JURNAL ILMU KEFARMASIAN INDONESIA
Indonesian Journal of Pharmaceutical Sciences
ISSN p-ISSN 1693-1831 (Print) e-ISSN 2614-6495 (Online) PUBLISHER : Faculty of Pharmacy Universitas Pancasila

Enhancing capsaicin solubility in lidocaine-based therapeutic deep eutectic solvents (THEDES): a COSMO-RS predictive study

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Received: 14 August 2025 / Accepted: 24 October 2025

ABSTRACT: Capsaicin, a potent analgesic, suffers from poor aqueous solubility and low bioavailability. Therapeutic deep eutectic solvents (THEDES) have emerged as a promising platform to enhance the solubility of poorly soluble drugs. This study employed the conductor-like screening model for real solvents (COSMO-RS) for the in-silico screening of capsaicin solubility in 34 lidocaine-based THEDES, comprising 10 hydrogen bond acceptors (HBAs) and 26 hydrogen bond donors (HBDs) at 1:1 and 1:2 molar ratios. The σ-profiles and σ-potentials of the components were analysed to understand the intermolecular interactions governing solubility. Our predictions revealed a remarkable solubility range from below 1 g/L to over 437 g/L. The betaine-lidocaine (1:1) system was identified as the optimal solvent, achieving a capsaicin solubility of 437.47 g/L at 333.15 K, attributed to betaine's zwitterionic nature facilitating multifaceted hydrogen-bonding. Small polyols like ethylene glycol also performed excellently. A consistent enhancement in solubility was observed in HBD-rich (1:2) compositions and with increasing temperature. Molecular interaction analysis confirmed a robust network of conventional and non-conventional hydrogen bonds within the optimal betaine-lidocaine-capsaicin system. This work demonstrates the power of COSMO-RS as a rational design tool for formulating high-loading THEDES-based drug delivery systems, with betaine-lidocaine emerging as a top candidate for advanced capsaicin topical formulations.

KEYWORDS: Capsaicin; COSMO-RS; lidocaine; solubility; therapeutic deep eutectic solvents (THEDES); in silico screening.

INTRODUCTION

Capsaicin (8-methyl-N-vanillyl-6-nonenamide), the primary pungent compound in chili peppers, is a potent pharmacological agent with well-documented analgesic, anti-inflammatory, and anti-cancer properties [1], [2], [3]. Its mechanism of action is primarily mediated through the transient receptor potential vanilloid 1 (TRPV1) channel, making it a valuable therapeutic candidate for managing neuropathic pain, arthritis, and psoriasis [4]. Despite this therapeutic promise, the clinical translation of capsaicin remains limited. In topical analgesic creams, for instance, its poor solubility restricts drug loading and leads to inconsistent pain relief; in systemic applications, its low bioavailability results in sub-therapeutic plasma concentrations, undermining its potential as an anti-inflammatory or anti-cancer agent [5].

Globally, chronic pain affects more than one in five adults and represents a major public health challenge, with profound impacts on quality of life, productivity, and healthcare costs [6]. Topical drug delivery has gained increasing attention as a safer and more patient-friendly alternative to systemic therapies, particularly in the context of the opioid crisis and the limitations of long-term NSAID use [6]. By enabling localized drug action with reduced systemic exposure, topical formulations offer a promising strategy for effective pain management while minimizing adverse effects [7]. Within this global therapeutic landscape, capsaicin stands out as a clinically relevant candidate whose utility is constrained primarily by formulation challenges [8].

Capsaicin is classified as a Biopharmaceutical Classification System (BCS) class II drug, characterized by low water solubility and high permeability [5]. To overcome the solubility limitations of lipophilic drugs like capsaicin, significant research has been directed towards advanced drug delivery systems [9]. Strategies that

How to cite this article: Asma N, Alwi RS, Ramadon D, Mun'im A. Enhancing capsaicin solubility in lidocaine-based therapeutic deep eutectic solvents (THEDES): a COSMO-RS predictive study. JIFI. 2025, 23(2): 336-347.

ISSN: 2614-6495

have been explored include nano crystallization, nano-emulsifying systems, and cyclodextrin inclusion complexes, all of which aim to enhance saturated solubility and dissolution rate [8], [10], [11]. However, these approaches often face limitations such as scalability, stability, or lack of synergistic therapeutic benefit, highlighting the need for alternative formulation strategies.

