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Revolutionising solvent systems: A new paradigm of deep eutectics, beyond conventional liquids

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Abstract

This review delves into Deep Eutectic Solvents (DESs) and Natural Deep Eutectic Solvents (NADES) as environmentally friendly substitutes, emphasizing their biodegradability, low toxicity, and recyclability, it addresses their development from hydrogen bond donors (HBDs) and acceptors (HBAs), increased solubility. The review explains the mechanisms behind eutectic formation and how intermolecular interactions contribute to their effectiveness. It throws a light on the experimental consideration followed by examination and future aspects. It also explores the wide range of applications for DESs and NADES, including in synthetic chemistry, natural product extraction, biocatalysts, and pharmaceutical formulations. The review also addresses challenges, such as high viscosity and poor ionic conductivity, and suggests future research to improve their performance. Overall, this work emphasizes the potential of DESs and NADES to drive more sustainable practices in chemistry and other fields.

Keywords: Deep Eutectic Solvents, Natural Deep Eutectic Solvents, biodegradability, low toxicity, recyclability, hydrogen bond donors, hydrogen bond acceptors, eutectic formation, synthetic chemistry, pharmaceutical formulations

Introduction

The term "solvents," derived from the Latin word meaning "to loosen," reflects their essential role in dissolving, suspending, or extracting various compounds without undergoing significant structural changes. Solvents, by their very nature as fluids, are crucial in a vast range of scientific and industrial applications, including synthesis[1], pharmaceuticals, nutrition, flavour research, materials science, and the painting industry. In the pharmaceutical field, solvents are particularly indispensable, used for dissolving active pharmaceutical ingredients (APIs) and excipients, as well as in formulation, coating, and other applications. Among solvents, water is the most widely recognized and versatile, owing to its ability to dissolve a wide array of substances.

In this context, substances like switchable solvents, ionic liquids, and deep eutectic solvents (DESs) have emerged as viable options. DESs, in particular, have garnered significant attention as a sustainable and cost-effective class of ionic liquids, offering promising solutions to enhance the efficiency of chemical processes.

DESs are formed by combining a quaternary ammonium or metal salt with a hydrogen bond donor (HBD)—such as acids, amides, amines, or alcohols—creating low-melting mixtures that exhibit reduced melting points compared to their individual components[8]. This allows DESs to exist as liquids at or below 100°C. The resulting mixtures are characterized by charge delocalization and strong hydrogen bonding, giving DESs a high degree of polarity. This polarity allows for diverse chemical interactions[3], while the composition of the DES can be tailored to display either acidic or basic behaviour, depending on the specific HBD used.

Deep Eutectic Solvents (DESs) are highly advantageous, being biodegradable, recyclable, and devoid of energy-requiring purification steps, thus a greener and safer option compared to conventional solvents[6]. Not withstanding difficulties such as high viscosity and low ionic conductivity, DESs are gaining prominence for their application in organic transformations and synthetic chemistry. Although they have been investigated in use in electroplating, their potential in the synthesis of organic materials is still unexplored[12], with much promise for the future. DESs are noted for a substantial depression of melting points due to increased intermolecular interactions, which increases their functionality and the range of their applications.

Natural Deep Eutectic Solvents System

Natural Deep Eutectic Solvents (NADES) are environmentally friendly liquid media with the ability to dissolve low water-soluble compounds, and they are thus potential substitutes for conventional organic solvents. Their most important characteristics—biodegradability, biocompatibility, and high polarity enable them to find applications in metabolomics, natural product studies, and synthetic chemistry. NADES are usually composed of natural metabolites such as sugars, organic acids, and amino acids, which are generated by intermolecular forces such as hydrogen bonding. Although their structural elaboration increases adaptability, it also makes it difficult to recognize multicomponent systems in nature.

NADES are similar to Deep Eutectic Solvents (DESs), a family of renewable solvents that exist through hydrogen bonding, but are commonly created from quaternary ammonium salts and organic acids. NADES and DESs are both extensively studied in green chemistry as they bring advantages such as recyclability, affordability, and minimal hazardous waste[13].Their applications in organic conversions as well as in drug synthesis indicate their potential in green chemical processes.

