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# Deep eutectic solvents in pharmaceutical applications: A review

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ABSTRACT

Deep eutectic solvents (DESs) have garnered significant attention in pharmaceutical research in recent years due to their high efficiency, facile separability and biocompatibility. Characterised by hydrogen-bond donors (HBDs) and hydrogen-bond acceptors (HBAs), DESs exhibit low toxicity, favourable biodegradability, and excellent solubilising properties, rendering them promising alternatives to conventional organic solvents in drug synthesis, natural active ingredient extraction and drug delivery. This review systematically evaluates the broad pharmaceutical applications of DESs, with particular emphasis on enhanced drug solubility and bioavailability. In plant extraction, DESs outperform traditional solvents (*e.g.*, diethyl ether) by improving the recovery efficiency of bioactive compounds. In drug synthesis, certain DESs function simultaneously as reaction media and catalysts, enhancing reaction efficiency and selectivity while minimising environmental impact. In drug delivery, DESs facilitate transdermal and oral absorption through interactions with biological membranes, making improved delivery efficiency. Despite these advantages, challenges remain, including high viscosity, formulation complexity, and unresolved regulatory considerations. Future research must focus on physicochemical optimisation, safety evaluation, and scalable production to fully realise the potential in pharmaceutical applications.

*Keywords*: deep eutectic solvents, plant extraction, drug synthesis, drug delivery, hydrogen bond interaction

## INTRODUCTION

DESs have emerged as versatile green solvents in fields such as green chemistry (1, 2), food analysis (3), and environmental engineering (4). Since their systematic introduction by Abbott *et al*. in 2003 (5), DESs have demonstrated cost-effectiveness, non-flammability, and facile synthesis (6). Structurally, DESs consist of eutectic mixtures with depressed melting points due to strong H-bond interactions (7). The extent of melting-point depression correlates with H-bond strength, a key determinant of their physicochemical behaviour (8). Based on their physicochemical characteristics, DESs are generally defined as eutectic systems formed by the combination of Lewis or Brønsted acids and bases, containing a variety of anions and/or cations. In practical preparation, DESs are most commonly

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synthesised by mixing HBDs and HBAs in a certain molar ratio (9). Among various DES systems, those based on choline chloride (ChCl) combined with urea, glycerol or organic acids have been the most extensively studied (10–12). This is not only because these DESs were among the earliest discovered, but also due to the low cost, availability, and environmental benignity of their components. With the continuous advancement of medicinal chemistry, an increasing number of novel DESs have been developed and are playing an increasingly important role in drug synthesis, plant extraction and drug delivery, providing innovative solutions to various complex challenges in pharmaceutical research and development (13, 14). Fig. 1 illustrates representative examples of traditional and emerging HBAs and HBDs commonly employed in the construction of DESs.

Research interest in DESs in the pharmaceutical field has increased steadily since 2011. Fig. 2a presents the number of publications on DESs in the pharmaceutical field, and Fig. 2b shows the number of related patents, with both datasets covering the period from 2012 to the present. As illustrated in Fig. 2, publications related to pharmaceutical applications of DESs emerged around 2011 and experienced rapid growth, peaking approximately in 2020. In parallel, the number of pharmaceutical patents involving DESs has shown an overall upward trend from 2010 to 2024, indicating the continuous deepening of basic research, technological development, and translational application of DESs in the pharmaceutical field. This growing research interest reflects the expanding application scope of DESs in pharmacy. For instance, DESs can enhance drug permeation through the skin, making them attractive for transdermal delivery systems (15); they can also serve as green and efficient extraction media for isolating active pharmaceutical ingredients (APIs) such as phenolic compounds from plant sources (16). Collectively, these research trends underscore

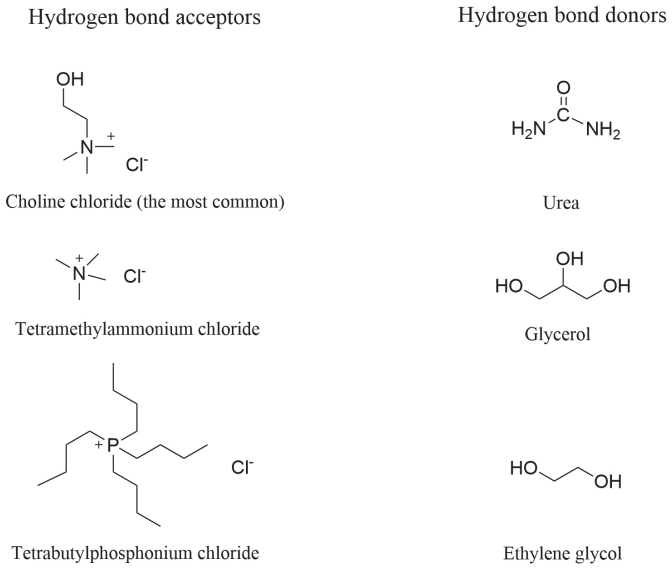


Fig. 1. Common examples of hydrogen bond acceptors and hydrogen bond donors used for the preparation of deep eutectic solvents.