Among these novel strategies, Deep Eutectic Solvents (DES) have emerged as an innovative and sustainable class of solvents with tunable properties. DES are eutectic mixtures formed by the complexation of a Hydrogen Bond Acceptor (HBA) and a Hydrogen Bond Donor (HBD) [12]. The strong hydrogen bond interactions within these mixtures result in a melting point significantly lower than that of the individual components, allowing for their existence as liquids at room temperature [12]. In contrast to ionic liquids, DES are formed from neutral compounds and are often cheaper, non-flammable, and have a low vapor pressure. When DES are designed for pharmaceutical applications, where their components are biologically compatible, they are termed Therapeutic Deep Eutectic Solvents (THEDES) [13]. Importantly, THEDES not only enhance drug solubility and permeability but may also provide synergistic therapeutic effects, making them particularly attractive for drugs like capsaicin whose clinical utility is constrained by formulation barriers [14].

Lidocaine, a widely used local anesthetic, has been frequently employed in THEDES studies as a model component due to its amphoteric molecular structure, featuring both a protonatable amine and an amide group that allow it to act as either an HBA or an HBD [15]. In this work, however, lidocaine is included only as a control system, while the primary focus is placed on the application of THEDES to enhance the solubility and therapeutic performance of capsaicin. This approach enables a direct evaluation of capsaicin-based THEDES without confounding contributions from lidocaine's pharmacological activity [16].

Nevertheless, the experimental screening of THEDES formulations is a time-consuming and resource-intensive process, requiring the synthesis and characterization of numerous candidate mixtures [17]. To address this bottleneck, in silico predictive tools offer a powerful alternative for rational solvent design. The Conductor-like Screening Model for Real Solvents (COSMO-RS) is a robust quantum chemistry-based method that predicts thermodynamic properties, such as activity coefficients and solubility, by computing the molecular surface charge densities (σ-profiles) of the components [18]. COSMO-RS offers several critical advantages over empirical screening approaches: it is an a priori predictive method capable of calculating thermodynamic properties for virtually any molecular system without requiring extensive experimental data; it accounts for dominant intermolecular interactions including electrostatic effects, hydrogen bonding, and van der Waals forces; and it enables rapid high-throughput virtual screening of thousands of solvent-solute combinations [19]. Unlike group contribution methods such as UNIFAC, COSMO-RS can handle novel chemical structures and functional group combinations not represented in existing parametrization databases, making it particularly valuable for exploring innovative solvent systems like THEDES [20]. Its success in predicting the solubility of various active pharmaceutical ingredients (APIs) in ionic liquids and DES, with root-mean-square errors typically below 0.7 log units, makes it an ideal tool for the rational design and high-throughput screening of THEDES formulations [21].

While previous studies have explored lidocaine-based DES [22], a systematic computational investigation specifically aimed at maximizing capsaicin solubility is lacking [23]. The rational selection of HBD partners and the optimization of their molar ratios with lidocaine remain underexplored through a predictive thermodynamic lens. Therefore, this study aims to bridge this gap by employing COSMO-RS for the *in-silico* screening and design of lidocaine-based THEDES for enhanced capsaicin solubility. This computational strategy provides a rational and efficient pathway for developing high-loading topical formulations of capsaicin, accelerating the discovery process and offering profound insights into the structure-property relationships that dictate drug solubilization in THEDES.

MATERIALS AND METHODS

Software and computational details

All computational predictions in this study were performed using the COSMO-RS method as implemented in the Amsterdam Modeling Suite (AMS), version 2023.105 [24]. The computational procedure involved two primary steps:

1. Quantum Chemical Calculations: The geometry of each molecule (capsaicin, lidocaine, and all HBDs/HBAs) was first optimized using Density Functional Theory (DFT) with the Generalized Gradient Approximation (GGA) and the Perdew-Burke-Ernzerhof (PBE) functional. A triple-ζ polarization (TZP) basis set was used for these optimizations. Subsequently, single-point energy calculations were conducted on the optimized geometries at the same level of theory (GGA-PBE/TZP) to generate the σ-profile for each compound. This process produced the necessary *.coskf files containing the screening charge density information.
2. COSMO-RS Thermodynamic Calculations: The *.coskf files were then used as input for the COSMO-RS module within AMS. The activity coefficients of capsaicin at infinite dilution (γ_i^{∞}) in various THEDES mixtures were calculated using the BP_TZVP_23.rc parameterization. All solubility predictions were performed across a temperature range of 298.15 K to 333.15 K to assess thermal effects.

Molecular structures were built and visualized using Avogadro 1.2.0; Non-covalent interaction analysis was performed using BIOVIA Discovery Studio Visualizer 2025; and LigPlot+ v.2.3.1 [25]. All graphs and data fitting were created using OriginLab 2024. The molecular structures and canonical SMILES strings were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/).

Selection of components in THEDES

The dataset comprises 34 distinct THEDES, resulting from various combinations of ten hydrogen-bond acceptors and twenty-six donors, as detailed in Table 1. A total of 749 measurements were conducted across temperatures ranging from 298.15 to 333.15 K. The selected HBDs represent categories, including amino acids, sugars, polyols, and quaternary amines. All compound names and abbreviations are listed in Table 1.