Nature of Solvents and Physicochemical Properties

The quest for environmentally friendly solvents has gained significant momentum in recent years, with eutectic solvents particularly and Deep Eutectic Solvents (DESs) emerging as promising alternatives to traditional organic solvents. These solvents, with their unique properties and sustainable nature, have opened new avenues in synthetic chemistry, natural product recovery, catalysis, and environmental science.

Understanding Eutectic Solvents

Eutectic solvents are a class of liquids formed by mixing a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA), typically a halide salt, in specific molar ratios. These mixtures exhibit a significant depression in melting point compared to their individual components, enabling them to exist as liquids at relatively low temperatures (often below 100°C). The unique intermolecular interactions, including hydrogen bonding, van der Waals forces, and occasional electrostatic interactions, endow eutectic solvents with remarkable properties that distinguish them from conventional solvents.

Properties of DESs: A Green Alternative

DESs possess a range of intrinsic properties that make them highly attractive for various applications. Their extensive hydrogen bonding network[4] contributes to:

- **High solubility** for diverse compounds, including poorly soluble natural products.
- **Tuneability**, allowing customization of solvent properties by altering the HBD and HBA.
- **High viscosity and density**, which can be modulated by the addition of water.
- **Low melting points**, enabling their use in temperature-sensitive applications such as biocatalysis.
- **Non-volatility and low vapor pressure**, reducing environmental contamination risks.
- **Non-flammability**, enhancing safety during storage and handling.

These properties, combined with their biodegradability, low toxicity, and chemical inertness, make DESs a cornerstone of green chemistry.

Biocompatibility of DES Components

Choline chloride (ChCl), a widely used HBA in DES formulations, exemplifies the safety and versatility of eutectic solvents. As a derivative of vitamin B4, ChCl is recognized as safe for consumption and plays essential metabolic roles. Paired with a variety of HBDs, including amines, alcohols, organic acids, and sugars, ChCl enables the creation of a vast library of DESs with tailored properties.

Unique Characteristics of DES

DES exhibit properties that make them particularly suited for biological and environmental applications:

- Their formation depends on the specific molar ratios of their components, typically near 1:1, creating stable, transparent liquids at room temperature.
- The electrochemical behaviour of DES, including conductivity, can be fine-tuned for specific applications. For example, DES matrices can improve the electrochemical detection[6] of natural products when used as reagents with buffer solutions.
- DES have shown high CO_2 solubility, surpassing that of aqueous amines, highlighting their potential in carbon capture and storage technologies.

Experimental Considerations

When preparing Deep Eutectic Mixtures, several critical steps must be followed to ensure the desired properties and functionality of the final mixture. The process involves the careful selection of components, their precise ratio, and the control of temperature during mixing and cooling. Here is a detailed explanation of the experimental considerations involved:

1. Selection of Components and Determination of Eutectic Composition

The first step in the preparation of DEMs is to choose appropriate components based on their compatibility and ability to form a eutectic mixture. A typical eutectic mixture is composed of a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA), often a salt or organic compound[2]. The ideal composition is determined by considering the chemical properties, such as polarity, hydrogen bonding capabilities, and melting point depression. The goal is to create a mixture where the melting point is significantly lower than the melting points of the individual components.

2. Heating the Mixture to Promote Eutectic Formation

Once the components are chosen, the mixture must be gently heated to ensure the complete dissolution and formation of the eutectic mixture. This can be done using equipment such as a heating mantle, water bath, or hot plate. The temperature should be carefully controlled to be slightly above the melting point of the individual components but well below their decomposition temperature to avoid any unwanted chemical reactions. The typical temperature range for this step is 50–80°C, depending on the specific DEM or being prepared.

3. Cooling and Checking for Recrystallization

After the eutectic mixture has been formed, the next step is to allow it to cool. The mixture should be checked at ambient temperatures for any signs of recrystallization, which would indicate incomplete eutectic formation[20]. If the mixture does not remain homogeneous or forms crystals, adjustments may be needed, either by modifying the component ratio or slightly increasing the temperature. For certain DEMs, such as those containing urea, moisture absorption from the air can occur, making it essential to handle these mixtures in a dry environment and store them in airtight containers to maintain their stability.

