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# Deep eutectic systems as enabling pharmaceutical formulations: mechanisms and applications

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ABSTRACT

New pharmaceutical chemical entities discovered in research often fail in development, due to poor biopharmaceutical performance, especially regarding aqueous solubility. Deep eutectic solvents or related systems (DES) are a new type of liquid with promising applications in solubility-enhancing pharmaceutics. DES are distinguished from the umbrella term eutectic solvents because their eutectic temperature is clearly lower than that of an ideal binary system from a thermodynamic viewpoint. DESs have been extensively studied and applied in the fields of green chemistry and chemical engineering, mainly for extraction purposes. Over the last decade, several studies have reported that DESs are excellent solubilizers of poorly soluble compounds, making them viable candidates for solubility-enabling formulations. This review aims to provide a thorough introduction to DESs and their material properties in comparison to other similar multicomponent systems, while also providing an overview of eutectic, DES, and therapeutic DES (THEDES) systems from the perspective of their potential application as enabling formulations. Additionally, an overview of computational studies on DESs is provided, where the techniques used to mechanistically study DES properties, including solubility and toxicity, are listed. The review concludes that DES liquids can be utilized as enabling formulations and that increased oral bioavailability would not only be beneficial from a biopharmaceutical perspective but also help reduce the amount of environmentally harmful active pharmaceutical ingredients (APIs). This increased bioavailability offers a further sustainability advantage, making this formulation strategy particularly attractive.

## 1. Motivation for using DES in oral pharmaceutics

With 40–60 % of new chemical entities failing to reach the pharmaceutical market for patient use, the poor solubility of compounds represents a hurdle in pharmaceutical research and development (Babu and Nangia, 2011; Kuentz et al., 2021). It is therefore of great importance to develop drug delivery systems to mitigate the issue of poor solubility in newly developed compounds (Babu and Nangia, 2011; Kuentz et al., 2021). Deep eutectic solvents (DESs) are a novel class of solvents capable of dissolving exceptional amounts of poorly water-soluble drugs (Abranches and Coutinho, 2023; Chakraborty et al., 2021; Chakraborty et al., 2023; Cysewski and Jeliński, 2019; Cysewski et al., 2024; Dwamena, 2019; Emami and Shayanfar, 2020; Faggian et al., 2016; Fourmentin et al., 2021; Fronduti et al., 2023; H. Palmelund et al., 2021; Hansen et al., 2021; Jeliński and Cysewski, 2018; Jeliński et al., 2019; Jeong et al., 2017; Li and Lee, 2016; Martins et al., 2019; Moermond et al., 2022; Mokhtarpour et al., 2020; Nasrallah et al., 2024; Palmelund et al., 2019; Smith et al., 2014; Sut et al., 2017; T. Jeliński et al., 2024; Wolbert et al., 2019). They are mixtures of hydrogen bond donating and accepting components that interact through hydrogen bonds, resulting in a significant reduction in the melting points (Hansen et al., 2021; Martins et al., 2019). The melting points are below the ideal eutectic systems, which distinguishes the DES from the simple eutectic systems (Martins et al., 2019). DESs are often liquid at either operating or physiological temperatures, and the large selection of component candidates allows for the tuning of factors such as toxicity, biodegradability, volatility, viscosity, and many other properties (Palmelund et al., 2019). This makes them attractive designer solvents in the fields of green chemistry and chemical engineering (Alonso et al., 2016; Chakraborty et al., 2021; Emami and Shayanfar, 2020; Fourmentin et al.,

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2021; García-Argüelles et al., 2013; Ramón and Guillena, 2019). In pharmaceutics, DESs are a novel field of study, where the solubilization of poorly water-soluble active pharmaceutical ingredients (APIs) has been repeatedly achieved through the application of various DESs (Fourmentin et al., 2021). Therefore, DESs have been frequently compared to ionic liquids, despite the differences in their molecular interactions. DESs are preferred over ionic liquids because of their lower toxicity (Fourmentin et al., 2021; Palmelund et al., 2019). The latter, in combination with the enhanced solubility of APIs, paved the way for research on DESs as potential candidates for bio-enabling formulations (H. Palmelund et al., 2021).

DES research has been on the rise, with >60 % of all DES-related publications published within the last three years, between 2021–2024. According to the Web of Science, approximately 14′295 hits show up when "deep eutectic" is searched. These are mostly reported in the field of chemistry (multidisciplinary, physical, and chemical engineering), accounting for approximately 62 % of all published documents. Only 1.9 % of all published data belong to the fields of pharmacology and pharmacy. Fig. 1 (adapted and modified from WebofScience.com) shows the overall growth in the number of DES publications since the pioneering work of Abbott et al. in 2001 (Abbott et al., 2001; Abbott et al., 2002).

The pioneering work on DES as a pharmaceutical enabling formulation was published by Palmelund et al. (H. Palmelund et al., 2021) who compared the in vitro and in vivo performances of nanocrystalline, amorphous, and DES-based formulations of aprepitant. As a result, improved in vitro performance of the DES was observed, and the in vivo performance of the DES was comparable to that of the nanocrystalline formulation but better than that of the amorphous formulation. This formulation was a simple and straightforward DES formulation, which could successfully be used as a formulation to enhance the solubility of the poorly soluble compound aprepitant (H. Palmelund et al., 2021).

However, DESs have rarely been considered for pharmaceutical applications so far, often due to the frequently occurring high viscosity and hygroscopicity, posing challenges in production and reproducibility (Dai et al., 2015; Emami and Shayanfar, 2020; H. Palmelund et al., 2021). Furthermore, liquid formulations, with high loads of dissolved API, carry the risk of drug re-crystallization in the gastrointestinal (GI) fluids, making them unattractive as potential enabling formulations (H. Palmelund et al., 2021; Taylor and Aulton, 2022). This review investigates and provides proof of concept for DES as novel enabling formulations, while providing computational insights into the different mechanistic aspects of DES formulations.

## 2. Deep eutectic solvents (DESs)

DESs are classified as a subcategory of eutectic systems (Hansen et al., 2021). The word 'eutectic' is the combination of the Greek words 'εὐ' and 'τηκein', directly translated to 'easily melting', coined by Frederick Guthrie in 1884 (Guthrie, 1884). Hence, eutectic systems refer to multicomponent systems with a molar ratio at which the lowest melting point is obtained (Chakraborty et al., 2021; Fourmentin et al., 2021). The components in eutectics interact through non-covalent bonds, including hydrogen bonding, London van der Waals interactions, and cohesive and adhesive forces, among others (Chakraborty et al., 2021). Eutectic mixtures follow a thermodynamic behavior that resembles that of an ideal system (Fourmentin et al., 2021). In such an ideal system, the enthalpy required to form the bonds between the two (or more) components is equal to the amount of enthalpic energy released from breaking the bonds to obtain individual components (Fourmentin et al., 2021). Solid-liquid (SL) behavior of such systems can be described by assuming the activity coefficient at unity ($\gamma_i = 1$), resulting in the Schröder van Laar (SvL) equation (Eq. (1)) below (Wolbert et al., 2019):

$$ln(x_i) = -\frac{\Delta_m H_i}{R}\left(\frac{1}{T} - \frac{1}{T_{m,i}}\right) \quad (1)$$

The SL equilibrium temperature (T) is accordingly related to the molar fraction ($x_i$), the enthalpy of fusion ($\Delta_m H_i$), and the melting point ($T_{m,i}$) of the component *i*. The red line in Fig. 2 (adapted and modified from (Martins et al., 2019)) showcases a hypothetical phase diagram of an ideal eutectic system with the dashed red line marking the obtained eutectic melting point ($T_{E,\ ideal}$) (Martins et al., 2019).

Traditionally, DESs were defined as liquids at room temperature,

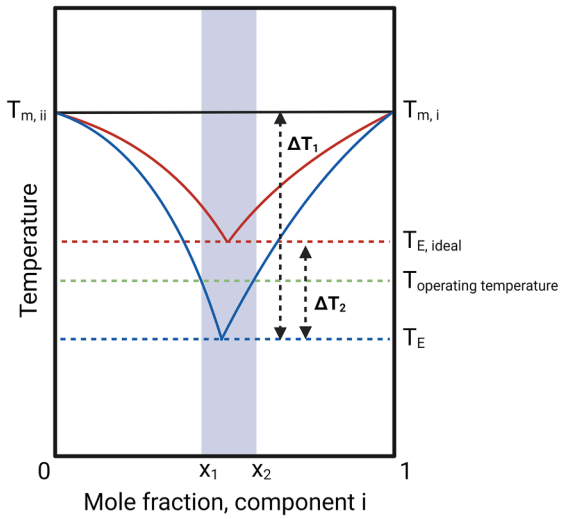


**Fig. 2.** Schematic representation of the comparison of the SLE of a simple ideal eutectic mixture (red line) and a deep eutectic mixture (blue line) modified from Martins et al. (Martins et al., 2019).

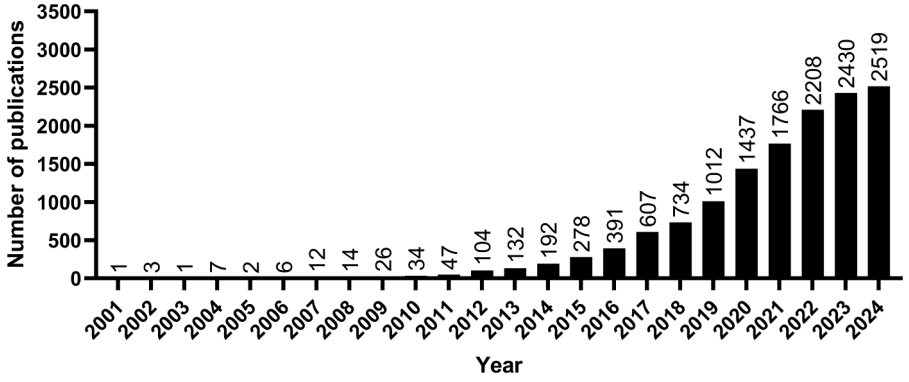


**Fig. 1.** Published articles on the topic of deep eutectic solvents in recent years, according to the Web of Science database (date of access: 09/10/2024).

made by mixing and heating of two (or more) solid components interacting through hydrogen bonding (Martins et al., 2019); this is marked as $\Delta T_1$ on Fig. 2. The first instance of a DES was introduced as 'reline' in the pioneering work of Abbott et al. in 2002 (Abbott et al., 2002). 'Reline' consisted of choline chloride and urea at the molar ratio of 1:2, with the eutectic melting point ($T_E$) of 12 °C (Abbott et al., 2002). This formulation showed a significant reduction in the melting point compared to the initial solid components, which were 302 °C for choline chloride and 133 °C for urea. However, this definition does not differ significantly from the definition of eutectics, whose melting points can be below operating temperatures (Chakraborty et al., 2021).

Thus, in 2019 Martins et al. (Martins et al., 2019) established that DESs show a clear negative deviation from the ideal eutectic behavior and must thereby always be characterized through phase diagrams to be accurately pointed out. An example of a SL line obtained from a DES is depicted as the blue line on Fig. 2, where the hypothetical eutectic point is marked as $T_E$ and the distinguishing negative deviation is demonstrated by $\Delta T_2$. Literature suggests that the characteristic negative deviation of DES is due to stronger interactions in the resulting mixture (Abdelquader et al., 2023; Chakraborty et al., 2021; Martins et al., 2019; Nasrallah et al., 2024). Additionally, recent data confirm that a negative Gibbs free energy value is the main contributor to the negative deviation in DES (Bruinhorst et al., 2024; Kollau et al., 2020). Bruinhorst et al. (Bruinhorst et al., 2024) demonstrated that, in the case of choline chloride DESs, the balance between the negative enthalpy and positive entropy is crucial for this characteristic. The negative enthalpy is governed by the favorability of hydrogen bond interactions, whereas the positive entropy is caused by the versatility of the hydrogen bond acceptor (choline chloride) (Bruinhorst et al., 2024; Kollau et al., 2020). The study performed by Kollau et al. (Kollau et al., 2020) further showed that assuming ideal entropy in DESs tends to underestimate the component contribution to entropy, which is affected by the molar volume and molecular size of the components.

The green line on Fig. 2 signals that the molar fractions between $x_1$ and $x_2$ result in liquid systems at operating temperatures, as the melting points are below this line. This puts emphasis on the nature of DES as eutectics, rather than a simple liquid at room temperature. However, the liquidus nature at the neighboring molar fractions have shown to possess beneficial properties as well, which can be utilized to tailor and optimize the systems according to their intended application (Abranches and Coutinho, 2023; Li and Lee, 2016). Nonetheless, recent studies have shown that the eutectic point is different from other molar fractions of the same components, as the lowest surface tension and highest activation energy for ionic conductivity were observed at this point (Fronduti et al., 2023). A lower surface tension indicates higher adhesive forces between the heteromolecular components in the DES, showing less structured short-range interactions while sustaining the least ionic transfer between the molecules (Fronduti et al., 2023). This further distinguishes the eutectic point of the DES from the long-range lamellar structure of the cohesive homomolecular structure observed in ideal eutectic systems (Abdelquader et al., 2023).

