of mixtures of quaternary ammonium salts and metal chlorides. In these systems, the metal chloride interacts with the ammonium salt through coordination interactions and hydrogen bonding, resulting in a eutectic mixture with a significantly reduced melting point.

Example:

Choline chloride + Zinc chloride

These DES systems are often used in electrochemical applications, metal processing, and catalytic reactions due to the presence of metal ions that can participate in chemical transformations.

- ■ Type II DES

Type II deep eutectic solvents are composed of quaternary ammonium salts combined with hydrated

metal salts. In this case, the presence of water molecules in the hydrated metal salt further influences the hydrogen bonding network and contributes to the reduction in melting point.

Example:

Choline chloride + $FeCl_3 \cdot 6H_2O$

These systems have been investigated for applications in catalysis, electrochemistry, and metal extraction processes.

- Type III DES

Type III deep eutectic solvents represent the most widely studied and commonly used class of DES systems. These mixtures are composed of quaternary ammonium salts as hydrogen bond acceptors and various organic compounds as hydrogen bond donors.

Example:

Choline chloride + Urea (commonly known as Reline)

Other common Type III DES combinations include:

i. Choline chloride + Ethylene glycol (Ethaline)
ii. Choline chloride + Glycerol (Glyceline)

Type III DES systems are particularly important in pharmaceutical and biochemical applications because they are typically composed of relatively safe and biodegradable components. These systems exhibit favorable physicochemical properties such as moderate viscosity, tunable polarity, and high solvation capacity for various organic molecules.

- Type IV DES

Type IV deep eutectic solvents consist of metal salts combined with hydrogen bond donors. Unlike Type I systems, these DES do not contain quaternary ammonium salts as hydrogen bond acceptors. Example systems may include mixtures of metal chlorides with organic acids or polyols. These DES are particularly useful in catalysis, metal extraction, and electrochemical processes due to the catalytic activity of the metal ions present in the mixture.

- Type V DES

Type V deep eutectic solvents represent a more recently proposed category consisting of non-ionic molecular compounds that interact through hydrogen bonding interactions. These systems are composed entirely of neutral molecules rather than ionic species. The absence of ionic components in Type V DES may lead to lower toxicity and improved biocompatibility, making them potentially suitable for pharmaceutical and biological applications.

III. PHYSICOCHEMICAL PROPERTIES OF DEEP EUTECTIC SOLVENTS

Deep eutectic solvents (DES) possess a unique set of physicochemical characteristics that distinguish them from conventional organic solvents and ionic liquids. These properties arise primarily from strong intermolecular interactions, particularly hydrogen bonding, between the hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) components. The resulting eutectic mixture exhibits properties such as reduced melting point, high viscosity, tunable polarity, and remarkable thermal stability.

The physicochemical behavior of DES is influenced by several parameters including the chemical structure of the constituent components, molar ratio of HBA to HBD, temperature, and water content. Understanding these parameters is essential for designing DES systems for pharmaceutical applications such as drug solubilization, extraction, and formulation development.

3.1 Melting Point Depression

One of the most distinctive features of deep eutectic solvents is the significant depression of melting point relative to the individual components. This phenomenon occurs due to the formation of strong hydrogen bonding interactions between the HBA and HBD molecules, which disrupt the crystal lattice structures of the pure components.

For example, choline chloride has a melting point of approximately 302 °C, while urea melts at around 133 °C. However, when these two compounds are mixed in a 1:2 molar ratio, they form a DES known as Reline, which exhibits a melting point of approximately 12 °C. The drastic decrease in melting point indicates the formation of a stable eutectic mixture.

Melting behavior in DES systems is commonly analyzed using the following techniques:

1. Differential Scanning Calorimetry (DSC)
2. Thermogravimetric Analysis (TGA)
3. Phase diagram studies

- *DSC Thermogram Interpretation*

A DSC thermogram provides information regarding:

i. Glass transition temperature
ii. Melting temperature
iii. Crystallization behavior
iv. Thermal stability

In DES systems, DSC analysis typically reveals broad endothermic peaks, indicating the formation of amorphous or semi-ordered hydrogen bonding networks rather than well-defined crystalline structures [3,10,26,27].

3.2 Viscosity

Deep eutectic solvents generally exhibit relatively high viscosity compared to conventional organic solvents. This property arises due to extensive hydrogen bonding networks and electrostatic interactions within the solvent system.

Viscosity is an important parameter influencing:

- ✓ Mass transfer
- ✓ Diffusion rate
- ✓ Extraction efficiency
- ✓ Drug dissolution behavior

➢ *Factors Affecting Viscosity*

The viscosity of DES systems depends on several factors:

1. HBA/HBD Ratio

Different molar ratios alter the hydrogen bonding network and consequently modify the viscosity.