Table 1. List of HBA and HBD screened for the development of lidocaine-based capsaicin-loaded THEDES.

Hydrogen Bond Acceptor (HBA)		Hydrogen Bond Donor (HBD)	
Abbrv.	**Name**	**Abbrv**	**Name**
Beta	Betaine	1,2pro	1,2 propanediol
CA	Citric acid	1,3buta	1,3 butanediol
CC	Choline chloride	Ara	Arabinose
CB	Choline Bicarbonate	AscA	Ascorbic acid
Gly	Glycerol	EG	Ethylene glycol
LA	Lactic acid	Fru	Fructose
Lido	Lidocaine	GA	Geranic acid
Lys	Lysine	Glu	Glucose
Mth	Menthol	Gly	Glycerol
Pro	Proline	Lido	Lidocaine
		MA	Malonic acid
		Mal	Maltose
		Man	d-Mannose
		MLA	Maleic acid
		OA	Oxalic acid
		PG	Propylene glycol
		Pro	Proline
		Sor	d-Sorbitol
		Suc	Sucrose
		TA	Tartaric acid
		TEG	Triethylene glycol
		U	Urea
		Xyl	Xylitol
		Xyls	d-Xylose

Abbreviations (Abbrv.) and full names of all compounds simulated in this study. Lidocaine was utilized in a dual role as both an HBA and an HBD. All molecular structures and data were retrieved from PubChem.

In silico solubility screening of THEDES

The screened THEDES were prepared conceptually with lidocaine serving as the functional solvent component, paired with a range of hydrogen bond donors (HBDs) or acceptors (HBAs) depending on the formulation strategy. Lidocaine was intentionally tested in two distinct stoichiometric roles: (A) lidocaine acting predominantly as a Hydrogen Bond Acceptor (HBA) in mixtures formulated at HBA:HBD = 1:1 and 1:2, and (B) lidocaine acting predominantly as a Hydrogen Bond Donor (HBD) in separate sets of mixtures at the same molar ratios. This design allows direct comparison between lidocaine-centered HBA- and HBD-type THEDES while keeping the molar ratios consistent across series. Mechanistically, lidocaine's tertiary amine provides HBA character, whereas its amide moiety and polar regions can participate in HBD-type or polar interactions, so lidocaine may contribute both interaction types depending on the partner compound and local microenvironment; the A/B labeling reflects the intended primary role in each screened series rather than an absolute exclusion of dual participation.

For each hypothetical THEDES, capsaicin solubility was predicted using COSMO-RS by calculating the activity coefficient at infinite dilution, ln(γi), and converting to mole-fraction solubility xi using the relation

$$ln(x_i) = -ln(\gamma_i)$$

where (x_i) is the mole-fraction solubility of capsaicin and (γ_i) is its activity coefficient in the THEDES solvent. This a priori computational workflow permits ranking of many candidate formulations rapidly and without synthesis. To contextualize this screening approach, we note that COSMO-RS-based pre-screening has frequently been used to prioritize solvent systems prior to bench testing, thereby reducing the number of experimental mixtures required and focusing laboratory resources on the most promising candidates.

Analysis of Molecular Interactions

For the top-performing THEDES candidate, a detailed analysis of molecular interactions was conducted. The σ-profiles, σ-potential, and σ-surface of capsaicin, lidocaine, and the HBA/HBD were analysed to understand their polarities and hydrogen-bonding tendencies.