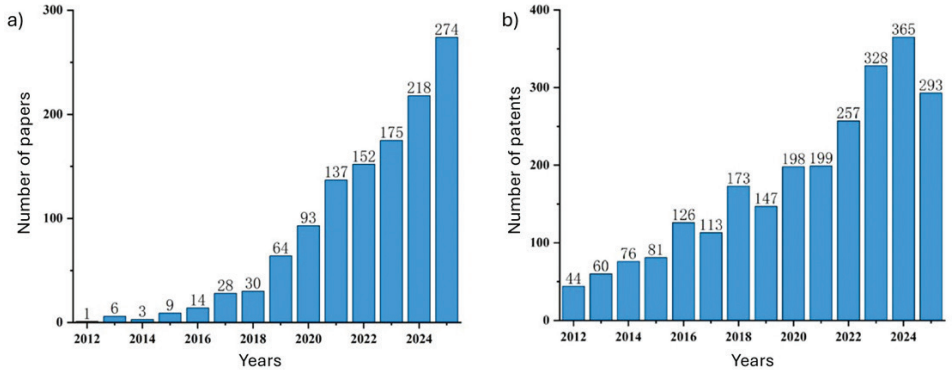


Fig. 2. a) Papers and b) patents published in the pharmaceutical field. (Data collected from online literature databases; slight discrepancies from actual values may occur.)

the importance of in-depth investigation into DESs in medicinal chemistry, as they hold substantial promise for advancing both fundamental research and practical pharmaceutical research and practical industrial applications.

Despite their great potential and extensive research in pharmaceutical applications, the fundamental understanding of toxicity and physicochemical properties of DESs remains insufficient (17, 18). From a thermodynamic perspective, DESs are typical eutectic systems formed by HBAs and HBDs, and their melting behaviour can be described using binary eutectic phase diagrams (19–21). As illustrated in Fig. 3, the phase diagrams reveal pronounced non-ideal interactions between the constituent components, leading to a melting point lower than that of either individual component, which is a direct reflection of the complex and dynamic hydrogen-bonding networks within DESs. However, unlike conventional binary eutectic systems, DESs often deviate significantly from ideal phase behaviour due to extensive, cooperative hydrogen-bonding interaction and strong specific intermolecular forces between components, resulting in the difficulty of systematic and quantitative prediction of their phase structures and physicochemical properties. Moreover, with

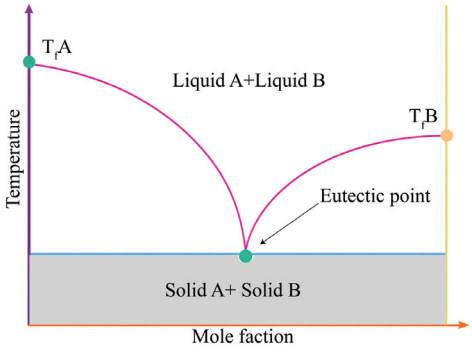


Fig. 3. Binary eutectic phase diagram.

the progress of research, several practical challenges in the application of DESs have become increasingly prominent. A major limitation is the inherently high viscosity of many DESs, which originates from their dense hydrogen-bonding networks (22). Elevated viscosity can hinder mass transfer by slowing the diffusion of reactants in extraction and catalytic processes; in industrial production, poor fluidity may also increase energy consumption, reduce process efficiency, and impose higher technical demands on equipment and process design (23). In addition, DESs face critical challenges related to irritation and potential toxicity in drug delivery applications (24, 25). These adverse effects may be partly attributed to the acidic HBD components in some DESs, which can result in a low pH of the solvent system and induce irritation to biological tissues. Furthermore, in transdermal drug delivery, certain DESs enhance drug permeation primarily by disrupting the highly ordered lipid organisation of the stratum corneum (26). While this mechanism effectively improves drug transport across the skin barrier, excessive disturbance of the lipid matrix may compromise the integrity of the skin barrier and induce local irritation or even cytotoxic effects on keratinocytes. Compared with traditional organic solvents, DESs exhibit extremely low vapour pressure, which may lead to solvent residue retention after use (27). When non-natural DESs are employed as drug delivery carriers, the lack of specific metabolic enzymes for their components in the human body may result in prolonged persistence and accumulation in organisms, potentially giving rise to long-term adverse biological effects (28). Finally, DESs represent a broad and structurally diverse class of solvent systems rather than a single, well-defined chemical entity. A vast number of DESs can be generated through different combinations of HBAs and HBDs, further complicating the establishment of unified structure-property relationships. Although significant progress has been made in the characterisation of individual DES systems, achieving a comprehensive and systematic understanding of the structure-function relationships of DESs remains a major challenge in the field (29).

The combinatorial diversity of HBAs and HBDs gives rise to an almost limitless number of DESs, each of which may exhibit distinct metabolic pathways and biological behaviours in organisms (30). This inherent structural and compositional variability has, to date, hindered the development of comprehensive and systematic metabolic assessments across different DES systems. Based on the nature of constituent components and the dominant interaction mechanisms governing their formation, DESs are commonly classified into five categories (Types I–V), as shown in Table I. Among these, Type III DESs, typically composed of quaternary ammonium salts and HBDs, are the most extensively investigated, particularly in pharmaceutical applications. The establishment of a rational and unified classification

*Table I. Composition of different DES types*

| Type of DES | Composition |
|---|---|
| Type I | Metal salts with quaternary ammonium salts |
| Type II | Metal salt hydrates with quaternary ammonium salts |
| Type III | Mixing quaternary ammonium salts with hydrogen bond donors |
| Type IV | Metal chlorides and hydrogen bond donors |
| Type V | Nonionic constituents both as hydrogen bond acceptors and hydrogen bond donors |

system for DESs is expected to provide a critical foundation for future studies aimed at correlating DES structures with their metabolic, toxicological, and biological properties, thereby facilitating more systematic and comparative investigations across diverse DES classes.