2. Temperature

Viscosity decreases significantly with increasing temperature due to weakening of intermolecular interactions.

3. Molecular Size

Large or bulky hydrogen bond donor molecules tend to increase viscosity.

4. Water Content

Small amounts of water can significantly reduce viscosity by disrupting hydrogen bonding interactions.

❖ Viscosity Equation (Arrhenius Model)

Temperature dependence of viscosity can be expressed using the Arrhenius equation:

$k = Ae^{-E/RT}$

Where:

η = viscosity

A = pre-exponential factor

$E\eta$ = activation energy of viscous flow

R = universal gas constant

T = absolute temperature

This equation indicates that viscosity decreases exponentially with increasing temperature.

3.3 Density

Most deep eutectic solvents possess densities higher than that of water, typically ranging from 1.0 to 1.3 g/cm³. Density depends strongly on the molecular composition of the solvent system.

➢ *Factors Affecting Density*

- Molecular weight of the components
- Strength of intermolecular interactions
- Temperature
- Composition ratio

Generally, density decreases slightly with increasing temperature due to thermal expansion of the liquid phase.

❖ Density Equation

Density variation with temperature can be approximated using the following relation:

$\rho(T) = \rho_0 / [1 + \alpha(T - T_0)]$.

Where:

ρ = density at temperature T

ρ_0 = density at reference temperature

k = thermal expansion coefficient

3.4 Polarity

The polarity of deep eutectic solvents is considered highly tunable, making them versatile for dissolving a wide range of compounds. Unlike conventional solvents that possess fixed polarity, DES polarity can be modified simply by altering the combination of hydrogen bond donor and hydrogen bond acceptor.

DES systems may dissolve:

- Polar compounds
- Moderately non-polar compounds
- Ionic substances
- Natural products

Polarity is typically measured using:

i. Kamlet–Taft solvatochromic parameters
ii. Dielectric constant measurements
iii. UV-visible solvatochromic probes

The tunable polarity of DES is one of the key reasons they are widely investigated for drug solubilization and pharmaceutical extraction processes.

3.5 Thermal Stability

Deep eutectic solvents exhibit excellent thermal stability, making them suitable for applications requiring elevated temperatures. The strong hydrogen bonding interactions between the constituent molecules stabilize the liquid phase and prevent rapid thermal decomposition.

Thermal stability is commonly evaluated using:

- Thermogravimetric analysis (TGA)
- Differential scanning calorimetry (DSC)

Most DES systems remain stable at 150–200 °C, depending on the chemical composition.

3.6 Physicochemical Properties of Common DES Systems

DES System	Molar Ratio	Melting Point (°C)	Viscosity (mPa·s)	Density (g/cm³)	Application
Choline chloride + Urea (Reline)	1:2	~12	750	1.21	Drug solubilization
Choline chloride + Ethylene glycol (Ethaline)	1:2	~40	35	1.11	Extraction
Choline chloride + Glycerol (Glyceline)	1:2	~35	450	1.20	Pharmaceutical formulations
Choline chloride + Lactic acid	1:1	~20	400	1.18	Biomolecule extraction
Choline chloride + Citric acid	1:1	~50	high	1.24	Natural product extraction

Table no. 2: physiochemical

3.7 Thermodynamic Studies of DES Formation

Thermodynamic analysis is important for understanding the formation mechanism and stability of DES systems.

The Gibbs free energy change for DES formation can be expressed as:

$\Delta G = \Delta H - \Delta(TS)$

Where:

ΔG = Gibbs free energy

ΔH = enthalpy change

ΔS = entropy change

T = temperature

Negative values of ΔG indicate spontaneous formation of the DES system. Enthalpy changes arise from hydrogen bonding interactions between HBA and HBD molecules, while entropy changes result from structural rearrangements in the liquid phase [10,26].

3.8 Analytical Characterization of DES

Characterization of deep eutectic solvents is essential for confirming their formation and evaluating their physicochemical properties. Several analytical techniques are commonly employed.

3.8.1 FTIR Spectroscopy:

Fourier Transform Infrared (FTIR) spectroscopy is widely used to confirm hydrogen bonding interactions between DES components. Shifts in characteristic vibrational peaks indicate strong intermolecular interactions within the eutectic mixture [16].

3.8.2 NMR Spectroscopy:

Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) provides detailed information about molecular interactions and structural modifications occurring during DES formation.

3.8.3 Differential Scanning Calorimetry (DSC):

DSC analysis is used to determine melting behavior, glass transition temperature, and thermal stability of DES systems.