RESULTS

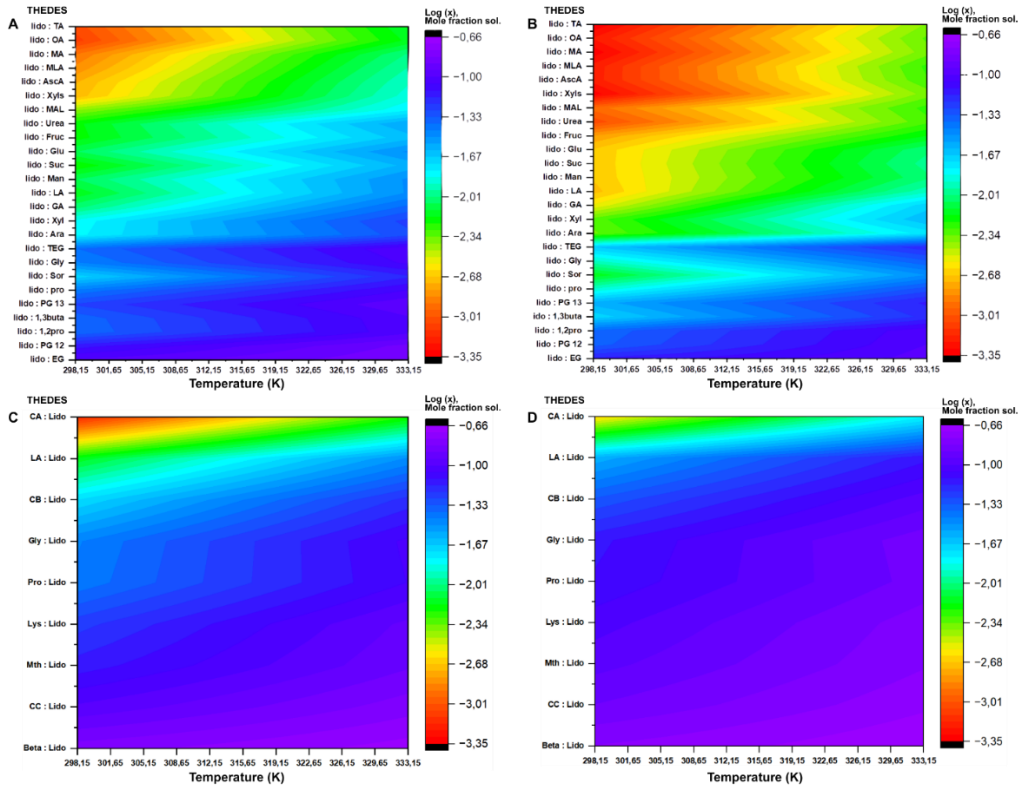

Figure 1. Contour plots of capsaicin mole fraction solubility (log x) predicted by COSMO-RS in lidocaine-based THEDES systems across 298.15--333.15 K. Lidocaine as HBA at 1:1 and 1:2 molar ratios (A, B), respectively; Lidocaine as HBD at 1:1 and 1:2 ratios (C, D). The colour scale represents solubility from low (red) to high (purple).

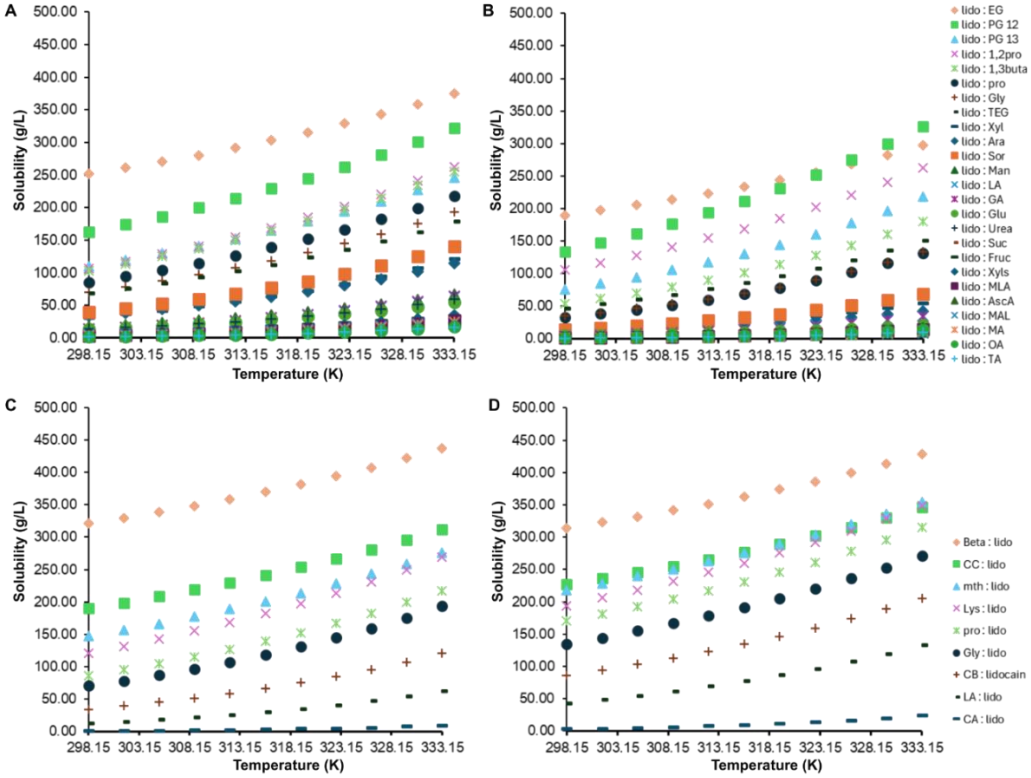

Figure 2. Scatter plot of the predicted solubility (g/L) of capsaicin in various lidocaine-based THEDES. Panels correspond to those in Figure 1.

Table 2. Predicted Absolute Solubility (g/L) of Capsaicin in High-Performing Lidocaine-Based THEDES.