Ultimately, the definition adopted in this review considers DESs as eutectic systems formed at a specific molar ratio between two (or more) hydrogen bond donating and accepting components interacting through transient interchangeable hydrogen bonds at different functional groups, resulting in a non-ideal negatively deviating thermodynamic behavior compared to ideal eutectic systems (Abdelquader et al., 2023; Ashworth et al., 2016; Martins et al., 2019).

### 2.1. Thermodynamic properties

Solubility of a component (i) in a multicomponent system can be described using the widely used general solubility Eq. (2) (Nordström and Rasmuson, 2009; Taylor and Aulton, 2022; Wolbert et al., 2019):

$$ln(a_i) = ln(x_i\gamma_i) = -\frac{\Delta_m H_i}{R}\left(\frac{1}{T}-\frac{1}{T_{m,i}}\right) + \frac{1}{R}\int_{T_{m,i}}^{T}\frac{\Delta_m C_{p,\,i}}{T}dT - \frac{1}{RT}\int_{T_{m,\,i}}^{T}\Delta_m C_{p,i}\,dT \quad (2)$$

where $\Delta_m C_{p,i}$ is the heat capacity upon melting and R is the ideal gas constant (Nordström and Rasmuson, 2009; Nordström and Rasmuson, 2008; Taylor and Aulton, 2022). The equation can be simplified to Eq. (1) (see above) to calculate the eutectic temperature or the ideal case, i.e., the $T_{E,\,ideal}$ (Wolbert et al., 2019). As the equilibrium temperature is presumed near the melting temperature, the simplified solubility equation omits the $\Delta_m C_{p,i}$ without notable impact on the accuracy (Nordström and Rasmuson, 2009; Nordström and Rasmuson, 2008; Taylor and Aulton, 2022). However, this depends on the melting temperature, as described in the work of Martins et al. (Martins et al., 2019). Nonetheless, Eq. (2) depicts the impact of the melting point ($T_{m,i}$), the melting enthalpy ($\Delta_m H_i$), and the activity coefficient ($\gamma_i$) on the SL equilibria (Abdelquader et al., 2023; Achkar et al., 2021; Chakraborty et al., 2021; Fourmentin et al., 2021; Hansen et al., 2021; Nordström and Rasmuson, 2009; Nordström and Rasmuson, 2008; Wolbert et al., 2019). Lower melting point of component *i* will consume more of the counter-component, whilst decreasing the eutectic point (Kollau et al., 2020; Kollau et al., 2018). The fading lines in the adopted Fig. 3-(a) represent this shift in the SL line compared to a hypothetical simple binary eutectic system at the molar ratio of 1:1 of components *i* and *ii*, shown as the dark blue solid line. Similarly, lower melting enthalpy and lower activity coefficients will result in lower eutectic points, as the steepness of the SL line shifts (see in Fig. 3-(b) and 3 -(c)) (Kollau et al., 2018; Wolbert et al., 2019). The lower melting enthalpy of component *i* increases the steepness of the slope of the SL line, in turn increasing the molar fraction of the counter-component *ii* (Fig. 3-(a)), resulting in less component *i* at the eutectic point (Kollau et al., 2018; Wolbert et al., 2019). However, the lower activity coefficient of the interaction between the two components results in steeper curves for both components, which correspondingly reduces the melting temperatures with no alteration of the molar fraction (Abdelquader et al., 2023; Kollau et al., 2018; Martins et al., 2019; Wolbert et al., 2019).

### 2.2. Preparation methods

DESs are prepared by the application of enough activation energy to break the existing bonds in the starting materials, and to form the subsequent new bonds between the component molecules (Fourmentin et al., 2021). Most methods involve heating and/or mixing (Fourmentin et al., 2021). Heating is often achieved in an oven, where the heat is set to temperatures between 40–100 °C (Abdelquader et al., 2023; Chakraborty et al., 2021; Fourmentin et al., 2021). Although the oven method is simple and easy to apply, the risk of degradation and esterification is higher due to longer heating times (Abdelquader et al., 2023; Fourmentin et al., 2021). In contrast, the fastest method for producing DESs involves the use of radiation energy in the form of ultrasonics or microwaves (Abdelquader et al., 2023; Javed et al., 2024). The radiation technique benefits from the fast transmission of the required activation energy; however, the pace of the interaction poses safety threats and carries some risk of uneven overheating (and consequent degradation) (Ijardar et al., 2022).

The grinding method also benefits from its simplicity and low energy input (Fourmentin et al., 2021). Grinding can be applied to components using a mortar and pestle or other milling instruments (e.g., a ball mill) (Długosz and Banach, 2024; Fourmentin et al., 2021). Because the method is devoid of heat, it is applicable to thermosensitive materials and APIs (Abdelquader et al., 2023; Długosz and Banach, 2024; Fourmentin et al., 2021). A downside of this method is excessive exposure to humidity (Fourmentin et al., 2021). As covered in the following Section

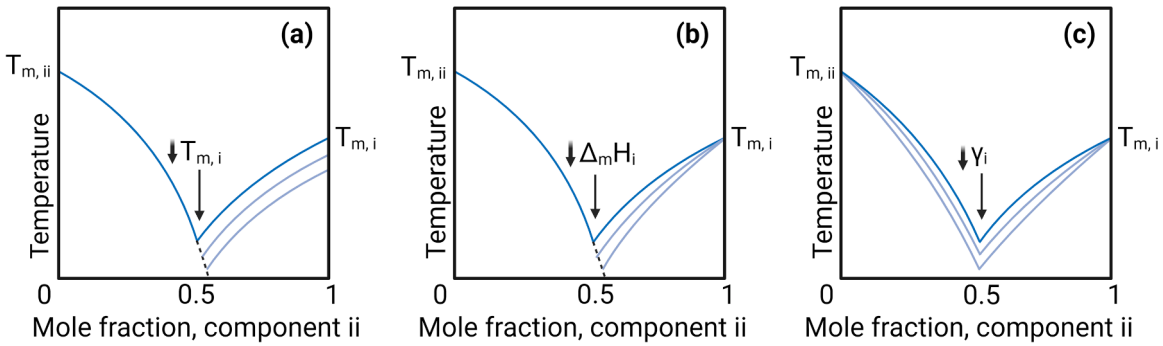


**Fig. 3.** Impact of melting point ($T_{m,i}$), enthalpy of fusion ($\Delta_m H_i$), and activity coefficient ($\gamma_i$) of component *i* on thermodynamic behavior of resulting mixtures with component *ii*, depicted in Figures (a), (b) and (c) respectively. Figure modified from Kollau et al. (Kollau et al., 2018).

2.3, DESs can be quite hygroscopic and eventually show deliquescence, so excessive water-uptake has an impact on the physicochemical properties of the final product (Achkar et al., 2019; Alizadeh et al., 2020; Hammond et al., 2017; Ma et al., 2018; Palmelund et al., 2020; Rozas et al., 2021). Stirring and heating plates combine two sources of energy, mechanical and heat, to overcome the activation energy (Abdelquader et al., 2023; Fourmentin et al., 2021). This method is most frequently utilized to produce DESs (Abranches and Coutinho, 2023; Fourmentin et al., 2021; Hansen et al., 2021; Martins et al., 2019). Another variation of the combined heating/mixing method is hot-melt extrusion (e.g., the twin screw extruder), which has recently been reported as an applicable approach for DES production (Crawford et al., 2016).

Another prevalent method for DES production is the solvent method (Chakraborty et al., 2021; Fourmentin et al., 2021). This method entails the solvation and mixing of the individual components in an organic solvent, followed by the evaporation of the excess organic solvent (Chakraborty et al., 2021; Fourmentin et al., 2021). The solvent method relies on the reported lack of volatility of DESs, as it is expected that the evaporation of the excess organic solvent leaves behind a uniform DES (Fourmentin et al., 2021). Nonetheless, the method can be disadvantageous as solvent residues are normally detected in the yielded DESs (Abdelquader et al., 2023; Chakraborty et al., 2021; Fourmentin et al., 2021; Javed et al., 2024). The excess organic solvent can be removed using a rotary evaporator or freeze-dryer (Abdelquader et al., 2023; Chakraborty et al., 2021; Fourmentin et al., 2021; Javed et al., 2024). All the enlisted preparation methods are also used at industrial scale. This includes industrial-scale ovens, extruders, freeze-dryers and rotary evaporators. Consequently, DESs are considered readily adaptable to established manufacturing techniques.

### 2.3. *Water as an impurity*

DESs often show higher viscosities, which prove to be a hurdle in pharmaceutical production (Ferreira and Sarraguça, 2024; Fourmentin et al., 2021; Negi et al., 2024). To mitigate this issue, researchers often add water to the DES to reduce the viscosity and to increase the ease of handling (Negi et al., 2024). Water affects intermolecular interactions and the nanostructure in DES and is therefore primarily categorized as an impurity in DES (Achkar et al., 2019; Fourmentin et al., 2021; H. Palmelund et al., 2021; Hammond et al., 2017; Ma et al., 2018; Pour et al., 2024). Moreover, water influences the phase-change thermodynamics, viscosity, and conductivity of DESs (Achkar et al., 2019; Fourmentin et al., 2021; Fourmentin et al., 2021; H. Palmelund et al., 2021; Hammond et al., 2017; Ma et al., 2018; Pour et al., 2024). Water results in the reduction of the melting point, viscosity, density and the solubilization properties of DESs, while increasing the conductivity and polarizability (Celebi et al., 2019; Fourmentin et al., 2021; Hammond et al., 2017). Water molecules have both hydrogen bond donating and accepting functional groups, which could potentially act as a form of "linker" between the hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) networks in the DES (Fourmentin et al., 2021; Hammond et al., 2017). However, the hydrogen bond network in the DES may also be interrupted by comparatively higher amounts of additional water in the system, which in turn impacts the physicochemical bulk properties (Fourmentin et al., 2021; Kaur et al., 2020; Ma et al., 2018; Rozas et al., 2021). Some studies have shown that the solubilization of APIs in some DESs can slightly increase in the presence of low concentrations of water, but it can be expected that the effects mitigated by water may also be negative for the solubilization of hydrophobic or lipophilic drugs (Sayad et al., 2021; T. Jeliński et al., 2024). As mentioned, water can also perturb the DES system after a certain concentration (>10 %) (Panbachi et al., 2023; Rozas et al., 2021). This often negatively impacts API solubilization (Fourmentin et al., 2021; H. Palmelund et al., 2021). Although water can be a beneficial co-solvent in DESs with APIs at lower concentrations, researchers must be mindful that water changes the properties of the DES.

Palmelund et al. (H. Palmelund et al., 2021) also established that most DESs are hygroscopic as a result of hygroscopic component incorporation, and that some DESs even deliquesce. It is hence of utmost importance to control the humidity of the production and storage environment for DESs (H. Palmelund et al., 2021). As described in Section 2.2 DESs are often produced using mixing and heating, which provides the energy to surpass the activation energy of DES formation. Some studies reduce the activation-energy by employing water in the production step (Achkar et al., 2019; Dai et al., 2015; Dai et al., 2013). This is usually combined with the solvent method, where the applied solvent can be water (Dai et al., 2013; Fourmentin et al., 2021). This method inevitably leaves traces of water in the system (H. Palmelund et al., 2021). As mentioned, methods with direct exposure to humidity, including the heating method in a water bath, and the milling/grinding method should be avoided as water can be taken up by the mix during processing (Fourmentin et al., 2021; H. Palmelund et al., 2021; Kaur et al., 2020; Ma et al., 2018; Rozas et al., 2021).

### 2.4. *Classification*

The constituents of a DES play an important role in determining its properties. The basic interacting components of a DES structure can be simplified to the formula $Cat^+X^-zY$, where $Cat^+$ denotes the cation (usually an ammonium, phosphonium, or sulfonium), $X^-$ the Lewis base (typically halide anions), and z represents the number of Y as Lewis or Brønsted acid (Smith et al., 2014). Thus, the DES are divided into four sub-categories depending on the type of components used to synthesize them. Table 1 summarizes the list of DES types I-V adopted from Chakraborty et al. (Chakraborty et al., 2021). The first three types described in the literature are made of an organic salt as the HBA, annotated as $Cat^+X^-$, and either a metal salt MCl (usually a chloride salt), a metal salt hydrate $MClx{\bullet}yH_2O$ (with y as the number of hydrates), or an organic compound (RZ, with the R alkyl group) as the HBD. These are known to be type I, II, and type III DES, respectively (Chakraborty et al.,

**Table 1**
Classification of DES according to interacting components (Smith et al., 2014). Adopted and modified from Chakraborty et al. (Chakraborty et al., 2021).

| Type | Composition | General formula | Term |
|---|---|---|---|
| I | Organic salt + metal salt | $Cat^+X^- zMCl_x$ | $M$ = Zn, Sn, Al, Ga, In |
| II | Organic salt + hydrated metal salt | $Cat^+X^- zMCl_x \bullet yH_2O$ | $M$ = Cr, Co, Cu, Ni, Fe, Ca |
| III | Organic salt + HBD | $Cat^+X^- zRZ$ | $R$= alkyl group and $Z$ = $CONH_2$, COOH, OH |
| IV | Metal chloride + HBD | $MCl_x + RZ$ | $M$ = Al, Zn and $Z$ = $CONH_2$, OH |
| V | Non-ionic HBD + non-ionic HBA | - | - |

2021; Fourmentin et al., 2021; Smith et al., 2014). Further DES types include the type IV made of an organic HBD with a metal halide as the HBA, and the recently described type V DES made of nonionic HBDs (mainly phenols) and nonionic HBAs (Abranches et al., 2019).