This review analyses DESs from both molecular and macroscopic perspectives, with a particular focus on their pharmaceutical applications, including natural active ingredient extraction, drug delivery, and drug synthesis. A defining feature of DESs is the presence of extensive hydrogen-bonding networks, and these interactions are central to understanding the behaviour and performance of DESs in pharmaceutical systems. In the extraction of bioactive compounds from natural sources, HBAs and HBDs within DESs can form stable hydrogen-bond complexes with polar functional groups (*e.g.*, carboxyl and amino groups) in herbal constituents. These specific interactions markedly enhance both the solubility and selectivity of target compounds, thereby significantly improving extraction efficiency.

In drug-delivery systems, DESs represent a promising approach for mitigating key formulation challenges in drug development, including poor solubility, low permeability, and inadequate chemical stability of APIs (31). Additionally, in pharmaceutical synthesis, hydrogen-bonding interactions between DESs and reaction substrates can promote the formation and stabilisation of reaction intermediate complexes, thereby enhancing reaction efficiency and selectivity (32).

Moreover, the relatively early stage of research and development of DESs, together with the lack of standardised characterisation and evaluation protocols, has resulted in significant knowledge gaps, particularly with respect to safety assessment, regulatory approval, and long-term application risks. For instance, the appropriate regulatory classification of DESs in pharmaceutical formulations, such as whether they should be considered co-solvents or pharmaceutical excipients, remains an open and actively debated question in the industry and regulatory agencies. In summary, despite their considerable promise in the pharmaceutical field, the further development and practical application of DESs face numerous unresolved challenges that must be systematically addressed in future research.

## DES USED AS EXTRACTION SOLVENT FOR NATURAL ACTIVE INGREDIENTS

Extraction technology is a fundamental and indispensable process in the pharmaceutical industry, particularly for the isolation and analysis of bioactive compounds from plant- and animal-derived materials (33), and it plays a crucial role in the advancement of pharmacological research and new drug development. However, conventional extraction methods often suffer from several limitations, including low extraction efficiency, difficulty in controlling solvent residues, and potential harm to human health and the ecological environment (34–36). Consequently, DESs, which have been systematically developed since the beginning of the twenty-first century, have emerged as promising alternatives to traditional organic solvents and ionic liquids in the extraction of natural active ingredients. Compared with conventional solvents, DESs generally exhibit superior extraction efficiency for natural APIs (37–39). They can markedly reduce solvent residues, thus improving the environmental sustainability of extraction processes.

Hu *et al*. (40) employed natural deep eutectic solvents (NADESs) for the green extraction of chlorogenic acid (CGA), ferulic acid (FA), hydroxysafflor yellow A (HSYA),

and anhydrosafflor yellow B (AHSYB) from herbal materials, aiming to enhance both extraction efficiency and the antioxidant activity of the extracts. Nine NADES formulations with different component combinations were systematically screened, and an L-proline:lactic acid system at a molar ratio of 1:2 was ultimately identified as the optimal extraction solvent. Compared with conventional solvents such as water and methanol, NADES tested exhibited markedly superior extraction performance: the extraction yields of CGA, HSYA, FA and AHSYB were increased by 60.4, 15.7, 103.3 and 70.8 %, resp. In addition, the extraction time using NADESs was significantly reduced, namely, to only 67 min, and the resulting extracts demonstrated strong antioxidant activity. These results highlight NADESs as highly effective extraction media that can not only directly isolate bioactive compounds from plant materials but also extract key precursors for subsequent chemical synthesis. *Torreya grandis* is a valuable tree species with significant nutritional and medicinal potential, and its kernels are rich in fatty acids and various bioactive compounds (41). After oil extraction, the remaining pomace still contains abundant flavonoids with antioxidant and anti-inflammatory properties. Owing to the multiple phenolic groups in flavonoids, strong hydrogen-bonding interactions can be established between flavonoids and DES components, thereby enhancing the solubility of flavonoids in the solvent and improving extraction efficiency. Using DES-based extraction technology, the maximum flavonoid yield from *T. grandis* pomace reached 12.741 mg $g^{-1}$. Consistently, as shown in Fig. 4, flavonoids extracted with 80 % choline chloride/acetamide exhibited higher

