INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Deep Eutectic Solvents and Eutectogels: Emerging Green Platforms for Pharmaceutical Applications

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ARTICLE INFO

Published: 09 Sept 2026
Keywords:
Eutectogels, Green solvents, Novel controlled, Transdermal drug delivery, Hydrogen Bond Donor, Hydrogen Bond Acceptor.
DOI:
10.5281/zenodo.22673205

ABSTRACT

Pharmaceutical therapy is still based on conventional dosage forms such tablets, capsules, creams, and injections; however, many medications have poor water solubility, low bioavailability, limited permeability, and stability problems that lower therapeutic efficacy. Deep Eutectic Solvents (DESs) and eutectogels have emerged as novel and sustainable pharmaceutical systems to overcome these constraints. Hydrogen bond donors and acceptors are combined to create DESs, which are liquids with special physicochemical characteristics that improve drug solubility, stability, and formulation flexibility. DESs are less expensive, simpler to manufacture, and frequently more environmentally better than traditional organic solvents. The benefits of both DESs and conventional gels are combined in eutectogels, which are created by integrating DESs into a three-dimensional gel network. Better drug loading, regulated drug release, increased penetration, and higher mechanical stability are all provided by these methods. As a result, eutectogels have drawn a lot of interest for applications involving topical, transdermal, and controlled drug administration. Additionally, by lowering the reliance on dangerous solvents in pharmaceutical production, DES-based formulations are consistent with green chemistry principles which demonstrates the potential of DESs and eutectogels as next-generation drug delivery vehicles, despite obstacles like toxicity assessment, regulatory approval, and large-scale production still existing. This review dives into the properties, preparation, applications of DESs and eutectogels.

INTRODUCTION

Deep Eutectic Solvents (DESs) are a potential class of green solvents because of their superior solubilizing capacity, simplicity in manufacture and adjustable physicochemical characteristics. Most pharmaceutical DESs and eutectogels are designed with biodegradable components and low

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

toxicity, which reduces the risk of soil contamination and the potential environmental impact compared to conventional solvents. Recently, eutectogels have been developed by incorporating DESs into gel matrices, combining the structural advantages of gels and DESs. These systems are attractive for pharmaceutical applications because of the higher drug loading, higher permeability and controlled drug release. This paper which discusses the principles, preparation methods, applications and possible future developments of DESs and eutectogels in drug delivery.

2. DEEP EUTECTIC SOLVENTS (DESs)

A liquid produced by combining two solid ingredients is called a deep eutectic solvent (DES) which is illustrated in Figure 1. Due of the significant melting point drop brought on by combining hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) molecules, DES research is gathering a lot of attention, especially in DESs that are liquids over a broad temperature range [1,2].

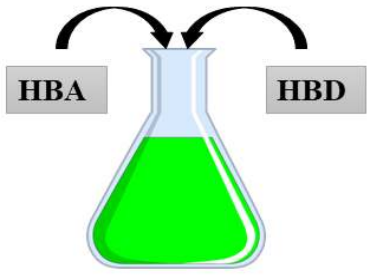

Figure 1. Deep Eutectic Solvent

2.1 Green Solvents

Deep eutectic solvents (DESs) are considered as a new generation of green solvents due to their unique properties such as simple synthesis, low cost, environmentally friendly, low volatility, high dissolution power, high biodegradability and feasibility of structural design.

2.2 Components Of Deep Eutectic Solvents

A hydrogen-bond donor (HBD) and a hydrogen-bond acceptor (HBA) are two of the components that combine to make the new and developing family of green solvents known as deep eutectic solvents (DESs). Table 1 lists a number of DES components. These components have high hydrogen-bond interactions when combined in specific molar or mass ratios, which significantly lowers the mixture's melting point relative to the separate components. As a result, a liquid phase that is much below the melting temperatures of the constituent parts is created.

Table 1. Commonly used HBD and HBA.

Hydrogen Bond Acceptors	Hydrogen Bond Donors
Choline chloride	Urea
Betine	Acetamide
Glycine	Oxalic acid
Proline	Glucose
Nicotinic acid	Lactic acid
Zinc chloride	Ethylene glycol

2.3 Types Of DESs

Based on the characteristics of HBD and HBA components, DESs have been divided into five categories [3-6] and is listed in Table 2.