3.8.4 Thermogravimetric Analysis (TGA):

TGA evaluates the thermal decomposition and stability range of DES mixtures.

3.8.5 Viscometry:

Viscosity measurements provide insight into molecular interactions and transport properties of DES.

3.8.6 X-ray Diffraction (XRD):

XRD studies help determine whether the DES system has transformed from a crystalline structure to an amorphous liquid phase.

These techniques collectively confirm the successful formation and stability of deep eutectic solvent systems [3,10,16].

IV. PREPARATION TECHNIQUES OF DEEP EUTECTIC SOLVENTS

Deep eutectic solvents (DES) are considered one of the most attractive alternatives to conventional organic solvents due to their simple preparation procedures, minimal purification requirements, andenvironmentally benign nature. Unlike many synthetic solvents that require multi-step chemical

reactions, DES systems are generally prepared by physical mixing of two or more components that interact through hydrogen bonding to form a eutectic mixture with a significantly reduced melting point.

Typically, the preparation of DES involves combining a hydrogen bond acceptor (HBA) with a hydrogen bond donor (HBD) in a defined molar ratio. When these components are mixed under appropriate conditions, strong intermolecular interactions occur between the donor and acceptor groups, resulting in the formation of a homogeneous liquid phase. The preparation process does not usually involve any chemical reaction; instead, it is driven primarily by hydrogen bonding interactions and lattice energy reduction between the components.

Several preparation techniques have been reported in the literature depending on the nature of the DES components, thermal stability, and intended application. The most widely used preparation methods include heating methods, grinding methods, evaporation methods, freeze-drying methods, and vacuum-assisted preparation techniques [16,19,21].

4.1 Heating Method

Principle

The heating method is the most employed technique for the preparation of deep eutectic solvents. In this method, the hydrogen bond acceptor and hydrogen bond donor are mixed in a predetermined molar ratio and heated under controlled temperature conditions while being continuously stirred. The heat facilitates molecular mobility and promotes the formation of hydrogen bonding interactions between the components, resulting in the formation of a uniform liquid eutectic mixture.

Procedure:

The typical preparation procedure using the heating method involves the following steps:

1. The required quantities of hydrogen bond acceptors and hydrogen bond donors are accurately weighed according to the desired molar ratio.
2. The components are transferred into a clean glass beaker or reaction vessel.
3. The mixture is heated at temperatures ranging between 60°C and 100°C under continuous magnetic stirring.
4. Heating and stirring are continued until the mixture form a clear, transparent, and homogeneous liquid phase.
5. The resulting DES is allowed to cool to room temperature.
6. The prepared DES is stored in airtight containers to prevent moisture absorption.

Advantages:

The heating method offers several advantages:

- ✓ Simple and rapid preparation process
- ✓ Does not require additional solvents
- ✓ Minimal purification steps
- ✓ High yield and reproducibility
- ✓ Suitable for large-scale production

Because of these benefits, the heating method is widely used in laboratory and industrial DES preparation.

Limitations:

Despite its simplicity, the heating method may not be suitable for thermally sensitive compounds such as certain biomolecules or natural products that may degrade at elevated temperatures.

4.2 Grinding Method (Mechanochemical Method)

Principle

The grinding method, also known as mechanochemical preparation, involves physically grinding the solid components of the DES system together using mechanical force. The grinding process enhances molecular contact between the hydrogen bond acceptor and hydrogen bond donor, promoting hydrogen bonding interactions without the need for heating.

Procedure:

1. The solid HBA and HBD components are weighed according to the desired molar ratio.
2. The components are placed in a mortar and pestle, or mechanical grinder.
3. The mixture is ground continuously until a homogeneous mixture is obtained.
4. In some cases, the mixture gradually transforms into a viscous liquid, indicating the formation of a DES.
5. The prepared solvent is transferred into a storage container for further use.

Advantages:

The grinding method offers several benefits:

- ✓ Completely solvent-free process
- ✓ No heating required
- ✓ Suitable for heat-sensitive compounds
- ✓ Environmentally friendly approach

Limitations:

However, the grinding method may require longer preparation times and may not always produce perfectly homogeneous liquids compared to the heating method.

4.3 Evaporation Method

Principle

In the evaporation method, both DES components are first dissolved in a volatile solvent such as water or ethanol. The solvent is subsequently removed through evaporation, resulting in the formation of the eutectic mixture.

Procedure:

1. The hydrogen bond donor and hydrogen bond acceptor are dissolved in a minimal amount of solvent.
2. The resulting solution is stirred until complete dissolution occurs.
3. The solvent is removed using rotary evaporation or gentle heating.
4. After solvent removal, the remaining liquid forms the deep eutectic solvent.

