Review

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Capric Acid–Based Therapeutic Deep Eutectic Systems: A Focused Review within the Framework of Deep Eutectic Solvents

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Abstract

Background/Objectives: Capric acid–based therapeutic deep eutectic systems (THEDES) are emerging as a distinct class of biofunctional matrices capable of reshaping drug solubilization, permeability, and bioactivity. **Methods**: Relevant studies on capric acid–based therapeutic deep eutectic systems (THEDES) were identified through targeted database searches and screened for evidence on their design, mechanisms, and pharmaceutical performance. **Results**: This review synthesizes current evidence on their structural design, mechanistic behavior, and pharmaceutical performance, revealing several unifying principles. Across multiple drug classes, capric acid consistently drives strong, directional hydrogen bonding and drug amorphization, enabling exceptional solubility enhancements and stabilized supersaturation. Its amphiphilic C10 chain further contributes to membrane fluidization, which explains the improved transdermal and transmucosal permeation repeatedly observed in capric acid-based THEDES. Additionally, synergistic antimicrobial and anticancer effects reported in several systems confirm that capric acid acts not only as a solvent component but as a bioactive co-therapeutic. Collectively, the reviewed data show that capric acid serves as a structurally determinant element whose dual hydrogen-bonding and membrane-interacting roles underpin the high pharmaceutical performance of these systems. However, gaps remain in long-term stability, toxicological profiling, and regulatory classification. Emerging Artificial Intelligence (AI) and Machine Learning (ML)-guided predictive approaches offer promising solutions by enabling rational selection of eutectic partners, optimal ratios, and property optimization through computational screening. **Conclusion**: Overall, capric acid-based THEDES represent a rationally designable platform for next-generation drug delivery, where solvent functionality and therapeutic activity converge within a single, green formulation system.

Keywords: therapeutic deep eutectic systems (THEDES); capric acid; deep eutectic solvents (DES); fatty acid-based eutectic systems; hydrogen bond interactions; artificial intelligence

1. Introduction

The growing demand for environmentally responsible and pharmaceutically acceptable alternatives to conventional organic solvents has driven significant interest in the development of advanced solvent systems. Traditional organic solvents are widely used in pharmaceutical processes; however, their volatility, toxicity, and poor biodegradability pose risks to both human health and the environment [1,2]. These concerns have accelerated the investigation of alternative solvent systems

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that combine functional performance with improved safety and environmental profiles. Among the alternatives investigated, deep eutectic solvents (DESs) have emerged as attractive candidates due to their ease of preparation, low cost, and potential for biocompatibility [3,4]. In recent years, a subclass known as therapeutic deep eutectic systems (THEDESs) has gained prominence. These systems incorporate at least one component with inherent pharmacological activity, enabling them to function simultaneously as solvent and therapeutic agent [5]. This dual role offers distinct advantages in drug formulation, particularly for compounds with poor aqueous solubility, low permeability, or instability in conventional vehicles [6–8]. Among fatty acids explored in THEDES development, capric acid (decanoic acid, C10:0) is especially attractive because of its natural origin, safety, and ability to form eutectic mixtures with various active ingredients [9–12].

Despite increasing reports on fatty acid-based DESs, a comprehensive evaluation of capric acid-based THEDESs remains lacking. The present review addresses this gap by providing a critical and focused analysis of capric acid-based THEDESs, with emphasis on their design principles, preparation methods, physicochemical characteristics, and pharmaceutical relevance. Particular attention is given to their role in enhancing drug solubility and bioavailability, modulating release kinetics, and supporting novel drug delivery strategies. This review also discusses the underlying mechanisms of drug–solvent interactions, safety considerations, and regulatory challenges, with the aim of supporting further research and translation into clinical and industrial applications.

2. Background on DES and THEDES

The development of non-toxic, biodegradable, and functionally versatile solvent systems has become a central theme in green chemistry and pharmaceutical formulation. Among the solvent systems under active investigation, ionic liquids (ILs) and DESs have gained substantial attention. ILs consist entirely of organic cations and inorganic or organic anions and are typically liquid at or near room temperature [13]. While they exhibit attractive physicochemical properties—such as negligible vapor pressure, tunable polarity, and high solvation capacity—their limited biodegradability, cytotoxicity concerns, and relatively high cost have restricted their widespread application in biomedicine [14].

DESs, by contrast, are formed through the association of a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA), resulting in an eutectic mixture with a melting point significantly lower than that of the individual components [12]. DESs can be readily prepared from a range of naturally derived components, including choline chloride, sugars, organic acids, and fatty acids, many of which are classified as Generally Recognized as Safe (GRAS) [15,16]. Due to their biocompatibility, low toxicity, and high solubilization potential, DESs are increasingly being explored in drug solubilization, extraction of bioactive compounds, biocatalysis, and pharmaceutical formulations [17–19].

An emerging extension of this field is the concept of deep eutectic systems (DESy). Unlike traditional DESs, which are prepared prior to application, DESy are formed in situ during the process of solubilization or formulation, with the target compound itself (e.g., an active pharmaceutical ingredient or bioactive molecule) actively participating in the eutectic interaction [20]. This innovation eliminates the need for pre-formed DESs, simplifying processing, reducing energy input, and enhancing formulation efficiency. DESy have already shown promise in areas such as prebiotic extraction and are increasingly being considered for pharmaceutical applications where solvent–drug synergy is desired [21].

A particularly significant advancement within this family is the development of THEDESs, which are defined as eutectic systems in which one or more components possess intrinsic pharmacological activity [22]. THEDESs represent a novel class of multifunctional systems capable of acting simultaneously as drug carriers and therapeutic agents. Their dual functionality allows for improved drug solubility, controlled release profiles, enhanced membrane permeability, and the potential for synergistic therapeutic effects [6–8]. THEDESs also offer formulation advantages by reducing the need for conventional excipients and enabling novel routes of administration, including

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transdermal and mucosal delivery. As summarized in Figure 1, ILs, DESs, DESy, and THEDESs differ in their composition, method of formation, and pharmaceutical role, reflecting a clear progression from structurally defined solvents to multifunctional, therapeutically active systems.