HBD	HBA:HBD Molar Ratio	Solubility at 298.15 K (g/L)	Solubility at 333.15 K (g/L)
Betaine	1:1	370.12	437.47
Betaine	1:2	345.54	408.38
EG	1:1	317.98	375.41
EG	1:2	277.10	327.46
PG	1:1	272.76	321.94
PG	1:2	239.52	282.90

Data obtained from COSMO-RS simulations. The betaine-based systems consistently outperform the polyol-based systems (EG, PG), with the 1:1 molar ratio yielding the highest solubility value at 333.15 K.

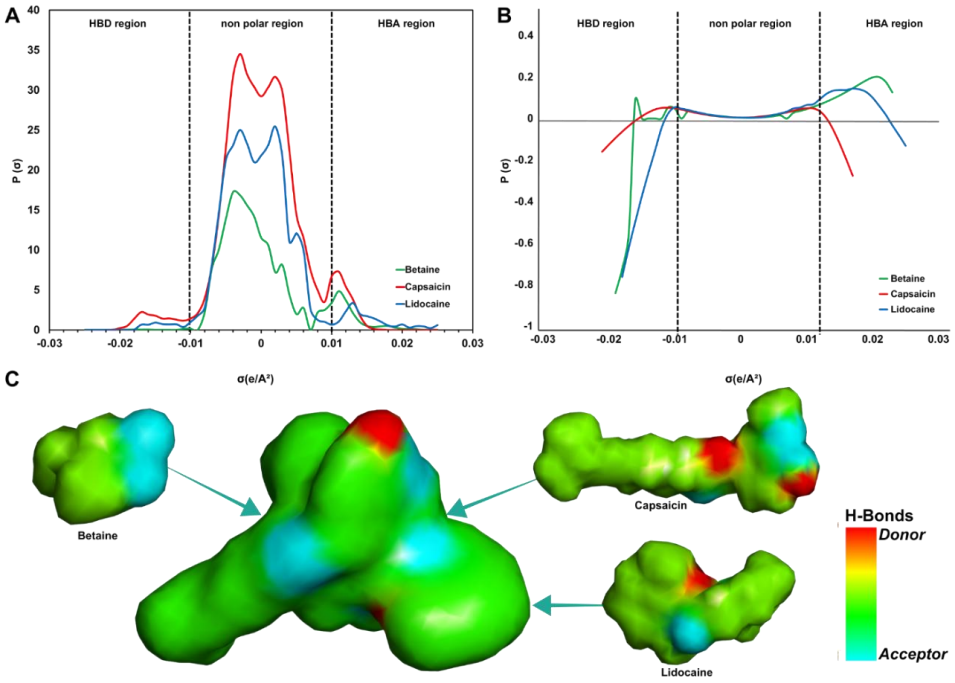

Figure 3. Molecular interaction analysis for the optimal system: (A) σ-profiles, (B) σ-potentials, and (C) σ-surfaces of capsaicin, lidocaine, and betaine.

Table 3. Hydrogen bond analysis for the betaine-lidocaine-capsaicin system. The conventional O-H···O bond between capsaicin and betaine is the strongest intermolecular interaction.

Donor Atom	Acceptor Atom	Distance (Å)	Angle D-H-A (°)	Interaction Type	Category
beta:H12	beta:O2	2.28	120.8	Intramolecular (Betaine)	C-H···O Hydrogen Bond
beta:H19	beta:O2	2.283	120.8	Intramolecular (Betaine)	C-H···O Hydrogen Bond
cap:H49	lido:O1	2.393	133.1	Capsaicin-Lidocaine	C-H···O Hydrogen Bond
lido:H22	beta:O1	2.392	153.4	Lidocaine-Betaine	C-H···O Hydrogen Bond
cap:H36	beta:O2	2.485	153.1	Capsaicin-Betaine	Conventional H-Bond
lido:H21	beta:O2	2.532	173.3	Lidocaine-Betaine	C-H···O Hydrogen Bond
cap:H48	beta:O1	2.522	174.3	Capsaicin-Betaine	C-H···O Hydrogen Bond
lido:H18	beta:O1	2.557	144.2	Lidocaine-Betaine	C-H···O Hydrogen Bond

The table lists all identified hydrogen bonds, sorted by H···Acceptor distance. The category distinguishes classical (X-H···O) from non-classical (C-H···O) interactions.