Within the individual DES categories, further subcategories can be described based on the properties of the constituting components, which ultimately impact the physicochemical properties of the DES formulation (Fourmentin et al., 2021). With the aim of selecting a physiologically applicable formulation, the type III DESs made of organic HBD and HBAs have been described as the most suitable candidate for pharmaceutical development, due to their lower toxicity (Abdelquader et al., 2023; Abranches and Coutinho, 2023; Fourmentin et al., 2021; Oyoun et al., 2023; Palmelund et al., 2019). Specifically, type III DES cover natural DES (NADES), therapeutic DES (THEDES), hydrophobic DES (HDESs), and low-transition-temperature mixtures (LTTMs). NADES are referred to as "natural" because they are composed of components of natural origin, including primary metabolites such as organic acids, amino acids, sugars, polyols, and choline derivatives, which exhibit low toxicity (Dai et al., 2013; Faggian et al., 2016; Fourmentin et al., 2021; Hayyan et al., 2016; Jeliński et al., 2019; Liu et al., 2018). Similarly, when a constituting component within the DES is an API, the DES is categorized as THEDES (Abdelquader et al., 2023). Such formulations benefit from higher bioavailability of the liquified API (Abdelquader et al., 2023; Aroso et al., 2016; Javed et al., 2024; Pereira et al., 2022). Another example of components reigning the properties of the final DES formulation is HDESs made of lipophilic components such as triglycerides of different fatty acid chain lengths (Dwamena, 2019; Fourmentin et al., 2021; Osch et al., 2020; Panbachi et al., 2025; Zainal-Abidin et al., 2021). HDESs are reported as viable alternatives to traditionally applied oils in various fields, including lipid based pharmaceutical formulation strategies and in environmental engineering applications (Dwamena, 2019; Florindo et al., 2018; Osch et al., 2020; Panbachi et al., 2024; Zainal-Abidin et al., 2021). Lastly, LTTMs present a rather novel class of mixtures referring to DES systems whose negative deviation compared to the ideal thermodynamic behavior is observed on the glass transition temperatures, rather than the melting point (Francisco et al., 2013). LTTMs require advanced techniques, such as Fourier-transform infrared (FTIR) spectroscopy, to be distinguished; however, they still present as a promising novel subcategory of DESs with beneficial properties for catalysis and material science (Balaraman and Rathnasamy, 2020; Zdanowicz et al., 2019). In summary, these subcategories of DES type III reflect the importance of classifying the interacting components within DES systems to determine their ultimate physicochemical properties in practice.

## 3. DESs as multicomponent systems

Pharmaceutical formulations often consist of various components (Fourmentin et al., 2021). The interaction between these components can affect the physicochemical properties of the system, which can be tailored according to the desired application (Berry and Steed, 2017; Cherukuvada and Nangia, 2013; Dai et al., 2015; Francisco et al., 2013; Palmelund et al., 2019; Zhuang et al., 2022). Often, the stability and the solubility (and in turn, the bioavailability) of APIs can be improved by incorporation into multicomponent systems (Berry and Steed, 2017; Cherukuvada and Nangia, 2013; Dai et al., 2015; Francisco et al., 2013; Palmelund et al., 2019; Zhuang et al., 2022). Such systems can be formed using an API and a suitable co-former selected based on the compatibility of the two (Berry and Steed, 2017; Cherukuvada and Nangia, 2013; Dai et al., 2015; Francisco et al., 2013; Palmelund et al., 2019; Zhuang et al., 2022). Salts, co-crystals, amorphous solid dispersions, ionic liquids, solutions, eutectic mixtures, LTTMs, and DESs are all examples of pharmaceutically applicable multicomponent systems (Berry and Steed, 2017; Cherukuvada and Nangia, 2013; Palmelund et al., 2019; Zhuang et al., 2022). The API can either be dissolved or act as a co-former in the systems (Berry and Steed, 2017; Cherukuvada and Nangia, 2013; Dai et al., 2015; Francisco et al., 2013; Palmelund et al., 2019; Zhuang et al., 2022). The melting point of a multicomponent system can vary, resulting in liquids at room temperature in some cases (Bica et al., 2011; Francisco et al., 2013). These include ionic liquids, DESs, and some eutectics and LTTMs (Askeland and Fulay, 2009; Francisco et al., 2013; Płotka-Wasylka et al., 2020). However, it is not uncommon to observe a change in the melting points of the components once they are incorporated into multicomponent systems (Berry and Steed, 2017). It is therefore important to distinguish the interactions, the component pKa differences and the phase behavior of the systems to assign the correct label to each system.

One of the main differences between the different multicomponent systems is the strength of the interactions between the constituents (Askeland and Fulay, 2009; Taylor and Aulton, 2022). Weaker interactions are observed in solid solutions and eutectics (Askeland and Fulay, 2009; Berry and Steed, 2017; Bica et al., 2011; Burrows et al., 2022). Metal alloys are the most prevalent examples of solid solutions (Askeland and Fulay, 2009; Burrows et al., 2022). Solid solutions occur between miscible elements that interact to form a homogeneous phase with crystalline structures reminiscent of the parent components (Askeland and Fulay, 2009; Berry and Steed, 2017). Nonetheless, new properties are attained in the solutions, such as lower melting points with larger malleability (Askeland and Fulay, 2009; Burrows et al., 2022). Solid solutions are formed across all compositions of the mixtures, resulting in a phase diagram with seemingly no $T_E$ (Askeland and Fulay, 2009; Berry and Steed, 2017). However, eutectic systems and solid solutions are similar, as they both consist of cohesive (homo--molecular) interactions (Abdelquader et al., 2023; Askeland and Fulay, 2009; Chakraborty et al., 2021; Cherukuvada and Nangia, 2013). These manifest as a single homogenous phase in solid solutions, and a two-phase mixture in eutectics (Abdelquader et al., 2023; Chakraborty et al., 2021). Fig. 4-(a) depicts a hypothetical phase diagram of a binary solid solution of components *i* and *ii* (Askeland and Fulay, 2009; Nugrahani and Jessica, 2021).

Hydrogen bonding, as an example of stronger interactions, makes up most of the primarily heteromolecular adhesive interactions observed in DESs, LTTMs, and co- crystals (Bica et al., 2011; Cherukuvada and Nangia, 2013; Fourmentin et al., 2021). As described in Section 2.4 the DES and the LTTMs are categorized as a sub-branch of eutectic mixtures with negatively deviating melting points in the case of DES, and glass transition temperatures in LTTMs (Francisco et al., 2013). In comparison to eutectics, and solid solutions, the phase behavior of co-crystals stands out, because they distinctively show two separate eutectic points (Berry and Steed, 2017). The two eutectic points in co-crystals occur at different compositions of the solids, due to the immiscibility of the two at certain ratios (Berry and Steed, 2017). This results in a distinct "W" shaped phase diagram (Berry and Steed, 2017; Nugrahani and Jessica, 2021). An example of a theoretical co-crystal phase diagram is presented in Fig. 4-(b) for a hypothetical binary mixture of components *i* and *ii*. It is also important to note that co-crystals differentiate from eutectics and solid solutions, in that they form new crystal lattices in the mixtures (Berry and Steed, 2017).

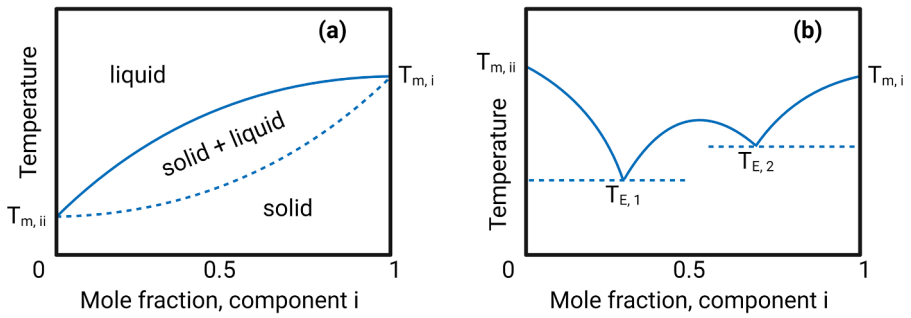


**Fig. 4.** Illustrated phase diagram of a hypothetical solid solution in (a) and "W"-shape phase diagram of a hypothetical co-crystal in (b), for proposed components *i* and *ii*, modified from Nugrahani et al. (Nugrahani and Jessica, 2021).

Stronger hydrogen bond interactions are expected to occur between the cation and anionic species in the makeup of salts and ionic liquids (Berry and Steed, 2017; Zhuang et al., 2022). Like co-crystals, salts are formed between basic and acidic components (Berry and Steed, 2017; Bica et al., 2011). However, the difference in pKa values between the acid and the base is often below 0 in co-crystals, whilst being larger than 3 units in salts (Berry and Steed, 2017; Quintano et al., 2023; Taylor and Aulton, 2022). The larger difference ensures that there are ionic species forming through proton transfer, which can result in a liquid at temperatures below 100 °C (Berry and Steed, 2017; Yoshizawa et al., 2003). The latter is obtained in ionic liquids, with pK differences above 10 units (Yoshizawa et al., 2003). Hence, ionic liquids have been described as liquid salts (Berry and Steed, 2017; Bica et al., 2011; Yoshizawa et al., 2003). Salts and co-crystal solid state engineering is frequently used to adjust API features, such as stability and solubility, in the pharmaceutical formulation development processes (Berry and Steed, 2017). Ionic liquids have also shown great properties such as extraordinary solubilization of poorly soluble compounds (Pedro et al., 2020; Shukla et al., 2023; Uddin et al., 2020; Yuan et al., 2022; Zhuang et al., 2022). However, ionic liquids can be disadvantageous due to toxicity (Emami and Shayanfar, 2020; Fourmentin et al., 2021; Zhuang et al., 2022).

In summary, pharmaceutical multicomponent systems resemble each other with major differences in interaction strengths and thermodynamic phase behaviors (Abdelquader et al., 2023; Berry and Steed, 2017; Bica et al., 2011; Cherukuvada and Nangia, 2013). The systems can be obtained based on the strength of the interactions and the balance between the cohesive and adhesive forces (Chakraborty et al., 2021; Fourmentin et al., 2021). The adhesive forces reign the interactions in co-crystals and DESs, whilst cohesive forces are seen as a single phase in solid solutions and a two-phase system in eutectics (Berry and Steed, 2017). Furthermore, the state of the material at operating temperatures differentiates the ionic liquids from salts, and most DESs from eutectics (Abdelquader et al., 2023). Lastly, salts and co-crystals are distinguished according to the pKa difference between their constituting components, resulting in protic interactions in salts (and ionic liquids), and hydrogen bonds in co-crystals (Berry and Steed, 2017; Bica et al., 2011; Cherukuvada and Nangia, 2013; Machado et al., 2016; Mohite et al., 2023; Nugrahani and Jessica, 2021) (Feeney and Crum, 2016; Radošević et al., 2015).

## 4. DES and eutectics in pharmaceutics

Research on DES, which is frequently presented as a new environmentally friendly 'green' solvent, has been on the rise in recent years (Achkar et al., 2021; Fronduti et al., 2023; Şahin et al., 2021; Zhang et al., 2017). This is due to the biodegradability, low toxicity, and low volatility of DESs, which can be tuned based on the starting materials used in production (Abdelquader et al., 2023; Emami and Shayanfar, 2020; Fourmentin et al., 2021; Hansen et al., 2021). DESs have mostly been studied for extraction, catalysis, and bio-catalysis (Álvarez et al., 2024). However, other applications, including pharmaceutical formulation development, have also been uncovered (Fourmentin et al., 2021). DESs can be used in a technical manner, such as a solvent for the synthesis, morphology control, and stabilization of APIs, excipients (mainly polymers), and other organic materials, or for functionalization in nanomaterials (Abdelquader et al., 2023; Chakraborty et al., 2021; Fourmentin et al., 2021; Oyoun et al., 2023). However, the main forte of the DES is their potential as drug delivery systems increasing bioavailability either through strong solvation of poorly water soluble drugs in DES vehicles, or by delivery of liquified APIs in the form of THEDESs (Abdelquader et al., 2023; Chakraborty et al., 2021; Fourmentin et al., 2021; Hansen et al., 2021; Ramón and Guillena, 2019). The following sections further elaborate on these topics based on a selection of key articles that have been repeatedly pointed out as leading works in pharmaceutical DES research.

