WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Deep Eutectic Mixtures (DEMs): Applications, Characterization, and Future Directions

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ABSTRACT :

Deep eutectic mixtures (DEMs) have gained considerable attention as a sustainable alternative to conventional solvents due to their low toxicity, biodegradability, and tunable properties. This review explores the foundational characteristics of DEMs, detailing their formation mechanisms, unique properties, and various classifications. Key applications in pharmaceuticals, green chemistry, and environmental sustainability are discussed, with a focus on how DEMs enhance solubility, improve drug delivery, and serve as eco-friendly solvent alternatives. The article concludes with a comparative analysis of DEMs and ionic liquids (ILs), highlighting advantages and limitations, and suggests directions for future research to expand DEM applications across multiple industries.

Keywords: Deep Eutectic Mixtures, Ionic Liquids, Hydrogen Bond Acceptor, Hydrogen Bond Donor, Volatile Organic Solvent, Fourier-transform infrared, Differential scanning calorimetry.

Introduction :

Deep eutectic mixtures (DEMs) are innovative solvents formed by combining hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs) to achieve a eutectic mixture with a significantly reduced melting point compared to the individual components. [9,20,25] Unlike ionic liquids, which consist entirely of ions, DEMs are composed of neutral or partially charged molecules stabilized through hydrogen bonding, giving them a distinctive structure and set of properties. Discovered in the early 2000s, DEMs have found applications in green chemistry due to their ability to replace volatile organic compounds (VOCs) [1,8,6,20] and reduce environmental impact. [9,20]

Deep eutectic mixtures (DEMs) are a type of binary or ternary solvent that has gained interest for their eco-friendly properties, cost-effectiveness, and versatility. [20] DEMs are typically composed of two or more components, one acting as a hydrogen bond donor (HBD) and the other as a hydrogen bond acceptor (HBA). When mixed at a specific molar ratio, they create a eutectic mixture with a melting point significantly lower than that of its individual components. [20,2] DEMs are similar in many ways to ionic liquids but are generally less expensive and often biodegradable, making them a favourable choice for various applications, particularly in green chemistry and industrial processes. [11]

Mechanisms behind DEMs Formation :

The interaction of the HBD and HBA plays a significant role in the development of a deep eutectic mixture. These interactions result in a complex hydrogen bonding network, reducing the melting point of the mixture. The main mechanisms contributing to this melting point depression include:

- **Hydrogen Bonding:** The hydrogen bonds formed between the HBDs (e.g., urea, glycerol) and HBAs (e.g., quaternary ammonium salts) disrupt the crystal lattice structure, resulting in a liquid state at a lower temperature. This interaction is essential, as it stabilizes the liquid phase and keeps the mixture from solidifying at room temperature. [7,14,21]
- **Electrostatic Interactions:** In some DEMs, especially those involving ionic compounds like choline chloride, electrostatic interactions between ions contribute to the stability of the eutectic mixture, preventing crystallization and further reducing the melting point. [24]
- **Van der Waals Forces:** Although weaker than hydrogen bonding and electrostatic interactions, van der Waals forces contribute to the overall interaction within the mixture, aiding in its stability and maintaining the liquid state at lower temperatures. [14,24]

Properties of DEMs

Deep eutectic mixtures have unique physical and chemical properties, making them suitable for a variety of applications. Key properties include:

1. **Thermal stability:** DEMs often exhibit high thermal stability, enabling their use in high-temperature applications. The stability largely depends on the components used in the mixture and their individual melting points and thermal resistance. [18]

2. **Low Volatility:** Most DEMs have negligible vapor pressure, making them a safer option for processes that require high temperatures without the risk of evaporation or emission of toxic fumes. [18]
3. **Ionic Conductivity:** Due to the presence of charged species, some DEMs exhibit high ionic conductivity. This makes them useful as electrolytes in applications like batteries and supercapacitors. [14,18,25]
4. **Tunability:** By varying the components and their molar ratios, the properties of DEMs can be tailored to specific applications. For instance, adjusting the HBD and HBA can modify properties like viscosity, polarity, and acidity. [18]
5. **Biodegradability and Low Toxicity:** Many DEMs, especially those made with naturally occurring substances, are biodegradable and exhibit low toxicity. This property makes them more environmentally friendly compared to traditional solvents and ionic liquids. [18]