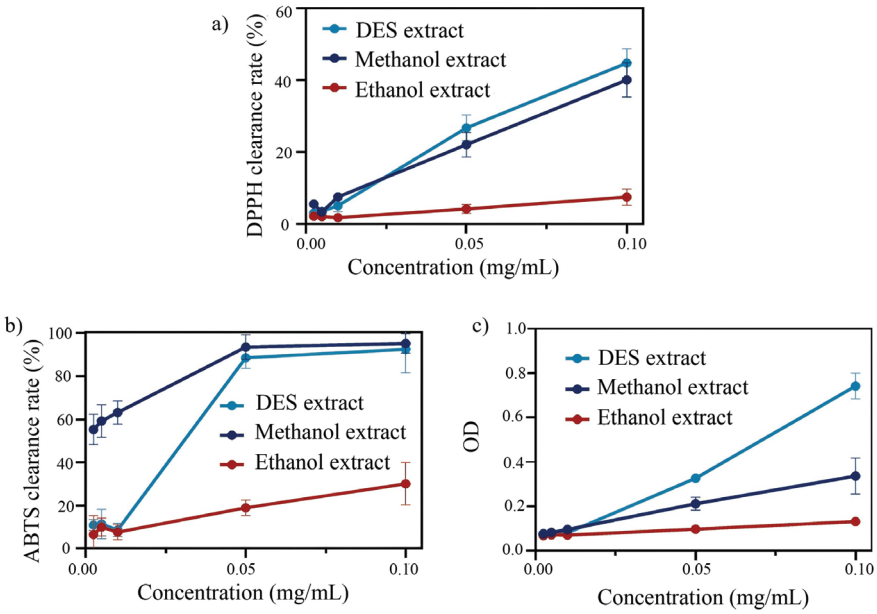


Fig. 4. Antioxidant activities of flavonoids from *T. grandis* pomace: a) DPPH radical scavenging; b) ABTS radical scavenging; c) $Fe^{2+}$ chelation, for extracts prepared with DES (80 % ChCl/acetamide), 90 % ethanol, and 90 % methanol. This indirectly reflects the extraction capabilities of different solvents for active ingredients (41).

2,2-diphenyl-1-picrylhydrazyl and 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) radical-scavenging activities, as well as stronger $Fe^{2+}$ chelating capacity, than those obtained using 90 % ethanol or 90 % methanol. These findings further demonstrate that NADESs not only improve the extraction yield of natural active ingredients but also preserve and even enhance their biological activity (*e.g.*, antioxidant functionality). Moreover, Meng *et al.* (42) reported an ultrasound-assisted DES-based extraction strategy for flavonoids from *Typha angustifolia* L. pollen, in which a choline chloride/1,2-propanediol system significantly outperformed conventional organic solvents. Compared with 75 % ethanol, this DES system achieved approximately 15–30 % higher total flavonoid yields, with improvements exceeding 30 % for isorhamnetin. These results further confirm the exceptional efficiency of DESs as alternative green solvents for the extraction of plant-derived bioactive compounds.

Li *et al*. (43) reported an ultrasound-assisted extraction of phenolic compounds from lettuce (*Lactuca sativa*) leaves using a natural DES composed of L-proline and lactic acid. Lettuce is a rich source of diverse bioactive constituents, including phenolic compounds, glycosylated flavonoids, sesquiterpene lactones (*e.g.*, lactucopicrin and lactucin), carotenoids, B vitamins, ascorbic acid and tocopherols. Using the NADES-based extraction approach, the total phenolic content reached 25.17 mg gallic acid equivalents per g dry mass of the raw material, which was significantly higher than that obtained using 50 % EtOH and water as extraction solvent. Notably, this value approaches the maximum phenolic yield achieved under fully optimised conventional extraction conditions, demonstrating the effectiveness of NADES-assisted extraction and highlighting its potential as a promising green strategy for the recovery of bioactive compounds from lettuce and other horticultural crops with medicinal value.

When DESs are employed as extraction media for bioactive compounds, solvent residue in the final product can be effectively controlled (44). For example, Sun *et al*. (45) reported an ultrasound-assisted extraction of flavonoids from hawthorn (*Crataegus pinnatifida*) using DESs. This approach not only significantly enhanced extraction efficiency but also enabled efficient solvent recovery after extraction. In that study, polyamide resin was used to recover the DES following flavonoid extraction, and it was collected after centrifugation and filtration, achieving a recovery rate of 91.5 ± 0.1 %, which is generally regarded as a high level of solvent recyclability. The ability to recover more than 90 % of the extraction solvent indicates that DESs can be efficiently reused, thereby yielding higher-purity extracted products. This substantial reduction in residual solvent content not only improves product quality but also offers important advantages for subsequent synthesis steps and downstream pharmaceutical processing.

Although traditional organic solvents can exhibit high extraction efficiency for certain plant-derived active compounds, most possess inherent toxicity and environmental hazards, which severely limit their suitability for industrial pharmaceutical production. In contrast, many components of DESs are of low toxicity or benign, environmentally friendly, and provide greater flexibility for green plant extraction processes (46–48). Artemisinin is a sesquiterpenoid compound isolated from *Artemisia annua* (49), and artemisinin-based therapies remain the fastest-acting antimalarial treatments currently available. At present, extraction from natural plant sources remains the primary route for artemisinin production. However, conventional organic solvents such as alcohols, ethers and alkanes are associated with significant toxicity and environmental risks, motivating the search for

greener alternatives. Consequently, increasing attention has been directed toward the use of DESs as environmentally sustainable extraction media. Cao *et al.* (50) explored the use of ammonium chloride-based DESs for the extraction and separation of artemisinin. Subsequently, Fan *et al.* (51) employed the conductor-like screening model for real solvents (COSMO-RS) to rationally design a novel benzoic acid/fenchyl alcohol-based NADES for artemisinin extraction. These DES systems demonstrated lower toxicity than traditional organic solvents, were easier to separate and recycle, and the NADES were recovered *via* a low-temperature liquid-liquid separation combined with anti-solvent crystallisation, resulting in substantially lower solvent residues. Collectively, these advantages underscore the potential of DES-based extraction strategies as greener, safer, and more sustainable alternatives for artemisinin production.