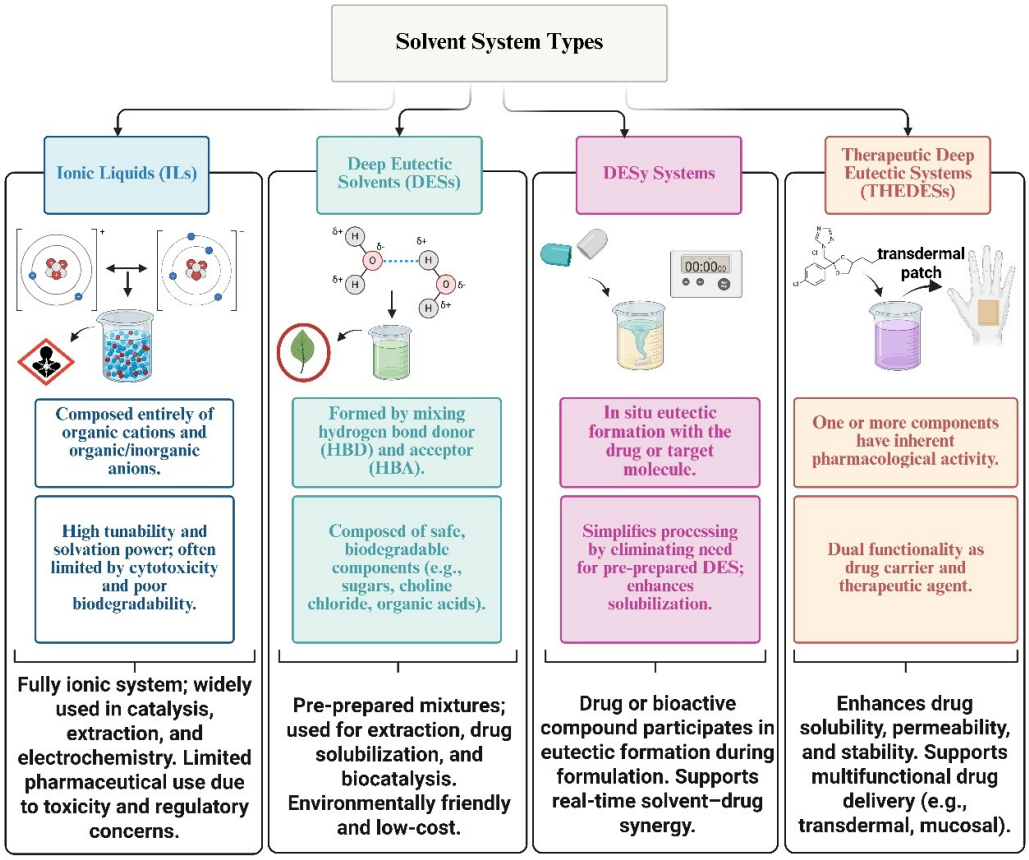

Figure 1. Comparison of ILs, DESs, DESy, and THEDESs based on composition, formation, and pharmaceutical function.

To facilitate a clearer comparison of these solvent systems, Table 1 summarizes the fundamental differences between them, highlighting their respective compositions, interaction mechanisms, physicochemical properties, and pharmaceutical relevance.

Table 1. Comparative overview of eutectic systems (ES), deep eutectic solvents (DES), ionic liquids (ILs), and in situ deep eutectic systems (DESy).

Feature	ES	DES	ILs	*DESy*
Composition	Organic/inorganic blends of solid compounds	Mixtures of H-bond donors and acceptors (ionic or non-ionic)	Pure salts: discrete organic cations and inorganic/organic anions	In situ mixtures formed with the active compound as part of the eutectic system
Melting Behavior	Sharp melting point at eutectic composition (solid or semisolid at RT)	Depressed melting point; liquid at or near room temperature	Liquid at room temperature due to bulky asymmetric ions	Formed dynamically during application; liquid under process conditions
Type of Interactions	Weak van der Waals and minimal hydrogen bonding	Extensive hydrogen bonding network	Electrostatic (ionic) interactions	Hydrogen bonding and solvation driven by target molecule–solvent synergy

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Polarity and Solubility	Moderate; limited to polar solutes	Polar; excellent for solubilizing poorly soluble APIs	Broad—dissolves both polar and non-polar compounds	Typically polar; designed to improve solubility of target APIs
Tunable Properties	Limited	Highly tunable via component selection and ratio adjustments	Highly tunable via cation/anion selection	Moderately tunable via selection of in situ interacting components and formulation conditions (e.g., temperature, water content).
Therapeutic Functionality	Typically absent	Possible if one or more components have inherent biological activity (THEDES)	Generally inert in drug delivery unless functionalized	Yes; active compound contributes to both therapeutic and solvent function
Toxicity and Biocompatibility	Depends on components	Often low (especially with natural components like fatty acids, amino acids, sugars)	Variable; some ILs have cytotoxicity and environmental concerns	Generally favorable if composed of GRAS or natural components
Environmental Impact	Moderate to high (based on solvents used)	Low (especially for NaDES and THEDES based on natural compounds)	Often high; requires careful design for biodegradability	Low; reduced processing steps and mild preparation conditions
Example Systems	Benzoic acid–urea	Choline chloride–urea, choline chloride–capric acid, menthol–ibuprofen	1-butyl-3-methylimidazolium chloride ([Bmim]Cl), [EtPy][BF_4]	In situ systems formed with kiwifruit or date seed polysaccharides
Applications	Melting point depression, food, metallurgy	Green extraction, pharmaceutical formulation, topical/transdermal delivery (THEDES)	Organic synthesis, catalysis, electrochemistry, solubilization	Prebiotic extraction, drug solubilization, biocompatible formulations
Reference	[23]	[24]	[25]	[20]

3. Capric Acid as a Functional Component in Multicomponent Therapeutic Deep Eutectic Systems

Capric acid is increasingly utilized as a hydrogen bond donor (HBD) in the design of THEDES. As illustrated in Figure 2, its chemical structure—characterized by a terminal carboxylic acid and a saturated 10-carbon alkyl chain—enables core structural contributions that support its functional integration in THEDES: hydrogen bonding capacity [11], membrane-modulating hydrophobicity [26], and biocompatible matrix formation [27].