### 4.1. Pharmaceutical eutectic mixtures

Eutectic mixtures refer to a mixture of components at a molar ratio where the melting point is the lowest (Ramón and Guillena, 2019). Eutectic mixtures follow an ideal thermodynamic phase behavior, with components forming solid solutions held together by adhesive interactions (Askeland and Fulay, 2009; Cherukuvada and Nangia, 2013). Their SL equilibria can be calculated using the SvL equation, which is often used as the blueprint method to distinguish simple eutectics from DESs (and THEDESs) (Martins et al., 2019; Wolbert et al., 2019). Eutectic mixtures are either purely made of APIs as constituting components, or of APIs with one or more counter excipients (Berry and Steed, 2017). The first instance of a eutectic mixture showing enhanced solubility of a drug was based on a study of sulfathiazole with urea, presented by Sekiguchi and Obi in 1961 (Sekiguchi and Obi, 1961). The mixture showed increased drug solubility as a result of enhanced surface area to volume ratio in aqueous dispersions (Bazzo et al., 2020; Sekiguchi and Obi, 1961). Since then, several eutectic mixtures have been presented, where enhanced solubility of an API was observed (Bazzo et al., 2020).

Improved bioavailability of the topically administered eutectic mixture of prilocaine and lidocaine granted the formulation market entry under the name EMLA®, in 1980 (Abdelquader et al., 2023; Lillieborg and Aanderud, 2017). EMLA® is a 5 % oil-in-water cream of a 1:1 eutectic mixture of prilocaine and lidocaine, with a $T_E$ of 17 °C, which is below the melting points of the starting materials; 68 °C for lidocaine and 37 °C for prilocaine (Lillieborg and Aanderud, 2017). It is widely acknowledged that the dermal and transdermal bioavailability of both APIs are increased with the application of EMLA® (Abdelquader et al., 2023; Lillieborg and Aanderud, 2017). Another eutectic mixture on the market with superior bioavailability is Fenoglide®, which is made of a eutectic mixture of fenofibrate and polyethylene glycol 8000 (Williams et al., 2016). The $T_E$ of the mixture is 57 °C at an approximate molar ratio of 1:4. Studies evaluating the drug release showed that the eutectic mixture had microcrystalline structures of 10 μm, which could be dissolved faster than the 100 μm crystalline structure of fenofibrate,

resulting in a 10-fold improvement in fenofibrate dissolution (Williams et al., 2016). Therefore, eutectics are recognized as pharmaceutically beneficial multicomponent systems with established practical use on the market (Lillieborg and Aanderud, 2017; Williams et al., 2016; Zainal-Abidin et al., 2021).

### 4.2. THEDESs as drug delivery systems

THEDESs are an alternative approach to DES drug delivery, where the API itself is a constituting component of the DES (Abdelquader et al., 2023; Aroso et al., 2015; Chakraborty et al., 2021; Silva et al., 2020). This enriches the formulation with therapeutic characteristics, hence the name therapeutic DES or THEDES (Fourmentin et al., 2021). The first instance of a THEDES was discovered by Bica et al. (Bica et al., 2011), who referred to it as "liquid co-crystals" made of a 1:1 molar ratio of lidocaine with either oleic acid or decanoic acid, resulting in melting points of $< 50$ °C. It was referred to as "liquid co-crystals" due to the observation of hydrogen bonding instead of protic interactions normally seen in ionic liquids (Bica et al., 2011). However, the term THEDES is often used in a broad manner in the literature to refer to all researched DES systems for pharmaceutical use (Abdelquader et al., 2023; Abranches and Coutinho, 2023; Oyoun et al., 2023). This includes DES and simple eutectic formulations with an API. As a result, papers on THEDESs can be found, where the study often reports on a DES used for solubilization of APIs rather than the API constituting a DES (Abdelquader et al., 2023; Javed et al., 2024; Oyoun et al., 2023). The interchangeable use of the two, accompanied by the frequently observed lack of thermodynamic characterization of the phase behavior, has led to the erroneous reporting of some systems (Abranches et al., 2019). However, from a practical perspective, the performance of a DES-based drug delivery system is repeatedly proven to be enhanced, which makes the discussion on the formulation nomenclature rather of academic interest (Abdelquader et al., 2023; Aroso et al., 2016; Fourmentin et al., 2021; Javed et al., 2024; S. Li et al., 2024; Sarraguça et al., 2022).

One of the few reported studies on the thermodynamic characterization of these systems is that of Wolbert et al. (Wolbert et al., 2019). The study aimed at developing a mechanistic approach to select the right THEDES forming excipients. They studied a list of THEDESs made of either phenylacetic acid, lidocaine or ibuprofen with a second component of either thymol, vanillin, lauric acid, para-toluic acid, benzoic acid or cinnamic acid. They developed THEDESs based on the novel approach of applying the UNIFAC(Do) to model DES phase behavior, which was then compared to the experimental findings. They found that the UNIFAC(Do) model could predict non- and near-ideal THEDESs; however, instances with lower experimental eutectic points than those predicted by the model were still observed for some mixtures. These included systems of lidocaine:lauric acid at the molar ratio of 1:1 with a $T_E$ of 7.05 °C, and others of lidocaine with either thymol or vanillin at an approximate molar ratio of 1:4 which appeared as liquidus amorphous solids at the operating temperature of 25 °C (Wolbert et al., 2019). The latter phenomenon was also observed for a system of ibuprofen:lidocaine at the molar ratio of 1:4 (Wolbert et al., 2019).

A recent study by Teixeira et al. (Teixeira et al., 2024) developed type V THEDESs based on the antimalarial APIs, quinine, pyrimethamine and 2-phenylimidazopyridine. They selected thymol, propyl gallate, and butylated hydroxyanisole based on COSMO-RS screening and compared the experimental SL phase behavior with each API to the ideal eutectic model calculated using the SvL equation. They found some co-crystals along the way with the classic "W" shaped phase diagrams, however they also successfully obtained THEDESs (Salehi et al., 2019). These included quinine with propyl gallate (1:1.5), with a negative deviation of $23.5 \pm 2.0$ K from the $T_E$, ideal of 399.6 K to $376.1 \pm 2$ K in the experimental observations, and quinine:thymol (1:3) with a deviation of $14.8 \pm 1.9$ K from 322.4 K to $307.6 \pm 1.9$ K. They also discovered pyridine:thymol, pyridine:butylated hydroxyanisole and 2-phenylimidazopyridine: butylated hydroxyanisole systems with less accentuated negative deviations and unclear molar compositions (Teixeira et al., 2024).

Other examples of more refined studies include "Formation of low melting point binary systems comprising ketoprofen and an amide local anesthetic" (Umerska et al., 2021) and "Anticrystal Engineering of Ketoprofen and Ester Local Anesthetics: Ionic Liquids or Deep Eutectic Mixtures?" (Umerska et al., 2020) by Umerska et al. (Umerska et al., 2021; Umerska et al., 2020). In both studies, the negative deviation of the eutectic point from the ideal thermodynamic behavior of ketoprofen-based THEDESs was clearly demonstrated. Additionally, the interactions were characterized using attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy to assess the hydrogen bonds (Umerska et al., 2021; Umerska et al., 2020). They found in the first article that the thermodynamic melting point and glass transition temperature of ketoprofen eutectic mixtures with benzocaine follow the ideal thermodynamic models depicted by SvL and Fox equations (Umerska et al., 2021). However, substantial negative deviations were shown between the $T_E$, ideal and the $T_E$ of the ketoprofen mixture with tetracaine and procaine, deeming them DESs (Umerska et al., 2021). The $T_E$ of the ketoprofen:procaine systems were observed between 30 and 80 mol % of ketoprofen with a $T_E$ of $\sim 30$ °C, above the calculated $T_E$, ideal of 46 °C (Umerska et al., 2021). The $T_E$ in the ketoprofen:tetracaine system occurred at a similar molar composition of 30–70 % ketoprofen, melting at 21–23 °C below the calculated value of 35.8 °C (Umerska et al., 2021). It is noteworthy that the exact detection of the eutectic composition could not be achieved owing to technical difficulties, such as overlapping peaks (Umerska et al., 2021). However, stronger interactions were observed in the DESs than in the eutectic mixture (benzocaine), as supported by ATR-FTIR data (Umerska et al., 2021). An interesting finding was that the ketoprofen:procaine mixture showed small traces of carboxylate anions, however the low amount did not qualify for ionic interactions (Umerska et al., 2021). Similarly, the second article discovered ketoprofen THEDESs in 2:1 mixture with either bupivacaine or mepivacaine (Umerska et al., 2020). The experimental $T_E$ of ketoprofen to mepivacaine was between $59.2 \pm 0.1$ °C and $64.9 \pm 4.5$ °C, which was notably below the calculated $T_E$, ideal value of 78.3 °C, as was the case of 2:1 ketoprofen with bupivacaine showing a calculated melting point of 69.2 °C, which was above the experimental $T_E$ of between $52.8 \pm 0.2$ °C and $54.9 \pm 1$ °C (Umerska et al., 2020). The anionic carboxylate moieties were also observed in these mixtures with no full proton transfer taking place (Umerska et al., 2021; Umerska et al., 2020).

Many recent THEDESs have shown improved in vitro behavior of APIs in THEDESs. Based on 72 h stability of liquid mixtures at operating temperatures, Balenzano et al. (2024) (Balenzano et al., 2024) developed THEDESs of 1:3 cannabidiol and caprylic acid (octanoic acid). The formulation formed nano droplets in partition tests and confirmed in vitro safety and permeability using Caco-2 cells (Balenzano et al., 2024). In another study by Song et al. (2024) (Balenzano et al., 2024), a THEDES of ascorbic acid and betaine (1:1) for transdermal delivery was similarly developed by using stability as the marker. They conducted in vitro permeability studies using porcine skin models, which showed improved permeability compared to other ascorbic acid formulations (Balenzano et al., 2024). This formulation was also tested in vivo for topical application in humans, with no signs of toxicity (Balenzano et al., 2024). Additionally, limonene:ibuprofen THEDESs were developed by Pereira et al. (Pereira et al., 2019) showing in vitro antiproliferative anticancer effects with improved drug bioavailability on HT29 and Caco-2 cell lines. A similar THEDES based on ibuprofen and perillyl alcohol was presented by Silva et al., (Silva et al., 2020) showing dose-dependent in vitro cell viability in colorectal cancer cell lines. Finally, Al-Akayleh et al. (Al-Akayleh et al., 2021) showed significant enhancement in risperidone ex vivo skin permeability tests using a THEDES of risperidone and capric acid (1.5:1). The same authors presented a very recent study on ketoconazole THEDES with capric acid at a molar ratio of 1:5, with thermodynamic characterization of the phase

behavior clearly showing a negative deviation from an ideal eutectic system predicted using the SvL equation (Al-Akayleh et al., 2024). Furthermore, the in vitro permeability was assessed using Franz cell diffusion cells separated by synthetic human skin membrane, Strat-M® (Al-Akayleh et al., 2024). Once again, it was found that the permeability of the THEDES across the membrane was substantially higher at a value of 59 %, compared to the 23 % of the commercial ketoconazole cream (Al-Akayleh et al., 2024).

Overall, these findings establish the usefulness of THEDESs for improving the bioavailability of poorly soluble compounds, as reiterated by others in the field (Aroso et al., 2016; Aroso et al., 2015; Chakraborty et al., 2021; Fourmentin et al., 2021; Javed et al., 2024; Pereira et al., 2022; Pereira et al., 2019; Rahman et al., 2021; Roda et al., 2020; S. Li et al., 2024; Silva et al., 2020). However, it has been repeatedly emphasized that more in vitro studies need to be conducted to fully characterize the properties of THEDESs (Abranches and Coutinho, 2023; Fourmentin et al., 2021). The THEDESs are beneficial, owing to the liquefaction of APIs (Abdelquader et al., 2023; Fourmentin et al., 2021; Taylor and Aulton, 2022). However, the selection of THEDES-forming drugs is limited, as DES components require certain molecular attributes to provide the distinguishable DES interactions (Wolbert et al., 2019). Moreover, THEDES drug loading is limited by the eutectic point rather than the solubility of the API in DES vehicles (see below), and as with all pharmaceutical DES-based formulations, in vivo studies on THEDESs remain scarce (Abdelquader et al., 2023; Abranches and Coutinho, 2023; Al-Akayleh et al., 2024; Fourmentin et al., 2021; H. Palmelund et al., 2021). THEDESs show great potential for pharmaceutical applications in general because of their enhanced API performance (Abdelquader et al., 2023; Aroso et al., 2016; Aroso et al., 2015; Fourmentin et al., 2021; Javed et al., 2024; Pereira et al., 2022; Pereira et al., 2019; Rahman et al., 2021; Roda et al., 2020; S. Li et al., 2024; Silva et al., 2020).