Anmol *et al.* (52) employed a NADES composed of ChCl, citric acid, urea and lactic acid to extract bioactive compounds from *Aconitum heterophylla*. The primary active component in the extract, lappaconitine, exhibits notable anticancer, analgesic and antifungal activities. The used NADES formulation not only achieved high extraction efficiency for lappaconitine but also consisted entirely of natural, non-toxic, and biodegradable components, complying with the requirements of green pharmaceutical production. Importantly, the authors further developed a solid-liquid separation strategy using HP-20 resin for effective NADES recovery after extraction, thereby minimising solvent consumption and enhancing the overall environmental sustainability of the extraction process. Citrus leaves are a commonly underutilised post-harvest byproduct of citrus fruits, rich in valuable bioactive compounds, particularly terpenoids and phenolic substances with antioxidant and anti-inflammatory activities. Domínguez-Rodríguez *et al.* (53) described the use of a NADES composed of ChCl and glycerol (molar ratio 1:2) as an extraction medium for the efficient isolation of bioactive terpenoids from citrus leaves. A comprehensive green assessment of the proposed biorefinery process revealed a green coefficient of 0.68. The green coefficient is a multi-parameter, weighted evaluation metric used to quantify the environmental friendliness of chemical processes, integrating factors such as resource utilisation efficiency, environmental impact and sustainability. A value of 0.68 indicates that the process is environmentally benign, safe and highly sustainable. Compared with conventional DESs, NADESs are generally considered greener and more environmentally compatible, as their constituents are derived primarily from natural compounds, including organic acids (54), amino acids (55) and carbohydrates (56). As a result, NADESs offer improved operational safety, superior biodegradability, and reduced toxicity, making them particularly attractive as extraction solvents. In summary, among the various classes of DESs, NADESs represent one of the most promising platforms for extraction applications, owing to their enhanced environmental compatibility and sustainability in process design.

In an experiment investigating the extraction and separation of active substances with different polarities from dried *Schisandra chinensis* fruit, Yan *et al.* (57) designed therapeutic deep eutectic solvents (THEDESs) composed of amino alcohols and phenolic compounds as switchable extraction media. Compared with conventional solvents (water, methanol and 70 % ethanol), the extraction efficiencies achieved using THEDESs were significantly enhanced, yielding 1.17–1.62 times higher yields for lignanoids and 1.39 times higher yields for polysaccharides. To elucidate the underlying extraction mechanism, density functional theory (DFT) calculations were employed, revealing that hydrogen bonding

plays a dominant role in improving extraction performance. The binding energies and the most probable binding sites between TRDESs and representative lignans and polysaccharides were calculated using DFT. The results indicate that, among all possible intermolecular interactions, hydrogen bonding exhibits the lowest binding energy, corresponding to the most stable interaction mode. Specifically, the hydrogen-bonding interaction energies between TRDESs and lignans and polysaccharides were calculated to be −4.7 kcal $mol^{-1}$ and −3.6 kcal $mol^{-1}$, resp. These values are substantially lower than those associated with non-hydrogen-bonding interactions involving –NH groups (−0.6 kcal $mol^{-1}$ for lignans and −0.06 kcal $mol^{-1}$ for polysaccharides). Because lower binding energy corresponds to stronger and more stable interactions, these results indicate that hydrogen bonding plays a decisive role in the dissolution, transport, and controlled release of target molecules during the extraction process. The unique ability of DES to achieve both high extraction efficiency and environmental friendliness is fundamentally attributed to its hydrogen-bonding characteristics. In particular, green and biocompatible components commonly used in NADES, such as sugars (58), amino acids (59) and lactic acid (60), can readily form hydrogen bonds with drug molecules containing polar functional groups. These hydrogen-bond interactions enhance the affinity between drug molecules and the HBDs or HBAs in the solvent system, thereby significantly improving the drug solubility of target compounds. Moreover, polar functional groups (*e.g.*, –OH, –COOH and $–NH_2$ groups) present in most natural bioactive molecules can form stable hydrogen-bonded complexes with HBDs or HBAs in DES. This results in the formation of an extended and stable solvent-solute hydrogen-bond network, which contributes to enhanced solubilization, stabilisation, and preservation of bioactive compounds within the extraction medium.

The high extraction efficiency of DES is mainly attributed to its strong hydrogen-bonding interactions and tunable polarity, two key physicochemical properties that significantly enhance the solubility and selectivity of target compounds. In addition, as reported in previous studies, the introduction of an appropriate amount of water as a cosolvent can partially disrupt the hydrogen-bond network of DESs, thereby reducing solvent viscosity and promoting solute diffusion, which further improves the overall extraction performance (61). Overall, NADES represent a class of green and low-toxic solvents that enable efficient extraction while simultaneously reducing solvent residues.

## DRUG SYNTHESIS

Drug synthesis represents a core component of pharmaceutical research and development, as it directly influences molecular structure construction, biological activity optimisation, and the technical feasibility of large-scale manufacturing for novel drug candidates (62, 63). Compared with conventional organic solvents, certain DESs exhibit superior process sustainability, as they are typically composed of low-cost, biodegradable, and pharmacologically safe components, feature improved operational safety, and can be efficiently recovered and reused. In this context, DESs have emerged as a promising solvent platform for pharmaceutical synthesis, owing to their outstanding green properties and unique capacity to modulate reaction environments (64). Broadly, the application of DESs in drug synthesis can be categorised into two main approaches: (*i*) their use as reaction solvents during drug synthesis processes, and (*ii*) the direct utilisation of DESs incorporating APIs as therapeutic systems (65).