4. Adjustment of Ratios for Optimal Eutectic Formation

If the resulting mixture does not form a clear, homogeneous solution, the ratio of the components may need to be adjusted. By slightly varying the proportions of the HBD and HBA or by increasing the temperature slightly, the eutectic formation can often be optimized. Stirring at specific temperatures, usually in the range of 50–100°C, will facilitate the formation of a uniform, transparent liquid, signifying successful eutectic mixture formation.

Analytical Techniques for Characterization of DEMs and

Several analytical techniques are employed to characterize the properties of DEMs and, ensuring they meet the desired criteria for various applications. These include thermal, structural, and viscosity measurements, among others.

1. Differential Scanning Calorimetry (DSC)

DSC is a key technique for studying the thermal properties of DEMs. It is used to determine the melting points, glass transition temperatures, and heat capacities of the mixtures. In particular, DSC helps identify the eutectic composition by observing a distinct melting endotherm that occurs at a temperature lower than that of the individual components. This observation confirms the formation of the eutectic mixture, which is crucial for determining the mixture's potential in various applications.

2. Thermogravimetric Analysis (TGA)

TGA is used to assess the thermal stability and decomposition behaviour of DEMs. This is particularly important to ensure that the mixture can withstand a range of temperatures without degrading during processing or in final applications. TGA helps to evaluate the stability of DEMs under different environmental conditions and provides insights into their handling characteristics.

3. Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectroscopy is utilized to investigate the molecular interactions between the components of DEMs, particularly focusing on hydrogen bonding between the HBD and HBA. By analysing chemical shifts in proton or carbon signals, NMR can reveal the nature of the interactions between the components. For example, shifts in proton NMR signals can confirm hydrogen bonding, and advanced techniques such as NOESY (Nuclear Overhauser Effect Spectroscopy) or COSY (Correlation Spectroscopy) can provide further insights into the spatial and dynamic interactions within the mixture.

4. X-ray Diffraction (XRD)

XRD is used to assess the crystallinity of DEMs. Most DEMs, including NADES, tend to form an amorphous or semi-crystalline phase. XRD analysis reveals the absence of sharp diffraction peaks, confirming the amorphous nature of the mixture. A broad hump in the XRD spectrum suggests that the DEM is in a disordered state, which is typical for deep eutectic mixtures, indicating their potential as efficient solvents or reagents in various applications.

5. Viscosity Measurements

The viscosity of DEMs is an important property, particularly for applications in solvents, lubrication, and pharmaceutical formulations. The viscosity can provide insight into the flow properties of the mixture, which can be crucial for processing and application performance. Viscosity measurements are often used to compare the behaviour of DEMs with their individual components, allowing researchers to assess any synergistic effects or changes in the mixture's flow characteristics upon mixing.

6. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy is employed to identify functional group interactions and confirm the presence of hydrogen bonding in DEMs. Shifts or broadening of peaks in the O-H or N-H stretching regions indicate hydrogen bonding interactions. Additionally, changes in carbonyl (C=O) or amine (N-H) stretches suggest specific functional group interactions between the components of the mixture. This analysis is critical for understanding the molecular interactions that contribute to the overall properties of DEMs.

Applications of DES

1. Green Catalysis and Synthetic Chemistry

DESs have become integral to modern synthetic chemistry as eco-friendly solvents. Their ability to facilitate organic transformations without requiring post-synthesis purification aligns with the principles of green chemistry. DESs have demonstrated:

- Enhanced reaction efficiency for catalytic processes.
- The capability to synthesize structurally diverse, drug-like small molecules.
- Superior performance in multi-component reactions, simplifying reaction setups and reducing waste.

2. Natural Product Extraction

The high solubility and low volatility of DESs make them ideal for extracting bioactive compounds from natural sources. For instance, adding water to ChCl-oxalic acid DES significantly reduces viscosity and enhances the extraction yield of flavonoids from grape skins. Such advancements demonstrate the potential of DESs to outperform conventional extraction methods in terms of efficiency and environmental impact.

3. Carbon Capture and Storage

Amine-based NADES species have shown exceptional CO_2 solubility, offering a sustainable alternative to aqueous amines for carbon capture. These solvents prevent increased vapor pressure during CO_2 dissolution, addressing one of the primary challenges in carbon capture technologies.