Table 2. Types of DESs and examples

Types	Expression (HBD + HBA)	Components	Examples
Type I	$Cat^+X^- + MX_y$	Quaternary ammonium salt (Cat^+X^-) and anhydrous metal halides (MX_y).	Choline chloride and aluminium chloride/ zinc chloride.
Type II	$Cat^+X^- + MX_y.nH_2O$	Quaternary ammonium salt (Cat^+X^-) and hydrated metal halides ($MX_y.nH_2O$).	Choline chloride and Chromium chloride hexahydrate.
Type III (pharmaceutical use)	$Cat^+X^- + RZ$	Quaternary ammonium salt (Cat^+X^-) and molecular hydrogen bond donors (RZ).	Choline chloride and urea, glycerol, sugars or organic acids.
Type IV	$MX_y + RZ$	Metal halides (MX_y) and organic hydrogen bond donors (RZ).	$ZnCl_2$ or $FeCl_3$ and ethylene glycol or urea.
Type V (pharmaceutical use)	$RZ + RZ'$	Neutral organic molecules, neither ionic salts nor metals, contain organic molecules.	Urea and acetamide.

Only Types III and V of the five categorized types of deep eutectic solvents have become widely used in pharmaceutical applications; Types I, II, and IV continue to play a minor role in pharmaceutical development. Active pharmaceutical ingredients (APIs) have been dissolved using Type III and V DESs [7-12]. Drug delivery has also made use of these kinds of DESs [13-17]. DESs have also been used in drug formulation as environmentally friendly solvents to dissolve APIs that are poorly soluble in water, as well as vehicles for the extraction of phytochemicals and the creation of medicinal products. Natural deep eutectic solvents (NADES) made from food-grade or metabolite components, like choline chloride mixed with sugars, polyols, or organic acids, have shown a remarkable ability to solubilize pharmaceutical ingredients and bioactive compounds while maintaining low cytotoxicity and good biocompatibility, making them appropriate as excipients in oral and transdermal formulations [18-22].

2.4 Natural Deep Eutectic Solvents (NADES)

NADES are biocompatible deep eutectic solvents solely composed of natural metabolites and are sustainable alternatives to the conventional solvents.

2.5 Therapeutic Deep Eutectic Solvents (Thedes)

THEDES are deep eutectic solvents where at least one of the components is an Active Pharmaceutical Ingredient (API) or a therapeutically active compound that forms a eutectic mixture with improved pharmaceutical properties, such as solubility, permeability, stability and bioavailability. Example: Lidocaine + Menthol → Lidocaine is the API.

2.6 Methods Of Preparation [22-24]

1. **Thermal mixing method (Traditional heating)**: HBA and HBD are stirred and heated (50-100°C) until a clear homogeneous liquid is formed. Easy, no solvent method but not for thermolabile compounds.

2. **Method of Vacuum Evaporation**: Components are dissolved in a volatile solvent, and the solvent is removed under reduced pressure. Good for volatile or heat sensitive materials. Moisture control is important.
3. **Solvent-Assisted (Co-solvent) Method**: A little water or ethanol is added to help in solubility and mixing of components. Then the solvent is evaporated to get a homogeneous DES.
4. **Ultrasound assisted method**: Ultrasonic waves promote the molecular diffusion and hydrogen-bond interactions. Offers faster and more efficient DES formation than conventional mixing.
5. **Mechanochemical method (Ball milling/Grinding):** DES are obtained by mechanical grinding of HBA and HBD in the absence of solvent. Eco-friendly, suitable for moisture-sensitive compounds.
6. **Microwave-Assisted Synthesis**: Microwave irradiation enables rapid and homogeneous heating of DES components. Reduces reaction preparation time and improves synthesis efficiency.

2.7 Characteristics Of DESs

1. **Phase Diagram**: Phase diagrams are used to determine the eutectic point (EP) which is the point with the minimum melting temperature of the mixture for example, Choline Chloride: urea (1:2) forms a DES with an EP of 12 °C [25].
2. **Melting point:** DESs have melting points much lower than their individual components due to strong hydrogen-bond interactions. For example, Choline Chloride: phenol (1:3) has an EP of −20 °C [26].
3. **Density:** The density of DESs is usually higher than water and it decreases with the increase of temperature depending on the nature of HBAs and HBDs [27].
4. **Viscosity:** Most DESs have high viscosities compared to ILs because of extensive hydrogen-bond networks, but some systems like Choline Chloride: Ethylene Glycol have low viscosity.
5. **Conductivity:** DESs have lower electrical conductivity compared to ILs. This is because the non-conductive HBD components dilute the ionic species.