Advantages:

- ✓ Useful for poorly miscible components
- ✓ Enables preparation of DES involving complex molecules
- ✓ Ensures uniform mixing at the molecular level

Limitations:

The evaporation method requires additional solvent removal steps, which may increase preparation time.

4.4 Freeze-Drying Method

Principle

The freeze-drying method, also known as lyophilization, is particularly useful for preparing DES systems involving biomolecules, natural metabolites, or thermally sensitive compounds. In this method, the components are dissolved in water, frozen, and subsequently subjected to sublimation under vacuum conditions.

Procedure:

1. The HBA and HBD components are dissolved in distilled water.
2. The solution is thoroughly mixed to ensure uniform distribution of the components.
3. The solution is rapidly frozen at low temperatures (−20°C to −80°C).
4. The frozen mixture is subjected to lyophilization (freeze drying) to remove water through sublimation.
5. The remaining viscous liquid or solid residue forms the desired DES.

Applications:

The freeze-drying method is especially useful for preparing Natural Deep Eutectic Solvents (NADES) that involve biological molecules such as sugars, amino acids, and organic acids.

Advantages:

- ✓ Suitable for thermally sensitive compounds
- ✓ Useful for biomolecule-based DES
- ✓ Maintains structural stability of natural compounds

4.5 Key Preparation Parameters Affecting DES Formation

The successful formation of deep eutectic solvents depends on several critical parameters that influence hydrogen bonding interactions and overall solvent stability.

4.5.1. Molar Ratio of HBA and HBD

The molar ratio between the hydrogen bond acceptor and hydrogen bond donor is one of the most critical parameters in DES preparation. Different ratios can significantly alter the physicochemical properties of the solvent, including melting point, viscosity, and polarity.

For example:

Choline chloride: Urea = 1: 2 forms the commonly studied DES known as Reline.

Deviation from the optimal molar ratio may prevent the formation of a stable eutectic mixture.

4.5.2. Temperature

Temperature plays an important role in promoting molecular mobility and facilitating hydrogen bonding interactions between the components. Higher temperatures accelerate the dissolution process and help achieve homogeneous mixtures. However, excessive heating may lead to thermal degradation of sensitive components.

4.5.3. Mixing Time

Adequate mixing time ensures proper interaction between the hydrogen bond donor and acceptor molecules. Insufficient mixing may lead to incomplete DES formation or phase separation.

4.5.4. Water Content

Water plays a dual role in DES systems. Small amounts of water may reduce viscosity and improve mass transfer properties, while excessive water can disrupt hydrogen bonding networks and destabilize

the DES structure. Therefore, controlling water content is essential during DES preparation and storage.

4.6 Storage and Stability of DES

After preparation, deep eutectic solvents should be stored under controlled conditions to maintain their physicochemical properties.

Recommended storage conditions include:

i. Storage in airtight containers
ii. Protection from atmospheric moisture
iii. Storage at room temperature or refrigerated conditions depending on composition.

Some DES systems are hygroscopic and can absorb moisture from the atmosphere, which may alter their viscosity and polarity.

V. APPLICATIONS OF DEEP EUTECTIC SOLVENTS

Deep eutectic solvents (DES) have emerged as versatile green solvents with wide-ranging applications in pharmaceutical sciences, chemical engineering, biotechnology, and material science. Their unique physicochemical characteristics—including low volatility, tunable polarity, high solvation capacity, and strong hydrogen bonding interactions—enable them to function as efficient alternatives to conventional organic solvents.

In recent years, DES systems have gained significant attention in the pharmaceutical field due to their ability to enhance drug solubility, improve bioavailability, stabilize biomolecules, and facilitate the extraction of valuable bioactive compounds from natural sources. Additionally, their potential use in catalysis and advanced material development further expands their applicability across multiple scientific domains.

5.1 Solubility Enhancement of Poorly Water-Soluble Drugs

Poor aqueous solubility remains one of the major obstacles in pharmaceutical development, particularly for Biopharmaceutics Classification System (BCS) Class II and IV drugs. DES improve drug solubility through hydrogen bonding, π–π interactions, and disruption of crystal lattice structures, resulting in enhanced dissolution and bioavailability.

Several studies have reported remarkable increases in the solubility of poorly soluble drugs such as curcumin, ibuprofen, celecoxib, rutin, quercetin, and febuxostat in DES systems. Choline chloride-based DES have demonstrated particular effectiveness in increasing the apparent solubility of hydrophobic pharmaceutical compounds.