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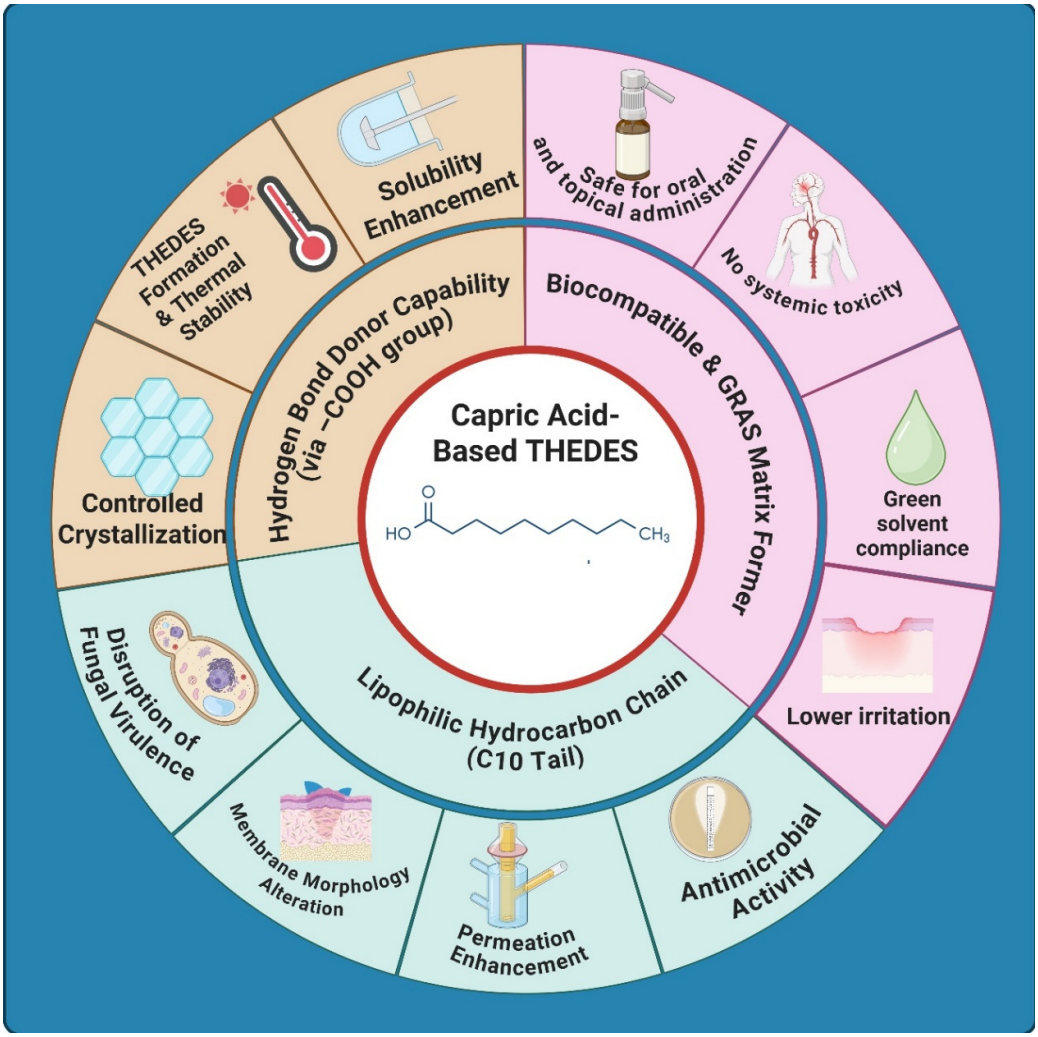

Figure 2. Schematic summary of the multifunctional roles of capric acid in THEDES.

The carboxyl group forms extensive hydrogen bonding networks with various HBAs, including drugs and amino acids, thus facilitating eutectic formation, enhancing thermal stability, and significantly improving the solubility and amorphization of poorly water-soluble active pharmaceutical ingredients (APIs) such as ibuprofen, rasagiline, and lidocaine [6,12]. Additionally, its long alkyl chain imparts amphiphilic characteristics that enhance membrane interaction and lipid fluidization, which in turn promote transdermal and mucosal drug permeation and contribute to antimicrobial efficacy by disrupting microbial membranes [28,29]. These biophysical effects extend to antifungal applications, where capric acid inhibits *Candida albicans* virulence mechanisms, including hyphal formation and biofilm development [30], and induces lipid membrane remodeling such as tubulation [26]. From a formulation standpoint, capric acid's GRAS classification and established biocompatibility make it an attractive choice for topical and oral routes, with in vivo studies confirming its low irritation and systemic safety in THEDES applications [12,31]. Notably, these properties are modulated by the physicochemical nature of the accompanying HBA, which plays a co-determinant role in defining viscosity, solubility, permeability, and biological performance of the final eutectic system. Therefore, capric acid's performance as a THEDES component should be interpreted within the broader context of eutectic pair selection and structural complementarity—factors that are essential for tailoring systems to therapeutic and delivery-specific needs.

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4. Preparation and Characterization of Capric Acid-Based THEDES

Capric acid-based THEDES are typically prepared through a simple, green synthesis route that relies on precise molar mixing of the hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) components under gentle heating and stirring [10,32]. Ratios are optimized based on phase diagrams to achieve eutectic formation, with systems becoming fully liquid at room temperature upon reaching the eutectic point [11].

