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DEEP EUTECTIC SOLVENTS AS EMERGING PLATFORMS FOR IMPROVING THE SOLUBILITY OF POORLY WATER-SOLUBLE DRUGS: A COMPREHENSIVE REVIEW

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ABSTRACT

Background: Insufficient aqueous solubility remains one of the most critical obstacles in the formulation and clinical performance of many contemporary drug molecules, particularly those classified under BCS classes II and IV. Traditional solubility enhancement strategies frequently exhibit limitations related to toxicity, formulation instability, and restricted applicability. **Purpose:** The present review aims to systematically examine the application of deep eutectic solvents (DESs) and therapeutic deep eutectic systems (THEDES) as novel solubilization tools for poorly water-soluble drugs, highlighting their mechanisms of action, formulation advantages, safety considerations, and translational challenges. **Methods:** An extensive review of the scientific literature was carried out using major electronic databases including PubMed, ScienceDirect, Google Scholar, and ACS Publications. Peer-reviewed studies published up to early 2025 were evaluated with emphasis on pharmaceutical DES design, solubility enhancement performance, physicochemical characterization, and biological evaluation. **Results:** DESs have demonstrated remarkable capability to enhance drug solubility by modulating hydrogen bonding interactions, solvent polarity, and microstructural organization of drug molecules. Numerous poorly soluble drugs, such as anti-inflammatory agents, anticancer compounds, and phytoconstituents, have shown substantial improvements in solubility and formulation performance when incorporated into DES-based systems. Nonetheless, concerns related to

viscosity, toxicity, and regulatory classification persist. **Conclusion:** Deep eutectic solvents represent a versatile and environmentally benign alternative to conventional solubilization approaches. Although their pharmaceutical potential is evident, further in-depth toxicological, in vivo, and regulatory studies are essential to facilitate their progression from laboratory research to clinical and commercial applications.

KEYWORDS: Deep eutectic solvents; solubility enhancement; poorly water-soluble drugs; THEDES; pharmaceutical formulations.

1. INTRODUCTION

Aqueous solubility is a decisive factor influencing drug dissolution, absorption, and bioavailability. The rapid advancement of drug discovery technologies has led to an increasing number of highly lipophilic molecules with limited water solubility, thereby complicating formulation development and clinical success. It is estimated that a significant proportion of newly developed drug candidates exhibit poor solubility, resulting in erratic absorption and low oral bioavailability.

Several formulation techniques—such as particle size reduction, solid dispersion systems, cyclodextrin complexation, lipid-based formulations, and cosolvency—have been employed to address this challenge. However, each of these approaches carries inherent drawbacks, including limited drug loading, physical instability, potential toxicity, or high manufacturing costs.

Deep eutectic solvents (DESs) have recently emerged as innovative solvent systems capable of overcoming many of these limitations. DESs are prepared by combining a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD), leading to extensive hydrogen bonding interactions and a significant depression in melting point relative to the individual components. When drug molecules participate directly in eutectic formation, the resulting systems are referred to as therapeutic deep eutectic systems (THEDES).

This review critically discusses the role of DESs in enhancing the solubility of poorly water-soluble drugs, focusing on their physicochemical principles, solubilization mechanisms, formulation strategies, and challenges associated with pharmaceutical translation.

2. MATERIALS AND METHODS

(Review Methodology)

2.1 Literature Search Approach

A structured literature search was conducted using PubMed, ScienceDirect, SpringerLink, Google Scholar, and ACS Publications. Search terms included *deep eutectic solvents*, *therapeutic deep eutectic systems*, *drug solubility enhancement*, and *pharmaceutical applications of DES*.

2.2 Selection Criteria

Original research articles, systematic reviews, and experimental studies written in English were considered. Publications focusing exclusively on industrial, metallurgical, or non-biomedical uses of DESs were excluded.

2.3 Data Compilation and Interpretation

Relevant data regarding DES composition, solubility improvement magnitude, physicochemical characterization, biological safety, and formulation feasibility were extracted and analyzed qualitatively.

3. RESULTS

3.1 Pharmaceutical Classification of DESs

Based on their chemical composition, DESs employed in pharmaceutical research are generally classified into four types. Among these, Type III DESs—comprising quaternary ammonium salts (e.g., choline chloride) and hydrogen bond donors such as organic acids, polyols, and sugars—are the most widely investigated due to their relatively favorable safety profiles.

Natural deep eutectic solvents (NADES), formed from naturally occurring metabolites, have gained additional interest owing to their improved biocompatibility and environmental sustainability.