### *Solvent function of DES in drug synthesis*

Numerous studies have validated the feasibility of DESs as green media for pharmaceutical synthesis. Das *et al.* (66) established a highly efficient and chemoselective one-pot three-component coupling reaction (3-CCR) for constructing densely functionalized 8,10-dimethyl-12-phenyl-8,12-dihydro-9*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)--dione frameworks. This transformation involved the coupling of aromatic aldehydes, 2-naphthol, and 6-amino-1,3-dimethyluracil in a DES composed of choline chloride and malonic acid [ChCl:$CH_2(COOH)_2$] at a 1:1 molar ratio. Under optimised conditions, the target products were obtained in moderate but meaningful yields of approximately 46 %, which is notable for the construction of such structurally complex fused heterocyclic derivatives. Importantly, the synthesised compounds displayed significant antiproliferative activity against multiple cancer cell lines, highlighting their potential pharmaceutical relevance. The effectiveness of this protocol is closely associated with the dual role of DES as a reaction medium: it facilitates substrate activation and stabilises key reaction intermediates *via* hydrogen-bonding interactions. Collectively, this synthetic strategy fully exploits the intrinsic merits of DESs, including ultra-low vapour pressure, non-flammability, high chemical and thermal stability, low toxicity and biodegradability. As a result, it provides a cost-effective, operationally straightforward, and environmentally benign synthetic route that proceeds under mild reaction conditions without harsh reagents or catalysts.

Cicco *et al*. (67) presented an enhanced, sustainable, and scalable synthetic strategy for tacrine, a well-established cholinesterase inhibitor used in the treatment of Alzheimer's disease, by replacing conventional volatile organic solvents with DES. This approach markedly reduced the environmental footprint of tacrine synthesis while achieving exceptionally high reaction efficiency under mild conditions. Notably, the yield of tacrine reached up to 98 % in the DES medium, in sharp contrast to only 48 % obtained using the traditional xylene-mediated reflux protocol. The remarkable improvement in synthetic performance can be attributed to the intensive hydrogen-bonding interactions between DES components and functional groups present in tacrine intermediates, which strengthen solvent-substrate affinity, stabilise transition states, and minimise side reactions and material losses during the transformation. These results clearly demonstrate that DESs outperform conventional organic solvents not only in environmental compatibility but also in boosting reaction efficiency and product yield for pharmaceutical synthesis.

### *Catalytic functions of DES in drug synthesis*

In addition, Mendes *et al.* (68) showed a novel DES-based catalytic system by combining a copper-manganese iminodiacetic acid one-dimensional coordination polymer with a ChCl/urea for the synthesis of a series of Morita-Baylis-Hillman adducts from indigo carmine derivatives. This combined system afforded excellent product yields ranging from 59 to 97 %, while significantly shortening reaction times, leading to substantially improved overall efficiency and reduced energy consumption. Similarly, Shirisha *et al.* (69) established a mild, green, and efficient synthetic strategy toward functionalized tacrine derivatives using biodegradable and recyclable DES both as solvent and catalyst. The DES was prepared from *N*,*N*′-dimethylurea and L-(+)-tartaric acid (molar ratio 3:1) at 80 °C and exhibited excellent biocompatibility and strong solubilising capacity for organic substrates. Within this solvent system, both C–C bond formation at C($sp^3$)–H sites and C–N bond

construction were successfully achieved for the synthesis of functionalized tacrine derivatives. Specifically, the condensation of 9-chloro-1,2,3,4-tetrahydroacridine with various aromatic aldehydes proceeded efficiently in the DES medium, enabling selective C($sp^3$)–H functionalization and yielding a series of structurally diverse unsaturated compounds in good yields. For the synthesis of substituted *N*-aryl tacrine derivatives, nucleophilic substitution between 9-chloro-1,2,3,4-tetrahydroacridine and various substituted anilines also proceeded smoothly in the DES, affording yields of up to 85 %, approximately 10 % higher than those obtained using the conventional $SnCl_2$/THF system, while avoiding the use of metal catalysts and thereby offering superior environmental sustainability. Overall, these studies demonstrate that the extensive hydrogen-bonding networks within DESs enable them to function not only as solvents, but also as catalytic media, effectively fulfilling dual roles as both solvent and catalyst in selected synthetic systems.

### *Drug-based deep eutectic systems*

Beyond their conventional role as solvents, DESs have increasingly been designed to incorporate pharmacologically active components, enabling their direct use as therapeutic systems and, in some cases, enhancing overall therapeutic efficacy. For instance, C. V. Pereira *et al*. (70) developed limonene-based therapeutic deep eutectic systems by combining limonene with menthol, ibuprofen (IBU) or fatty acids, and demonstrated their antiproliferative activity against HT29 colorectal cancer cells. Notably, the IBU-limonene system (1:4) inhibited cancer cell proliferation while maintaining normal cell viability, indicating selective activity. Mechanistically, this system did not induce cell-cycle arrest or apoptosis but instead reduced intracellular ROS levels and increased nitric oxide production. In addition, terpene-NSAID THEDES have been reported by J. Pereira *et al*. (71) to enhance drug solubility and bioavailability, supporting their potential as drug delivery systems. Moreover, Santos *et al*. (72) designed THEDESs composed of citric acid, ethambutol and water, as well as systems containing L-arginine, for potential use in tuberculosis therapy. Incorporation of ethambutol into the THEDES drastically improved its physicochemical properties: solubility was increased by 27.5-fold (from 4.64 to 127.6 mg $mL^{-1}$), and membrane permeability was significantly enhanced, suggesting great potential for improved drug bioavailability and pharmacokinetic performance. In a related study, Yang *et al*. (73) prepared and characterised a series of matrine-based THEDESs composed of matrine and medium- to long-chain fatty acids. Systematic evaluation of their physicochemical properties provided an important foundation for the future medical application of matrine-based DES formulations.