4. Advanced Monitoring Techniques

The electrochemical properties of NADES facilitate their use in sophisticated monitoring systems. Phase metering devices, for example, distinguish NADES from eluting analytes during the recovery of natural products, enabling precise analysis and optimization of extraction processes.

Challenges and Future Directions

Despite their promising attributes, DESs and NADES face challenges that must be addressed to unlock their full potential:

1. **High Viscosity**: The inherent viscosity of DESs can limit their applicability, particularly in large-scale extractions. Strategies such as water addition and the design of low-viscosity DESs are being explored to overcome this limitation.

2. **Lack of Systematic Correlations**: The relationship between the components of DESs and their resulting properties remains poorly understood. Comprehensive studies are needed to establish predictive models for DES behaviour.

3. **Scalability and Cost**: While DESs are considered cost-effective, their industrial scalability requires further investigation to ensure consistent quality and performance.

Applications of Deep Eutectic Solvents (DESs)

1. **Biotechnological and Medicinal Applications:** The potential applications of Deep Eutectic Solvents (DESs) in biotechnology and medicine significantly overlap, offering promising opportunities for the development, delivery, and analysis of pharmaceutical and biological

materials. DESs are particularly advantageous in the formulation of drug delivery systems, as they act as solubilizing agents for drugs, improving their bioavailability. In the field of biomedicine, DESs are increasingly being used in the development of biodegradable elastomers, which have applications as drug delivery systems, scaffolds for tissue engineering, and regenerative medicine. These polymeric materials are versatile, especially in the creation of temperature-sensitive systems for controlled drug release. Furthermore, DESs' ability to stabilize and protect biological molecules makes them ideal candidates for use in preserving cellular structures and bioactive compounds.

One of the critical concerns in biomedicine is the treatment of bacterial infections caused by medical procedures such as the implantation of devices, which often leads to the formation of biofilms—clusters of bacteria that are highly resistant to conventional antibiotics. DESs have shown promise in disrupting these biofilms, making them potential candidates for novel antibacterial therapies.

1. **Therapeutic Applications:** DESs are increasingly recognized for their utility in therapeutic applications across various fields, particularly in anticancer treatment and molecular biology. Due to their remarkable properties, DESs are being explored as drug delivery carriers, scaffolds for tissue engineering, and in gene therapy. Their ability to stabilize and transport biomolecules has made them indispensable in the development of bio-imaging systems and shape-memory polymers that respond to environmental stimuli such as temperature, thus enabling controlled drug release. DESs also show considerable promise in regenerative medicine[9], with their potential to support the healing of damaged tissues and organs by providing a controlled microenvironment conducive to cellular growth and regeneration.

2. **Stabilization and Preservation of Biological Molecules:** A recent patent by Goldsborough and Bates (2014) highlights the potential of DESs in molecular cell biology. Their research demonstrated that DES mixtures could stabilize and preserve biological molecules, such as RNA, DNA, and proteins, in various phases—whether solid, liquid, or gel. This finding is particularly significant for applications where the preservation of biological specimens is crucial, including in the storage and transportation of cells, tissues, and biological fluids like blood, serum, and plasma. Furthermore, DESs maintain the native morphology of cells in a variety of biological materials, including urine and cerebrospinal fluid, which is critical for preserving their functional integrity.

3. **Molecular Analytical Techniques:** In molecular biology, DESs are utilized in several techniques to fix cells and maintain their structure and morphology. These include applications such as cell counting, immunohistochemistry, histochemistry, and various staining and colouring methods. DESs have shown exceptional ability to stabilize cells during these processes, improving the accuracy and reliability of diagnostic and research procedures.

4. **Electroplating and Metal Processing:** DESs have found a significant application in electroplating, particularly when dealing with metals that are typically difficult to plate or process using conventional methods. Unlike traditional aqueous or organic solvents, DESs offer higher solubility for metal salts, as well as enhanced conductivity, making them ideal for electrochemical processes. Their low water content and non-volatility are additional advantages, as they help prevent corrosion and minimize environmental impacts during metal processing. These characteristics make DESs a sustainable and efficient alternative to traditional plating techniques.