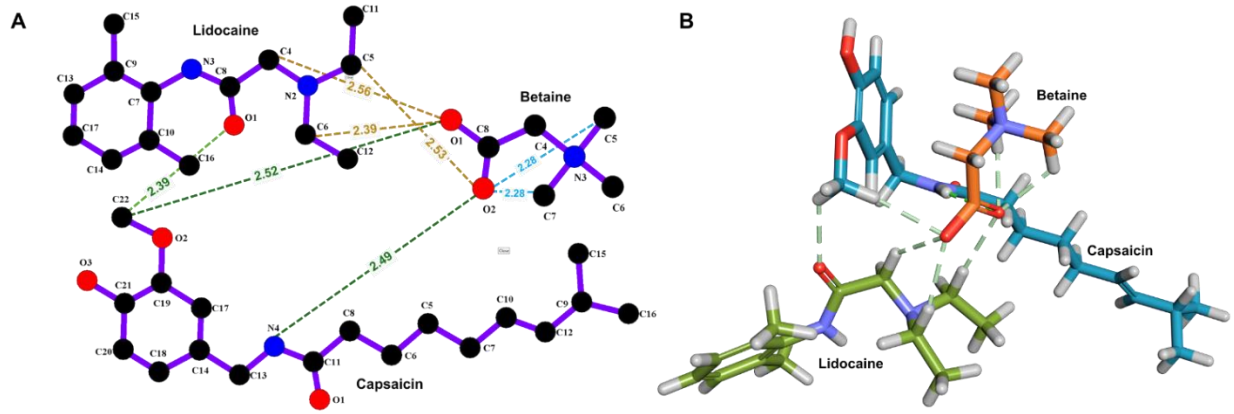

Figure 4. Two-dimensional (A) and three-dimensional (B) representations of molecular interactions in the capsaicin-lidocaine-betaine complex.

▪ DISCUSSION

Comprehensive Solubility Screening via COSMO-RS

The COSMO-RS method was employed to systematically predict capsaicin solubility across a comprehensive library of 34 lidocaine-based THEDES, yielding 749 data points over the temperature range 298.15 K to 333.15 K. The predicted mole-fraction solubility (log x) provides a detailed map for evaluating the efficacy of different hydrogen bond donors (HBDs) and acceptors (HBAs), as visualized in the contour plots of Figure 1. The screened HBDs/HBAs span representative chemical classes including small polyols (ethylene glycol, glycerol), short-chain alcohols, organic acids (e.g., citric, lactic), betaines/zwitterions, amino-acid derivatives, and amides, allowing assessment of diverse polarity, hydrogen-bonding capacity, and ionic character.

A pivotal finding was the strong dependence of capsaicin solubility on both the co-former chemical nature and the HBA:HBD molar ratio; predicted solubilities spanned more than three orders of magnitude, underscoring that rational component selection and stoichiometry are critical to optimize drug loading. Figure 1 shows that HBD-rich compositions (panels B and D) and elevated temperature systematically increase predicted capsaicin solubility, with zwitterionic co-formers (notably betaine) and small polyols occupying the highest-solubility regions [26]. The contour plots (Figure 1) summarize three clear trends: (1) HBD classes with multiple hydroxyl groups and small polyols consistently promote higher solubility [27], (2) zwitterionic co-formers (e.g., betaine) produce exceptionally high solubilities, likely via multifaceted electrostatic and hydrogen-bonding interactions [26], and (3) increasing temperature and HBD-rich compositions (HBA:HBD = 1:2) generally shift solubility contours upward, indicating enhanced solvation at elevated temperatures and in HBD-excess matrices [28]. These plot-level observations guided selection of top candidate THEDES for deeper molecular interaction analysis.

Identification of high-performing THEDES formulations

The analysis revealed distinct performance trends among the different classes of co-formers. Small and flexible polyols, particularly ethylene glycol (EG) and propylene glycol (PG), consistently emerged as top-performing co-formers in the screening analysis [23]. The Lido:EG system at a 1:1 molar ratio demonstrated a predicted solubility of log(x) = –0.99 at 298.15 K, underscoring the efficiency of these low-molecular-weight solvents. Their superior performance can be attributed to their high conformational flexibility and capacity to establish extensive hydrogen-bond networks, which effectively disrupt the capsaicin crystal lattice without introducing significant steric hindrance [23]. Remarkably, the betaine–lidocaine (Beta:Lido) system exhibited the highest solubility overall, achieving log(x) = –0.77 at 298.15 K at a 1:2 molar ratio. This enhanced performance is directly linked to the zwitterionic nature of betaine, which provides dual hydrogen-bonding functionality through its quaternary ammonium (HBD) and carboxylate (HBA) groups, thereby enabling multifaceted interactions with both lidocaine and capsaicin [29]. In contrast, co-formers with greater molecular complexity and strong self-association tendencies, such as sugars (e.g., sucrose, glucose; log(x) ≈ –2.2 to –2.0)

and di-/tricarboxylic acids (e.g., oxalic acid, tartaric acid; log(x) ≈ –3.1 to –3.0), demonstrated markedly lower predicted solubility. Although sugars are rich in hydrogen-bond donors, their pronounced intramolecular self-association restricts their capacity to interact effectively with capsaicin [30]. These findings highlight that solubility enhancement is not solely dependent on the presence of hydrogen-bonding groups, but also on the ability of solvent components to disrupt the intrinsic crystal lattice of the solute.