Types of DEMs

DEMs can be categorized based on the type of HBAs and HBDs used, each with distinct properties:

- **Type I:** A combination of salts and hydrogen bond donors (e.g., choline chloride + urea), commonly used for general solvent applications. [3,9,14]
- **Type II:** Combinations of metal salts and HBDs, useful in catalytic and electrochemical applications. [3,9,14]
- **Type III:** Include non-ionic compounds or complex donors, offering diverse properties for niche applications. [9,14,22]

Pharmaceutical Applications of DEMs

Drug Solubilization and Bioavailability Enhancement

One of the major challenges in drug formulation is the low solubility of many active pharmaceutical ingredients (APIs) in traditional solvents, which limits their bioavailability. DEMs can significantly improve the solubility of poorly water-soluble drugs, which is essential for enhancing their absorption and therapeutic effectiveness. For instance, DEMs have been shown to increase the solubility of drugs like fexofenadine, demonstrating their potential in pharmaceutical formulations.

- ✓ **Improves Solubility:** The hydrogen bonding and ionic interactions within DEMs allow them to dissolve both hydrophobic and hydrophilic substances, making them ideal solvents for drugs with poor water solubility. [11]
- ✓ **Enhanced Bioavailability:** By dissolving APIs effectively, DEMs improve the bioavailability of drugs, making them more readily absorbed by the body. This is particularly useful for oral and transdermal drug delivery systems. [11]

Extraction of APIs

DEMs are highly effective in the extraction of bioactive compounds from natural sources. Due to their selective solvating ability, DEMs can extract APIs from plant materials with high efficiency, which is useful for obtaining pharmacologically active substances.

- ✓ **Green Extraction Method:** DEMs are considered more environmentally friendly than organic solvents, making them suitable for "green" pharmaceutical extractions. [18] They allow for cleaner and more efficient isolation of APIs, reducing the need for hazardous chemicals. [1,6,20]
- ✓ **Higher Purity and Yield:** The high selectivity of DEMs in dissolving specific compounds helps in extracting APIs in pure form and with greater yield compared to traditional methods.

Drug Delivery Systems

DEMs have unique characteristics that make them ideal carriers in drug delivery systems. [14,15] Their ability to act as solvents and stabilizers enhances the effectiveness of various delivery mechanisms.

- ✓ **Topical and Transdermal Delivery:** DEMs can penetrate biological membranes, making them ideal for skin and transdermal drug delivery applications. They enhance skin permeability, facilitating the transport of APIs across the skin barrier. [11]
- ✓ **Oral and Injectable Formations:** Due to their biocompatibility and relatively low toxicity, certain DEMs are suitable for oral and parenteral drug formulations, providing a stable medium for drug administration and reducing potential side effects.

Stabilization of Sensitive Compounds

DEMs can help stabilize drugs that are sensitive to environmental conditions, such as temperature, humidity, or light. Their ability to maintain stable conditions for sensitive APIs makes them ideal for prolonging the shelf life and efficacy of pharmaceuticals.

- ✓ **Enhanced Stability:** The hydrogen bonding within DEMs can protect sensitive drugs from degradation by stabilizing their structure, thus prolonging their shelf life. [11,19]
- ✓ **Temperature and pH Resistance:** Some DEMs have shown stability across a broad range of temperatures and pH levels, making them useful for storing unstable or reactive APIs. [11,19]

Enzyme and Protein Stabilization

Many pharmaceutical applications require the use of enzymes and proteins, which can be sensitive to traditional solvents. DEMs provide a more compatible environment for these biomolecules, making them an excellent choice for enzyme-based pharmaceuticals and protein therapies.

- ✓ **Protein Solubility and Stability:** DEMs stabilize the three-dimensional structure of proteins, allowing them to function efficiently over extended periods. [11,19]
- ✓ **Improved Enzyme Activity:** DEMs can enhance the activity and selectivity of enzymes used in drug synthesis and bio-catalytic reactions, increasing the efficiency and reducing the cost of pharmaceutical manufacturing processes. [11,19]

Biocompatible Solvents for Controlled Release Formulations

DEMs are increasingly used in controlled release formulations, where their low toxicity and biodegradability play a significant role. DEMs can act as carriers for the slow release of APIs, allowing for consistent and prolonged therapeutic effects.