### 4.3. DES as a solubilizing vehicle

DESs are known for their outstanding solubilization capacity for poorly soluble compounds, which have been reported in many literature articles showing solubility improvements far beyond that of the aqueous API solubility (Abdelquader et al., 2023; Aroso et al., 2016; Chakraborty et al., 2021; Chakraborty et al., 2023; Cysewski and Jeliński, 2019; Faggian et al., 2016; Fourmentin et al., 2021; H. Palmelund et al., 2021; Huber et al., 2022; Javed et al., 2024; Jeliński et al., 2019; Li and Lee, 2016; Lu et al., 2016; Morrison et al., 2009; Oyoun et al., 2023; Palmelund et al., 2019; Panbachi et al., 2024; Panbachi et al., 2025; Sut et al., 2017). Evidently, Morrison et al. (Morrison et al., 2009) provided the first evidence of DESs as strong solubilizers for API compounds in 2009, where the solubility of a list of APIs was tested in urea:choline chloride (1:2) and malonic acid:choline chloride (1:1) DESs (Morrison et al., 2009). The APIs included benzoic acid, danazol, griseofulvin, AMG517, and itraconazole, for which the solubilities improved 5–22′000 fold compared to the aqueous solubility (Fourmentin et al., 2021; Morrison et al., 2009). In 2013, Dai et al. (Dai et al., 2013) investigated the solubility of a series of poorly water-soluble compounds, including rutin, quercetin, cinnamic acid, carthamin, 1,8-dihydroxyl anthraquinone, taxol, and ginkgolide B, in some NADESs. These included 1,2-propanediol:choline chloride:water 1:1:1, glucose:choline chloride:water 1:2:3, lactic acid:glucose:water 5:1:3 and xylitol:choline chloride:water 1:2:3 (Dai et al., 2013; Fourmentin et al., 2021). In all cases, solubility enhancements were observed, with a soaring 400′000 fold improvement in quercetin solubility in xylitol:choline chloride: water 1:2:3 (Dai et al., 2013; Fourmentin et al., 2021). In another study, Choi et al. (Choi et al., 2011) showed rutin solubility improvements between 50–100 fold compared to that in water (Fourmentin et al., 2021), with the highest solubility in aconitic acid:choline chloride (1:1) NADES (Fourmentin et al., 2021). They also found that the water-insoluble compound paclitaxel could be dissolved up to 0.81 mg/mL in glucose:choline chloride:water (1:1:1) NADES (Choi et al., 2011; Fourmentin et al., 2021). Additionally, Mokhtarpour et al. (Mokhtarpour et al., 2020) discovered an astounding 136′744-fold improvement in celecoxib solubility compared to water (at 313.15 K) in a DES of choline chloride:malonic acid at a 1:1 mol ratio. They also demonstrated solubility improvements between 127–6′739 folds higher for other DES systems with other APIs such as naproxen, acetaminophen, meloxicam, piroxicam, and betamethasone, in comparison to water at 313.15 K (Mokhtarpour et al., 2020).

Lu et al. (Lu et al., 2016) compared the solubility of a series of non-steroidal anti-inflammatory drugs (NSAIDs) in DESs made of chlorine chloride, betaine, choline bitartrate, tetra- propylammonium bromide and ethylammonium chloride with co-formers of ethylene glycol, 1,2-propanediol, glutaric acid, malonic acid, levulinic acid, lactic acid and urea. The NSAIDs studied were aspirin, acetaminophen, ketoprofen, naproxen and ibuprofen (Lu et al., 2016). They found that solubility elevations of 17- to 5′477-fold was achieved in DESs (Lu et al., 2016). In 2016, Li and Lee (Li and Lee, 2016) found between 28 and 53′600-fold improvement in the solubility of itraconazole, piroxicam, lidocaine, and posaconazole in so-called “DES-derivatives”, referring to DESs at different molar compositions surrounding the eutectic point resulting in liquids at room temperature (Li and Lee, 2016). The derivatives consisted of choline chlorides with carboxylic acids such as glycolic acid (Fourmentin et al., 2021; Li and Lee, 2016). In the same year, Faggian et al. (Faggian et al., 2016) investigated the solubility of rutin in a series of NADESs and compared the data to solubility in water and two organic solvents, ethanol and methanol. They observed that rutin solubility in NADESs was enhanced by 0.7-fold in glucose:fructose:water (1:1:1) NADES to 24.5-fold in proline:glutamic acid (2:1), compared to its solubility in water (Faggian et al., 2016). In the following year, Sut et al. (Sut et al., 2017) investigated the solubility of berberine in a list of NADESs and observed the same trend of solubility enhancement in DES compared to water. They also found enhanced solubility of berberine in some urea, lactic acid, and amino acid-based NADESs compared to its solubility in ethanol (Sut et al., 2017). The best solubility (25 mg/mL) was obtained in proline:malic acid:lactic acid:water (1:0.2:0.3:0.5) (Sut et al., 2017).

One of the more notable works on DES as pharmaceutical formulations is the work of Palmelund et al. (Palmelund et al., 2019), where they studied the solubility improvement of 11 APIs in six DESs. They found that in all cases, DESs improved the solubility of APIs compared to water (Palmelund et al., 2019). They then compared the finding to the API solubility in conventional pharmaceutical solvents (PEG 300, ethanol and glycerol), showing that the solubility of four APIs was higher in DESs compared to classic solvents (Palmelund et al., 2019). They reported that the solubility of paracetamol was 1.3- to 9.7-fold higher in a choline chloride:lactic acid:water (1:0.9:0.6) DES than in the compared solvents (Palmelund et al., 2019). Additionally, a pronounced solubility improvement with a log scale of 4.91 was seen for celecoxib in the same DES, in mole/mole comparison to water (Fourmentin et al., 2021; Palmelund et al., 2019).

### 4.4. Advanced bio-enabling DES formulations

Palmelund et al. (H. Palmelund et al., 2021) expanded their work by showcasing the first case of a DES as an enabling formulation, where aprepitant was used as the poorly soluble model drug. Three formulation approaches for aprepitant were compared through in vitro drug release and permeability and in vivo rat studies (H. Palmelund et al., 2021). Aprepitant dissolved in DES was compared with the marketed nanocrystalline form (EMEND®) and the amorphous solid form of the same API. The DES formulation consisted of a 1:2 molar ratio of choline chloride and levulinic acid loaded with either 3.5 mg/g of dissolved aprepitant alone or 5 mg/g of aprepitant in a suspension with 10 % HPMC. For the in vitro studies, the HPMC was pre- dissolved in the release medium, which was FaSSIF. The DES formulation showed

enhanced in vitro drug release and permeability and was recognized as an SDDS (H. Palmelund et al., 2021). It was also reported that the precipitation inhibiting polymer hindered absorption and compromised DES permeability (H. Palmelund et al., 2021). Nonetheless, the in vivo bioavailability of DES was 34 ± 4 %, on-par with the 36 ± 3 % of the nanocrystalline formulation, which were both above the 20 ± 4 % of the amorphous formulation (H. Palmelund et al., 2021). This study was performed on a simple crude DES, which built the foundation for DES as a potential novel bio-enabling formulation approach (H. Palmelund et al., 2021).

Panbachi et al. (Panbachi et al., 2023) developed the polymer-embedded DES (PEDES) formulation with the aim of reducing the risk of drug precipitation following oral administration and addressed the hypothesis that directly including a polymeric precipitation inhibitor (PI) in a DES mixture could be suitable as a novel bio-enabling formulation principle. Following broad formulation screening, a PEDES embedding 15 % w/w of polyvinyl pyrrolidone K30 (PVP) in L-carnitine:ethylene glycol (1:4, molar ratio) DES was successfully formulated as a supersaturating formulation using indomethacin as model compound (Panbachi et al., 2023). The obtained drug solubility of 175.6 mg/mL in DES was >312′000-fold higher than the aqueous solubility, and upon release (in phosphate buffer, pH 6.5), a maximum apparent supersaturation of 9.8 was recorded, whereby the release kinetics displayed a suitable "parachute effect" (Panbachi et al., 2023). Furthermore, the binding of water was evaluated using time-domain NMR in pure DES and compared to that of PEDES with either PVP or HPMCAS, showing that PVP resulted in larger fractions of water due to the hygroscopicity of the polymer (Panbachi et al., 2023). In conclusion, PEDES appears to be a viable novel formulation approach (Panbachi et al., 2023).

In 2024, Panbachi et al. (Panbachi et al., 2024) tackled another literature-inspired DES system, namely a hydrophobic DES (HDES), which was found to be a good candidate as an enabling formulation due to substantial improvements in venetoclax solubility. This system, made of decanoic acid and dodecanoic acid at the molar ratio of 2:1, was presented as a novel alternative to oil phases in LBFs, as it showed greatly enhanced drug solubilization compared to conventional glyceride- based vehicles (Panbachi et al., 2024). To facilitate better aqueous dispersion of the hydrophobic formulation, the surfactant Tween 80 was added and tested at concentrations of 10, 20, and 30 % w/w (Panbachi et al., 2024). This study provided insights into the impact of different surfactant concentrations on the resulting droplet diameter, API solubilization capacity, short-term stability, freezing point, and API release of the venetoclax-loaded formulations (Panbachi et al., 2024). The API release from the formulations was studied using a classic USP II setup with FeSSIF at four different surfactant concentrations of 0, 10, 20, and 30 % (w/w) Tween 80, showing higher release with higher amounts of surfactant, while negatively impacting the solvation capacity, freezing point, and stability of the API in DES (Panbachi et al., 2024). Ultimately, the combination of HDES with surfactant provides a novel LBF with high pharmaceutical potential, although the components must be finely balanced to keep the integrity of the solubilizing HDES, while enabling sufficient dispersion and drug release (Panbachi et al., 2024).

Lastly, with increasing evidence of notable solubility improvement brought by DES, Panbachi et al. (Panbachi et al., 2025) utilized a THEDES for a fixed-dose enabling formulation of abiraterone acetate (AbAc) in 2025. In this study, the potential anticancer effects of ibuprofen (IBU) were harnessed in THEDES to dissolve higher amounts of AbAc, an antitumor agent (Panbachi et al., 2025). Four IBU-based combinations were studied: 1:4 molar ratio with octanoic acid (OctA), 1:5 with nonanoic acid (NonA), 1:3 with decanoic acid (DeA) or 1:2 with dodecanoic acid (DoA). The listed THEDESs can dissolve AbAc amounts up to 1311.0 ± 125.4 mg/g in IBU:OctA THEDES, 1151.7 ± 22.2 mg/g in IBU:NonA, 1160.4 ± 33.5 mg/g in IBU:DeA, and 231.3 ± 10.7 mg/g in IBU:DoA (Panbachi et al., 2025). In vitro dissolution of the simultaneously released drugs reached 37.8 ± 9.0 % to 64.2 ± 1.0 % for IBU and 5.0 ± 3.3 % to 19.4 ± 0.1 % for AbAc (Panbachi et al., 2025). This increased to between 60.4 ± 2.8 % to 79.4 ± 5.0 % of released IBU, and 23.6 ± 1.0 % to 57.3 ± 5.8 % of released AbAc, with 20 % (w/w) Tween 80 in the formulations (Panbachi et al., 2025). This research project laid the groundwork for the development of a novel combination formulation approach, where ibuprofen-fatty-acid THEDES were utilized as a solubilizer for the poorly soluble AbAc (Panbachi et al., 2025).

The very recent work of Li et al. (M. Li et al., 2024) is another noteworthy example of DES enabling formulation, where Artemisinin was formulated into a microemulsifying formulation based on a THEDES with ibuprofen:menthol at the molar ratio of 1:3. The "deep" eutectic point was accurately characterized using a binary phase diagram, comparing the experimental to the ideal thermodynamic behavior (M. Li et al., 2024). Subsequently, a water-based microemulsion was formulated using ternary phase diagrams, resulting in the selection of a microemulsion with a composition of 53.2 % water, 44.8 % Tween 80: Span® 20 (1:1)+ethanol surfactant mixture, and 2 % DES (M. Li et al., 2024). They found that the DES increased the solubility of artemisinin by approximately 400-fold, from 0.07 mg/mL in water to 30 mg/mL in DES (M. Li et al., 2024). The microemulsion consisted of droplets in the 50–60 nm droplet size range and as the formulation was intended for transdermal application, the permeation behavior was characterized using Franz cell diffusion cells separated by poly(ether sulfone) membranes. The performance of the DES-based microemulsions was compared to that of pure DES, isopropyl myristate, a surfactant mixture (Tween 80:Span® 20 (1:1) with ethanol), and a separate microemulsion of isopropyl myristate, with applied drug loadings of 0.4 and 0.6 %. Their findings demonstrated that the DES-based microemulsion showed increased flux and accumulated permeability compared with other formulations (M. Li et al., 2024).