Characterization of the eutectic nature and molecular interactions is routinely performed using thermal techniques such as Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA), revealing clear endothermic transitions and phase stability of the eutectic systems. In the Gefitinib/Capric acid system, DSC confirmed a homogeneous liquid phase at the eutectic ratio, and TGA demonstrated thermal stability within acceptable pharmaceutical handling ranges [7]. FTIR spectroscopy consistently shows red-shifts in O–H and C=O vibrational bands, supporting extensive hydrogen bonding between carboxyl and hydroxyl groups of the HBD and HBA respectively [11]. In addition, 1H and13C NMR confirm structural integration through chemical shift perturbations, particularly at the hydrogen bonding sites of active pharmaceutical ingredients like Gefitinib and risperidone [7,32]. Phase behavior analyses indicate polymorphic transitions and suppressed crystallinity, a crucial factor in enhancing drug solubility. Morphological studies using microscopy further corroborate the homogeneity of THEDES formulations at room temperature [11]. Rheological assessments demonstrate that viscosity is highly tunable depending on molar ratio, temperature, and water content. Lower viscosity is generally favored to enhance drug diffusion and spreadability, and capric acid-based systems have shown viscosity reductions of up to 70% compared to conventional solvents [10]. Overall, capric acid-based THEDES offers a highly tunable, biocompatible, and efficient platform for drug solubilization and delivery, provided that rigorous preparation and analytical characterization protocols are followed.

5. Role of CA in Promoting Real DES Formation: Insights from Solid–Liquid Phase Diagrams

A pivotal step in validating CA–based THEDES is the comparison of theoretical and experimental solid–liquid phase diagrams. This analysis not only determines the eutectic composition but also reveals the extent to which CA drives systems toward *genuine DES behavior* rather than simple ideal eutectic mixing—a recurring concern among experts in the DES field. Across the investigated systems, CA consistently induces *strong negative deviations from ideality*, a defining thermodynamic signature of real DES formation and a performance level rarely achieved by many commonly used conformers.

In both the ketoconazole–CA (KCZ–CA) and clotrimazole–CA (CLOT–CA) systems, CA demonstrated a remarkable capacity to disrupt the ideal melting behavior predicted by theoretical models, leading to pronounced shifts in eutectic composition and substantial depressions in eutectic temperature. The KCZ–CA mixture exhibited a eutectic point at a KCZ molar fraction of 0.16, while the CLOT–CA mixture reached its eutectic composition at a CLOT molar fraction of 0.25. In each case, the experimental melting curves deviated significantly from ideal predictions, and the resulting mixtures readily transitioned into stable liquids at their eutectic ratios. These pronounced non-idealities reflect CA's exceptional hydrogen-bond-donating ability, hydrophobic compatibility with lipophilic drugs, and its unique capacity to dramatically reduce crystallinity—features that surpass the behavior commonly observed with other fatty acids or conventional DES coformers.

In conclusion, the consistent negative deviations, marked melting-point depressions, and substantial eutectic shifts observed across drug–CA combinations clearly establish CA as a *superior and highly effective coformer* for generating real DESs. Its ability to reliably enforce non-ideality positions CA as an outstanding hydrogen bond donor for the development of pharmaceutical THEDES with enhanced functional performance.

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6. Pharmaceutical Applications

Capric acid-based THEDES have shown remarkable potential in addressing key formulation challenges such as poor drug solubility, low bioavailability, and suboptimal stability. By incorporating active pharmaceutical ingredients (APIs) into a eutectic matrix with capric acid, these systems can dramatically improve the dissolution of hydrophobic drugs. Notably, BCS Class II drugs like risperidone and gefitinib have exhibited solubility enhancements on the order of 104–105-fold when formulated with capric acid [6,29].

For example, a eutectic of risperidone with capric acid achieved a 70,000-fold increase in solubility compared to water [29], while a gefitinib–capric acid THEDES (optimal 80:20 molar ratio) yielded a 30,000-fold solubility boost over aqueous media [7]. Such massive solubilization stems from strong hydrogen-bond interactions and amorphization of the drug within the fatty-acid matrix, effectively overcoming crystalline lattice energy.

This improved thermodynamic solubility translates into faster dissolution rates and can significantly enhance oral or topical bioavailability of poorly water-soluble compounds [33]. Furthermore, the microenvironment of the THEDES can stabilize labile drugs, as the hydrogen-bonded network and low water activity help prevent degradation pathways (e.g., hydrolysis or oxidation) [34]. The viscous, non-volatile nature of capric acid eutectics limits API exposure to oxygen, thereby reducing oxidative instability of sensitive molecules [34]. Overall, the capric-acid THEDES serves as a solvating and protective matrix that maintains drug molecules in a supersaturated yet stabilized state until administration.

Beyond solubility benefits, capric acid-based THEDES have been shown to improve drug permeability and pharmacokinetic profiles. The amphiphilic capric acid moiety can fluidize biological membranes and act as a penetration enhancer, which is especially useful for transdermal and transmucosal delivery [34]. Likewise, risperidone-capric acid THEDES showed markedly higher skin permeation (with melting-point depression to ~17 °C at a 40:60 w/w ratio) and caused no irritation on rat skin [29]. In the case of droperidol (a sedative with low oral bioavailability), forming a THEDES with capric acid enabled a solvent-free liquid formulation that demonstrated superior intestinal absorption in ex vivo gut models [12]. The droperidol–CA system exhibited significantly higher flux across everted intestinal sacs compared to solid drug, highlighting how THEDES can enhance transmucosal delivery and potentially replace injectable administration with oral dosing.

Similarly, aripiprazole (an antipsychotic) was converted into a capric acid eutectic at certain ratios, yielding a clear, H-bond-stabilized liquid that avoids crystalline precipitation and is expected to improve oral uptake and onset of action [12]. These examples underscore that capric acid THEDES can tackle multiple biopharmaceutical hurdles simultaneously – increasing drug solubility, maintaining supersaturation, and facilitating membrane permeation – thereby boosting overall drug bioavailability.

