



Contents lists available at Journal of Pharmacological Horizons

Journal of Pharmacological Horizons

Journal homepage: www.lakshmi Biosciences.com

REVIEW ARTICLE

Deep Eutectic Solvents in Pharmaceutical Drug Delivery: Structure–Property Relationships, Mechanistic and Computational Insights, and Translational Challenges

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ARTICLE HISTORY

OPEN ACCESS

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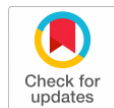
RECEIVED 05 June 2026

REVISED 01 July 2026

ACCEPTED 13 July 2026

PUBLISHED 30 July 2026

DOI: <https://doi.org/10.67796/jph.v1i1.7>



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Abstract: Volatile organic solvents remain central to pharmaceutical extraction and formulation despite well-documented toxicity, flammability, and regulatory limits on residual-solvent content. Deep eutectic solvents (DESs) liquid systems formed when a hydrogen-bond acceptor (HBA) and a hydrogen-bond donor (HBD) combine to produce a eutectic mixture with a melting point far below that of either parent component have emerged as tunable, low-cost, and often biodegradable alternatives with growing relevance to drug delivery. This review synthesises current knowledge on DES classification (Types I–V), natural, therapeutic and hydrophobic subclasses, structural hydrogen-bonding chemistry, and the six principal preparation routes (hot-melt extrusion, conventional heating, vacuum evaporation, grinding, freeze-drying, and ultrasound-/microwave-assisted synthesis). Fourteen representative DES systems are examined in terms of structure–property relationships, and the density, viscosity, polarity, and surface-tension behaviours of DESs are related to their hydrogen-bonding architecture. The review evaluates DES integration into polymeric drug carriers (hydrogels, nanoparticles, electrospun fibres, films, and scaffolds), oral bioavailability enhancement for Biopharmaceutics Classification System (BCS) Class II/IV drugs, and self-assembled DES-based nanomicelles for transdermal delivery. Mechanistic contributions membrane fluidisation, polymer plasticisation, supersaturation maintenance, mucoadhesion, and nanocarrier stabilisation are discussed alongside computational approaches (molecular dynamics, density functional theory, and COSMO-RS) that rationalise these effects. DES- and THEDES-based platforms offer a compositionally flexible, often GRAS-compatible strategy for solubility and permeability enhancement, but translation is constrained by unpredictable DES–polymer interactions, regulatory ambiguity around eutectic mixtures as novel excipients, and a scarcity of in vivo pharmacokinetic and long-term toxicological data. Closing these gaps through standardised characterisation, computational screening, and harmonised regulatory frameworks will be essential for clinical translation.

Keywords: Deep eutectic solvents; natural deep eutectic solvents; therapeutic deep eutectic systems; drug delivery; oral bioavailability; transdermal permeation; polymeric drug carriers; green chemistry.

1. INTRODUCTION

Over the past two decades, deep eutectic solvents (DESs) have evolved into a highly promising class of designer solvents that bridge green chemistry, materials science, and pharmaceutical engineering. Extraction and formulation processes have traditionally relied on volatile organic solvents such as methanol, ethanol, chloroform, dichloromethane, and n-hexane. While effective, these solvents are associated with toxicity, flammability, environmental persistence, limits on residual-solvent content in finished pharmaceutical products [1,2,30]. Growing environmental awareness, tighter regulatory frameworks, and global sustainability initiatives have intensified the search for safer, greener alternatives [31]. DESs were first systematically defined in 2003 as eutectic mixtures formed by combining a hydrogen-bond acceptor (HBA) with a hydrogen-bond donor (HBD); the resulting liquid has a melting point dramatically lower than that of either component alone [1]. The archetypal example is choline chloride and urea at a 1:2 molar ratio: both components individually possess high melting points, yet the mixture melts at approximately 12 °C. This depression arises because hydrogen-bonding interactions and charge delocalisation within the newly formed supramolecular structure disrupt the ordered crystalline lattice that would otherwise stabilise the solid state [1]. Unlike conventional solvents, which consist of a single defined molecular species, DESs are built around a dynamic, structured hydrogen-bonding network; their behaviour therefore arises from cooperative molecular interactions rather than from an individual compound. A defining feature of DES chemistry is tunability: viscosity, polarity, density, electrical conductivity, and solvation capacity can be adjusted by varying the HBA/HBD pair, their molar ratio, or the water content of the system. This flexibility enables researchers to design DESs for specific pharmaceutical or extraction applications, a capability that underlies the emergence of natural deep eutectic solvents (NADESs) systems composed entirely of naturally occurring metabolites such as sugars (glucose, fructose), amino acids (proline), organic acids (citric acid, lactic acid), and polyols (glycerol) [2].

Because their components are biologically derived, NADESs are particularly attractive for pharmaceutical and nutraceutical use: they generally show improved biocompatibility, minimal volatility, and lower cytotoxicity than many ionic liquids [34]. From a formulation standpoint, DESs offer several concurrent advantages: enhanced solubilisation of poorly water-soluble drugs; improved extraction efficiency for bioactive phytochemicals; modulation of drug-release kinetics within polymeric matrices; permeability enhancement across

biological membranes; and, in some designs, direct incorporation of the active pharmaceutical ingredient (API) into the solvent structure itself.

This last capability underlies therapeutic deep eutectic solvents (THEDES), in which the API itself becomes part of the eutectic mixture, functioning simultaneously as a structural component of the solvent and as the therapeutic agent [3]. This strategy departs from the conventional use of pharmacologically inert solvents and excipients: by incorporating the API directly into the eutectic network, THEDES formulations can enhance solubility, improve physicochemical stability, and increase bioavailability, often without additional solubilising excipients.

The application space of DESs has expanded considerably beyond extraction chemistry into advanced drug-delivery technology. In oral delivery, DESs enhance the dissolution and intestinal permeability of poorly soluble drugs, particularly those in BCS Classes II and IV [4], addressing one of the most persistent bottlenecks in oral formulation science. In transdermal delivery, amphiphilic DESs self-assemble into reverse nanomicellar architectures that promote deeper skin penetration and support controlled, sustained drug release [5].

Despite this progress, several practical challenges constrain translation: manufacturing scalability, control of the characteristically high viscosity of many DES systems, long-term physicochemical stability, and comprehensive toxicological evaluation remain open questions, as does regulatory clarity for DES-based excipients. This review therefore aims to (i) consolidate current understanding of DES classification, structural chemistry, and preparation methods; (ii) relate the physicochemical behaviour of representative DES systems to their pharmaceutical performance; (iii) critically evaluate DES-enabled polymeric, oral, and transdermal delivery platforms and their underlying mechanisms; and (iv) identify the regulatory, safety, and scale-up gaps that must be addressed to advance DES-based technologies toward clinical use.

Several recent reviews have addressed DES classification, extraction chemistry, or a single delivery route in isolation. The present review differs in scope: it is, to our knowledge, among the first to integrate structure–property analysis of fourteen representative DES systems with a mechanistic account of DES-mediated solubilisation and permeability enhancement, a dedicated evaluation of computational approaches (molecular dynamics, density functional theory, and COSMO-RS) that rationalise these mechanisms, and a cross-cutting assessment of DES performance across polymeric, oral, and transdermal delivery platforms within a single translational framework. By explicitly linking

hydrogen-bonding architecture to physicochemical behaviour and, in turn, to pharmaceutical performance and regulatory status, this review aims to provide formulators with a more mechanistic and decision-oriented basis for DES selection than is available in the existing literature.

2. CLASSIFICATION AND STRUCTURAL CHEMISTRY OF DEEP EUTECTIC SOLVENTS

2.1 General Classification

DESs are commonly categorised into five types according to the chemical nature of their constituents [1,2,93] (Table 1). Type III DESs have received the greatest attention in pharmaceutical and food applications because of their comparatively low toxicity and good biological compatibility [1]. These formulations are typically biodegradable, inexpensive, and readily available, most commonly pairing choline chloride with urea, glycerol, lactic acid, or related

organic acids; this favourable safety and cost profile makes Type III systems the preferred starting point for translational work [6].

2.2 Natural Deep Eutectic Solvents (NADESs)

NADESs are a biologically inspired DES subclass composed entirely of primary metabolites found in living systems [2,41]. They have been proposed to function as alternative intracellular solvent environments that help organisms particularly plants solubilise and stabilise otherwise poorly water-soluble compounds and are thought to mimic physiological conditions more closely than conventional solvents. Representative NADES pairings include choline chloride with glucose, proline with malic acid, citric acid with fructose, and betaine with glycerol [7]. Their enhanced biocompatibility makes NADESs particularly attractive for pharmaceutical extraction, nutraceutical formulation, and transdermal applications.

Table 1. General classification of deep eutectic solvents.

Type	General composition	Representative example
I	Quaternary ammonium salt + metal chloride	Choline chloride + ZnCl ₂
II	Quaternary ammonium salt + hydrated metal chloride	Choline chloride + CoCl ₂ ·6H ₂ O
III	Quaternary ammonium salt + hydrogen-bond donor	Choline chloride + urea, glycerol, or an organic acid
IV	Metal chloride + hydrogen-bond donor	ZnCl ₂ + urea
V	Non-ionic hydrogen-bond donor–acceptor systems	Thymol + menthol

2.3 Therapeutic Deep Eutectic Solvents (THEDES)

THEDES systems incorporate the API directly into the eutectic mixture, where it functions as either the HBA or the HBD [8]. This integration can increase apparent solubility, reduce crystallinity, enhance permeability, and improve thermal stability. Typical THEDES formulations combine nonsteroidal anti-inflammatory drugs (NSAIDs) with choline chloride or selected organic acids; the strong supramolecular hydrogen bonding within these systems disrupts the drug's rigid crystalline lattice, lowering lattice energy so that the solid-state drug becomes less tightly packed, which in turn

promotes improved dissolution and potentially greater bioavailability.