Another example is the so-called desosomes and desimicelles recently developed by Said et al. (Said et al., 2024) to enhance the in vivo and in vitro performance of lornoxicam. Desosomes and desimicelles are DES-based vesicular and micellar nanocarriers, respectively (Said et al., 2024). Their DES was prepared based on choline chloride with glycerin at a molar ratio of 1:2 with incorporated cetyl trimethyl ammonium bromide:cholesterol 1:1 and Tween 40 in the desosomes, and 10 mM cetyl trimethyl ammonium bromide in the desimicelles, respectively. The formulations demonstrated elevated solubility and entrapment efficacy, while also providing sustained release owing to diffusion-dependent release (Said et al., 2024). Compared to other lornoxicam formulations, such as the pure form, marketed Edurepan® suspension, and niosome formulation, an in vivo anti-inflammatory response was observed earlier with a noticeable reduction in cytokine levels (Said et al., 2024). They also found that the micellar desimicelles resulted in larger anti-inflammatory effects (1.25-fold COX2 inhibition) compared to the vesicular desosomes (Said et al., 2024).

In 2023, Chakraborty et al. (Chakraborty et al., 2023) presented a celecoxib-carrying DES formulation with enhanced in vitro and in vivo performance. The DES was made of choline chloride and malonic acid at the molar ratio of 1:1. This DES dissolved 13.1 μg/g of celecoxib, resulting in an approximately 10′000-fold improvement in solubility compared to that in water (Chakraborty et al., 2023). The 8 mg/g of the DES was loaded with celecoxib, and the in vitro dissolution tests showed supersaturations of up to 2-fold sustained over the 2 h test compared to the crystalline celecoxib (Chakraborty et al., 2023). In vivo rat studies showed a 2.76-fold improvement in maximum plasma concentration ($C_{max}$) levels, 1.52 times reduction in the time to reach it ($t_{max}$), and 1.81 times improvement in the area under the curve ($AUC_{0-\infty}$) of the profile compared to crystalline celecoxib (Chakraborty et al., 2023).

Currently, few examples of pharmaceutically applicable DES-based enabling formulations have been developed in the literature, despite the promising usefulness of DESs (Chakraborty et al., 2023; H. Palmelund et al., 2021; M. Li et al., 2024; Said et al., 2024). It is often intended that the developed liquid is administered in the form of an oral capsule or bulk liquid (H. Palmelund et al., 2021), similar to many LBFs (Feeney

and Crum, 2016; Holm et al., 2023; Machado et al., 2016; Mohite et al., 2023). Hence, concrete examples of DESs as enabling formulations with proven in vitro and in vivo efficiencies build the roadmap to move DESs from the laboratory-stage to actualization as a pharmaceutical product on the market.

### 4.5. Oral safety and toxicity

Although some in vivo studies have been performed on DESs, toxicity remains an underexplored area in DES research (García et al., 2023; H. Palmelund et al., 2021; Hayyan et al., 2015; Said et al., 2024; Sut et al., 2017). DESs are often developed for dermal, transdermal, and nasal administration (Abdelquader et al., 2023; Chakraborty et al., 2021; Fourmentin et al., 2021; Javed et al., 2024). However, when oral administration is considered, toxicity and oral tolerability become issues for some reported systems (Fourmentin et al., 2021; Hayyan et al., 2016; Hayyan et al., 2015). Some studies on cell lines and ex vivo tissues have been reported; however, the data on human clinical trials in the literature almost exclusively focus on the dermal/transdermal application of DESs (Al-Akayleh et al., 2021; Al-Akayleh et al., 2024; Fourmentin et al., 2021; Hayyan et al., 2016; Javed et al., 2024).

Hayyan et al. (Hayyan et al., 2015) provided the first data sets on the cytotoxicity of DES. They examined the cytotoxicity of choline chloride-based DESs with a 1:3 molar ratio of glycerine, ethylene glycol, triethylene glycol, and urea on selected cancer cell lines. The cell lines included prostate cancer, malignant melanoma, hepatocellular cancer, breast cancer, oral carcinoma, and normal oral keratinocytes (Fourmentin et al., 2021; Hayyan et al., 2015). The impact of DES on the cells was studied using MTT cell viability assay (Fourmentin et al., 2021; Hayyan et al., 2015). They saw negligible selectivity towards cancer cells compared to the normal keratinocytes and found that the generation of reactive oxygen species (ROS) was mainly attributed to the observed apoptosis of the cells (Hayyan et al., 2015). However, emphasis was also placed on membrane alterations by the properties of DES resulting in cell apoptosis, as a result of increased polarity at cell surfaces (Hayyan et al., 2015; Mbous et al., 2017; Radošević et al., 2015).

It has also been verified that the toxicity of DES as a mixture can vary from that of the individual components, owing to the potential synergistic or antagonistic effects of the components in DESs (Hayyan et al., 2015; I.P.E. Macário et al., 2018; Radošević et al., 2015). The latter was recorded in DESs with urea, where the toxicity of urea was reduced in the DES compared to that of the pure component (Hayyan et al., 2015). Composition-specific toxicity was also observed, showing immediate death in rodents (mice) ingested with choline chloride:urea at a molar ratio of 1:3, while a molar ratio of 1:2 resulted in a median lethal dose (LD50) of 5.64 g/kg (Fourmentin et al., 2021; Hayyan et al., 2015). Additionally, Radošević et al. (Radošević et al., 2015) demonstrated increased toxicity of choline chloride in DES systems with oxalic acid due to synergistic effects. This was confirmed in channel catfish ovary and human breast cancer cell lines, which showed lower half maximal effective concentration (EC50) values of 218.7 mg/L and 559.0 mg/L for DES, respectively, compared to the EC50 value of 633.0 mg/L for neat oxalic acid and >2000 mg/L for pure choline chloride (Radošević et al., 2015). This has resulted in the implementation of some NADESs based on nutraceuticals as anticancer therapies, with heightened anti-cancer in vivo (and in vitro) properties (Fourmentin et al., 2021; Javed et al., 2024; Mbous et al., 2017; Pereira et al., 2022; Sun et al., 2020). NADESs are also repeatedly found to be less toxic than other DESs, despite their other disadvantages, such as higher viscosity (Hayyan et al., 2016; Mbous et al., 2017; Paiva et al., 2014).

A study performed by Benlebna et al. (Benlebna et al., 2018) provided the first data points for the oral toxicity of DES by studying its in vivo toxicity in rats. The rats were orally administered 3 mL of betaine: glycerol DES at a molar ratio of 1:2 with green coffee bean extract twice daily using a gavage. They found it difficult to administer the liquid due to its high viscosity (Benlebna et al., 2018), which could have compromised the reproducibility of the results. This is especially important because no control group was studied. Nonetheless, the rats did not survive past 5–10 days after the first administration, where high blood lipid levels and enlargement of the stomach were observed, likely due to increased water uptake (Benlebna et al., 2018), or force-feeding using syringes filled with viscous DES, which could have posed gavage problems. In summary, the lack of a control group and the application volume used pose questions about the validity of the study, and more data are certainly needed before conclusions are made regarding the toxicity of the applied formulation. Interestingly, Chen et al. (Chen et al., 2017) found a choline chloride:glycerol (1:2) DES carrying salvianolic acid B to be suitable for pharmaceutical applications based on toxicity studies in rodent animal models. The acute toxicity of the formulation was determined by oral gavage of a dose varying between 5′236 to 11′800 mg/mL in mice (Chen et al., 2017). They found the LD50 to be 7′733 mg/kg, with observations in the mice varying from initially active to subsequently sedentary with breathlessness, convulsions, and tremors. Thirty of the 70 mice died within the first 4 h after administration, whereas the surviving mice returned to normal within the 2-hours post gavage. They determined that the DES was non-toxic because of its higher LD50 (Chen et al., 2017).

As described in Section 4.3, some DES have been reported to have increased in vivo (and ex vivo) bioavailability (Al-Akayleh et al., 2021; Al-Akayleh et al., 2024; Faggian et al., 2016; H. Palmelund et al., 2021). Most of these studies did not report toxicity in their models. Examples include the studies conducted by Palmelund et al. (H. Palmelund et al., 2021) and Al-Akayleh et al. (Al-Akayleh et al., 2021; Al-Akayleh et al., 2024). Faggian et al. (Faggian et al., 2016) orally administered proline: glutamic acid (2:1) loaded with rutin in Balb/c mice, finding enhanced bioavailability of rutin in DES, seen through increased and prolonged plasma rutin concentrations compared to an aqueous suspension of rutin (Faggian et al., 2016). Toxicity was not observed in this case, where a dose of 10 mg/kg was used (Faggian et al., 2016). Similarly, Sut et al. (Sut et al., 2017) measured higher concentrations of absorbed berberine in mice administered DES formulations via gavage, with seemingly no toxicity. They dissolved berberine into three DESs of proline:malic acid (2:1), proline:urea (2:1), and lactic acid:proline:malic acid:water (1.0:0.2:0.3:0.5), and administered a dose of 50 mg/kg to the mice in the applied models (Sut et al., 2017).

The disadvantage of DESs for pharmaceutical applications is the current lack of a comprehensive assessment of the toxicity of orally administered DES. This includes information on the long-term toxicity associated with repeated exposure and the long-term stability of the API in the vehicle (Fourmentin et al., 2021). Current data suggest that the toxicity of DESs is often component-dependent (Abranches and Coutinho, 2023; Fourmentin et al., 2021; García et al., 2023; Hayyan et al., 2015; Juneidi et al., 2016) and that synergistic effects can be observed between DES components, resulting in dose-dependent toxicity (Abranches and Coutinho, 2023; García et al., 2023; Hayyan et al., 2015). However, the opposite can also be true, where the toxicity of components is dampened when incorporated into a DES owing to antagonistic effects (Hayyan et al., 2015; I.P.E. Macário et al., 2018; Radošević et al., 2015). Furthermore, data are often lacking to ensure that the API maintains the same chemical structure while remaining devoid of toxic degradation species over time in DESs. Despite the limited data, it is established that DESs are generally less toxic than conventional ionic liquids, making them important candidates for future use in pharmaceuticals (Hayyan et al., 2015; Oyoun et al., 2023; Paiva et al., 2014; Płotka-Wasylka et al., 2020). Nonetheless, there is a consensus among researchers that more studies are required to provide additional data on the toxicity and safety of orally administered DESs, especially for future regulatory requirements (Fourmentin et al., 2021; García et al., 2023; Paiva et al., 2014).

## 5. In silico models on pharmaceutical DESs

The rise of DESs as novel mixtures has nearly been simultaneous with the progression of computational tools in the pharmaceutical sector in the 21st century (Abbott et al., 2001; Abbott et al., 2002; Kuentz and Bergström, 2021). Hence, the characterization of DES properties can be facilitated by using different computational models. Currently, the thermodynamic behavior, interactions, solubility, and toxicity of DESs have been attempted to be predicted using computational models (Fourmentin et al., 2021; Tolmachev et al., 2022). Often computational tools are applied to better mechanistically understand individual DESs and therefore, characteristics cannot be predicted based on other systems (Kollau et al., 2020). Such a broader scope to more generally predict DES properties would be important as it builds the foundation for databases used to further develop and improve predictive models. In the following sections, examples of engraining work are presented to discuss the applicability of computational in silico models to advance the development of DES as pharmaceutical formulations.

### 5.1. Prediction of thermodynamic properties

#### 5.1.1. Phase diagram predictions

The prediction of DES phase behavior is of interest to developers to avoid the costly trial-and-error approach to formulation development (Bannigan et al., 2021). Wolbert et al. (Wolbert et al., 2019) presented the pioneering UNIFAC(Do) model, where activity coefficients of DES components were predicted to form SL equilibria. This was done at various molar fractions resulting in a phase diagram for each mixture. The group studied 11 THEDES candidates based on lidocaine, ibuprofen, and phenylacetic acid with counter components such as thymol, vanillin, lauric acid, para-toluic acid, and cinnamic acid. In addition to predicting the phase behavior, the main aim was to detect the DES-forming excipient for each API using the UNIFAC(Do) computational approach (Wolbert et al., 2019). It was observed that the phase diagram of lidocaine-THEDESs, which all formed liquids at room temperature, could not be correctly estimated due to the amorphous solidification (Wolbert et al., 2019). However, the phenylacetic acid and ibuprofen THEDESs showed melting points above room temperature but below 37 °C. When compared to the experimental findings, they found that all tested systems, excluding lidocaine:lauric acid and lidocaine:vanillin THEDESs, could be predicted with UNFIAC(Do) with an accuracy of ± 3 °C (Wolbert et al., 2019). They concluded that excipients need to have low melting points, similar to the melting points of the selected APIs, with as low as possible activity coefficients throughout all compositions of the THEDES (Wolbert et al., 2019). They found that the UNIFAC(Do) model could predict non- and near-ideal THEDESs; however, instances with lower experimental eutectic points than those predicted by the model were still observed for some mixtures (Wolbert et al., 2019).