Another important application of capric acid-based eutectics is in topical and transdermal drug delivery. Many active agents suffer from poor skin penetration or require high solvent content in creams. THEDES offers a way to combine the drug with a fatty acid that both solubilizes the API and enhances its diffusion through skin. A striking case is the capric acid–ketoconazole (KCZ) THEDES developed for fungal infections. Ketoconazole, an antifungal that is poorly water-soluble and limited in skin uptake, formed a room-temperature eutectic with capric acid (optimized at 1:5 molar ratio) that showed dramatic improvements in therapeutic performance [6]. The KCZ–CA eutectic exhibited a 6.2-fold higher transdermal flux in Franz cell studies compared to a commercial ketoconazole cream, and it halved the minimum inhibitory concentration (MIC) against Candida albicans (indicating enhanced antifungal potency).

This dual enhancement – increased permeation and a 2× stronger antifungal effect – is attributed to the intimate hydrogen bonding between ketoconazole's imidazole ring and capric acid's carboxyl, which creates a stable liquid complex that both delivers more drug into the skin and leverages capric acid's inherent antimicrobial activity.

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In general, capric acid and other medium-chain fatty acids are known to disrupt microbial membranes; when used as part of a THEDES, they can synergize with antimicrobial drugs. For example, eutectic mixtures of capric with lauric or myristic acid show significant activity against Gram-positive bacteria (S. aureus, MRSA, C. albicans), including the ability to dissolve and remove biofilms by ~80–90% within minutes [35].

When combined with conventional antibiotics, such as in a capric acid–levofloxacin DES, the fatty acid can provide a complementary antibacterial effect and improve drug solubility, potentially overcoming resistance mechanisms [36]. This highlights the multifunctional role of capric acid in THEDES: it acts as a solvent, an absorption enhancer, and an active adjuvant (antimicrobial or anti-inflammatory) that can augment the pharmacodynamics of the co-formulated API.

Indeed, a gefitinib–capric acid eutectic not only increased drug solubility enormously but also produced a synergistic cytotoxic effect on EGFR-positive cancer cells in vitro, lowering the IC_50 by significantly more than gefitinib alone [7]. Such synergism suggests that capric acid's bioactivity (e.g., mild anticancer or permeation-facilitating properties) can enhance the therapeutic outcome of the primary drug.

Capric acid-based THEDES are also versatile in terms of dosage form design. Being liquids or low-melting semi-solids, they can be directly incorporated into various formulation types without traditional organic solvents [12]. Topical gels and ointments can be formulated by simply mixing a capric acid eutectic with gelling agents or emulsifiers, yielding drug-loaded gels that maintain high API solubility at skin temperature [5]. Transdermal patches and films have been developed by impregnating polymer matrices with drug–capric acid DES: for instance, incorporating a deep eutectic solution of a drug into an ethylcellulose film led to improved drug permeation and antifungal efficacy in a skin model [6]. Because THEDES can dissolve a large drug payload in a small volume, patch reservoirs or dissolvable films can deliver higher doses through the skin compared to conventional formulations.

Additionally, injectable depots represent an emerging application of DES technology. While capric acid-based systems have mostly been explored for oral and topical routes so far, the concept of using a biocompatible eutectic as a long-acting injectable is highly promising [12]. Deep eutectic formulations can be designed to be biodegradable, low-toxicity liquid implants that solidify or form microemulsions upon injection, thus slowing drug release [37]. A recent proof-of-concept in this arena employed a choline geranate-based deep eutectic mixture to create a subcutaneous depot for apomorphine, converting a thrice-daily injection therapy into an every-other-day regimen [38]. The depot, which self-emulsified in situ, entrapped the drug and extended its release over ~48 hours. The inherent low volatility and mild melting point of capric acid eutectics make them stable under physiological conditions, and their Generally Recognized as Safe (GRAS) status suggests good biocompatibility [34]. Any residual fatty acid would be metabolized via normal lipid pathways. This approach could be transformative for depot delivery of drugs like antipsychotics or analgesics, reducing dosing frequency and improving patient compliance.

Collectively, capric acid-based therapeutic deep eutectic systems represent a novel and highly adaptable platform in pharmaceutics. They enable unprecedented solubility increases for poorly soluble drugs, stabilize and protect actives within a green solvent matrix, and concurrently enhance drug release kinetics and absorption across biological barriers, as shown in Table 2.

Table 2.

Components with CA	Ratio	Observation	Application	Reference
Tetradecanoic acid (myristic acid)	CA: Myristic acid = 82:18 (mol%) or 78:22 (wt%)	Smooth, homogeneous, congruent melt; no	As a phase change material (PCM) of potential interest for passive temperature control in buildings	[39]

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		phase separation		
Myristic acid, Lauric acid, Steric acid	Molar Ratio (CA: Myristic acid)		Synergistic antimicrobial activity	[35]
	3:1	Pasty-like solid		
	Molar Ratio (CA: Lauric acid)			
	2:1	Transparent liquid		
	Molar Ratio (CA: Stearic acid)			
	4:1	White solid		
Thymol, Menthol	(Thymol: CA)		Reported physical properties and their dependence on constituents/composition of the NADESs will enhance their utility and help establish them as novel alternate media in science and technology.	[40]
	0.33: 0.67	Homogeneous liquid		
	0.50: 0.50	Homogeneous liquid		
	0.67: 0.33	Homogeneous liquid		
	(Menthol: CA)			
	0.33: 0.67			
	0.50: 0.50	Homogeneous liquid		
	0.67: 0.33	Homogeneous liquid		