### *Hydrogen-bond-mediated reaction regulation*

The role of DESs in pharmaceutical drug synthesis is closely associated with their extensive hydrogen-bonding interactions (74). When used as reaction media, DESs are capable of dissolving both polar and weakly polar drug precursors through their structured hydrogen-bond networks, a property that is particularly beneficial for poorly soluble APIs. These interactions improve dispersion and enhance effective contact between reactants and catalysts, thereby improving reaction efficiency and overall synthetic performance (75, 76).

When employed as reaction media or carriers, the HBD components of DESs, such as carboxylic acids and phenols (77), can significantly influence substrate orientation, thereby promoting regioselective and enantioselective transformations. Furthermore, the extensive hydrogen-bonding networks within DESs can modulate electron distribution between reactants, effectively lowering activation energy barriers and accelerating reaction kinetics (78–81). In addition, many DES components possess inherent biological activity, such as IBU, limonene and matrine, enabling the one-step construction of THEDESs with combined solubilising and therapeutic functions. Collectively, these characteristics underscore the potential of DESs as versatile and multifunctional platforms for pharmaceutical drug synthesis.

## DRUG DELIVERY

In pharmaceutical formulation development, solvent selection constitutes a critical factor that directly determines the efficiency, safety, and clinical outcome of drug delivery. The use of conventional organic solvents (*e.g.*, methanol, acetonitrile, dichloromethane) is frequently restricted by inherent toxicity, insufficient biocompatibility and environmental hazards (82, 83). Therefore, the development of green, safe, and efficient alternative solvent systems has become an important direction in modern pharmaceutical research and development. Within this context, DESs have attracted considerable interest owing to their high drug-solubilization capacity, favourable biocompatibility and inherent sustainability (84, 85). The distinctive hydrogen-bonding networks in DESs can effectively improve the solubility and permeability of poorly water-soluble drugs, thereby enhancing their bioavailability (defined as the proportion of the unchanged drug entering the systemic circulation) (86, 87). Consequently, DESs have become increasingly important in a wide range of drug--delivery applications, including oral, transdermal, and other advanced delivery strategies.

### *Oral drug delivery*

Panbachi *et al*. (88) proposed a novel hypothesis for the oral delivery of drugs using DESs. By incorporating polymeric precipitation inhibitors into DES formulations, they developed a polymer-embedded deep eutectic system. After systematic formulation screening, a DES composed of L-carnitine and ethylene glycol (molar ratio 1:4) combined with 15 % (*m*/*m*) polyvinylpyrrolidone was constructed. This system effectively inhibited drug precipitation, maintained a supersaturated state, and presented a pronounced "spring-and-parachute" release profile. Consequently, drug absorption and systemic exposure were significantly improved, accompanied by enhanced formulation stability and robustness, demonstrating its great potential as a versatile platform for oral delivery of poorly soluble drugs.

DESs can be directly employed as filling liquids in soft capsules, an oral dosage form in which a liquid, solution, emulsion, or semi-solid system is encapsulated within a capsule shell (89). In addition, DES-based systems can be transformed into preferred amorphous solid formulations through drying and subsequent processing, improving drug carrier nanofibers, rather than acting as drug carriers, thereby opening new avenues for oral drug delivery. IBU is a widely used non-steroidal anti-inflammatory drug characterised by poor aqueous solubility, low dissolution, and limited formulation compatibility. To overcome

these drawbacks, Marincaș *et al*. (90) prepared IBU-loaded nanofibers based on polycaprolactone (PCL), and two DESs (ChCl-acetic acid and ChCl-glycerol). These nanofibrous systems could be further processed into granules and deliver IBU to targeted intestinal sites through fibre degradation, dissolution, or diffusion. Although the incorporation of DESs did not significantly alter the adsorption-desorption behaviour of IBU, it remarkably improved nanofiber morphology and reduced the strong hydrophobicity of the PCL, thereby enhancing wettability, dissolution, and oral bioavailability of IBU.

### *Transdermal drug delivery*

Compared with oral delivery, DESs show more prominent advantages in transdermal delivery systems (91, 92). Conventional transdermal drug delivery is often limited by the extremely low permeability of the stratum corneum, which forms a dense lipid barrier that prevents most drug molecules from penetrating into the skin. To overcome this bottleneck, Li *et al.* (93) developed a series of DESs composed of oxymatrine (OMT) and fatty acids with varying alkyl chain lengths as a novel transdermal penetration enhancer. Their results demonstrated that quercetin exhibited significantly enhanced and composition-dependent solubility in different OMT-long chain fatty acids DES formulations, with saturation solubilities of 4.3 ± 0.47, 5.0 ± 0.22, and 3.9 ± 0.33 mg $mL^{-1}$ in OMT-capric acid, OMT-lauric acid and OMT-myristic acid DES, resp. These values represent a remarkable 390–500-fold increase in the solubility of quercetin compared with its aqueous solubility. In parallel, the DES systems substantially improved the skin permeability of OMT, highlighting their strong potential for transdermal drug delivery. Collectively, this study provides valuable guidance for the rational design of future DES-based transdermal formulations. Beyond their role as penetration enhancers, DESs have also been explored in microneedle-assisted transdermal drug delivery. Microneedle delivery is an emerging and minimally invasive technique that employs arrays of microscopic needles to breach the skin barrier and deliver drugs directly to the epidermal or dermal layers (94, 95). Microneedle patch therapy offers improved patient compliance and reduced risk compared with conventional administration routes (96). However, its broader application is often constrained by low drug-loading capacity, particularly when the active pharmaceutical ingredient or carrier exhibits poor solubility (97–99). Recent studies have demonstrated that incorporating deep eutectic solvent-based matrices can effectively overcome this limitation. For example, eutectogel microneedle patches prepared using a choline chloride:1,2-propanediol (1:2) NADES significantly enhanced the solubilization and loading of hydrophobic drugs such as curcumin and docetaxel, enabling sustained transdermal delivery over several days (100).