Panbachi et al. (Panbachi et al., 2024) expanded on the work of Wolbert et al. (Wolbert et al., 2019) to predict the phase behavior of a mixture of decanoic acid and dodecanoic acid using the UNIFAC model in comparison to the ideal thermodynamic behavior (Eq. (1)), and the experimental output. The UNIFAC model resulted in a eutectic temperature only 0.03 °C lower than the ideal value and was thus closer to the actual experimental value of 19.70 ± 0.11 °C (Panbachi et al., 2024). Despite the eutectic melting values being very similar to the experimental output, the UNIFAC model was in this case apparently not much more accurate than the ideal approach for the system studied (Panbachi et al., 2024). This is in agreement with the pioneering work of Wolbert et al. (Wolbert et al., 2019) on the UNIFAC modelling of therapeutic DES, which indicated that model precision depends to some extent on the specific system studied (Panbachi et al., 2024). While the model precision in the study was adequate for the purpose of characterizing a fatty acid mixture, a main drawback of UNIFAC modelling is generally the availability of group contributions and all possible interaction terms, which generally limits current UNIFAC modelling of complex APIs (Panbachi et al., 2024). Hence, it can be argued that the current UNIFAC(Do) models are more applicable for the thermodynamic predictions of DESs (Panbachi et al., 2024).

Focusing on the negative deviation of the DES phase behavior from the ideal thermodynamic phase equilibria, Kollau et al. (Kollau et al., 2020) developed an entropy-based predictive model for the free energy of mixing in DES. This study emphasized that correct entropy estimations are critical for explaining thermodynamic non-ideal negative deviations that occur due to excess entropy and enthalpic contributions. They argued that the component molar volume should be adequately reflected in predicting the entropic contribution to excess free energy (Kollau et al., 2020) analogous to the Flory-Huggins model (Salehi et al., 2019). This was tested on DESs made of erythritol, pimelic acid, succinic acid, and tetrapentylammonium bromide, in which the developed models showed the necessity of molecular volumes for the accurate prediction of phase behavior (Kollau et al., 2020).

Unconventionally, Nasrallah et al. (Nasrallah et al., 2024) developed a tool to predict the ternary phase diagram of THEDESs in water to enhance the formulation development process. Their hypothesis was that ternary phase diagrams could be used as a tool to best select the co-forming excipient that would result in the highest amount of drug solubilization in water (Nasrallah et al., 2024). Water was used as a representative hypothetical gastric fluid. The two-suffix Margules equation was used to model the ternary phase diagrams of the API, excipient, and water. As expected, the properties of the excipient (such as its melting point) govern the molar ratio and melting temperature of the eutectic point (Nasrallah et al., 2024). They found that some excipients displayed stronger interactions, which resulted in eutectic points below that of the $T_{E,ideal}$ (Nasrallah et al., 2024). These systems showed higher solubilization in water, affirming the hypothesis that ternary phase diagrams can enable better excipient selection (Nasrallah et al., 2024). This data supports the notion that the negative thermodynamic deviation in DESs grants better solubilization of APIs in aqueous liquids compared to APIs incorporated into simple eutectics (i.e., systems with ideal thermodynamic behavior) (Nasrallah et al., 2024).

In summary, the prediction of DES phase diagrams appears to be more challenging than that of other less complex mixtures, and the negative deviation from ideal behavior requires an adequate thermodynamic description, whereby the entropic contribution to the free energy of mixing is critical and should consider the molar volume (Kollau et al., 2020; Wolbert et al., 2019). Further studies comparing the experimental phase behavior to the predicted models are still required to establish the key properties for the accurate prediction of any DES type (Nasrallah et al., 2024; Wolbert et al., 2019).

#### 5.1.2. DES solubilization prediction

DESs have become increasingly known for their strong solubilization capacities (Chakraborty et al., 2021; Emami and Shayanfar, 2020; Fourmentin et al., 2021; Nasrallah et al., 2024). This is especially interesting for pharmaceutical formulation developers because of the recurring solubility enhancement of APIs in DESs (Chakraborty et al., 2021; Emami and Shayanfar, 2020; Fourmentin et al., 2021; Nasrallah et al., 2024). Many computational studies have been performed on various DESs to describe the relationship between their structures and resulting properties (Tolmachev et al., 2022). A few studies have investigated the predictability of API solubility in DESs (Chakraborty et al., 2021; Cysewski and Jeliński, 2019; Fourmentin et al., 2021; Jeliński and Cysewski, 2018; Jeliński et al., 2019; Palmelund et al., 2019; Salehi et al., 2019). This has been mostly carried out by systematically comparing computationally described properties with experimental solubility results (Chakraborty et al., 2021; Cysewski and Jeliński, 2019; Fourmentin et al., 2021; Jeliński and Cysewski, 2018; Jeliński et al., 2019; Palmelund et al., 2019; Salehi et al., 2019). In the following, some of the central studies devoted to developing computational approaches to predict the solubility of compounds in DESs are reported.

As mentioned, the interactions within a DES are often considered the main reason for the solubility-augmenting property of DESs (Fourmentin et al., 2021; Nasrallah et al., 2024). This was specifically presented in the work of Nasrallah et al. (Nasrallah et al., 2024) described in the previous section, who showed that the THEDESs showing stronger interactions, resulted in negative deviations from the ideal thermodynamic phase equilibria, which in turn resulted in larger solubilization of the API in water (Nasrallah et al., 2024). In addition to modelling the activity coefficients using the two-suffix Margules equation, they compared the interactions between the three components (API, excipient, and water), showing that the API-excipient interaction should generally be higher than the interaction between API-water to enable better solubilization of the THEDES-bound API in water (Nasrallah et al., 2024). Their model assisted in understanding that the API-excipient interaction in a THEDES plays a vital role in the final solubility improvement in the third aqueous component (Nasrallah et al., 2024). Considering the third component as a hypothetical gastric fluid, this model is highly beneficial for selecting components that result in the highest uptake (Nasrallah et al., 2024).

Cysewski and Jeliński (Jeliński and Cysewski, 2018) used the Conductor-like Screening Model for Real Solvents (COSMO-RS), which combines quantum chemical and statistical thermodynamics calculations, to screen NADES for solubilization of rutin (Jeliński and Cysewski, 2018). A list of 126 NADESs with different compositions of carboxylic acids and amino acids were studied for the solvation of rutin. They calculated the activity coefficients for the compound and found a correlation coefficient ($R^2$) of 0.167 with the resulting experimental solubility outputs (Jeliński and Cysewski, 2018). They argued that the model was unrealistic due to the assumption that all species in the system are neutral and undissociated (Jeliński and Cysewski, 2018). It was declared that future models must take into account all ionic forms that could occur in DESs (Jeliński and Cysewski, 2018). Hence, they advanced the calculation using an infinite dilution approximation to obtain an $R^2$ of 0.974 (Jeliński and Cysewski, 2018). It is often learned that the low accuracy of the COSMO-RS predicted solubility values is either due to the lack of enthalpy of fusion inputs or other solid-state complications such as polymorphic changes of the residual solid (Cysewski et al., 2024; Palmelund et al., 2019). COSMO-RS was also applied by Palmelund et al. (Palmelund et al., 2019) to predict the solubility of a list of 11 APIs in DESs made of choline chloride with each urea (1:2), glycerol (1:2), lactic acid with water (1.0:0.9:0.6), or glucose with water (1.0:0.4:1.0). This was in addition to two systems betaine:glycerol:water (1:2:1) and lactic acid:glucose:water (1.0:0.2:1.2). They studied the relative solubility of APIs in DESs using the COSMO-RS approach and compared it with the experimental output. They found that COSMO-RS could enable the ranking of API-DES relative solubilities as the relative solubility of APIs in DESs could be predicted with acceptable precision ($R^2 = 0.82$) (Palmelund et al., 2019); however, the prediction of absolute solubility values proved to be more challenging.

In another study, Jeliński et al. (Jeliński et al., 2019) utilized the quantum chemistry of COSMO-RS to interpret the elevated solubility of curcumin in gastric fluids when formulated as a NADES of choline chloride with glycerol (1:1). They generated different binary dimers consisting of curcumin, choline chloride, and glycerol and assessed the affinity between the pairs using Gibbs free energy calculations. The most probable molecular configuration was estimated using the COSMO for Configurations (COSMOconf) tool, whereas the properties were estimated based on the thermodynamic COSMO-RS predictions. They generated affinities for three homomolecular pairs and compared them with the affinities obtained for three heteromolecular constructs. They found that the affinity between curcumin and choline chloride is similar to that of the binary choline chloride system, which were both larger than the affinity between curcumin and glycerol, glycerol-glycerol dimer, and the heteromolecular DES components (choline chloride and glycerol) (Jeliński et al., 2019). The latter showed affinities similar to those of the homomolecular dimer of curcumin (Jeliński et al., 2019). The molar ratio of the components within the DES influenced the propensity of certain interactions because of the higher exposure of the interacting surfaces of the components with a larger molar volume (Jeliński et al., 2019). Therefore, they deduced that the higher affinity of curcumin in heteromolecular interactions with the DES components allowed for better bulk solubilization of the compound in simulated gastric fluids (Jeliński et al., 2019).

Panbachi et al. (Panbachi et al., 2025) applied COSMO-RS modelling to perform qualitative evaluation of component interactions using quantum chemistry-derived σ-profiles of IBU-based THEDESs with different fatty acids to understand the impact of alkyl chain length on THEDES characteristics. An example of such modelling is given in Fig. 5 below. They found that despite the similarity in hydrogen bond donating and accepting properties, only one 'deep' eutectic system in a series of four IBU:fatty acid eutectic systems was formed (Panbachi et al., 2025). It was argued that other factors, such as a shorter fatty acid carbon chain length, could result in less of the neutral component (the alkyl chain) on the interacting molecule, which may lead to less steric hindrance, or that other factors, such as apolar hydrophobic interactions or the number of interacting molecules, contribute to the higher overall free energy of mixing in the DES-forming systems (Panbachi et al., 2025). Hence, it was proposed that this technique can be applied to comparatively study simple formulations from a compositional viewpoint to exhibit complexity at the microstructural level (Panbachi et al., 2025).

Cysewski and Jeliński (Cysewski and Jeliński, 2019) later expanded the findings by applying the same model to study the elevated solubilization of a list of sulfonamides (sulfanilamide, sulfacetamide, sulfamethoxazole, sulfamethazine, probenecid and sulfasalazine) in NADESs (Cysewski and Jeliński, 2019). The NADESs in their study consisted of choline chloride and glycerol at a molar ratio of 1:1 (Cysewski and Jeliński, 2019). Gibbs free energy quantum calculations from COSMO-RS were used to assess the molecular affinities between the individual DES components and sulfonamides in both homo-and heteromolecular dimer setups. Similar to the previously studied curcumin, all sulfonamides showed higher affinity in a sulfonamide-choline chloride pair, in comparison to all pairs with glycerol and the affinity of the API to itself (Cysewski and Jeliński, 2019). As a result, they demonstrated that an artificial neuronal network based on the affinity input (calculated Gibbs free energy), was able to predict the ranking API-NADES solubility outcomes (Cysewski and Jeliński, 2019). Using the same Gibbs free energy-based affinity model, Chakraborty et al. (Chakraborty et al., 2023) applied density functional theory (DFT) calculations (similar to the quantum- chemistry in the COSMO-RS model), to understand the enhanced solubility of celecoxib in a DES made of choline chloride and malic acid (1:1) (Chakraborty et al., 2021). They also found that it was the affinity of the hetero-molecular interactions between the DES components and the celecoxib that enabled better solubilization (Chakraborty et al., 2023).

More recent studies by Cysewski et al. (Cysewski et al., 2024) used COSMO-RS-predicted solubilities based on the so-called COMSO moment approach, whereby descriptors of the σ-potentials were employed in a machine learning approach with a multi-layer perception regressor. They found that the model could accurately describe the solubility of ibuprofen and flurbiprofen in 36 different combinations of choline chloride or betaine with ethylene glycol, diethylene glycol, triethylene glycol, 1,3-butanediol, 1,2-propanediol, and glycerol co-formers were trained, with low deviations (root mean square deviation of 0.016 for the training set, 0.118 for the test, and 0.136 for the validation) (Cysewski et al., 2024). Similar to the previously described studies, they also found that the standard COSMO-RS approach could not predict the absolute solubilities with sufficient accuracy (Cysewski et al., 2024). In a following study Jeliński et al. (T. Jeliński et al., 2024) used the same descriptor approach again for a machine learning with support vector regressor resulting in similar accuracy. This was done to predict the solubility of ferulic acid in the DESs described in their previous study (Cysewski et al., 2024; T. Jeliński et al., 2024).

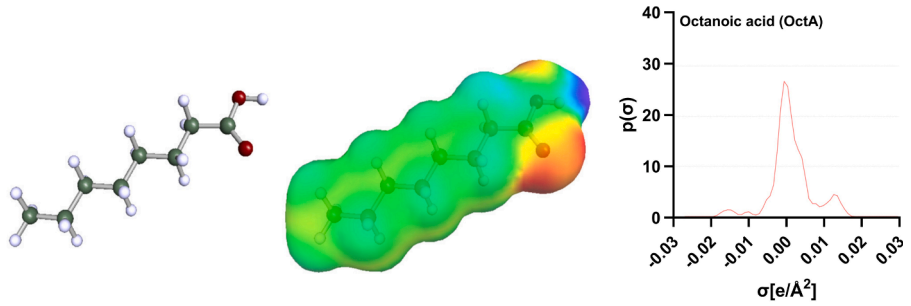


**Fig. 5.** .Chemical structures and sigma surfaces calculated using the conductor-like screening model for real solvents (COSMO-RS) of octanoic acid. The molecular structure is presented on the left side of the Figure, whereas the sigma surface and sigma profile are given in the middle and right panels, respectively. Modified from (Panbachi et al., 2025).