2.4 Hydrophobic Deep Eutectic Solvents (HDES)

While most DESs are hydrophilic, hydrophobic DESs (HDES) have been developed specifically to improve the solubility of lipophilic compounds [9], commonly pairing menthol with fatty acids, or thymol with decanoic acid. HDES systems are particularly relevant to transdermal delivery because their lipophilic character improves compatibility with stratum corneum lipids.

2.5 Structural Chemistry and Hydrogen-Bonding Network

The defining feature of DES chemistry is an extensive hydrogen-bonding network: the HBA (commonly a quaternary ammonium salt such as choline chloride) interacts with the HBD through strong hydrogen bonding, disrupting the individual crystalline structures of both components, reducing lattice energy, delocalising charge, and forming a stable supramolecular liquid. Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and molecular dynamics simulations have consistently shown that the strength and spatial arrangement of these hydrogen bonds govern key DES properties, with viscosity, polarity, and solvation capacity all directly influenced by how the intermolecular network is organised [10,32]. Water content exerts a further regulatory effect on DES behaviour. Small additions of water can substantially lower viscosity and improve mass transfer, which is beneficial for extraction and formulation processing; however, excess water can weaken or disrupt the hydrogen-bonding network that defines the DES, altering and in extreme cases eliminating its characteristic identity and performance [11].

3. Preparation Methods of Deep Eutectic Solvents

DESs can be prepared using several complementary methods, each offering distinct advantages in yield, scalability, and compatibility with thermolabile components.

3.1 Hot-Melt Extrusion

Hot-melt extrusion (HME) transforms solid starting materials into uniform, continuous extrudates through the combined application of heat, pressure, and mechanical shear, and is particularly attractive for scale-up within continuous manufacturing frameworks. Crawford et al. reported a production rate of approximately 6 kg/h for a Type III DES (choline chloride:urea, 1:2) using a twin-screw extruder, with a space-time yield nearly four orders of magnitude higher than that achieved by conventional heating and stirring [12]. HME has also been used to produce a therapeutic DES based on metronidazole and maleic acid for intravaginal administration [13]; however, the literature currently lacks studies applying extrusion-based DES manufacture to solid oral dosage forms a clear gap for future process development.

3.2 Heating Method

Conventional heating remains the most widely used DES preparation technique: components are mixed and stirred at controlled temperature until a clear, homogeneous liquid forms. Its simplicity, minimal equipment requirements, and low cost make it especially popular at laboratory scale. Optimal preparation temperatures are typically below 100 °C, most often in the 80–90 °C range [14]; both temperature and heating–stirring duration must be carefully controlled, since insufficient temperature or processing time can leave components incompletely interacted, favouring unwanted crystal formation [15]. Continuous stirring for approximately 8–12 h is usually required to achieve complete dissolution and a stable hydrogen-bonded network.

3.3 Vacuum Evaporation

The solvent-assisted vacuum-evaporation method, first described by Dai et al. [16], dissolves the HBA and HBD in a suitable solvent most commonly water after which the solvent is removed by rotary evaporation at approximately 50 °C, and the resulting liquid is further dried over silica gel to constant weight. Although this route facilitates uniform molecular-level mixing, it carries the practical limitations of low overall yield and a comparatively time-consuming process. A representative example is the preparation of the choline-and-geranic-acid eutectic system (CAGE): choline bicarbonate (80% solution) is added to purified geranic acid (1:2 molar ratio) and stirred overnight at 40 °C; water is removed by rotary evaporation (60°C,2h) followed by vacuum-oven drying (60°C,48h). The API is then incorporated into a measured volume of CAGE and solubilised by sonication or stirring, yielding a system suitable for oral drug-delivery development [17].

3.4 Grinding Method

Neat grinding combines the selected components in a defined molar ratio and mechanically grinds them manually with a mortar and pestle, or by high-energy milling until a uniform liquid forms, relying on mechanical rather than thermal energy to drive HBA–HBD interaction. Florindo et al. [18] observed that simple room-temperature grinding was, in some cases, more effective than conventional heating at lowering the viscosity of the resulting DES and reported improved tunability when the HBA:HBD molar ratio was varied. The approach nonetheless carries limitations, including relatively low product yield, undesirable temperature rise during high-energy milling, and practical difficulty in handling hygroscopic materials; for these reasons, neat grinding is

generally considered less scalable than solvent-assisted vacuum evaporation.

3.5 Freeze-Drying

Freeze-drying (lyophilisation) is a scalable but comparatively time-consuming route in which each component is first dissolved separately in water at the desired molar ratio, the solutions are combined, and the mixture is frozen and subsequently dried under reduced pressure to yield a clear, viscous liquid. Zhang et al. reported that conventional heating suits liquid acids best, whereas freeze-drying is preferable for thermally sensitive or unstable components, and that systems with multiple hydrogen-bond donors (carboxyl or hydroxyl groups) may perform better when dried by freeze-drying or rotary evaporation rather than direct heating [19]. Gutierrez et al. further demonstrated that DESs prepared by freeze-drying aqueous component solutions preserved the structural and functional properties of incorporated preformed liposomes, highlighting the potential of freeze-dried DESs as solid platforms for advanced drug-delivery systems [20]. While not typically the first-line method, freeze-drying therefore offers clear advantages for composite delivery systems involving thermosensitive actives.

3.6 Ultrasound- and Microwave-Assisted Methods

NADESs prepared by alternative energy-assisted techniques generally show properties comparable to those obtained by conventional methods, but ultrasound-assisted (UA) and microwave-assisted (MA) routes are markedly faster and more energy-efficient. In ultrasonic preparation, high-frequency sound waves generate cavitation bubbles whose collapse releases localised energy that accelerates HBA–HBD interaction; sonication is typically applied for at least 30 min, or in shorter repeated cycles until a uniform liquid forms. Microwave-assisted synthesis instead exploits dipole rotation and rapid molecular collisions under microwave irradiation,

forming the eutectic mixture within a very short time depending on applied power and stirring; energy consumption can be up to 650-fold lower than conventional heating [21,22]. Both techniques require careful temperature control when thermally sensitive components amino acids or sugars, for example are involved, since overheating can compromise starting-material stability.

4. REPRESENTATIVE DEEP EUTECTIC SOLVENT SYSTEMS: STRUCTURE–PROPERTY RELATIONSHIP

To ground the classification above in concrete chemistry, this section examines fourteen representative DES systems spanning hydrophilic, hydrophobic, natural, and metal-salt-based classes, relating each pairing's hydrogen-bonding or coordination chemistry to its measured physicochemical behaviour and principal application domain.

4.1 Reline (Choline Chloride–Urea, 1:2)

Reline is the landmark DES, first reported by Abbott et al. in 2003 and still the benchmark for the field [23]. Choline chloride (ChCl) melts at 302 °C and urea at 133 °C, yet their 1:2 mixture is liquid at just 12 °C. This depression reflects strong N–H···Cl[−] hydrogen bonds between urea's two amino groups and the chloride anion of ChCl, producing a stable [Cl(urea)₂][−] complex that disrupts both crystal lattices simultaneously. Reline is non-toxic and biodegradable and supports applications ranging from metal dissolution to pharmaceutical excipient work; its principal limitation is a moderate viscosity (~750 cP at 25 °C) that slows mass transfer. It remains the most extensively studied DES owing to its low cost, biodegradability, and broad applicability in extraction, catalysis, and electrochemistry.

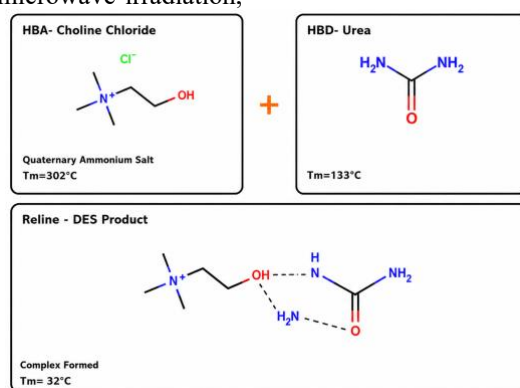


Fig. 1. Molecular structure of Reline (choline chloride:urea, 1:2). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

4.2 Glyceline (Choline Chloride–Glycerol, 1:2)

Glycerol's three hydroxyl groups make it an unusually effective hydrogen-bond donor, producing one of the deepest eutectic depressions in the ChCl family the mixture remains liquid down to -40°C through a dense, interlocking $\text{Cl}\cdots\text{H}-\text{O}$ network [24]. Glyceline is entirely non-toxic, since glycerol is both a food ingredient and a biodiesel by-

product, but this comes at the cost of very high viscosity (~ 376 cP even at 40°C) and low conductivity. It is well suited to biocatalysis, as lipases and other enzymes remain active within it, and functions as a biocompatible cryoprotectant medium in which DNA and proteins are stable a distinctive feature among DES solvents. Principal applications include biomass processing, enzymatic reactions, and green synthesis.