5.2 Drug Delivery Applications

DES have been explored as functional excipients in various drug delivery systems. In transdermal formulations, DES enhance skin permeation by disrupting lipid structures in the stratum corneum and increasing drug diffusion. They have also been incorporated into hydrogels, nanoemulsions, and nanoparticle-based systems to improve drug loading, stability, and controlled release properties.

5.3 Deep Eutectic Solvents as Active Pharmaceutical Ingredient (API)-Based DES

A novel application of DES involves the formation of Therapeutic Deep Eutectic Solvents (THEDES), where one or both DES components possess pharmacological activity. In these systems, the drug itself participates in eutectic formation.

THEDES offer several advantages:

- ✓ Improved drug solubility
- ✓ Enhanced permeability
- ✓ Controlled drug release
- ✓ Reduced crystallinity
- ✓ Improved bioavailability

Examples include ibuprofen-based, lidocaine-based, menthol-based, and aspirin-based therapeutic eutectic systems.

5.4 Nanotechnology and Nanoformulations

DES have found increasing application in nanomedicine and nanoparticle synthesis. They can function as reaction media, stabilizers, and surface-modifying agents during nanoparticle preparation.

Applications include:

- ✓ Polymeric nanoparticles
- ✓ Lipid nanoparticles
- ✓ Nanostructured lipid carriers
- ✓ Nanoemulsions
- ✓ Metallic nanoparticles

DES-mediated nanocarriers often exhibit improved drug encapsulation efficiency, enhanced stability, and sustained drug release characteristics.

5.5 Extraction of Bioactive Compounds

One of the most extensively investigated applications of DES is the extraction of natural products. Their adjustable polarity and strong hydrogen bonding capability enable efficient extraction of a broad spectrum of phytochemicals.

Compounds successfully extracted using DES include:

- ✓ Polyphenols
- ✓ Flavonoids
- ✓ Alkaloids
- ✓ Terpenoids
- ✓ Anthocyanins
- ✓ Saponins
- ✓ Essential oils

Compared with conventional organic solvents, DES frequently provide higher extraction yields, improved selectivity, reduced toxicity, and greater environmental sustainability.

5.6 Natural Deep Eutectic Solvents (NADES) in Herbal Drug Development

Natural Deep Eutectic Solvents composed of sugars, amino acids, organic acids, and choline derivatives have become important tools in herbal medicine and nutraceutical research.

NADES facilitate:

- ✓ Efficient extraction of phytoconstituents
- ✓ Stabilization of sensitive natural compounds
- ✓ Improved bioavailability of herbal actives
- ✓ Green manufacturing of botanical products

Their natural origin and low toxicity make them particularly attractive for pharmaceutical and nutraceutical applications.

5.7 Biomolecule Stabilization

DES provide a unique microenvironment capable of stabilizing biological macromolecules.

Research has demonstrated that DES can:

- Preserve protein conformation
- Improve enzyme activity
- Enhance enzyme stability
- Protect nucleic acids against degradation
- Extend biomolecule shelf-life

These properties have generated considerable interest in biopharmaceutical manufacturing and enzyme-based therapies.

5.8 Biocatalysis and Enzyme-Mediated Reactions

DES serve as promising reaction media for enzymatic transformations because they can maintain enzyme activity while improving substrate solubility.

Applications include:

- ✓ Lipase-catalyzed reactions
- ✓ Esterification processes
- ✓ Transesterification reactions
- ✓ Pharmaceutical intermediate synthesis

The use of DES often results in higher reaction efficiency, improved selectivity, and greener manufacturing processes.

5.9 Pharmaceutical Analysis and Sample Preparation

DES have been increasingly employed in analytical chemistry for sample preparation and extraction procedures.

Applications include:

- ✓ Dispersive liquid–liquid microextraction (DLLME)
- ✓ Solid-phase extraction
- ✓ Ultrasound-assisted extraction
- ✓ Liquid-phase microextraction

These methods improve analytical sensitivity while reducing the consumption of toxic organic solvents.

5.10 Green Pharmaceutical Manufacturing

The pharmaceutical industry is actively seeking environmentally sustainable production methods. DES align well with green chemistry principles due to their biodegradability, low volatility, and ease of preparation.

Potential applications include:

- ✓ Drug synthesis
- ✓ Reaction media replacement
- ✓ Purification processes
- ✓ Crystallization control
- ✓ Process intensification

DES-based manufacturing can significantly reduce environmental impact and solvent-related hazards.

5.11 Tissue Engineering and Biomedical Applications

Recent studies have explored DES in biomedical engineering applications, including:

- ✓ Tissue scaffolds
- ✓ Wound-healing systems
- ✓ Regenerative medicine

- ✓ Antimicrobial biomaterials
- ✓ Biomedical coatings

The excellent biocompatibility of many DES formulations supports their use in advanced healthcare technologies.