Computational models to predict the solubility of compounds in DESs have been developed over the past few years (Mokhtarpour et al., 2020; Palmelund et al., 2019; T. Jeliński et al., 2024). It seems that for the time being, ranking of solubility enhancements can be predicted using a standard COSMO-RS approach (Palmelund et al., 2019), whilst Gibbs free energy models can also simultaneously provide qualitative understanding of the solubility enhancements using affinity (Chakraborty et al., 2023; Cysewski and Jeliński, 2019; Jeliński and Cysewski, 2018; Jeliński et al., 2019). Given sufficient experimental results, the use of COSMO-moments of the σ-potentials to predict solubility seems to be an attractive option for solubility prediction as a strategy of theory-guided data science (Cysewski et al., 2024). Evidently, the constituting structure in DESs results in strong solvation characteristics (Chakraborty et al., 2023; Cysewski and Jeliński, 2019; Jeliński et al., 2019; Nasrallah et al., 2024). As pharmaceutical DES systems are still in their infancy, it is necessary to provide more experimental data to facilitate the development of training sets for future computational models. Therefore, computational models are necessary to mechanistically advance the understanding of experimental observations. As a final note, it can be anticipated that more machine learning algorithms will be tested on DESs for accurate prediction of their properties, and potential artificial intelligence-based models will also be developed (Ayres et al., 2021; Baum et al., 2021; K. Shahbaz et al., 2012; K. Shahbaz et al., 2012).

### 5.2. *Modeling of structural and dynamic properties of DES*

The molecular structures of DESs have been extensively studied; however, no single, uniform explanation has emerged for the interactions within them. The hydrogen-bonding interactions between the different functional groups in a DES are often described as an "alphabet soup of hydrogen bonds" (Ashworth et al., 2016). Despite the absence of a regular repeating structure, the liquid state of a DES remains stable, largely owing to the high entropy of the mixture. This entropy is enough to counterbalance the enthalpic energy typically required for liquefaction. Molecular dynamics (MD) simulations serve as a useful tool for gaining a basic understanding of the molecular setup within such DES systems, especially in the case of an external component, such as a drug (Panbachi et al., 2024) or precipitation-inhibiting polymer (Panbachi et al., 2023).

To gain qualitative molecular insights into the structure of a PEDES of L-carnitine:ethylene glycol (1:4) with 15 % w/w polyvinylpyrrolidone, a full atomistic MD simulation was conducted by Panbachi et al. (Panbachi et al., 2023) in 2024. The MD simulation showed that all components interacted with each other to some extent, and PVP showed no indication of pronounced deswelling (Panbachi et al., 2023). Thus, the microscopic view mirrored the homogeneous macroscopic appearance of the PEDES (Panbachi et al., 2023). This study presents a novel understanding of how the applied API (indomethacin) and the precipitation-inhibiting polymer were located within the DES, achieved by MD simulations, which further supplied the stability and solubility studies (Panbachi et al., 2023).

In a later study, Panbachi et al. (Panbachi et al., 2024) carried out a mechanistic study on molecular positioning of venetoclax in a HDES using MD simulations. In this case, MD simulations were performed on pure HDES (decanoic acid:dodecanoic acid at a molar ratio of 2:1) and HDES with 5 % w/w venetoclax to study the molecular architecture of the formulation mechanistically (Panbachi et al., 2024). An example of the results is provided in Fig. 6. The number of interactions, including the hydrogen bonding, hydrophobic, and the insignificant but present pi-pi and cation-pi interactions were reported to evaluate the DES construction (Panbachi et al., 2024). The distribution of API appeared to be comparatively homogeneous in the model system, indicating good solubilization without signs of phase separation from either the drug or any other HDES component (Panbachi et al., 2024). The system showed a balance between the inter-component and drug-component hydrogen bond interactions (Panbachi et al., 2024). Nonetheless, hydrophobic interactions were slightly higher between decanoic acid and the drug, whereas some drug-drug interactions were observed (Panbachi et al., 2024). This was used as a potential explanation for the results of the stability tests conducted (Panbachi et al., 2024). Nevertheless, with the much lower number of drug molecules in the simulation compared to the DES components, these findings were not evaluated quantitatively and should be regarded as qualitative information (Panbachi et al., 2024). This self-cohesion tendency of venetoclax in this case underlines the importance of excipient interactions, with special focus on cases of a hydrophobic compound precipitating upon dispersion in an aqueous environment (Koehl et al., 2021; Panbachi et al., 2024).

The previously described studies prove that, at the current stage, only qualitative data can be obtained from MD simulations of DESs. In the first case, MD simulations complemented the experimental work, and structural insights were obtained regarding the polymer dispersion in the selected DES vehicle and the interactions between the API and PEDES components (Panbachi et al., 2023). In the latter study the excellent solubilization capacity of the HDES was studied by MD simulations and a notable finding was that the drug interacted with the solvent components to a certain extent, enabling API solubilization without disruption of the hydrogen bonding network of the DES vehicle (Panbachi et al., 2024). Despite its qualitative nature, MD simulation is a useful tool with great potential for further examination of the molecular constitution of novel mixtures with non-ideal thermodynamic traits such as DES.

### 5.3. *Pharmacokinetic modelling*

A series of studies have attempted to predict the toxicity of DES using computational models. Hayyan et al. (Hayyan et al., 2016) used COSMO-RS to simulate interactions between NADES and phospholipids covering cells, demonstrating that strong interactions can occur resulting in the depletion of cell membrane surfaces. They concluded that the

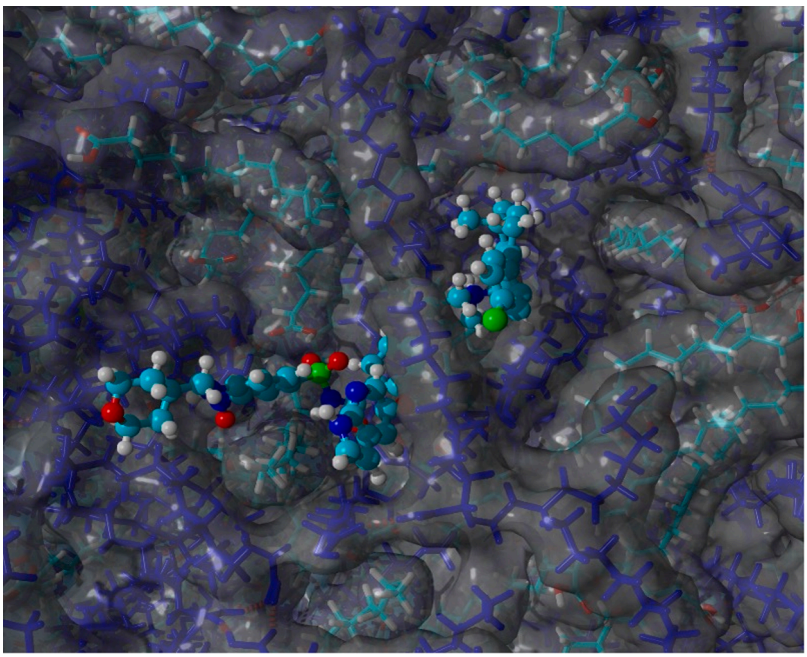

**Fig. 6.** Molecular dynamics simulation of a DES made of 1:2 molar ratio of dodecanoic acid:decanoic acid with 5 % w/w venetoclax. Dark blue tube-stick models are given for dodecanoic acid and the turquoise tube-stick models represent decanoic acid. The turquoise ball and stick molecules in the center represent the drug venetoclax. Modified from Panbachi et al. (Panbachi et al., 2024).

toxicity of DES components should be considered, and that DESs with organic acid components were associated with higher toxicity (Hayyan et al., 2016). A review by Halder et al. (Halder and Cordeiro, 2019) reported the same findings using multitasking quantitative structure–toxicity relationship molecular descriptors of DESs on various biological targets. They found that the main contributors to DES toxicity were polarizability, electronegativity, HBD component, and topological properties (Halder and Cordeiro, 2019). They concluded that sugar and amide HBDs result in intermediate toxicity, followed by sugar alcohols and straight-chain alcohols resulting in low level toxicity (Fourmentin et al., 2021; Halder and Cordeiro, 2019). Similarly, the mixture toxicity theory was utilized by Macário et al. (I.P.E. Macário et al., 2018; I.P.E. Macário et al., 2018) to expand the understanding of the ecotoxicity of some choline chloride-based DESs on marine organisms. They found antagonistic effects between most DES components, such that lower toxicity was found in DESs compared to the individual components (I.P.E. Macário et al., 2018). The same group provided ecotoxicity predictions of various ammonium chloride-based DESs with either ethylene glycol or 1-propanediol on marine bacteria (I.P.E. Macário et al., 2018). They furthered the understanding of DES toxicity using mixture toxicity theory, affirming that DES toxicity differs from the starting materials, as both synergistic and antagonistic phenomena can occur (I.P.E. Macário et al., 2018).

Although the prediction of DES toxicity is still at an early stage, previous studies are promising, in that computational tools will likely be used in the future to assist scientists in the selection of candidate mixtures (Halder and Cordeiro, 2019; Hayyan et al., 2016; I.P.E. Macário et al., 2018; I.P.E. Macário et al., 2018). Nonetheless, research on DES toxicity prediction is still encouraged, and modelling should, at this stage, primarily be used to facilitate the understanding of experimentally documented observations.

## 6. Conclusion and outlook

To tackle the biopharmaceutical obstacle of poor water solubility of APIs, the given review presents different studies on DESs as a new enabling formulation approach. Studies show that solubility enhancements of DESs are remarkable, and that novelty is achieved in the form of advanced approaches to formulation or high drug solubility.

The review also demonstrated that each DES-based formulation has specific characteristics that can overcome the limitations of some of the already-established enabling formulations in the field. For example, precipitation inhibiting formulations (PEDES, HDES, DES microemulsions) can be applied to mitigate the issue of drug re-crystallization observed when liquid vehicles with high drug loads release the API. Furthermore, THEDESs are thermodynamically stable systems, which is not the case for solid dispersions or other kinetically stabilized supersaturating formulations. Finally, employing THEDES as a solubilizing vehicle for poorly water-soluble compounds demonstrated that DESs can be utilized to provide a pharmacologically synergistic combination product with high drug loads. This can be a particular advantage in therapies where polypharmacotherapy may lead to a lack of patient compliance. Collectively, these studies demonstrate the potential and versatility of DESs as enabling formulation.

Future work should include the characterization of the molecular architecture within the DES, either in the form of computational techniques or further analytical approaches (such as NIR or FTIR). Additionally, the interactions between components within a DES mixture play a vital role in correctly assigning DESs (Abranches and Coutinho, 2023; Fourmentin et al., 2021). This was established through the cautionary case of the CAGE (choline bicarbonate:geranic acid (1:2)) developed by Banerjee et al. (A. Banerjee et al., 2018). The group categorized CAGE as a DES, however, Rogers and Gurau (Rogers and Gurau, 2018) challenged this notion in an open letter stating that their results indicated that the CAGE was an ionic liquid instead of a DES (A. Banerjee et al., 2018; A. Banerjee et al., 2018; Rogers and Gurau, 2018). The paper was then later modified to correctly report an ionic liquid, rather than a DES (A. Banerjee et al., 2018). In this regard, the work of Umerska et al. (Umerska et al., 2021; Umerska et al., 2020) set a good example for future studies by assessing the chemical structure of molecules in an API-containing DES to ensure that the reigning interactions are hydrogen bonds. Hence, further emphasis on the characterization of DES interactions is anticipated in future studies.

Although the content of this review provides evidence of improved in

vitro results, in vivo examination of the systems were lacking. Although proof of enhanced in vivo performance of DES drug delivery systems is repeatedly shown (Faggian et al., 2016), the mechanism behind the release/partition of API from the drug- loaded DESs are not yet established. Hence, future assays studying the separation of API from a DES carrier could provide valuable information regarding the in vitro properties of enabling DES formulations. A recent study provided a foundation for future assays by demonstrating that some APIs are stabilized as nanocolloids in bulk DES (Zhu et al., 2023). To this end, future studies should provide information on drug release dynamics, intercomponent interactions, interactions with API, and in vivo evidence of improved bioavailability.

In anticipation of future clinical trials, it is important to consider the regulatory aspects of DESs. Currently there are no relevant guidelines referring specifically to DESs. However, it is possible to follow the established framework used for regulatory submissions of novel formulations composed of co-processed materials. Such assessments should begin with the inclusion of the complete toxicological profiles of all incorporated components as well as the DES system as a whole.

## CRediT authorship contribution statement

**Shaida Panbachi:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Josef Beránek:** Writing – review & editing. **Martin Kuentz:** Writing – review & editing, Resources, Conceptualization.

## Declaration of competing interest

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

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## Data availability

Data will be made available on request.

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