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Gefitinib	(Gefitinib: CA) 80: 20 ≤70: 30 Extreme ratios	Homogeneous liquid Clear liquid Pasty Powder/solid	Enhance Gefitinib solubility and exhibit a synergistic cytotoxic effect against EGFR-expressing cell lines	[7]
Tetrabutylammonium chloride (TBAC), methyl tricaprylmethylammonium chloride (TOMAC)	(TBAC:CA) 1:2 (TOMAC:CA) 1:2	Clear, viscous fluid Clear, viscous fluid	Have the potential to be a novel class of lubricants	[41]
Cineole	(Cineole: CA) 1: 1	Clear, low-viscosity liquid	Very low viscous and dense fluid, with suitable properties for several solubilization technologies. its suitability to penetrate and stabilize cell membranes may lead to adverse outcomes when living organisms are exposed to this hydrophobic deep eutectic solvent.	[27]
Droperidol	(Droperidol: CA) 0.9:0.1 (D1)	Clear eutectic liquid; ^{1}H NMR showed $\Delta\delta$ = +0.08–0.09 ppm at	Solvent-free THEDES platform for enhancing droperidol solubility and intestinal permeability; suitable for green	[12]

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		protons adjacent to piperidine N; DOSY confirmed reduced CA diffusion; DSC showed no melting peaks; highest intestinal flux (1.182 mg cm^{-2} s^{-1} at 15 min).	pharmaceutical formulation.	
	0.8:0.2 (D2)			
	0.7:0.3 (D3)			
	≤0.6:0.4 (D4–D8)	Homogeneous liquid; similar NMR shifts; DSC revealed CA recrystallization on cooling (−8.1 °C); slightly lower flux than D1.		
		Partial melting; depressed CA melting at 17.7 °C in DSC; signs of phase separation.		
Aripiprazole	(Aripiprazole: CA)	Pasty mixtures; recrystallization and Tg observed in DSC; weak interaction. Clear eutectic	Hydrogen-bond-stabilized eutectic systems enabling	[12]

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	0.9:0.1 (A1) 0.8:0.2 (A2)	liquid; downfield shifts in amide (Δδ = +0.62 ppm) and piperazine CH_2 (Δδ = +0.10 ppm); strong H-bonding confirmed.	improved solubility and biopharmaceutical performance of aripiprazole.	
	≤0.7:0.3 (A3–A8)	Similar spectral shifts: eutectic liquid maintained; no residual crystallinity.		
		Heterogeneous pastes; DSC showed unincorporated CA (e.g., CA melting at 18.7 °C in A3); weak or absent interactions.		
Lauric acid	(Lauric acid: CA) 1:2	Clear, homogeneous liquid; lowest density (0.859 g/cm³); Newtonian flow; visually stable. Lycopene yield 7.51 mg/100 g FW, total carotenoids 8.04 mg/100 g.	Green solvent for lycopene extraction; practical operating window established.	[42]
Lauric acid	(CA : Lauric Acid) 1:1	Transparent liquid; thicker	Alternative HNADES	[42]

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		flow (shear-thickening). Lycopene 2.98 mg/100 g.	with moderate performance.	
	2:1		Lower-performing variant.	
		Transparent liquid; more viscous feel; Lycopene 3.19 mg/100 g.		
Dodecanoic acid	(Dodecanoic cid:CA) 1:2	Clear, uniform liquid; noticeably viscous; stable hydrophobic phase. Effective for Cu^{2+}, Co^{2+}, Ni^{2+} extraction	Green solvent for metal recovery; applicable in wastewater treatment.	[43]
Matrine	(Matrine:CA) 1:1	Slightly yellowish homogeneous liquid; density and viscosity decrease with temperature; moderate thermal stability	better antibacterial activity on *S. aureus* as compared with matrine	[44]
Polyethylene glycol	Weigh% Mass Ratio (polyethylene glycol:CA) 1:1	Congruent eutectic at ~22.9 °C with high latent heat (173.9 J g^{-1}); reduced supercooling, faster crystallization, stable after 200 cycles, negligible corrosion.	Thermal energy storage for solar passive buildings; energy saving (≈4.9 $kWh \cdot kg^{-1} \cdot yr^{-1}$), cost-effective, and carbon neutral within ~3 years.	[45]

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Mirtazapine	(Mirtazapine:CA) 1:2	Light-yellow transparent viscous liquid; no crystals (polarized microscopy)	Transdermal delivery of MTZ to bypass first-pass metabolism; promising topical antidepressant THEDES.	[46]
Levofloxacine:	(CA:Levofloxacin) 9:1, 8:2, 7:3 (DES liquids formed at these ranges; eutectic ~80:20–70:30	Clear liquids (THDES); DES formation confirmed by ^{1}H NMR & ATR-FTIR (H-bonding) and DSC (melting point depression; excess CA signal decreases with more LEV).	Green THDES to enhance LEV performance: solubilization + antibacterial synergy; potential to combat resistance.	[36]
Ketoconazole:	Molar Ratio (Ketoconazole: CA) 1:5	Clear, stable liquid at room temperature for ≥5 months.	Enhanced antifungal efficacy, solubility, and transdermal permeability using a green, stable THEDES system.	[6]
Oxymatrine:	(Oxymatrine: CA) 1: 1	Stable transparent DES.	Biocompatible, low-toxicity enhancer; suitable when high safety is prioritized.	[47]
Ibuprofen:	(Ibuprofen: CA) 1:3	Clear, stable liquid at 37 °C.	Effective transient eutectic solubilizer; excellent for dual-drug oral systems when combined with surfactant; balances high solubility and moderate release.	[48]
	(Clotrimazole:CA) 1:1	Solid at RT (not a DES)	Therapeutic DES (THEDES) for enhanced antifungal potency and skin permeation	[49]

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1:2	Transparent liquid; physically stable ≥1 year
1:3	(DES candidate)
1:4	Eutectic point; transparent liquid
1:5	Transparent liquid; physically stable (DES candidate)
	Solid at RT (not a DES)

7. Mechanisms of Drug–Solvent Interactions

The molecular structure of capric acid, characterized by a terminal carboxylic acid group and a long hydrophobic alkyl chain, confers versatility in its interactions with both hydrophilic and hydrophobic moieties. As mentioned earlier, DESs are primarily formed through strong hydrogen bonding between a HBD and a HBA, which leads to lattice disruption and a marked decrease in the melting point of the resulting mixture. The carboxylic acid group in capric acid can function as both a hydrogen bond donor, through its hydroxyl hydrogen, and as a hydrogen bond acceptor, through carbonyl oxygen, facilitating extensive hydrogen-bonding networks within deep eutectic systems.