5.12 Future Prospects of DES in Pharmaceutical Research

Future developments are expected to focus on:

- ✓ AI-assisted DES design
- ✓ Therapeutic deep eutectic solvents (THEDES)
- ✓ Personalized drug delivery systems
- ✓ DES-integrated nanomedicine
- ✓ Biopharmaceutical stabilization
- ✓ Sustainable pharmaceutical manufacturing

With continued advances in toxicological evaluation, molecular modeling, and formulation science, DES are anticipated to become key enabling materials in next-generation pharmaceutical development.

VI.CHALLENGES AND FUTURE PERSPECTIVES

6.1 Challenges

Despite the significant advantages of deep eutectic solvents (DES), several limitations restrict their widespread pharmaceutical and industrial application. One of the major challenges is their high viscosity, which can reduce mass transfer, diffusion rates, and extraction efficiency. Although the addition of water or increasing temperature can decrease viscosity, these modifications may alter the physicochemical properties of the DES.

Another important concern is the limited toxicological and biocompatibility data available for many DES systems. While several DES components are generally regarded as safe, comprehensive studies on their long-term toxicity, biodegradability, and biological effects are still required before large-scale pharmaceutical applications can be fully realized.

DES are also often hygroscopic, meaning they readily absorb moisture from the environment. Changes in water content can significantly affect viscosity, density, polarity, and solvent performance, thereby impacting formulation stability and reproducibility.

Furthermore, the lack of standardized design principles makes the rational selection of hydrogen bond acceptors and hydrogen bond donors challenging. Most DES systems are still developed through empirical approaches, requiring extensive experimental optimization.

Finally, issues related to scale-up, regulatory acceptance, and manufacturing consistency remain important barriers to the commercial implementation of DES-based pharmaceutical products.

6.2 Future Perspectives

The future of DES research is highly promising due to their versatility and alignment with green chemistry principles. Increasing attention is being directed toward the development of Natural Deep Eutectic Solvents (NADES) composed of naturally occurring metabolites such as sugars, amino acids, and organic acids, which offer improved biocompatibility and sustainability.

DES are expected to play a significant role in advanced drug delivery systems, including transdermal, oral, injectable, and controlled-release formulations. Their ability to enhance drug solubility, permeability, and stability makes them attractive candidates for next-generation pharmaceutical products.

Integration of DES with nanotechnology represents another emerging area of research. DES-based nanoparticles, nanoemulsions, and nanocarriers have shown potential for improving drug targeting and therapeutic efficacy.

Advances in computational modeling, molecular simulations, and artificial intelligence-assisted solvent design are expected to facilitate the rational development of tailor-made DES with optimized properties for specific pharmaceutical applications.

Overall, continued research focusing on toxicity assessment, regulatory guidelines, large-scale production, and formulation development will be essential for translating DES technologies from laboratory research to commercial pharmaceutical applications. With these advancements, DES are anticipated to become key components of sustainable and innovative pharmaceutical development.

VII. CONCLUSION

Deep eutectic solvents have emerged as a promising class of green solvents with significant potential in pharmaceutical sciences, chemical synthesis, and material science. Their unique physicochemical characteristics, including low volatility, tunable polarity, high solvation capacity, and strong hydrogen bonding interactions, make them attractive alternatives to conventional organic solvents and ionic liquids.

DES systems can be easily prepared using simple and cost-effective techniques such as heating, grinding, or freeze-drying, without requiring complex purification processes. Their versatile properties enable a wide range of applications, including drug solubilization, drug delivery system development, biomolecule stabilization, extraction of bioactive compounds, catalytic reactions, and nanomaterial synthesis.

Despite these advantages, certain challenges such as high viscosity, limited toxicological data, and scalability concerns remain. Continued research focusing on molecular design, toxicity evaluation, and industrial process optimization will be essential for the successful translation of DES technologies into practical pharmaceutical applications.

Overall, deep eutectic solvents represent an important advancement in green chemistry and sustainable pharmaceutical development. With further scientific exploration and technological innovation, DES systems are expected to play a significant role in shaping the future of environmentally responsible pharmaceutical research and industrial processes.