2.8 Routes Of Delivery

1. **Intravenous (IV) Drug Delivery:** THEDES can enhance the stability, solubility, and bioavailability of drugs used in IV infusion. They enable rapid and efficient delivery of poorly soluble drugs into the bloodstream [28].
2. **Implantable Drug Delivery Systems:** THEDES can be incorporated into implants to improve sustained drug release and therapeutic efficacy. They help maintain prolonged drug action for long-term treatment [29,30].
3. **Intramuscular (IM) Drug Delivery:** THEDES-based injectable formulations can improve drug stability, solubility, and controlled release. They provide prolonged therapeutic effects through sustained drug absorption [31].
4. **Subcutaneous (SC) Drug Delivery:** THEDES can enhance the solubility, stability, and prolonged release of drugs administered subcutaneously. They support improved absorption of drugs delivered beneath the skin [32-34].
5. **Eye Drug Delivery:** THEDES may enhance drug retention, penetration and sustained-release in ocular tissues. They can enhance ocular bioavailability and reduce the frequency of administration [35-37].

6. **Vaginal Delivery of Drugs:** A THEDES with metronidazole has been developed for intravaginal use in the treatment of bacterial vaginosis. PCL (polycaprolactone) matrix showed better onset of action and controlled drug release up to 7 days showing advantages over oral therapy [55].

2.9 Pharmaceutical Applications

1. **Tuberculosis:** Encapsulation of L-arginine-based THEDES matrices in lipidic structures such as glycerol monostearate using green supercritical CO_2 fluid technology. These micro-sized formulations prepared by Particle from Gas Saturated Solution (PGSS) methods exhibit high encapsulation efficiency and faster drug release profiles [39,40].
2. **Cancer:** THEDES are used to create anticancer nano-systems by combining lipids, synthetic polymers or natural terpenes (menthol) with drugs. These strategic combinations result in synergistic antiproliferative effects and low toxicity compared with conventional therapies [41,42].
3. **Microbial Infections:** Combining known antimicrobial agents like benzalkonium chloride with acrylic or methacrylic acids in deep eutectic solvents results in enhanced overall pathogen inhibition. This unique eutectic formulation efficiently manages and optimizes the drug release characteristics, offering novel approaches for antimicrobial treatment [43,44].
4. **Hepatotoxicity:** To get over significant biopharmaceutical restrictions, silymarin is synthesized into solid dispersion eutectic combinations using poly-vinylpyrrolidone K30 (PVP K30). The anti-inflammatory and hepatoprotective properties of the active component are enhanced by this architecture, which effectively produces a significant five-fold increase in drug solubility [45].

3. EUTECTOGELS

Eutectogels are something new that is being talked about as a type of soft material that is made out of eutectic solvents and polymeric gel network. Eutectogels are defined as gels in which the liquid phase is composed of deep eutectic systems (DESs) or natural deep eutectic systems (NADESs). These materials have unique properties because of their eutectic components, hydrogen bond acceptors and donors that are mixed together. The resulting gels take the benefits of DESs like; low volatility, biodegradable, soluble to a wide variety of chemicals, and possibly biocompatible [46]. Eutectogel 3D network is illustrated in Figure 2 [47].

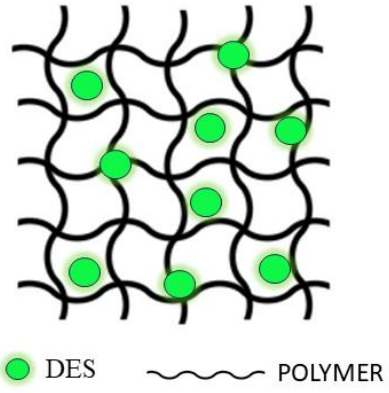

Figure 2. Eutectogel 3D Network

3.1 Types Of Eutectogels

It can be categorized as polymeric eutectogels, supramolecular eutectogels and biopolymer-based eutectogels depending on the network forming material. Polymeric eutectogels are made from synthetic polymers as gel matrix [48,49], supramolecular eutectogels are made by self-assembly driven by non-covalent interactions and biopolymer-based eutectogels are made from natural polymers such as chitosan, alginate, cellulose, starch, gelatin, agarose, dextran and silk fibroin [50]. According to the crosslinking

mechanism, eutectogels can be divided into chemically crosslinked eutectogels including permanent covalent networks endowing them with high stability and mechanical strength, and physically crosslinked eutectogels stabilized through hydrogen bonding, electrostatic interactions or other supramolecular forces [51]. Eutectogels can be homogeneous with uniform network structure and ionic distribution, or heterogeneous with phase-separated or templated architectures and compartmentalized properties, depending on their structure. Based on the function of the deep eutectic solvent (DES), the eutectogels are divided into solvent-type eutectogels, in which the DES is merely the solvent in the gel network, and monomer-derived eutectogels, in which the DES acts as both solvent and reactive monomer in the process of gel formation.