5. **Fuel Oil and Hydrocarbon Separation:** Another area of growing interest in DES research is their application in the removal of sulphur compounds from fuel oil. The use of DESs in the distillation process of aromatic hydrocarbons and the creation of aliphatic hydrocarbons has proven to be particularly effective. Recent studies on lab-scale liquid-liquid extraction techniques have shown that DESs can significantly improve the selectivity and efficiency of these separation processes. This makes DESs highly suitable for applications in petrochemical industries where the separation of complex hydrocarbons is essential for refining and fuel production.

6. **Biocatalysis:** Biocatalysis, which involves the use of natural catalysts such as enzymes or cells to accelerate chemical reactions, has long been recognized for its efficiency, specificity, and eco-friendliness. The integration of DESs in biocatalysis has led to significant advances in the design and application of these catalysts. By offering a unique environment for the catalysts, DESs enhance the efficiency of enzymatic processes and allow for the rational design of biocatalysts with improved properties. These advances hold immense potential for various applications, including in biotechnology, pharmaceuticals, and environmental science, where the need for sustainable and efficient chemical processes is ever-increasing.

Advantages and Limitations of DESs

DESs offer several advantages that make them a compelling alternative to traditional organic solvents:

1. **Environmental Benefits:** DESs are considered "green solvents" because of their low toxicity, high biodegradability, and the fact that they are typically produced from abundant and inexpensive natural resources[23]. Unlike volatile organic solvents (VOCs), DESs are non-volatile, reducing air pollution and contributing to safer working environments.

2. **Recyclability and Biodegradability:** DESs can be recycled and reused in multiple processes, which makes them more sustainable and cost-effective over the long term compared to conventional solvents that often require expensive disposal methods.

3. **Elimination of Energy-Intensive Purification:** Traditional organic solvents often necessitate energy-consuming purification steps after their use in industrial processes.

4. DESs, on the other hand, frequently do not require post-synthesis purification, thus reducing both environmental impact and processing costs.

Despite these advantages, DESs have some inherent limitations that need to be addressed for broader applications:

1. **High Viscosity:** DESs are known for their high viscosity, which can hinder their ability to dissolve certain compounds or limit their efficiency in applications such as extraction or catalysis. Researchers are exploring ways to modify DESs, such as adding water or optimizing the HBD and HBA combinations, to reduce viscosity and enhance their solubility properties.

2. **Poor Ionic Conductivity:** Many DESs exhibit low ionic conductivity, which can be a disadvantage in applications that require the transport[19] of ions, such as electrochemical reactions or energy storage devices. Improving ionic conductivity while maintaining other desirable properties remains an ongoing area of research.

3. **Limited Exploration in Organic Synthesis:** Although DESs have been extensively explored in applications such as electroplating and metal recovery, their potential in organic material synthesis is still underutilized. The ability of DESs to enhance organic transformations in synthetic chemistry remains an exciting area for future investigation.

Conclusion

In summary, Deep Eutectic Solvents (DESs) provides green substitutes for conventional solvents with features such as biodegradability, recyclability, low melting points, and high solubility. They are versatile and useful for green chemistry, organic synthesis, natural product extraction, and industries such as pharmaceuticals, biotechnology, and carbon capture. Yet, problems including high viscosity, low ionic conductivity, and limited utilization in organic synthesis exist. Even with these constraints, further research and development may unlock their full potential, making chemical processes more sustainable and efficient.

Deep Eutectic Solvents (DESs) with tunable properties has a high prospect for the design cost-efficient synthetic protocols. Their ease in experimentation coupled with high synthetic efficiency renders DESs suitable for organic transformations. These solvents are not only useful for educational and pharmaceutical research but also hold great promise for industrial use, especially in the synthesis of drug-like small molecules with varied structures and molecular complexity. Their future development will lead to more sustainable and efficient approaches to organic synthesis. Their ability to be versatile, have low volatility, high solubility, and react efficiency enhancement makes them priceless resources for applications ranging from synthetic chemistry to carbon sequestration and biocatalysis. With further research bringing forth new opportunities for their application, DESs have the potential to revolutionize solvent systems by presenting a cleaner, safer, and more efficient alternative to industrial processes. The application of DESs across pharmaceutical, environmental technology, and other sectors has the potential to unlock a cleaner and high-performance future in chemistry and production.

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