Some of us also reported the successful fabrication of capric acid and menthol DES further enhancing the drug solubility of hydrophobic model drugs fluconazole and mometasone furoate. FTIR analysis suggested the contribution of CA carboxylic acid group as HBD and HBA Another notable structural change in the capric acid–menthol system was the disruption of the hydrocarbon side chains, indicating the presence of hydrophobic interactions, such as van der Waals forces [10,50].

Building on this work, Al-Akayleh et al. have fabricated capric acid–gefitinib DES, enhancing gefitinib aqueous solubility by 30,000-fold and confirmed CA hydrogen bond interactions through hydroxyl hydrogen and carbonyl oxygen as confirmed by FT-IR and NMR [7] Furthermore, Alkhawaja et al. reported the fabrication CA aripiprazole and CA droperidol DESs reporting enhanced permeability, and NMR revelated CA interacts only via its –OH group of the carboxylic acid, acting exclusively as a hydrogen bond donor[12]. Understanding the nature of interactions between CA and other components of DES is vital, as it allows monitoring their impact on the characteristics of the final formulation.

8. Safety, Toxicity, and Regulatory Considerations

The safety and biocompatibility of pharmaceutical excipients — both alone and in combination with APIs are critical determinants for whether a formulation can progress from the laboratory into clinical development and regulatory approval [51]. The safety of pharmaceutical excipients is highly dependent on the intended route of administration. Decanoic acid (capric acid) is recognized by the

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U.S. FDA as Generally Recognized As Safe (GRAS) when used in food product manufacturing or as a food additive under 21 CFR §§ 172.210, 172.860, 173.340, and 178.1010 [52].

When the API is combined with capric acid to form a DES, the molecular interactions between the components may modify their physicochemical and biological behavior. Consequently, each DES formulation is expected to exhibit a distinct safety profile that requires independent evaluation. However, the overall safety and toxicity of DESs have not yet been fully characterized, and the potential formation of degradation products from the API–capric acid system represents an additional concern that must be addressed [53]. Previous evaluations of the risperidone–capric acid DES demonstrated favorable dermal compatibility, with no observable irritation or tissue damage. Histological analysis further confirmed the absence of inflammatory or structural alterations in the treated skin, supporting the formulation's safety for topical application [29].

9. Challenges and Future Perspectives

Despite their promising advantages, capric acid-based THEDES still face major challenges in achieving pharmaceutical viability. Stability remains a central concern — these eutectic mixtures are often hygroscopic, and uncontrolled moisture absorption can disrupt their hydrogen bonding balance and alter physicochemical behavior, affecting drug solubility and shelf-life. For instance, hydrophobic THEDES demonstrate improved stability compared to hydrophilic DESs, but their long-term stability under humidity fluctuations remains insufficiently characterized [5,37]. Although certain formulations show thermal stability up to 200 °C, oxidative degradation or compositional drift may still occur over time, warranting thorough shelf-life testing [54].

Viscosity also poses a technical bottleneck. Capric acid-based THEDES generally display higher viscosities than conventional solvents, limiting mass transfer and process scalability [29]. Experimental and modeling data show that viscosity in these eutectic systems is strongly temperature-dependent and can be mitigated via mild heating or the incorporation of small fractions of co-solvents like water or polyols [55,56]. However, such modifications risk altering the eutectic structure or drug solubility profile, underscoring the need for careful balance between viscosity control and formulation integrity [40].

From a manufacturing and scale-up perspective, translating laboratory-scale THEDES formulations to industrial production presents nontrivial difficulties. Large-batch synthesis demands strict process controls, optimized mixing protocols, and consistent sourcing of pharmaceutical-grade components like capric acid and co-formers [12]. Moreover, rheological complexity and temperature sensitivity make scaling viscosity-dependent operations (e.g., blending or spray-drying) challenging without pilot-scale optimization [57]. Addressing these interrelated issues—moisture sensitivity, viscosity control, and scalability—through formulation engineering and robust process design is thus essential to unlock the full pharmaceutical potential of capric acid-based THEDES.

In addition to these formulation and process challenges, significant knowledge gaps persist regarding the toxicological and pharmacokinetic behavior of THEDES. Although many individual components used in eutectic systems (e.g., capric acid, menthol, amino acids) are Generally Recognized as Safe (GRAS), their combination can give rise to novel physicochemical interactions that alter biological performance and toxicity profiles. Recent studies demonstrate that THEDES may exhibit distinct cytotoxicity or biocompatibility behaviors compared to their isolated components, emphasizing the need for formulation-specific safety evaluation [37,58].

From a regulatory standpoint, the lack of a defined classification framework continues to impede industrial and clinical translation. As noted by Abdelquader et al., 2023, current guidelines do not specify how THEDES should be regulated within the pharmaceutical context, and their distinction from related systems such as co-crystals or ionic liquids remains conceptually and terminologically unclear [59]. This definitional ambiguity complicates safety testing and regulatory approval, underscoring the need for harmonized evaluation standards and classification criteria.

Furthermore, the lack of standardized assays for biodegradability, cytotoxicity, and irritation prevents reliable cross-study comparisons and complicates regulatory evaluation. Harmonizing

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these protocols within existing EMA excipient frameworks, as proposed in recent green chemistry studies [60], will be essential to build regulatory confidence and facilitate THEDES qualification as safe, bioactive pharmaceutical matrices.

Looking forward, emerging research directions are exploring multi-drug and multifunctional THEDES as next-generation drug delivery systems. The principle underlying the well-known lidocaine–prilocaine eutectic (melting point ≈18 °C) is now being extended to capric acid-based eutectics capable of co-delivering synergistic drug combinations. Notably, levofloxacin–capric acid THEDES exhibited superior antibacterial efficacy against resistant strains, owing to capric acid's intrinsic membrane-disruptive activity coupled with enhanced drug solubility [36]. Such systems exemplify the potential of THEDES as dual-function platforms that integrate solvent functionality with therapeutic bioactivity, opening avenues for fixed-dose, biocompatible liquid formulations in transdermal, oral, or parenteral delivery routes.