3.2 Characteristics Of Eutectogels

1. High mechanical strength, toughness, flexibility, and stretchability [52,53].
2. Excellent moisture absorption and water-retention properties [54].
3. Good ionic and electrical conductivity suitable for biosensors and drug delivery systems [55,56].
4. Anti-freezing behavior and stability at sub-zero temperatures [54].
5. Biocompatibility, low cytotoxicity, particularly when prepared using NADES [57].
6. Self-healing capability due to reversible hydrogen-bond interactions [52].

3.3 Development Of Eutectogels Using Various Polymers

Synthetic Polymers

1. Polyvinyl alcohol (PVA) [58]
2. Polyacrylic acid (PAA/AA) [59]
3. Polyacrylamide (PAM) [60]

Natural Polymers

1. Sodium alginate (SA) [54]
2. Cellulose and bacterial cellulose [61,62]
3. Chitosan [63]
4. Gelatin [57]
5. Xanthum gum [64]

3.4 Methods Of Preparation

1. **Free Radical Polymerization:** DES, monomers, and initiators are mixed and polymerized using UV light or heat to create eutectogels [58,59].
2. **Solvent exchange method:** hydrogels are made first and then soaked in DES to substitute water [65,66].
3. **Ion exchange method:** Crosslinking is done by ion substitution where Ca^{2+} typically replaces Na^{+} in alginate systems [54,67].
4. **One-Pot Preparation:** Addition of everything in one pot and transform it in eutectogels [53,68,69].
5. **Freeze Thaw Method:** both freezing and thawing in repeated cycles produce eutectogels [70,71].

3.5 Pharmaceutical Applications Of Eutectogels

1. **Topical and Transdermal Drug Delivery:** Improve drug solubility, skin penetration, and prolonged release of active pharmaceutical ingredients [72,73].
2. **Wound Healing and Tissue Repair:** Keep the area moist, promote tissue regeneration, and preserve bioactive molecules [74,75].
3. **Oral and Buccal Mucoadhesive Drug:** Delivery Enhance drug solubility, mucoadhesion, and bioavailability at mucosal surfaces [76].
4. **Nanomedicine and Targeted Drug Delivery:** Enhance drug encapsulation,

stability, and controlled release using nanogel systems [77,78].

3.6 Key Challenges Of Eutectogels [79]

1. **Low Conductivity:** Eutectogels display low conductivity compared to DESs in the liquid state, restricting their widespread applications.
2. **Weak Mechanical Properties:** Most synthesized eutectogels exhibit low mechanical strength (in the kP_a range), necessitating the need for more robust materials.
3. **Moisture Susceptibility:** The hygroscopic nature of DESs due to extensive hydrogen bonding makes them vulnerable to moisture, affecting weatherability and performance.
4. **Small Voltage Window:** Moisture absorption in eutectogels adversely affects their electrochemical properties, reducing their voltage window.
5. **Necessity of Greener Polymers:** There is an urgent need to replace harmful polymers (polyacrylic acid and polyacrylamide) with green polymers (polylactic acid and polyvinyl alcohol).
6. **Restrictive Variety of HBAs:** Most eutectogels rely on the use of ChCl as the hydrogen bond acceptor, and other types of HBAs have not been explored much.
7. **Inadequate Research on Metal Salt Eutectogels:** The use of different metal salts (LiCl, $ZnCl_2$, $FeCl_3$, and others) as HBAs to synthesize eutectogels that can provide improved conductivity needs more attention.

FUTURE OUTLOOK

DESs and eutectogels can be considered prospective green platforms for pharmaceutical development in the future due to their excellent biocompatibility, versatile properties, and capacity to increase drug solubility and delivery. The main objectives of future studies may involve the investigation of the long-term safety of these substances and further enhancement of formulation approaches as well as application in targeted delivery, nanomedicine, regenerative medicine, and other sophisticated areas.

CONCLUSION

Deep eutectic solvents and eutectogels are new generations of eco-friendly pharmaceutical compounds. The exceptional properties of these substances that consist in the ability to increase drug solubility, stability, permeation, and release make them promising materials for modern pharmaceutical practice. Further efforts can be devoted to the overcoming of the existing limitations in terms of toxicity, scalability, and regulatory acceptance of these materials.

Declaration Of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors sincerely thank all contributors who supported this work.

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HOW TO CITE: Senthil Prabhu R, Varshini K, Yogashruthi S, Deep Eutectic Solvents And Eutectogels: Emerging Green Platforms For Pharmaceutical Applications, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 9, 914-926, https://doi.org/10.5281/zenodo.22673205