Mesoporous silica nanoparticles (MSNs) represent a promising class of inorganic drug carriers; nevertheless, limitations related to solubility and skin permeability have hindered their clinical translation. To overcome these challenges, Zhao *et al.* (101) proposed a DES-mediated transdermal delivery system based on amino acids and citric acid. This system significantly promoted skin penetration of MSNs, and nanoparticles were successfully detected in systemic circulation, confirming that DESs can effectively overcome the skin barrier and achieve non-invasive transdermal delivery of nanocarriers.

### *Injectable drug delivery*

DESs also exhibit great potential in injectable formulations, particularly for poorly soluble drugs that cannot be prepared as aqueous injections. Conventional injectable

solvents (*e.g.*, ethanol, propylene glycol) often cause vascular irritation, systemic toxicity and poor stability, limiting their clinical application. Kim *et al.* (102) reported a lipid-based DES system for efficient solubilization of verteporfin, a promising therapeutic agent with potential roles in cardiovascular protection and immune modulation. The DES, composed of choline and oleic acid, spontaneously form stable nanocomplexes (< 100 nm) and significantly improves cellular internalisation and intracellular retention of verteporfin. This study demonstrated that DESs can serve as safe and effective solubilising vehicles for intravenous delivery of poorly soluble drugs.

### *Mechanistic basis of DESs in drug delivery*

In summary, the unique hydrogen-bonding structure of DESs is the fundamental mechanism underlying their excellent performance in drug delivery systems. On one hand, DESs can destroy the crystal lattice of drugs, stabilise amorphous or supersaturated states, and greatly improve the solubility and oral bioavailability (103). On the other hand, DESs can interact with skin lipids and increase membrane fluidity to promote transdermal permeation without permanently damaging the skin barrier. In addition, the structural tunability and molecular compatibility of DESs allow flexible design for oral, transdermal, injectable and microneedle delivery platforms. Most DES components (choline, amino acids, organic acids, polyols) are biodegradable, low-toxic and pharmaceutically acceptable, ensuring high biological safety. Collectively, these advantages make DESs highly promising next-generation delivery systems that can significantly improve the efficacy, safety and sustainability of pharmaceutical formulations.

## CONCLUSIONS

DESs have emerged as highly promising green solvent systems in the pharmaceutical field owing to their unique physicochemical properties, excellent biocompatibility and designable structure, making them ideal alternatives to traditional organic solvents and even ionic liquids. This review systematically summarises the rapidly expanding applications of DESs across three core pharmaceutical domains: natural active ingredient extraction, drug synthesis and drug delivery. In each field, DESs exhibit distinct advantages in improving efficiency, enhancing sustainability, reducing toxicity, and boosting product performance, highlighting their irreplaceable role in the development of modern green pharmacy.

Notably, DESs should no longer be regarded as conventional replacement solvents, but as multifunctional integrated platforms that simultaneously regulate solvation behaviour, intermolecular interactions, mass transfer efficiency, and formulation performance through tailorable hydrogen-bonding networks. Their greatest value lies in the unified integration of extraction, synthesis and delivery, within a single green solvent system, which simplifies pharmaceutical processes, reduces raw material and energy consumption, lowers environmental pollution, and enhances the safety and stability of final products. This integrated advantage is difficult to achieve using traditional solvent systems.

Despite the remarkable progress achieved in pharmaceutical applications of DESs, several critical challenges still restrict their large-scale industrial translation and clinical application: (*i*) high intrinsic viscosity of most DESs, which impedes mass transfer and

processing operability, (*ii*) lack of systematic and comprehensive toxicological and metabolic data to support long-term safety assessments, (*iii*) unclear regulatory status (*e.g.*, classification as co-solvent, excipient or carrier) and absence of unified quality control standards, (*iv*) difficulties in structure-property relationship prediction caused by the extreme diversity of HBA-HBD combinations. To address these challenges, future research should focus on rational molecular design of DESs with reduced viscosity, improved biodegradability and enhanced biocompatibility, systematic safety evaluation, scalable and economical preparation processes, and collaboration with regulatory authorities to establish standardised evaluation systems. Only in this way can DESs truly progress from laboratory research to industrial production and fully realise their enormous potential in promoting the green, sustainable, and high-quality development of the pharmaceutical industry.

*Abbreviations, acronyms, symbols.* – AHSYB – anhydrosafflor yellow B, API – active pharmaceutical ingredient, 3-CCR – three-component coupling reaction, CGA – chlorogenic acid, ChCl – choline chloride, COSMO-RS – conductor-like screening model for real solvents, DES – deep eutectic solvent, DFT – density functional theory, FA – ferulic acid, GAE – gallic acid equivalent, HBA – hydrogen bond acceptor, HBD – hydrogen bond donor, HSYA – hydroxysafflor yellow A, IBU – ibuprofen, MSNs – mesoporous silica nanoparticles, NADES – natural deep eutectic solvents, PCL – polycaprolactone, THEDES – therapeutic deep eutectic systems, TRDES – therapeutic-responsive deep eutectic solvents, VOCs – volatile organic compounds

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