Addressing these toxicological, pharmacokinetic, and regulatory gaps, alongside continued innovation in multi-component formulation design, will be key to advancing capric acid-based THEDES from laboratory concept to clinical reality.

Crucially, the integration of Artificial Intelligence (AI) and Machine Learning (ML) is emerging as a transformative force in the rational design of DES and THEDES. Traditional experimental screening of eutectic systems is slow and resource-intensive due to the near-limitless combinations of hydrogen bond donors and acceptors. Recent AI-based methodologies now enable predictive and generative exploration of this vast formulation space, significantly reducing reliance on trial-and-error synthesis [61].

Among the most impactful advances is the use of ML models combined with COSMO-RS molecular descriptors to predict drug solubility in DES. For example, Cysewski et al., 2024 demonstrated that ML algorithms could accurately forecast the solubility of poorly water-soluble drugs (ibuprofen, ketoprofen) across multiple DES compositions, eliminating the need for extensive experimental screening [62]. This predictive capability holds particular relevance for capric acid-based THEDES, where AI could rapidly identify the optimal co-former type and molar ratio to maximize drug solubility and minimize formulation time.

Beyond solubility, ML models have been successfully applied to predict key physicochemical properties such as viscosity, melting point, and miscibility. A recent study achieved $R^2 \approx 0.99$ in predicting DES viscosities across 670 systems using CatBoost regression and COSMO-RS-derived σ-profiles [63].

Similarly, XGBoost-based models accurately predicted DES melting points within ±2 K of experimental data, offering powerful tools for screening stable, low-melting eutectic mixtures [64]. Neural-network approaches have also shown promise in modeling viscosity and density across diverse DES compositions and temperature ranges [65,66].

Beyond prediction, generative AI is now being explored for inverse design—creating entirely new eutectic systems optimized for multiple objectives such as low viscosity, high thermal stability, and enhanced solvation capacity. The combination of transformer-based and explainable AI (XAI) frameworks has been proposed to design DES formulations meeting automatically specified property targets [67]. In the context of capric acid-based THEDES, such approaches could enable computational pre-selection of formulations that remain liquid at physiological temperatures, dissolve target drugs at therapeutic levels, and exhibit low cytotoxicity and manageable viscosity—all before physical synthesis.

While AI/ML offers tremendous promise in streamlining THEDES innovation, it also introduces new considerations [68]. One is the importance of model interpretability and regulatory acceptance [69,70]. Especially in pharmaceuticals, "black-box" models that cannot explain their decisions may face skepticism from regulators who demand understanding of how a formulation works and assurance of its safety. To address this, researchers have begun employing explainable AI techniques (e.g., SHAP analysis) to identify which molecular features drive desirable properties [71]. Ensuring transparency in AI-driven formulation design will likely be necessary for it to gain trust in a highly

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regulated field [72–74]. Furthermore, the quality and representativeness of training data directly affect AI model outputs [75–78]. If certain chemical spaces (say, choline chloride-based DES) are over-represented, the model might be biased and less accurate for others like fatty-acid-based systems [79]. Therefore, expanding high-quality experimental datasets – including those specifically featuring capric acid and other natural components – is critical to improve model generalizability.

Equally important is the issue of reproducibility [80,81]. Because THEDES properties can be sensitive to raw-material variability (e.g., purity, water content, fatty-acid isomer distribution) and to procedural details (such as mixing order, equilibration time, or storage conditions), AI predictions and supporting experiments must be consistent and verifiable across laboratories. Finally, issues of accessibility and equity should not be overlooked [82]. High-performance AI tools, along with large proprietary datasets, may be available only to well-funded institutions or countries, potentially widening the gap in global green chemistry research. Promoting open-source algorithms, publicly accessible data repositories, and collaborative international initiatives will be essential to ensure that AI-driven THEDES innovation advances sustainability equitably worldwide.

10. Conclusions

Capric acid–based THEDES represent a distinct and rapidly evolving class of biofunctional eutectic systems whose value extends far beyond conventional solvent replacement. This review demonstrates that capric acid introduces a unique synergy of strong, directional hydrogen bonding, membrane-modulating amphiphilicity, and intrinsic bioactivity, enabling it to serve simultaneously as a solubilizer, permeability enhancer, and therapeutic co-agent. This multifunctionality underpins several unprecedented outcomes reported across recent studies—including 10^4–10^5-fold solubility enhancement for BCS II drugs, synergistic antimicrobial and anticancer effects, and transdermal fluxes surpassing commercial formulations—all achieved without reliance on volatile organic solvents. Critically, the role of capric acid is not generic but structurally determinant: its carboxyl group governs eutectic formation and drug amorphization, while its C10 chain drives membrane interactions and microbial disruption. These mechanisms collectively establish capric acid-based THEDES as purpose-built therapeutic matrices, capable of reshaping pharmacokinetics and enabling alternative administration routes, including solvent-free oral, transmucosal, and transdermal delivery. Despite these advances, gaps persist in long-term stability, viscosity control, toxicological profiling, and regulatory classification. The emerging integration of AI-guided formulation offers transformative potential to address these challenges by predicting optimal compositions, accelerating discovery, and providing mechanistic interpretability. Overall, capric acid-based THEDES stand at the forefront of next-generation green pharmaceutical technologies—systems in which the solvent is no longer passive but an active determinant of therapeutic performance. Their continued development may redefine how poorly soluble or permeation-limited drugs are formulated, delivered, and clinically optimized.

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Abbreviations

The following abbreviations are used in this manuscript:

CA	Capric Acid
ILs	Ionic Liquids
THEDES	Therapeutic Deep Eutectic Systems
DES	Dee Eutectic Solvent
DESy	Deep Eutectic System

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