The impact of molar ratio and temperature

Two key thermodynamic parameters were found to exert a decisive influence on capsaicin solubility. First, the molar ratio of the components played a critical role, with hydrogen bond donor (HBD)-rich compositions consistently outperforming equimolar systems. For example, the solubility of the lidocaine:ethylene glycol (Lido:EG) system improved from log(x) = –0.99 at a 1:1 ratio to –1.15 at a 1:2 ratio. This enhancement highlights that an excess of HBD molecules provides a more versatile and robust solvation environment, likely driving the system closer to its eutectic point and thereby maximizing its capacity to disrupt the capsaicin crystal lattice [31]. Second, temperature exerted a monotonic positive effect across all systems, consistent with an endothermic dissolution process [32]. The observed correlation not only confirms the thermodynamic stability of the solutions within the studied range but also suggests practical advantages for therapeutic applications, as drug solubility is expected to increase at skin temperature, potentially improving the efficiency of topical delivery formats [33].

Absolute solubility and formulation implications

Translating mole fraction to absolute solubility (g/L) provides a more direct metric for pharmaceutical formulation (Figure 2, Table 2). The predictions revealed remarkable variation, from concentrations exceeding 400 g/L to values below 1 g/L. The Beta:Lido (1:1) system achieved an unprecedented capsaicin solubility of 437.47 g/L at 333.15 K. The polyol-based systems also demonstrated excellent performance, with Lido:EG and Lido:PG reaching 375.41 g/L and 321.94 g/L, respectively, at the same temperature. This data offers critical guidance for formulators: the Beta:Lido combination is ideal for high-loading applications where maximum drug potency is required, while the EG and PG formulations offer excellent alternatives with established safety profiles and high solubilizing power. The general superiority of HBD-rich (1:2) compositions suggests that maximizing hydrogen bond donor availability is a key strategy for enhancing drug solubilization in DES-based systems [34].

Translating mole fraction predictions into absolute solubility (g/L) yields a formulation-relevant metric (Figure 2, Table 2). Predicted values ranged from below 1 g/L to exceptionally high concentrations (exceeding 400 g/L) under the conditions studied; notably, the Beta:Lido (1:1) system reached 437.47 g/L at 333.15 K, while polyol-based systems Lido:EG and Lido:PG reached 375.41 g/L and 321.94 g/L, respectively, at the same temperature. These results indicate clear formulation pathways: Beta:Lido is a top candidate for very high-loading topical formulations, and EG/PG systems are strong, safety-familiar alternatives for high-solubility formulations.

We note two important qualifiers to aid interpretation. First, COSMO-RS generates a priori thermodynamic predictions that depend on computed intermolecular descriptors and ideal-mixture assumptions; in some solvent classes, particularly those with strong ionic or complex aggregation behaviour, COSMO-RS may overestimate absolute solubility relative to experimental values [35]. Therefore, exceptionally large numerical predictions (e.g., >100 g/L) should be treated as indicators of strong solvation potential and prioritized for experimental validation rather than accepted as final formulation specifications. Second, molecular interaction analysis of the top systems provides mechanistic insight that supports the numerical ranking: betaine (the "Beta" co-former) is a zwitterionic molecule that can engage in multifaceted electrostatic interactions and both conventional and non-conventional hydrogen bonds with capsaicin, producing complementary polarity and multiple binding modes that collectively enhance apparent solubility. Small polyols (EG, PG) favor solubilization through dense donor/acceptor hydrogen-bond networks and effective disruption of capsaicin self-association [36], explaining their consistently high performance.

Figure 2 highlights three visually apparent trends that guide formulation choices: (1) solubility increases with temperature for nearly all THEDES series, (2) HBD-rich compositions (HBA:HBD = 1:2) generally show higher absolute solubility than 1:1 counterparts, and (3) co-former classes cluster by performance — zwitterions and small polyols occupy the highest-solubility region, while long-chain alcohols and non-polar

co-formers cluster at the low-solubility end. These observations prioritize Beta:Lido and polyol systems for follow-up experimental screening.