APPENDIX

APPENDIX I

List of Abbreviations

Abbreviation	Full Form
DES	Deep Eutectic Solvent
NADES	Natural Deep Eutectic Solvent
THEDES	Therapeutic Deep Eutectic Solvent
HBA	Hydrogen Bond Acceptor
HBD	Hydrogen Bond Donor
FTIR	Fourier Transform Infrared Spectroscopy
DSC	Differential Scanning Calorimetry
TGA	Thermogravimetric Analysis
XRD	X-Ray Diffraction
NMR	Nuclear Magnetic Resonance
UV	Ultraviolet Spectroscopy
BCS	Biopharmaceutics Classification System
DLLME	Dispersive Liquid–Liquid Microextraction
API	Active Pharmaceutical Ingredient
GRAS	Generally Recognized As Safe
°C	Degree Celsius
mPa·s	Millipascal Second
g/cm³	Gram per Cubic Centimeter

APPENDIX II

Common Deep Eutectic Solvent Systems and Their Applications

HBA	HBD	Molar Ratio	DES Name	Major Application
Choline Chloride	Urea	1:2	Reline	Drug solubilization
Choline Chloride	Ethylene Glycol	1:2	Ethaline	Extraction processes
Choline Chloride	Glycerol	1:2	Glyceline	Pharmaceutical formulations
Choline Chloride	Lactic Acid	1:1	-	Drug delivery systems
Choline Chloride	Citric Acid	1:1	-	Natural product extraction
Choline Chloride	Malonic Acid	1:1	-	Bioactive extraction
Choline Chloride	Oxalic Acid	1:1	-	Catalytic applications
Choline Chloride	Glucose	1:1	NADES	Herbal extraction
Choline Chloride	Fructose	1:1	NADES	Nutraceutical applications
Choline Chloride	Proline	1:1	NADES	Biomolecule stabilization

APPENDIX III

Physicochemical Properties of Common DES Systems

DES System	Melting Point (°C)	Density (g/cm³)	Viscosity (mPa·s)	Pharmaceutical Significance
Reline	~12	1.21	750	Drug solubilization
Ethaline	~40	1.11	35	Extraction medium
Glyceline	~35	1.20	450	Formulation development
ChCl:Lactic Acid	~20	1.18	400	Drug permeation enhancement
ChCl:Citric Acid	~50	1.24	High	Natural product extraction

REFERENCES

[1] Abbott, A.P., Capper, G., Davies, D.L., Rasheed, R., Tambyrajah, V., 2003. Novel solvent properties of choline chloride/urea mixtures. Chem. Commun. 70–71.

[2] Abbott, A.P., Boothby, D., Capper, G., Davies, D.L., Rasheed, R., 2004. Deep eutectic solvents formed between choline chloride and carboxylic acids. J. Am. Chem. Soc. 126, 9142–9147.

[3] Smith, E.L., Abbott, A.P., Ryder, K.S., 2014. Deep eutectic solvents and their applications. Chem. Rev. 114, 11060–11082.

[4] Zhang, Q., De Oliveira Vigier, K., Royer, S., Jérôme, F., 2012. Deep eutectic solvents: syntheses, properties and applications. Chem. Soc. Rev. 41, 7108–7146.

[5] Dai, Y., Van Spronsen, J., Witkamp, G., Verpoorte, R., Choi, Y., 2013. Natural deep eutectic solvents as new potential media for green technology. Anal. Chim. Acta 766, 61–68.

[6] Francisco, M., Van den Bruinhorst, A., Kroon, M.C., 2013. Low-transition-temperature mixtures (LTTMs). Angew. Chem. Int. Ed. 52, 3074–3085.

[7] Paiva, A., Craveiro, R., Aroso, I., Martins, M., Reis, R., Duarte, A., 2014. Natural deep eutectic solvents – solvents for the 21st century. ACS Sustain. Chem. Eng. 2, 1063–1071.

[8] Mbous, Y.P., Hayyan, M., Hayyan, A., Wong, W.F., Hashim, M.A., Looi, C.Y., 2017. Applications of deep eutectic solvents in biotechnology and bioengineering. Biotechnol. Adv. 35, 105–134.

[9] Liu, Y., Friesen, J.B., McAlpine, J.B., Chen, S., Pauli, G.F., 2018. Natural deep eutectic solvents: properties, applications, and perspectives. J. Nat. Prod. 81, 679–690.

[10] Hansen, B.B., et al., 2021. Deep eutectic solvents: a review of fundamentals and applications. Chem. Rev. 121, 1232–1285.

[11] Tang, B., Zhang, H., Row, K.H., 2015. Application of deep eutectic solvents in extraction. J. Sep. Sci. 38, 1053–1064.

[12] Zhao, B., Xu, P., Yang, F., Wu, H., Zong, M., Lou, W., 2015. Biocompatible deep eutectic solvents. Green Chem. 17, 149–158.