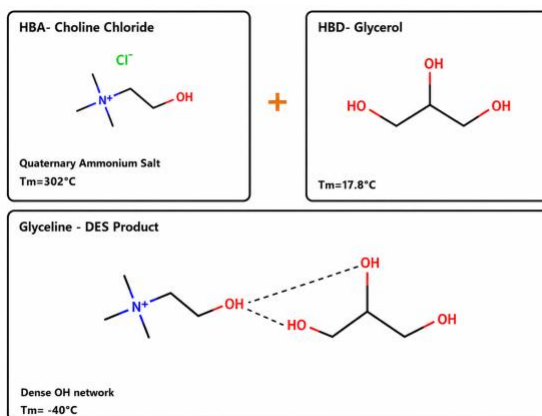


Fig. 2. Molecular structure of Glyceline (choline chloride: glycerol, 1:2). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

4.3 Ethaline (Choline Chloride–Ethylene Glycol, 1:2)

Ethylene glycol carries only two hydroxyl groups and a shorter carbon chain than glycerol, making Ethaline considerably less viscous (~ 37 cP at 25°C) and far more conductive (~ 7.6 mS/cm at 25°C) than its glycerol counterpart [25]. This favours electrochemical applications, particularly electrodeposition of zinc, copper, and silver,

where ionic mobility is critical. Its eutectic melting point (approximately -66°C) is the deepest in this series, reflecting clean, efficient hydrogen-bond donation by ethylene glycol. Because ethylene glycol is moderately toxic it is a major component of automotive antifreeze Ethaline is less suitable than Glyceline or Reline for biomedical applications; its principal uses lie in metal processing, electrodeposition, and CO_2 absorption.

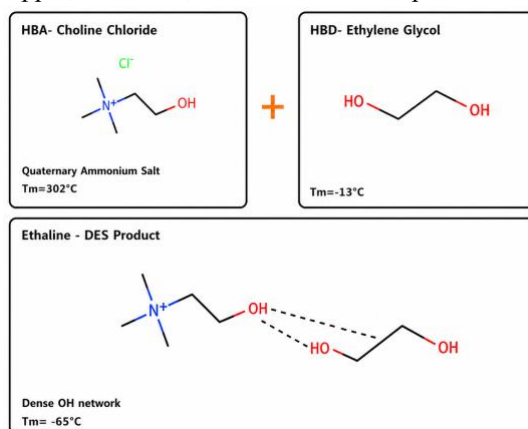


Fig. 3. Molecular structure of Ethaline (choline chloride: ethylene glycol, 1:2). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

4.4 Oxaline (Choline Chloride–Oxalic Acid)

Oxaline is a strongly acidic DES, with solution pH reaching as low as 1–2 [26]. Oxalic acid's two carboxyl groups, positioned on a very short two-carbon chain, both donate strongly to Cl^- , forming tightly bound ion clusters. The resulting DES dissolves metal oxides (Fe_2O_3 , CuO , ZnO) effectively without requiring mineral acids such as HCl or

H_2SO_4 , offering a greener alternative for hydrometallurgical leaching and rust or scale removal. Its 1:1 stoichiometry (rather than the 1:2 ratio typical of most ChCl systems) reflects the stronger acid–base interaction between the components. Viscosity is high, but oxide-dissolving performance exceeds that of most other DES systems; oxalic acid itself occurs naturally in rhubarb and spinach.

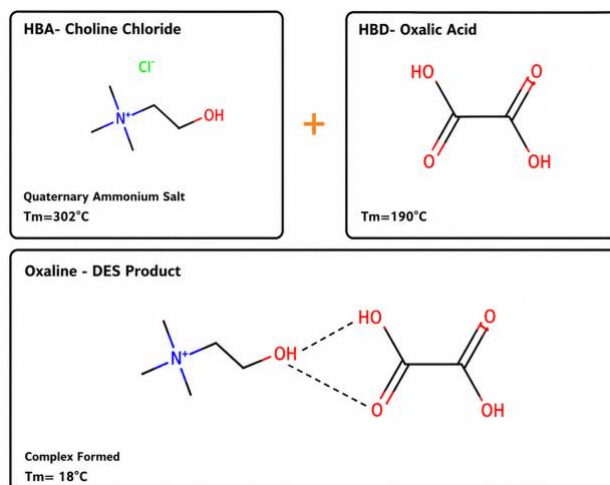


Fig. 4. Molecular structure of Oxaline (choline chloride:oxalic acid). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

4.5 Maline (Choline Chloride–Malonic Acid)

Malonic acid (propanedioic acid) shares the two $-\text{COOH}$ groups of oxalic acid but adds a $-\text{CH}_2-$ methylene spacer that confers greater rotational flexibility [27]. This structural difference produces a somewhat less acidic DES (pH ~2–4, concentration-dependent) with a lower melting point (~10 °C)

than Oxaline; the $-\text{CH}_2-$ bridge also allows conformations that maximise hydrogen bonding with Cl^- , contributing to effective lattice disruption. Maline supports lipase-catalysed reactions, extraction of polyphenols from plant matrices, and use as a mild acid medium in pharmaceutical synthesis and is considered more biocompatible than Oxaline owing to its milder acidity.

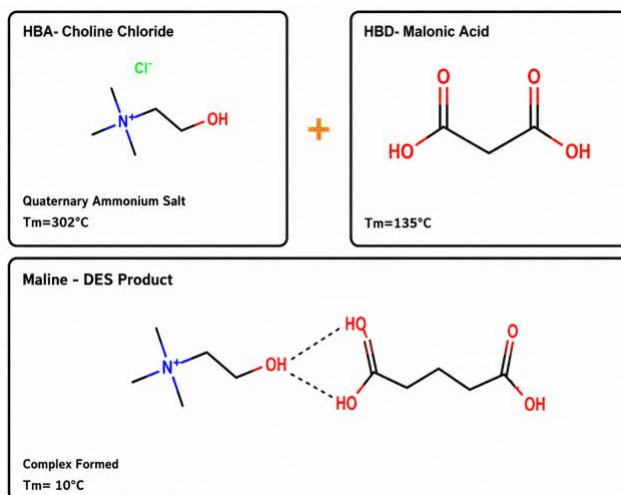


Fig. 5. Molecular structure of Maline (choline chloride:malonic acid). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

4.6 Choline Chloride–ZnCl₂ (Type I/II)

This system differs fundamentally from the hydrogen-bonded examples above: zinc chloride is a strong Lewis acid that reacts with chloride ions from ChCl to form complex anions such as ZnCl_4^{2-} and $\text{Zn}_2\text{Cl}_6^{4-}$ [28]. It is this Lewis acid–base complexation not hydrogen bonding that disrupts both crystal lattices and generates the liquid mixture ($T_m \approx -28^\circ\text{C}$), yielding a highly ionic, dense fluid ($\sim 1.63\text{ g/cm}^3$) with properties markedly different from Type III systems. It is used extensively in electrodeposition of zinc alloys and as a Lewis acid catalyst for organic reactions such as Diels–Alder cycloadditions; the presence of Zn^{2+} renders it moderately toxic and unsuitable for biological applications.

4.7 Betaine–Malic Acid (Type I)

This is the only fully natural-origin system among the examples considered here. Betaine (trimethyl glycine, found in sugar beet) and malic acid (found in apples, grapes, and wine) are both primary metabolites classified as Generally Recognised as Safe (GRAS) [29]. The interaction mechanism is unusually rich: betaine is a zwitterion bearing a permanent positive charge on its quaternary nitrogen and a carboxylate ($-\text{COO}^-$) at the opposite end, allowing it to act as both a hydrogen-bond acceptor (via $-\text{COO}^-$) and a hydrogen-bond donor (via its N^+-CH_2 chain), while malic acid contributes three donor sites (two $-\text{COOH}$ and one $-\text{OH}$). The resulting hydrogen-bond network is thought to mimic an intracellular liquid phase in plant cells. Betaine–malic acid DES is particularly effective at extracting polar bioactives anthocyanins, flavonoids, and phenolic acids from plant material and is used in food-safe extraction and cosmetic formulation.

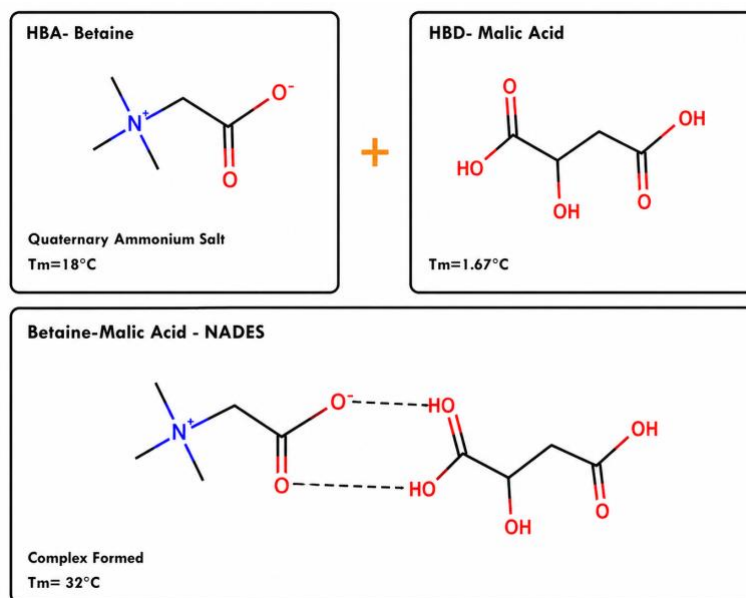


Fig. 6. Molecular structure of the betaine–malic acid deep eutectic system. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

4.8 Choline Chloride–Lactic Acid DES (1:2)

The ChCl:lactic acid system (1:2) exhibits a significantly depressed melting point ($\approx -40^\circ\text{C}$), attributable to extensive hydrogen bonding between the chloride anion and the bifunctional lactic acid molecule, which contributes both carboxylic ($-\text{COOH}$) and hydroxyl ($-\text{OH}$) groups to a highly cooperative hydrogen-bonding network. This dual hydrogen-bond-donor functionality contributes to both strong eutectic

behaviour and moderate Brønsted acidity within the system [7]. The DES shows high efficiency in biomass pretreatment, particularly lignocellulosic fractionation, where its moderate acidity selectively dissolves hemicellulose while preserving cellulose crystallinity; its relatively low viscosity compared with sugar-based DESs further enhances mass transfer, making it suitable for catalytic transformation of biomass-derived substrates.