3.2 Mechanistic Basis of Solubility Enhancement

Multiple mechanisms contribute to the enhanced solubilization of drugs in DESs. These include strong hydrogen bonding between the API and DES components, reduction in drug lattice energy, and optimization of solvent polarity. In some systems, drugs exist in a micro-heterogeneous or colloidal state, which contributes to unusually high apparent solubility.

3.3 Evidence of Solubility Improvement

Numerous studies report dramatic solubility enhancement for drugs such as ibuprofen, curcumin, paclitaxel, rutin, and dapsone when formulated in DESs. In certain cases, solubility increases of several hundred-fold compared to water have been documented.

3.4 Influence of Water on DES Performance

The controlled addition of water to DESs significantly alters viscosity and solvent structure. Moderate hydration often improves drug solubility and processability; however, excessive water disrupts eutectic interactions, resulting in diminished solubilization capacity.

4. DISCUSSION

The findings reviewed herein indicate that DESs offer a highly adaptable and efficient approach for addressing solubility limitations of poorly water-soluble drugs. Their compositional flexibility enables rational design of solvent systems tailored to the molecular characteristics of individual APIs.

Nevertheless, several limitations must be addressed. Elevated viscosity can impede drug release and manufacturing operations. Toxicological behavior varies significantly depending on DES composition, underscoring the necessity for case-specific safety evaluations. Furthermore, ambiguity regarding regulatory classification of DESs—as excipients or active components—poses a substantial barrier to industrial adoption.

Future research should prioritize in vivo pharmacokinetic investigations, standardized toxicity assessments, and the development of regulatory frameworks to support pharmaceutical use of DES-based formulations.

4.1 Toxicological and Biocompatibility Considerations

Although deep eutectic solvents (DESs) are frequently described as environmentally friendly and biocompatible solvent systems, their toxicological profiles depend strongly on the nature and ratio of the constituent components. DESs composed of naturally occurring metabolites such as sugars, amino acids, and organic acids (commonly termed Natural Deep Eutectic Solvents – NADES) generally demonstrate improved safety compared with synthetic DESs.

Several in vitro studies have evaluated cytotoxicity using mammalian cell lines and demonstrated that DES systems based on choline chloride combined with glycerol, urea, or organic acids show relatively low toxicity at moderate concentrations. However, certain DES

formulations may exhibit increased membrane permeability or enzyme inhibition due to strong hydrogen bonding interactions with biomolecules. Consequently, systematic toxicological profiling—including cytotoxicity, hemocompatibility, and long-term exposure studies—is required prior to pharmaceutical application.

Furthermore, the presence of water significantly modifies DES physicochemical properties and may alter biological interactions. Hydrated DES systems often exhibit lower viscosity and improved diffusion properties, which may positively influence drug absorption.

4.2 Applications of DES in Advanced Drug Delivery Systems

Beyond simple solubilization, DESs are increasingly being investigated as multifunctional excipients in advanced drug delivery systems. Their tunable polarity and strong intermolecular interactions allow them to participate in the design of transdermal, topical, and oral delivery systems.

For example, DES-based formulations have been explored for:

- Transdermal drug delivery, where DESs act as penetration enhancers by disrupting lipid structures of the stratum corneum.
- Nanoformulations, including DES-assisted nanoparticle preparation and drug nanocrystal stabilization.
- Protein and peptide stabilization, where DESs provide protective microenvironments that reduce denaturation.
- Green extraction of bioactive compounds, enabling simultaneous extraction and formulation of plant-derived therapeutics.

In addition, therapeutic deep eutectic systems (THEDES), in which the active pharmaceutical ingredient (API) itself participates as a component of the eutectic mixture, offer a unique approach for improving both solubility and bioavailability.

4.3 Industrial and Regulatory Perspectives

Despite promising experimental findings, translation of DES-based drug formulations into pharmaceutical products faces several regulatory and manufacturing challenges. Regulatory agencies such as the FDA and EMA currently lack clear classification frameworks for DES-based excipients. It remains uncertain whether DES components should be evaluated individually or as novel chemical entities.

From an industrial perspective, challenges include:

- High viscosity affecting large-scale processing
- Lack of standardized preparation protocols
- Limited long-term stability data
- Absence of pharmacopeial monographs

Future research should therefore emphasize standardized safety testing, pharmacokinetic studies, and scalable manufacturing approaches. Establishing regulatory guidelines will be essential to facilitate commercialization of DES-based pharmaceutical formulations.

5. CONCLUSION

Deep eutectic solvents represent a promising and sustainable platform for improving the solubility of poorly water-soluble drugs. Their ability to enhance solubility through multiple physicochemical mechanisms distinguishes them from conventional approaches. Despite encouraging experimental evidence, comprehensive safety evaluation and regulatory clarification remain essential prerequisites for their successful clinical translation.

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