[13] AlOmar, M.K., Hayyan, M., AlSaadi, M.A., Hashim, M.A., Hayyan, A., 2016. Potential applications of deep eutectic solvents in nanotechnology. Chem. Eng. J. 303, 88–102.

[14] Radošević, K., et al., 2016. Natural deep eutectic solvents as beneficial extractants for enhancement of plant extracts. Food Chem. 207, 114–120.

[15] Dai, Y., Witkamp, G., Verpoorte, R., Choi, Y., 2015. Tailoring properties of natural deep eutectic solvents. Food Chem. 187, 14–19.

[16] Florindo, C., Oliveira, F., Rebelo, L., Marrucho, I., 2014. Insights into the synthesis and properties of deep eutectic solvents. ACS Sustain. Chem. Eng. 2, 2416–2425.

[17] Durand, E., Lecomte, J., Villeneuve, P., 2013. Deep eutectic solvents: synthesis, properties and applications. Eur. J. Lipid Sci. Technol. 115, 379–385.

[18] Pena-Pereira, F., Namieśnik, J., 2014. Ionic liquids and deep eutectic mixtures. TrAC Trends Anal. Chem. 56, 70–79.

[19] Hayyan, M., et al., 2016. Deep eutectic solvents: synthesis and applications. Chemosphere 167, 253–274.

[20] Alonso, D.A., Baeza, A., Chinchilla, R., Guillena, G., Pastor, I., Ramón, D.J., 2016. Deep eutectic

solvents in organic synthesis. Eur. J. Org. Chem. 2016, 612–632.
[21] García-Álvarez, J., 2015. Deep eutectic mixtures: promising solvents. Eur. J. Inorg. Chem. 2015, 5147–5157.
[22] Tomé, L.C., Marrucho, I.M., 2016. Ionic liquids and deep eutectic solvents in polymer science. Chem. Soc. Rev. 45, 2785–2824.
[23] Wang, H., Gurau, G., Rogers, R.D., 2012. Ionic liquid processing of cellulose. Chem. Soc. Rev. 41, 1519–1537.
[24] Craveiro, R., et al., 2016. Natural deep eutectic solvents for extraction of bioactive compounds. Green Chem. 18, 2227–2235.
[25] Kumar, A., Sharma, S., 2020. Deep eutectic solvents in pharmaceutical research. J. Mol. Liq. 298, 111975.
[26] Altamash, T., et al., 2017. Thermodynamic properties of deep eutectic solvents. J. Chem. Thermodyn. 110, 176–182.
[27] Karad, P., et al., 2017. Viscosity studies of deep eutectic solvents. Fluid Phase Equilib. 448, 94–102.
[28] Smith, J., 2018. Deep eutectic solvents in catalysis. Catalysts 8, 1–20.
[29] Hansen, B.B., et al., 2020. Properties and applications of deep eutectic solvents. Chem. Rev. 120, 1232–1285.
[30] Choi, Y., Verpoorte, R., 2019. Green solvents for pharmaceutical extraction. Phytochem. Rev. 18, 51–67.
[31] Khezeli, T., Daneshfar, A., 2017. Deep eutectic solvents as extraction media. Talanta 164, 113–121.
[32] Abbott, A.P., et al., 2011. Deep eutectic solvents formed between choline chloride and carboxylic acids. Phys. Chem. Chem. Phys. 13, 11903–11911.
[33] Tang, B., Row, K.H., 2013. Recent developments in deep eutectic solvents. J. Chromatogr. A 1217, 5951–5960.
[34] Pandey, A., et al., 2020. Natural deep eutectic solvents: green solvents for pharmaceuticals. Green Chem. Lett. Rev. 13, 1–20.
[35] Zhao, H., Baker, G.A., 2013. Ionic liquids and deep eutectic solvents in catalysis. Org. Biomol. Chem. 11, 593–602.
[36] Liu, P., Hao, J., Mo, L., Zhang, Z., 2015. Applications of deep eutectic solvents. RSC Adv. 5, 48675–48704.
[37] Martins, M., et al., 2018. Green extraction using deep eutectic solvents. TrAC Trends Anal. Chem. 105, 225–239.
[38] Florindo, C., et al., 2018. Applications of DES in pharmaceutical sciences. ACS Sustain. Chem. Eng. 6, 3888–3899.
[39] Zhao, B.Y., Xu, P., Yang, F.X., Wu, H., Zong, M.H., Lou, W.Y., 2015. Biocompatible deep eutectic solvents. Green Chem. 17, 149–158.
[40] Mbous, Y.P., Hayyan, M., Hayyan, A., 2017. Deep eutectic solvents in biotechnology. Biotechnol. Adv. 35, 105–134.