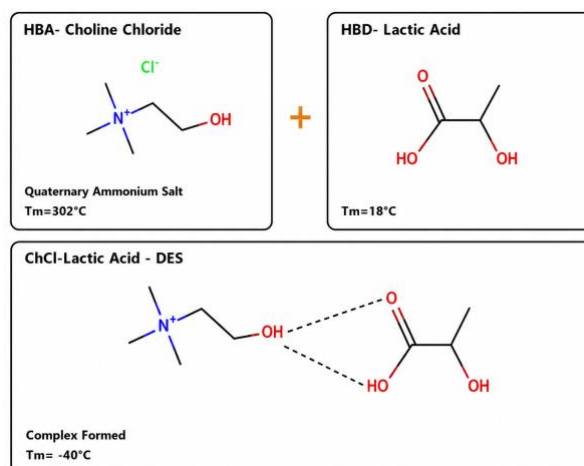


Fig. 7. Molecular structure of the choline chloride–lactic acid deep eutectic system (1:2). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

4.9 Choline Chloride–Caprolactam DES (1:3)

The ChCl–caprolactam system (1:3, $T_m \approx -6^\circ\text{C}$) employs ϵ -caprolactam, a cyclic amide, as the hydrogen-bond donor [11]. Its amide group enables bidirectional hydrogen bonding donation via the N–H group and acceptance via the carbonyl oxygen which markedly enhances the DES's ability to

disrupt intermolecular hydrogen bonding within cellulose and promote its dissolution. This DES shows low volatility and good thermal stability, favouring polymer-processing applications, and has been widely explored for dissolution and modification of polyamide materials such as Nylon-6; its moderate polarity and non-acidic character further extend its utility to materials science and solvent engineering.

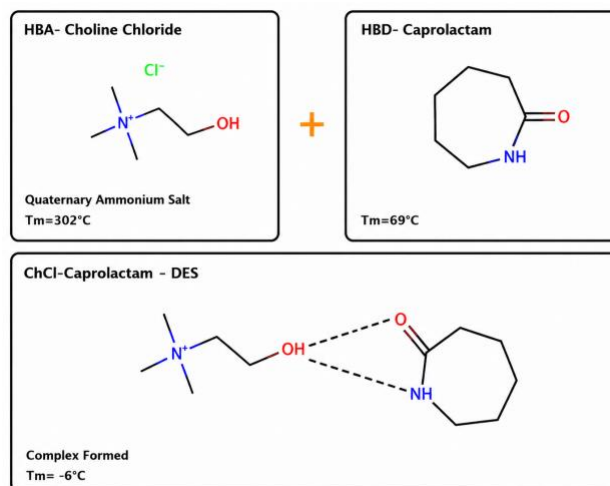


Fig. 8. Molecular structure of the choline chloride–caprolactam deep eutectic system (1:3). (A higher resolution / colour version of this figure is available in the electronic copy of the article)

4.10 Choline Chloride–Levulinic Acid DES (1:2)

The ChCl:levulinic acid system (1:2, $T_m \approx -10^\circ\text{C}$) is a sustainable, biomass-derived solvent in which levulinic acid a recognised platform chemical interacts strongly with chloride ions through its carboxylic group while participating in secondary interactions via its ketone functionality [78].

This DES shows moderate acidity and strong solvation capacity for carbohydrates and lignin derivatives, making it highly effective in biomass valorisation, particularly the conversion of cellulose and sugars into value-added chemicals such as 5-hydroxymethylfurfural, a key intermediate in bio-based fuel and polymer production [79].

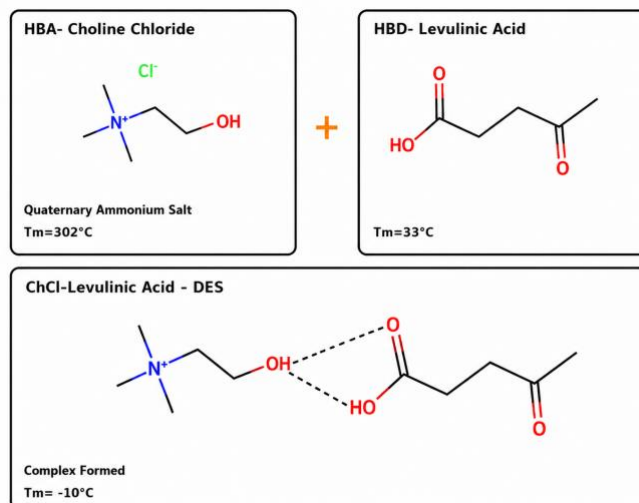


Fig. 9. Molecular structure of the choline chloride–levulinic acid deep eutectic system (1:2). (A higher resolution / colour version of this figure is available in the electronic copy of the article)

4.11 Choline Chloride–Citric Acid DES (1:1)

The ChCl–citric acid system (1:1, $T_m \approx 69^\circ\text{C}$) features citric acid, a tricarboxylic acid capable of forming a dense hydrogen-bonding network [80]. Strong interactions between its multiple carboxyl groups and the chloride anion produce a relatively high melting point, requiring operation at elevated temperature ($\geq 70^\circ\text{C}$). Despite this constraint, the DES

exhibits high polarity and strong acidity, making it highly effective for extracting bioactive compounds such as polyphenols and anthocyanins, while citric acid's inherent metal-chelating properties further extend its applicability to systems involving metal-ion coordination in food, pharmaceutical, and environmental contexts [81].

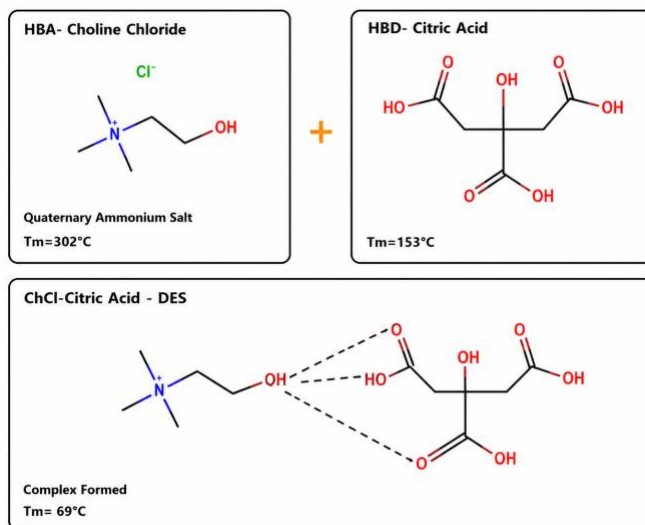


Fig. 10. Molecular structure of the choline chloride–citric acid deep eutectic system (1:1). (A higher resolution / colour version of this figure is available in the electronic copy of the article)

4.12 Sugar-Based DES and NADES Systems

Sugar-based DESs, including ChCl–sorbitol (1:1) and ChCl–glucose systems, belong to the broader NADES class and are

characterised by extensive hydrogen bonding arising from the multiple hydroxyl groups of sugar molecules, producing highly structured liquid networks [39]. A defining feature of this group is extremely high viscosity, which can exceed

10,000 mPa·s and significantly limits mass transfer and diffusion; this property can nonetheless be advantageous where high-viscosity media are required, such as biomolecule stabilisation, controlled-release systems, and specialised electrochemical environments. Their non-toxic, biodegradable nature further supports sustainable and biocompatible applications [44]

4.13 Non-Choline-Chloride Hydrogen-Bond Acceptors

Beyond choline chloride, alternative HBAs tetrabutylammonium bromide (TBAB), methyltriphenylphosphonium bromide (MTPB), and other

phosphonium salts have been extensively investigated, typically offering enhanced hydrophobicity, thermal stability, and tunable physicochemical properties relative to ChCl-based systems [40,48]. Phosphonium-based DESs, commonly paired with ethylene glycol, diethylene glycol, or glycerol at molar ratios near 1:4, show reduced hydrogen-bonding density and larger ionic size, contributing to lower viscosity and distinct polarity profiles suited to high-temperature processes, electrochemistry, and non-polar compound extraction [82,92].