Molecular-Level insight into the optimal betaine-lidocaine system

To decipher the exceptional performance of the Beta:Lido system, a detailed analysis of molecular interactions was conducted using σ-profiles, σ-potentials, and σ-surfaces (Figure 3). The σ-profile analysis revealed that betaine exhibits a broad and intense peak in the strong hydrogen bond donor (HBD) region ($\sigma < -0.01$ e/Å^2), confirming its pronounced proton-donating capacity [37]. Lidocaine displayed significant density in both HBD and hydrogen bond acceptor (HBA) regions ($\sigma > +0.01$ e/Å^2), consistent with its amphoteric nature [38], while capsaicin showed peaks primarily in the HBD region (phenolic OH) alongside a large non-polar domain ($\sigma \approx 0$), reflecting its amphiphilic character [39]. Complementary insights were obtained from σ-potential analysis, where betaine exhibited pronounced negative μ(σ) values in the HBA region, signifying its strong preference to act as an acceptor, while positive values in the HBD region confirmed its donor capability [40]. This balanced σ-potential profile positions betaine as an effective "molecular bridge" that facilitates cooperative interactions among the components. Visualization of σ-surfaces further highlighted the spatial distribution of polarity, with betaine dominated by intense polar patches indicative of abundant hydrogen-bonding sites. Lidocaine presented a mixed distribution of polar and non-polar regions, whereas capsaicin exhibited a large hydrophobic domain accompanied by localized polar zones. Collectively, these complementary properties explain the superior solubility of the Beta:Lido system. Betaine efficiently solvates the polar head of capsaicin, while maintaining compatibility with lidocaine, which in turn contributes additional solvation capacity and modulates the hydrophobic environment to accommodate capsaicin's extended alkyl chain [41].

A detailed analysis of the ternary system (betaine, lidocaine, capsaicin) revealed a complex and robust network of hydrogen bonds stabilizing the complex (Figure 4). The interactions include both strong conventional (O-H···O) and multiple weaker, non-classical (C-H···O) hydrogen bonds (Table 3). The strongest intermolecular interaction was a conventional H-bond between the phenolic hydrogen of capsaicin (cap:H36) and a carboxylate oxygen of betaine (beta:O2), with a short distance of 2.485 Å and a near-linear D-H-A angle of 153.1°, indicating a very strong and stable interaction. An extensive array of C-H···O bonds (distances from 2.280 Å to 2.557 Å) further stabilizes the system. Notably, a C-H···O bond between capsaicin (cap:H49) and lidocaine (lido:O1) provides a direct molecular link between the active pharmaceutical ingredient (API) and the anesthetic component, which physically confirms the hypothesized synergy of the formulation. This multifaceted hydrogen-bonding network is consistent with the exceptionally high solubility predicted by COSMO-RS and provides atomistic validation for the performance of the Beta:Lido formulation.

Limitations of the study

Notwithstanding the powerful utility of COSMO-RS as an efficient high-throughput screening tool, it is important to acknowledge the inherent limitations of a purely in-silico approach. The results presented here are thermodynamic predictions that require experimental validation, which we have designated as a critical next step. While COSMO-RS is well suited for qualitative screening and ranking, its quantitative accuracy may need empirical calibration against measured data [18], [21]. The current model addresses equilibrium solubility only and does not capture kinetic factors such as dissolution rate, nor does it predict final formulation properties including viscosity, rheology, or long-term physical stability. Biological endpoints relevant to topical applications—such as skin permeation, local metabolism, and cytotoxicity—are beyond the scope of these calculations. Therefore, although the computational findings provide valuable guidance for prioritizing solvent candidates and reducing experimental burden, laboratory synthesis, physicochemical characterization, and biological testing remain indispensable to confirm performance and to establish the clinical viability of the most promising THEDES formulations.

▪ CONCLUSION

This study establishes COSMO-RS as an efficient, generalizable in-silico platform for rationally screening Therapeutic Deep Eutectic Solvents (THEDES) to address poor API solubility. By evaluating 34 lidocaine-based formulations across two stoichiometries (1:1 and 1:2) and a temperature range, we identified compositional rules that consistently favor capsaicin solubilization: HBD-rich matrices and elevated temperature increase predicted solubility, and co-former chemistry—particularly zwitterionic character and

dense hydrogen-bonding capacity—strongly determines performance. The betaine–lidocaine (Beta:Lido) combination emerged as the top candidate, achieving the highest predicted loading under the tested conditions, while small polyols (e.g., ethylene glycol, propylene glycol) offered robust, safety-familiar alternatives. Mechanistic interrogation using σ-profiles and σ-potentials provided interpretable, atomistic-level criteria (complementary electrostatics and multiple donor/acceptor interactions) that explain the relative rankings and can be applied when screening other APIs and solvent classes.

These computational findings produce a prioritized, testable shortlist to guide formulation development and reduce experimental workload, but they remain thermodynamic predictions that require empirical follow-up. Planned next steps include equilibrium solubility measurements, activity-coefficient validation where feasible, physicochemical characterization of lead formulations (viscosity, rheology, stability), and biological evaluation (ex vivo permeation, in vitro cytotoxicity, and targeted in vivo studies as appropriate). By combining COSMO-RS pre-screening with focused experimental validation, the workflow presented here accelerates the discovery of clinically relevant topical capsaicin formulations and offers a scalable pre-screening strategy adaptable to other APIs and solvent design problems.

Acknowledgements: N. A. expresses gratitude to LPDP for the financial support provided during her academic studies.

Funding: This research was funded by the Indonesia Endowment Fund for Education (LPDP) scholarship program.

Conflict of interest statement: The authors declared no conflict of interest

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