- ✓ **Extended-Release Profiles:** DEMs can be used to design formulations that release APIs gradually, leading to sustained therapeutic effects and improved patient compliance.
- ✓ **Reduced Toxicity:** Many DEMs are derived from natural compounds, making them biocompatible and reducing potential toxicity compared to synthetic solvents. [18]

Synthesis of Pharmaceutical Compounds

DEMs serve as an efficient medium for organic synthesis, providing an eco-friendly alternative to traditional solvents. Their unique properties allow for faster reaction rates and higher yields in the synthesis of pharmaceutical compounds.

- ✓ **Catalysis in Drug Synthesis:** DEMs can act as both solvents and catalysts in various reactions, reducing the need for additional catalysts and improving the overall efficiency of drug synthesis. [14]
- ✓ **Green Chemistry Applications:** The low toxicity and biodegradability of DEMs align well with green chemistry principles, making them an attractive choice for pharmaceutical companies focusing on sustainable practices. [20]

Analytical Methods for Characterizing DEMs

Spectroscopy Techniques

Fourier-transform infrared (FTIR), nuclear magnetic resonance (NMR), and Raman spectroscopy [14,17] are used to study DEM structure and interactions, providing insight into molecular behaviour and hydrogen bonding within mixtures. [5,13,14]

Thermal Analysis

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) are employed to assess thermal stability, melting behaviour, and decomposition profiles of DEMs, essential for application-specific optimization. [14,17]

Microscopy and Imaging

Microscopic techniques, such as electron microscopy, are utilized to observe particle dispersion and structural uniformity in DEM-based formulations, especially valuable for pharmaceutical and materials science applications. [16]

Rheological and Viscosity Studies

Rheological measurements provide data on viscosity and flow properties, which are critical for pharmaceutical formulations and industrial processes that require specific flow characteristics. [10]

Comparative Analysis of DEMs and Ionic Liquids

Both DEMs and ILs exhibit low melting points and solvent versatility, yet they differ significantly in composition and application. DEMs are cost-effective, biocompatible, and simpler to prepare than ILs, making them an attractive alternative for applications requiring safe, sustainable, and scalable solutions.

Challenges and Limitations of DEMs :

Stability Concerns

While DEMs are generally stable, certain mixtures may degrade under extreme pH or temperature conditions, which can limit their use in specific applications. Addressing these limitations requires careful selection and optimization of components. [12]

Scalability Issues

Scaling up DEM production for industrial applications remains challenging due to consistency and purity requirements. Future research into production methods is essential to make DEMs more accessible for widespread use. [12]

Toxicity and Regulatory Hurdles

Some DEM components may have toxicity concerns, and regulatory standards for pharmaceutical use are stringent. Additional toxicology studies are necessary to ensure that DEMs meet regulatory requirements for broader adoption. [12]

Future Directions and Research Prospects

Enhanced Drug Delivery Systems

Future research on DEMs could focus on developing advanced drug delivery systems, such as nanoencapsulation, to enable targeted and controlled release of therapeutics.[14]

New Formulations and Compositions

There is potential to explore novel HBA and HBD combinations to create DEMs with custom properties tailored to specific applications, expanding their versatility across multiple fields.

Expansion into Other Fields

Beyond pharmaceuticals and green chemistry, DEMs could play transformative roles in fields like cosmetics, food science, and agriculture, where safe, eco-friendly solvents are increasingly in demand.

Summary and Conclusion :

Deep eutectic mixtures present a promising avenue for addressing challenges in both pharmaceuticals and green chemistry. Their unique properties and versatility make them well-suited to a wide range of applications, from drug delivery to sustainable industrial processes. Continued research into the characterization, application, and optimization of DEMs will be essential for unlocking their full potential and overcoming existing limitations, supporting the development of safer, more sustainable technologies across various sectors.

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