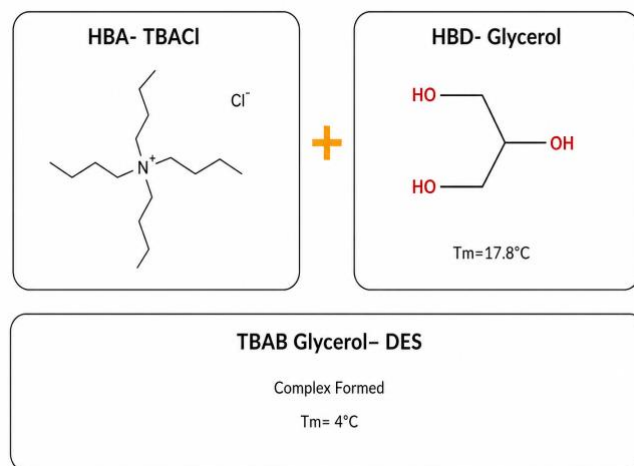


Fig. 11. Molecular structure of a tetrabutylammonium bromide (TBAB)–glycerol deep eutectic system. (A higher resolution / colour version of this figure is available in the electronic copy of the article)

4.14 Metal Salt-Based (Lewis Acidic) DES

Metal-salt-based DESs, such as ZnCl_2 –urea (1:3.5, $T_m \approx 9^\circ\text{C}$) and ZnCl_2 –acetamide (1:4, $T_m \approx 8^\circ\text{C}$), form a distinct class characterised by strong Lewis's acidity, in which the metal centre acts as an electron-pair acceptor while coordinating ligands stabilise the complex through oxygen or nitrogen donor atoms [83]. These systems show high ionic conductivity and strong catalytic activity, suiting acid-catalysed organic reactions including Friedel–Crafts alkylation and polymerisation; AlCl_3 –urea DES, notably, has been successfully applied in aluminium electrodeposition where conventional aqueous electrolytes are ineffective [84]. Related hydrophobic systems such as thymol–menthol (2:1, $T_m \approx -2^\circ\text{C}$) extend this structural diversity further: composed of non-polar, naturally derived components, they rely primarily on weak hydrogen bonding and van der Waals interactions and are consequently immiscible with water, enabling phase separation in aqueous systems [45]. This

property makes them well suited to liquid–liquid extraction of hydrophobic compounds such as lipids, essential oils, and pharmaceuticals; variants including thymol–decanoic acid and menthol–lauric acid extends the class further, adding antimicrobial activity and enhanced lipid solubility [33]. Natural amino-acid-based DESs, exemplified by proline–malic acid (1:1, $T_m \approx -33^\circ\text{C}$) and proline–lactic acid (1:3, $T_m \approx -45^\circ\text{C}$), are similarly attractive for their biocompatibility and tunable properties, with proline acting as a hydrogen-bond acceptor through its pyrrolidine nitrogen and the organic acids serving as donors; the proline–lactic acid pairing shows particularly low viscosity and enhanced extraction efficiency for polar plant metabolites, including phenolics, alkaloids, flavonoids, and anthocyanins [50]. The betaine–glycerol system (1:2, $T_m \approx -45^\circ\text{C}$) similarly represents a fully biodegradable, non-toxic DES pairing a zwitterionic HBA with a polyol HBD, offering high polarity and moderate viscosity for efficient extraction of bioactive compounds such as polyphenols from green coffee beans,

with additional utility in cosmetics, pharmaceuticals, and food processing [47]. Finally, ternary NADES systems such as glucose–fructose–sucrose (1:1:1) provide insight into the possible biological role of eutectic mixtures: these systems mimic intracellular environments and have been proposed as evidence that NADES may function as a natural liquid phase within living cells, with their dense hydrogen-bonding network and high viscosity enabling stabilisation and solubilisation of otherwise poorly soluble biomolecules – a concept with implications for both fundamental biology and bio-inspired solvent design [51].

Taken together, these fourteen systems illustrate a consistent structure–property logic: melting-point depression scales with hydrogen-bond donor density and geometric complementarity

to the chloride (or metal) acceptor, viscosity tracks the strength and connectivity of the hydrogen-bond network (sugar- and citric-acid-based systems being the most viscous, glycol-based systems the least), and polarity and acidity are set primarily by the functional groups of the HBD. This structure–property mapping provides a rational basis for selecting or designing a DES for a specific pharmaceutical task for example, favouring low-viscosity glycol- or acid-based systems for extraction efficiency, or GRAS-compatible natural pairings such as betaine–malic acid or proline–lactic acid where biocompatibility is paramount.

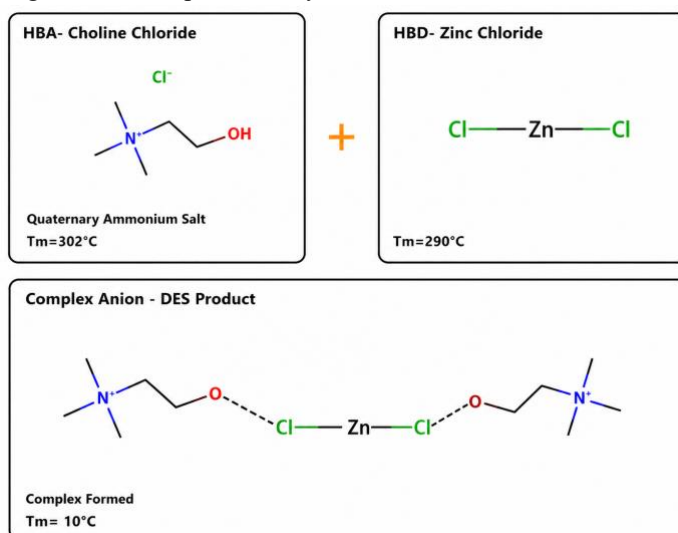


Fig. 12. Structure of the complex anion formed in a metal salt-based (Lewis acidic) deep eutectic system. (A higher resolution / colour version of this figure is available in the electronic copy of the article)

5. PHYSICOCHEMICAL PROPERTIES OF DEEP EUTECTIC SOLVENTS

5.1 Density

Density is a key physicochemical property because it directly influences diffusivity, miscibility, and overall process performance; from an industrial perspective, it also affects equipment design and energy requirements, since higher-density DESs demand greater power input during agitation, stirring, or pumping [16]. Density is strongly influenced by temperature, pressure, and HBA:HBD molar ratio: most DESs exhibit densities of 1.04–1.63 g/cm³, higher than water (1 g/cm³) [52], although exceptions exist Ribeiro et al. developed low-density hydrophobic DESs using DL-menthol as the HBA combined with acetic, pyruvic, lactic, or lauric acid, yielding systems with lower density and viscosity (5–100 cP)

than water [53], with comparable findings reported by Martins et al. for terpene–monocarboxylic-acid hydrophobic systems [54]. Temperature and pressure further modulate density: Leron et al. observed that ChCl:glycerol density decreases with increasing temperature owing to thermal expansion, and increases under higher pressure owing to compression [55], with comparable trends reported for ChCl:levulinic acid, Glyceline, and Ethaline [56,57,35,36,37]. As Shahbaz et al. explain, rising temperature enhances molecular motion, creating greater intermolecular spacing and thereby reducing density [58,38]. Molar ratio also matters: Manurung et al. observed an initial density decrease with increasing choline chloride concentration in ChCl:D-glucose DES, followed by a sharp increase beyond a 2:1 ratio, possibly reflecting excess halide ions contributing to a more compact structure [59]; in ChCl:ethylene glycol systems, density instead decreased with

increasing ethylene glycol content, consistent with ethylene glycol's lower intrinsic density [60]. HBD structure exerts a further effect: Yusof et al. found that density decreased as the carbon-chain length of the HBD increased across TBAB

systems paired with ethylene glycol, 1,3-propanediol, and 1,5-pentanediol, attributable to steric hindrance that weakens hydrogen-bond interactions and increases free volume [61].

Table 2. Comparative structure–property analysis of representative deep eutectic solvent systems.

DES System	Components (HBA:HBD)	Molar Ratio	Type	T _m (°C)	Interactions	Viscosity	Polarity	Acidity	Major Applications	Advantages	Limitations
ChCl–Lactic acid	Choline chloride : Lactic acid	1:2	Hydrophilic DES	–40	Strong H-bonding between –COOH and –OH groups	Moderate	High	Moderate (Brønsted acid)	Biomass pretreatment, hemicellulose extraction	Selective dissolution, low melting point	Water sensitivity
ChCl–Caprolactam	Choline chloride : Caprolactam	1:3	Hydrophilic DES	–6	Amide N–H···O=C hydrogen bonding	Moderate	Medium	Low	Cellulose dissolution, polymer processing	Good thermal stability	Limited acidity
ChCl–Levulinic acid	Choline chloride : Levulinic acid	1:2	Hydrophilic DES	–10	Carboxyl and ketone hydrogen bonding	Moderate	High	Moderate	Biomass conversion to 5-HMF	Renewable origin	Moderate viscosity
ChCl–Citric acid	Choline chloride : Citric acid	1:1	Hydrophilic DES	69	Multiple –COOH hydrogen bonding	High	Very high	Strong	Polyphenol and anthocyanin extraction	Strong acidity, excellent chelation	High operating temperature
ChCl–Sorbitol	Choline chloride : Sorbitol	1:1	NADES	Variable	Extensive hydroxyl hydrogen-bonding network	Very high	High	Neutral	Biomolecule stabilization	Non-toxic, biodegradable	Extremely high viscosity
ChCl–Glucose	Choline chloride : Glucose	5:2	NADES	Variable	Extensive hydroxyl hydrogen-bonding network	Very high	High	Neutral	Biomolecule stabilization	Non-toxic, biodegradable	Extremely high viscosity
TBAB-based DES	Tetrabutylammonium bromide : HBD	~1:4	Non-ChCl DES	Variable	Ionic interactions with weak H-bonding	Low–Moderate	Tunable	Low	Electrochemistry, catalysis	High thermal stability	Potential toxicity
MTPB-based DES	Methyltriphenylphosphonium bromide : HBD	~1:4	Non-ChCl DES	Variable	Ionic interactions with weak H-bonding	Low–Moderate	Tunable	Low	Electrochemistry, catalysis	High thermal stability	Higher cost, possible toxicity
ZnCl ₂ –Urea	Zinc chloride : Urea	~1:3.5	Metal-based DES	~8–9	Lewis acid coordination	Low–Moderate	Medium	Strong (Lewis acid)	Catalysis, electrodeposition	High catalytic activity	Corrosive, moisture sensitive

ZnCl ₂ –Acetamide	Zinc chloride : Acetamide	~1:4	Metal-based DES	~8–9	Lewis acid coordination	Low–Moderate	Medium	Strong (Lewis acid)	Catalysis, electrodeposition	High reactivity	Corrosive, moisture sensitive
Thymol–Menthol	Thymol : Menthol	2:1	Hydrophobic DES	2	Weak H-bonding and van der Waals interactions	Low	Low	Neutral	Lipid extraction, liquid–liquid extraction	Water immiscibility	Limited polar solubility
Proline–Malic acid	L-Proline : Malic acid	1:1	NADES	–33	Amino acid–acid hydrogen bonding	Moderate	Medium–High	Moderate	Plant metabolite extraction	Biocompatible	Moderate viscosity
Proline–Lactic acid	L-Proline : Lactic acid	1:3	NADES	–45	Strong hydrogen-bonding network	Low–Moderate	High	Moderate	Flavonoid extraction	Low-viscosity NADES	Limited hydrophobic scope
Betaine–Glycerol	Betaine : Glycerol	1:2	NADES	–45	Zwitterion–polyol hydrogen bonding	Moderate	High	Neutral	Polyphenol extraction	Non-toxic, stable	Moderate viscosity
Glucose–Fructose–Sucrose	Glucose : Fructose : Sucrose	1:1:1	Ternary NADES	Variable	Dense hydrogen-bonding network	Very high	High	Neutral	Biomolecule stabilization	Biological relevance	Poor mass transfer

5.2 Viscosity

Viscosity reflects a liquid's resistance to flow and is a decisive parameter in solvent selection: highly viscous systems are harder to pump, stir, filter, and handle, and demand greater processing energy, so viscosity influences both formulation performance and equipment design [62]. In DESs, viscosity depends strongly on HBA/HBD identity, temperature, and water content, and is governed primarily by extensive hydrogen bonding together with electrostatic and van der Waals interactions [63]; many DESs are 100–1000-fold more viscous than conventional organic solvents or water because their strong hydrogen-bonding networks reduce the mobility of free molecular species [64]. While this structural rigidity is advantageous in some contexts, excessive viscosity can limit extraction processes that require efficient mass transfer, whereas low-viscosity DESs show higher diffusivity and markedly improved extraction efficiency for pigments and other bioactive compounds [65]. Temperature is inversely related to viscosity: sugar-based systems such as ChCl:glucose (1:1) exhibit extremely high viscosity (~34,400 mPa·s at 323.15 K), whereas ChCl:urea (1:2) shows much lower viscosity (~750 mPa·s at 298.15 K) [66]. Polyalcohol-

based DESs typically show lower viscosity than sugar- or organic-acid-based systems, likely because smaller polyalcohol molecules engage in comparatively weaker intermolecular interactions, whereas urea-based DESs tend toward higher viscosity owing to stronger hydrogen bonding, and diacid pairings (e.g., oxalic acid) are generally more viscous than monoacid pairings (e.g., levulinic acid) owing to their greater number of hydrogen-bonding sites [67]. Component ratio also matters increasing HBD mole fraction in allyl-triphenyl-phosphonium-bromide (ATPPB) systems paired with diethylene glycol (DEG) or triethylene glycol (TEG) significantly reduces viscosity by weakening salt–HBD hydrogen bonds, whereas increasing HBD molecular weight or alkyl chain length (DEG → TEG) tends to increase viscosity [3]. Excessive viscosity complicates decantation, dissolution, and filtration [68]; controlled water addition is a practical mitigation strategy, since small amounts of water disrupt inter-component hydrogen bonding and lower viscosity without substantially compromising solvation capacity [65]. DESs based on levulinic acid, ethylene glycol, or phenol show particularly favourable low-viscosity behaviour, and around 10% water can markedly reduce viscosity while preserving solvent performance; however,

dilution beyond 50% water can destabilise the hydrogen-bonding network of NADESs, reducing solubilisation efficiency.

5.3 Polarity and Solvation Capacity

Polarity is a fundamental determinant of a solvent's capacity to dissolve and extract a given compound [69]. In NADESs, polarity can be adjusted, most commonly through controlled water addition; because many NADESs are inherently hydrophilic and highly polar, they show strong solubilising capacity for polar compounds and, in some cases, even for certain water-insoluble substances [43]. Polarity varies systematically with HBD identity: organic-acid-based DESs are generally the most polar, often exceeding the polarity of water, followed by amino-acid- and sugar-based systems, while polyalcohol-based DESs tend to be less polar, in some cases approaching menthol-based systems [70]. This tunability supports selective extraction of a wide range of phytochemicals, frequently outperforming traditional solvents such as methanol, ethanol, water, or acetone. Because early DES systems were predominantly hydrophilic limiting their use for non-water-soluble substances hydrophobic DESs were developed, first reported in 2015, and have since been applied successfully to extract volatile fatty acids and biomolecules such as vanillin and caffeine [71]. The choice between hydrophilic and hydrophobic DESs depends on the target compound and matrix. Consistent with the principle that “like dissolves like,” optimal extraction occurs when solvent polarity closely matches solute polarity [65]: Xu et al. reported poor extraction of citrus-peel flavonoids using highly polar sugar-based DESs, likely because these flavonoids carry multiple methoxy ($-\text{OCH}_3$) groups and are relatively non-polar, whereas a ChCl :levulinic acid system of comparatively lower polarity proved more effective, illustrating the importance of matching solvent polarity to solute chemistry [72].

5.4 Surface Tension

Surface tension, the cohesive force acting at a liquid's surface, governs how a solvent spreads, penetrates, and interacts with solid materials, and is particularly relevant to extraction, absorption, adsorption, heat exchange, fluid transport, and industrial system design [73]. Solvents with lower surface tension penetrate solid matrices more readily, improving extraction efficiency. Alkyl-chain length, temperature, hydrogen-bond strength between HBA and HBD, molecular weight, and viscosity all influence DES surface tension; stronger hydrogen bonding generally raises surface tension, whereas increasing temperature weakens these interactions and lowers it [74]. Molar ratio also contributes increasing

choline chloride proportion in ChCl :glycerol systems reduce surface tension by weakening HBA–HBD interactions [42]. Ghaedi et al. reported that ATPPB-TEG DES showed lower surface tension than ATPPB-DEG DES, attributed to weaker hydrogen bonding in the former; notably, viscosity alone did not explain the difference, since ATPPB-DEG had lower viscosity than ATPPB-TEG at equivalent molar ratio and temperature yet higher surface tension, indicating that hydrogen-bond strength and alkyl-chain structure are more decisive than viscosity in determining surface behaviour [49]. Molecular weight further affects surface characteristics, with lower-molecular-weight DESs generally showing lower surface tension: Chen et al. found that betaine-based DESs exhibited higher surface tension than chloride-based DESs relative to their pure components [60], and Hayyan et al. observed that glucose-based DESs displayed higher surface tension than carboxylic-acid-based systems at equivalent molar ratio, likely reflecting glucose's multiple hydroxyl groups and consequently stronger hydrogen bonding [61]. Bi et al. further demonstrated a decreasing surface-tension trend among alcohol-based DESs linked to structural differences in the alcohol component [62]. Collectively, these findings confirm that hydrogen-bonding strength, molecular structure, and alkyl-chain configuration are central determinants of DES surface behaviour, with direct consequences for extraction efficiency for example, in flavonoid recovery from plant materials.

6. DEEP EUTECTIC SOLVENTS IN POLYMERIC DRUG CARRIERS

Incorporating DESs into polymer-based drug delivery systems adds a valuable layer of multifunctionality, merging the structural advantages of polymers with the strong solubilising and stabilising properties of DESs. Rather than acting solely as environmentally friendly solvents, DESs can function as active formulation components that interact with polymer matrices at the molecular level [63]. These interactions can alter polymer network architecture, improve drug loading capacity, enable more controlled release profiles, and enhance overall formulation stability, positioning DES–polymer systems as a strategic advance in designing smarter, more efficient delivery platforms [64].

6.1 Structural Integration

DESs can be seamlessly incorporated into a wide range of polymeric drug-delivery platforms, including hydrogels, nanoparticles, electrospun fibres, films, and three-dimensional scaffolds. Within these systems they perform multiple functional roles acting as plasticizers, solubilising agents, porosity enhancers, or bioactive components,

depending on formulation design [65]. When used as plasticisers, DESs lower the glass transition temperature (T_g) of polymers by increasing chain mobility and expanding free volume within the network, improving flexibility, swelling behaviour, and overall mechanical adaptability [66]. Their strong hydrogen-bonding interactions further promote uniform drug distribution throughout the polymer matrix; this molecular-level stabilisation minimises phase separation and reduces the likelihood of drug recrystallisation, supporting long-term formulation stability [67].

6.2 Modulation of Drug Release

Incorporating DESs into polymer matrices markedly influences drug-release behaviour by modifying the internal microstructure and dynamic properties of the polymer network. By enhancing chain mobility and regulating water uptake, DESs can shift the release mechanism from Fickian diffusion toward anomalous (non-Fickian) transport or swelling-controlled release [3]. In hydrophilic polymer systems, DES addition generally promotes greater swelling and opens diffusion pathways, accelerating release; hydrophobic DES-based systems, conversely, may extend release duration by strengthening drug–matrix interactions and increasing affinity within the polymer environment. Hydrogen-bond interactions between DES components and the API can also maintain the drug in an amorphous, molecularly dispersed state, supporting sustained supersaturation and dissolution-driven release that ultimately improves bioavailability [68].

6.3 Therapeutic DES Systems (THEDES) in Polymer Carriers

THEDES formulations represent a more advanced approach in which the API becomes an integral part of the eutectic structure itself. By participating directly in the hydrogen-bonded network, the API experiences reduced melting point and disrupted crystalline lattice, enhancing molecular miscibility within polymer matrices [68]. When incorporated into polymer carriers, THEDES can achieve higher drug loading, more controlled diffusion profiles, and improved bioavailability compared with traditional solid dispersions [65], merging solubilisation and delivery into a single, unified molecular framework—a notable departure from conventional formulations built around passive excipients.

6.4 Stability and Regulatory Considerations

Despite this promise, DES–polymer systems face practical and regulatory challenges. Because DESs are inherently hygroscopic and rich in hydrogen-bonding interactions, their incorporation into polymeric matrices can increase moisture

sensitivity and affect storage stability, requiring careful environmental control to maintain product consistency and shelf life [69]. Thermal sterilisation, commonly used in pharmaceutical manufacturing, may alter DES composition or disrupt polymer–DES interactions, so detailed compatibility and stability studies are needed before large-scale application. Regulatory considerations are further complicated for THEDES formulations, in which structural integration of the API into the eutectic system blurs the conventional distinction between “excipient” and “active ingredient” [43]; clearer regulatory guidance will be essential to support development and approval pathways. Progress toward clinical translation will require comprehensive *in vivo* evaluation, toxicological assessment, and scalable manufacturing studies to ensure DES–polymer hybrid platforms meet the safety, efficacy, and quality standards expected of pharmaceutical products.

7. MECHANISMS OF DES-MEDIATED DRUG SOLUBILIZATION AND DELIVERY

DESs do far more than simply improve drug solubility: they enhance overall delivery performance through several interconnected physicochemical and biological mechanisms that act at the molecular, membrane, and polymer-matrix levels, jointly improving permeation, controlled release, stability, and ultimately bioavailability. Membrane permeation enhancement is among the most important of these mechanisms. Choline salts, organic acids, and terpenes can interact with biological lipid bilayers, transiently disturbing or fluidising membrane structures; this increases membrane flexibility, lowers barrier resistance, and allows drugs to partition more efficiently into lipid domains, improving absorption across transdermal, buccal, nasal, and intestinal routes. Terpene-based systems such as choline–geranic acid (CAGE) have demonstrated enhanced skin permeability by extracting lipids and increasing diffusion across the stratum corneum; importantly, these effects are typically reversible and concentration-dependent, positioning DESs as safer, more controllable alternatives to traditional chemical penetration enhancers [70]. A second key mechanism is polymer plasticisation and matrix modulation. When DESs are incorporated into hydrogels, films, nanoparticles, or electrospun fibres, they lower the polymer’s glass transition temperature by increasing chain mobility and free volume, improving flexibility, swelling, and water uptake, and enabling fine-tuning of release kinetics across Fickian, anomalous, or erosion-controlled regimes [71]. DESs additionally provide stabilisation benefits by modulating the drug’s microenvironment: their structured hydrogen-bond networks and reduced water activity can protect sensitive compounds—peptides, antioxidants, and acid-sensitive drugs

from hydrolytic or oxidative degradation, extending shelf life and improving therapeutic reliability [65]. A further contribution is the maintenance of thermodynamic activity and supersaturation: DESs can hold drugs in a molecularly dispersed or amorphous state, reducing recrystallisation risk during storage or after administration, and sustaining the high concentration gradient across biological membranes that drives absorption – an effect especially relevant to THEDES, where the API itself forms part of the eutectic network [72]. Finally, DESs can enhance bioadhesion and mucosal interaction, with hydrogen-bonding capability enabling interaction with mucin glycoproteins to increase mucosal residence time (useful for ocular, nasal, and buccal delivery) and can improve nanocarrier formation and drug encapsulation by reducing interfacial tension in nanoparticle and micelle-based systems. Collectively, these mechanisms position DESs not merely as solvents but as multifunctional delivery enhancers operating synergistically across biological and formulation levels.

8. Deep Eutectic Solvents in Oral Drug Delivery

Oral administration dominates the pharmaceutical market, yet poorly soluble drugs BCS Classes II and IV continue to pose major formulation challenges. DESs enhance solubilisation, dissolution rate, intestinal permeability, and overall bioavailability for such drugs; API–ionic-liquid systems and THEDES represent emerging strategies in oral formulation, and surface-active ionic liquids together with DESs may further improve membrane transport and micellar solubilisation. Table 3 summarises representative DES-based oral delivery systems reported in the literature, spanning solubility enhancement, mechanism of action, and safety considerations.

9. Self-Assembled DES-Based Nanomicelles for Transdermal Delivery

Self-assembled DES-based nanomicelles have recently attracted attention as an innovative transdermal delivery strategy, combining the strong solubilising capacity of DESs with the organised architecture of amphiphilic nanocarriers. In these formulations, DES components – typically a choline-derived HBA and an HBD such as fatty acids, terpenes, or other organic acids – either directly contribute to micelle formation or act as supportive co-solvents that facilitate self-assembly of surfactants or amphiphilic polymers into nanosized structures. Formation is driven by multiple intermolecular forces: hydrophobic interactions among lipid-like DES components encourage aggregation, while hydrogen bonding within the eutectic network and electrostatic stabilisation at the interface maintain structural integrity. On

introduction into an aqueous environment, these systems spontaneously organise into nanomicelles with a hydrophobic inner core – ideal for encapsulating poorly water-soluble drugs – and a hydrophilic outer shell that enhances stability and promotes effective interaction with the skin surface. A key advantage of DES-based nanomicelles lies in their dual functionality: beyond improving drug solubility, the DES itself can act as an effective permeation enhancer. Terpene- or fatty-acid-containing systems, such as choline–geranic acid formulations, interact directly with the lipid matrix of the stratum corneum, fluidising skin lipids, disturbing tightly packed ceramide structures, and expanding intercellular diffusion pathways to facilitate deeper drug penetration. This enhancement generally proceeds through partial lipid extraction, increased membrane fluidity, and temporary disruption of highly ordered lipid domains – changes that are typically reversible and do not cause permanent tissue damage. DES-based formulations have been shown to improve model-drug permeation by altering stratum corneum organisation, underscoring their potential in advanced transdermal delivery. At the nanoscale, micelle formation substantially improves delivery performance. Particle sizes generally below 200 nm provide a large surface area and intimate contact with the skin, enhancing absorption, while the hydrophobic core maintains poorly soluble drugs in solution and sustains a strong thermodynamic activity gradient that drives diffusion across the skin barrier. The internal hydrogen-bonding network within DES-containing micelles further stabilises the incorporated drug, reducing the risk of crystallisation or chemical degradation, while lowered interfacial tension promotes spontaneous nanoscale aggregation and higher encapsulation efficiency. Mechanistically, drug delivery from DES-based nanomicelles proceeds through several coordinated processes: a fraction of the drug exists in free form and can directly partition into the stratum corneum; the nanomicelles themselves interact closely with the skin surface, enabling localised release at the interface; and the DES components may partially disrupt the skin's lipid matrix, expanding diffusion pathways and enhancing drug mobility within the tissue. Depending on formulation, overall release may be diffusion-controlled or partition-controlled, and careful adjustment of DES composition and surfactant concentration allows the design of sustained, controlled-release transdermal systems. Recent work has extended this concept by incorporating THEDES into nanomicellar platforms, in which the API itself becomes part of the eutectic structure rather than being simply dissolved within it – an approach that can significantly increase drug loading and often eliminates the need for additional solubilising excipients. Aroso et al. were among the first to

highlight the pharmaceutical significance of therapeutic DES systems, demonstrating their potential to enhance drug bioavailability and laying the foundation for THEDES as multifunctional delivery platforms [68]. Taken together, DES-

based nanomicelles combining solubilisation, permeation enhancement, and controlled release in a single platform represent a strong candidate strategy for next-generation, non-invasive transdermal therapies.

Table 3. Representative deep eutectic solvent-based systems for oral drug delivery.

S. No	Focus	DES composition & type	Physicochemical characteristics	Solubility / bioavailability outcome	Mechanism of enhancement	Safety / toxicology	Limitations	Ref.
1	Role of ionic liquids and DES in oral pharmaceuticals	ChCl-based NADES and conventional DES; organic acids, sugars, amino acids; eutectogels	Low melting point; tunable viscosity; high density	Up to 400,000-fold solubility increase (quercetin); major C _{max} and AUC improvements	Hydrogen bonding; crystallinity reduction; permeability enhancement	Component-dependent toxicity; limited long-term oral data	Scale-up challenges; viscosity control needed	[4]
2	DES and pharmaceuticals general overview	Primarily Type III DES; ChCl-based systems	Improved API stability; hydrolysis prevention	Ibuprofen: 12-fold solubility increase	Improved dissolution and membrane interaction	Insufficient IC ₅₀ data; chronic toxicity unknown	In vivo PK/PD validation needed	[73]
3	DES in metabolic-disease API delivery	ChCl/betaine + menthol/fatty acids; NADES and THEDES; gel systems	Improved lipophilicity; enhanced permeability	RA-XII: 17.5-fold solubility, 11.6-fold bioavailability increase	Reduced crystallinity; enhanced intestinal transport	IC ₅₀ 37–1260 mM (system-dependent)	Sustained-release Optimisation needed	[74]
4	DES as pharmaceutical excipients (ibuprofen, mefenamic acid)	ChCl/menthol + PEG/Miglyol; Type III and V	Low surface tension; density and T _g evaluated	Ibuprofen ≤ 379.7 mg/g; mefenamic acid ≤ 17.1 mg/g	Improved wetting and molecular dispersion	Menthol GRAS; limited chronic toxicity data	Bioavailability not directly measured	[63]
5	DES for dapsone (topical)	ChCl + ascorbic acid (2:1) / propylene glycol (1:3); conventional	High viscosity; characterised by DSC and FTIR	Dapsone solubility: 380 mg/L → 500 mg/mL	Hydrogen bonding; enhanced dermal permeation	Biodegradable; cytotoxicity not reported	No systemic PK data	[75]
6	Hydrophobic DES for transdermal delivery	Menthol + fatty acids; HDES systems	Amphiphilic; self-assembled nanostructures	Improved lipophilic-drug solubility; enhanced skin flux	Stratum corneum lipid disruption; nanoscale penetration	Generally low acute toxicity; irritation studies needed	Long-term dermal safety data limited	[76]
7	NADES for phytochemical extraction and oral use	ChCl + organic acids/sugars; fully bio-derived	High polarity; water-dependent viscosity	Significant enhancement for flavonoids and alkaloids	Strong H-bond network; improved molecular stabilisation	Better biocompatibility than synthetic ionic liquids	GI-interaction studies lacking	[77]

10. MECHANISTIC INSIGHTS FROM COMPUTATIONAL MODELING

Molecular-level understanding of DES behaviour has advanced considerably through computational tools such as molecular dynamics (MD) simulation and quantum-chemical calculation, which consistently show that the extensive

hydrogen-bonding network formed between HBAs and HBDs plays a central role in governing drug solubilisation and transport [85]. Density functional theory (DFT) investigations further reveal that strong hydrogen bonding between drugs and DES components can lower the crystal lattice energy of solid drugs and stabilise them in a molecularly dispersed state, providing a theoretical explanation for the enhanced solubility frequently observed experimentally [88]. MD simulations additionally demonstrate nanoscale structural heterogeneity within DESs, with dynamic hydrogen-bond clusters creating microenvironments capable of accommodating both hydrophilic and lipophilic molecules – a structural basis for polarity-tunable solvation behaviour [87]. Thermodynamic modelling has clarified the driving forces behind drug partitioning into DES systems: free-energy calculations indicate that solubilisation is largely enthalpy-driven, arising from favourable hydrogen-bonding and van der Waals interactions, balanced against entropic penalties associated with solvent reorganisation. In transdermal applications, MD simulations of DES interactions with lipid bilayers provide atomistic insight into permeation enhancement, showing increased disorder in lipid tails, reduced membrane thickness, and enhanced lateral diffusion – changes consistent with stratum corneum fluidisation – while coarse-grained simulations have predicted the spontaneous self-assembly of terpene-based hydrophobic DES systems into nanomicelles, driven by hydrophobic interactions and stabilised by hydrogen bonding. Beyond structural analysis, predictive tools such as COSMO-RS (Conductor-like Screening Model for Real Solvents) are widely used to estimate drug solubility in DES formulations: by analysing σ -profiles and chemical-potential differences, this approach enables rational component selection prior to laboratory experimentation, reducing formulation time while offering deeper insight into polarity matching and hydrogen-bonding capacity [86]. Rheological modelling combined with molecular simulation has further linked DES viscosity to hydrogen-bond-network density, helping explain diffusion-controlled release patterns observed in polymer–DES hybrid systems. Collectively, these computational approaches now provide a powerful framework for the rational design and optimisation of DES-based pharmaceutical systems, complementing and, in several respects, accelerating experimental formulation development.

11. CHALLENGES AND FUTURE PERSPECTIVES

Although interest in incorporating DESs into polymer-based drug delivery systems is steadily increasing, several challenges continue to limit broader application. Uncertain formulation compatibility, potential alterations in drug

stability, regulatory ambiguity, and limited manufacturing scalability remain significant barriers, and addressing them will require a coordinated, multidisciplinary effort combining fundamental mechanistic research with applied pharmaceutical development. A major difficulty is the unpredictability of interactions within complex, multicomponent DES–polymer formulations. Because DESs are highly tunable, even small compositional changes particularly in the HBD-to-HBA ratio can influence polymer integrity, drug compatibility, and release kinetics. While this flexibility is a core strength of DES technology, it also introduces variability that complicates formulation stability and reproducibility: the same strong intermolecular interactions that enhance solubility and permeability may, in some formulations, destabilise polymer matrices, alter release behaviour, or promote phase separation [24,77]. The absence of detailed structure–activity relationship models further limit the ability to predict how compositional changes will affect polymer morphology and drug-release mechanisms [25]. Moisture uptake, oxidative degradation, and phase instability must also be carefully monitored, since they directly affect shelf life and batch-to-batch consistency – underscoring the need for systematic optimisation strategies and real-time analytical monitoring tools such as rheometry and near-infrared spectroscopy to ensure reliable DES–polymer compatibility. From a regulatory standpoint, DES-based systems currently occupy a grey area. Although individual components such as choline chloride, lactic acid, and glycerol may be classified as Generally Recognised as Safe (GRAS), the eutectic mixture itself is often treated as a novel chemical entity, and regulatory bodies including the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have not yet issued specific guidance on DES use in pharmaceutical products [91]. This lack of clarity can delay approval timelines, discourage industrial investment, and create uncertainty throughout product development. These limitations notwithstanding, DES technology offers substantial opportunities for innovation. Its compositional flexibility makes DESs attractive platforms for responsive, personalised drug delivery systems targeting oncology, transdermal, mucosal, and implantable applications. THEDES in which the solvent itself carries pharmacological activity introduce dual-function systems that act simultaneously as carrier and co-therapeutic agent, potentially simplifying formulations, reducing excipient burden, lowering required dosages, and enhancing localised bioavailability [46]. Integration of DES with advanced polymer technologies, including stimuli-responsive hydrogels, electrospun nanofibres, and 3D-printed scaffolds, further expands this potential, and combining these platforms with artificial

intelligence and machine learning could enable systematic exploration of the vast combinatorial DES compositional space, supporting predictive modelling of stability, safety, and release kinetics. Such data-driven approaches are likely to accelerate rational formulation design and support regulatory acceptance by improving reproducibility and risk assessment. Future progress will depend on strong collaboration across pharmaceutical sciences, materials engineering, and biotechnology. Research must extend beyond *in vitro* studies to prioritise *in vivo* investigations of pharmacokinetics, biocompatibility, and therapeutic performance under physiologically relevant conditions. Integrating DES-based matrices with targeted delivery strategies—ligand-mediated targeting, stimuli-responsive release, and programmable

12. CONCLUSION

Deep eutectic solvents have progressed from a niche green-chemistry curiosity to a structurally versatile platform with genuine relevance across oral, transdermal, and polymer-based drug delivery. Their defining feature—a tunable hydrogen-bonding network formed between an HBA and an HBD—accounts for the wide-ranging control that formulators can exert over melting point, viscosity, polarity, and surface tension, and this structure–property relationship underlies every application surveyed in this review, from biomass-derived extraction solvents through therapeutic deep eutectic systems in which the API itself becomes structurally integral to the delivery vehicle. Across the systems examined here, three consistent themes emerge. First, natural and Type III DES compositions offer the most immediately translatable combination of low toxicity, biodegradability, and formulation performance, making them the logical starting point for pharmaceutical development. Second, DES-mediated mechanisms of solubility and permeability enhancement—membrane fluidisation, polymer plasticisation, supersaturation maintenance, and nanocarrier stabilisation—are increasingly well supported by both experimental and computational (MD, DFT, COSMO-RS) evidence, giving formulators a mechanistic rather than purely empirical basis for DES selection. Third, translational progress remains constrained less by chemistry than by systems-level gaps: unpredictable DES–polymer interactions, an absence of structure–activity relationship models, incomplete long-term stability and toxicological data [89,90], and an unresolved regulatory classification for eutectic mixtures as pharmaceutical excipients. Closing these gaps will require standardised physicochemical characterisation protocols, expanded *in vivo* pharmacokinetic and biocompatibility studies, and computational screening frameworks capable of navigating the very large DES compositional space

implantable devices—may enable precise spatial and temporal control of drug action, and THEDES-based codelivery approaches, in which the solvent itself contributes therapeutic activity, may enhance synergistic effects while reducing formulation complexity. Ultimately, successful translation of DES–polymer platforms will require harmonised regulatory frameworks, comprehensive toxicological evaluation, long-term stability studies, and quality-control standards aligned with Good Manufacturing Practice (GMP). As bioinspired design principles, computational modelling, and high-throughput screening tools continue to mature, they will play a central role in mapping the expansive compositional landscape of DESs and guiding their safe, effective integration into next-generation drug delivery systems.

efficiently. Achieving regulatory clarity—potentially through harmonised guidance from agencies such as the FDA and EMA on the classification of DES and THEDES systems—will be equally important for industrial adoption. With these foundations in place, DES- and THEDES-based platforms are well positioned to move from promising laboratory-scale demonstrations toward validated, GMP-compliant drug delivery technologies.

AUTHORS' CONTRIBUTIONS

All authors contributed substantially to the conception, literature review, writing, revision, and final approval of the manuscript. All authors have accepted responsibility for the content of the manuscript and consented to its submission. They have reviewed the final version and approved it for publication.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

No new datasets were generated or analyzed during the current study. All data supporting the findings of this review are available within the published literature cited in the References section.

FUNDING

The authors received no specific funding for this work.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the support provided by the Department of Pharmaceutics, Dr. K. N. Modi Institute of Pharmaceutical Education and Research, Modinagar, Ghaziabad, Uttar Pradesh, India, the Department of Pharmaceutics, I.T.S College of Pharmacy, Muradnagar, Ghaziabad, Uttar Pradesh, India, and the Department of Pharmacology, IIMT College of Medical Sciences, IIMT University, Meerut, Uttar Pradesh, India, for providing an academic environment that facilitated the preparation of this review article.

PUBLISHER'S NOTE

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