Biointerface Research in Applied Chemistry
Platinum Open Access Journal (ISSN: 2069-5837)

Review
Volume 12, Issue 1, 2022, 847 - 860
https://doi.org/10.33263/BRIAC121.847860

Deep Eutectic Solvents as an Alternate to Other Harmful Solvents

T. Raja Sekharan [1,2], R. Margret Chandira [1,*], Shunmugaperumal Tamilvanan [3], S.C. Rajesh [4], B.S. Venkateswarlu [1]

[1] Department of Pharmaceutics, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed to be University), Salem-636308, Tamil Nadu, India
[2] Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy, Anaikuttam-626130, Sivakasi, Tamil Nadu, India
[3] Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER)-Guwahati, C/O NETES Institute of Technology & Science, Mirza, Assam, India
[4] Department of Pharmaceutical Analysis, Sankaralingam Bhuvaneswari College of Pharmacy, Anaikuttam-626130, Sivakasi, Tamil Nadu, India
* Correspondence: mchandira172 @gmail.com;

Scopus Author ID 36114451300
Received: 23.02.2021; Revised: 6.04.2021; Accepted: 8.04.2021; Published: 26.04.2021

Abstract: Solvents generally in liquid form, are used to dissolve, dilute, suspend any substances or extract other materials. More than one-third of the drugs listed in the various Pharmacopeias fall into the poorly water-soluble or water-insoluble categories. For more than 200 years, traditional solvents could be used as a solvent for substances that were insoluble in water. But the usage of these types of solvents should be decreased because these types of solvents are volatile, flammable, and often toxic. Also, the industrialist's usages in different types of processes prove the risk for workers. In recent years, several solvents have been proposed to be the greener replacement for traditional solvents. Replacing hazardous chemicals with more environmentally friendly alternatives is a matter of current interest, in line with the philosophy of Green Chemistry. The use of nontraditional or nonconventional solvents such as supercritical fluids (SCFs) such as Carbon dioxide (CO_2) and water, fluorous solvents, solventless reaction Ionic liquids (ILs) and their derivatives [polymeric ILs and magnetic ILs], and deep eutectic solvents (DESs) are alternatives for environmentally unfriendly traditional solvents. Among them, DES is a neoteric class of green solvents defined as a mixture of two or more compounds that are typically solid at room temperature, but when combined at a particular molar ratio, changes into a liquid at room temperature. It is assumed that eutectic mixtures show low volatility, have a broad liquid range, and are water-compatible, non-flammable, non-toxic, biocompatible, and eco-friendly. Eutectic solvents have been useful in several pharmaceutical fields, such as the increase of drug solubility, permeation, and absorption.

Keywords: green solvent; deep eutectic solvents; natural deep eutectic solvents; therapeutic deep eutectic solvents; polymeric deep eutectic solvents; hydrophilic deep eutectic solvents; hydrophobic deep eutectic solvents.

Abbreviation:
API: Active Pharmaceutical Ingredients; DES: Deep Eutectic Solvents; ILs: Ionic Liquids; HBA: Hydrogen Bond Acceptor; HBD: Hydrogen Bond Donor; CHCl: Choline chloride; NADES: Natural Deep Eutectic Solvent; THEDES: Therapeutic Deep Eutectic Solvent; PODES; Polymeric Deep Eutectic Solvent.

1. Introduction

The word “Solvents” gets from the Latin term, which generally means “loosen”. Solvents, which are normally large in fluid-structure, are utilized to break up, weaken, suspend any substances, or take out different materials, as a rule with no concoction change either in the solvents or additional materials [1]. Solvents are nearly being used in all the sort of ventures. Solvents are essential to most regions of science, including synthesis, testing, pharmaceutical, nourishment and flavor science, and the materials and painting industry [2]. Solvents are fundamental in all the pharmaceuticals territory, including dissolving active pharmaceutical ingredients (API) and different excipients, for scientific reason, for covering, and so forth. Among all the solvents, water is the most widely recognized dissolvable on the planet [3].

The choice of water as a dissolvable is because of various reasons, little of them are: (a) It is low-priced and promptly accessible in an unadulterated form; (b) It is non-lethal; (c) It isn’t extremely thick and can be effectively poured starting with one vessel then onto the next. Activities, for example, crystallization and filtration, can be promptly completed; (d) It is a decent dissolvable for dissolving a wide assortment of solutes [4].

Still, numerous substances are not dissolvable or can counter with water, and a few responses are impractical in water because of dissolvable impacts [3]. More than 33% of the medications recorded in different Pharmacopeias fall into the inadequately water-solvent or water-insoluble classifications. The rise of huge quantities of ineffectively solvent medication applicants has prompted the need for creating systems to conquer the impediments in tranquilize item advancement related to poor dissolvability [5]. The drug/excipients/other substances which are not soluble in water can be dissolved in traditional/conventional organic solvents [6]. Traditional organic solvents are often regulated as volatile organic compounds (VOCs) [7].

VOCs and petrochemical solvents are utilized to break down certain API. However, the utilization of these kinds of solvents ought to be diminished, the fact that these sorts of solvents can evaporate at room temperature, unstable, unpredictable, combustible, and frequently lethal. Additionally, the industrialist’s utilization in various sorts of procedures demonstrates laborers' hazard. Thorough security necessities method ought to be followed during usage [8]. However, a major number of solvents utilizing are hazardous to human healthiness and nature. Developing new green solvents is one of the key subjects in Green Chemistry [3].

Green chemistry is defined as the design of chemical products. The procedure involved should lessen and/or reduce/remove the use of dangerous substances [9]. Green solvents are always being developed to alternate hazardous solvents with better healthiness, protection, and ecological properties [10].

Green solvents like supercritical fluids, supercritical water, ionic liquids, DES, switchable solvents, supramolecular solvents, surfactants, etc. [11] can replace conventional organic solvents. Our study in this review covers a detailed summary of DESs as a green solvent.

2. Eutectic Mixtures (EM)

Eutectic mixtures from the Greek word meaning *eutēktos meaning “easily melted”* [5]. In the formulation, eutectic mixtures have been used to improve drug solubility, permeation, and absorption. For emulsion preparation, EM has been used as an oil phase [12].

2.1. Chemistry of DESs.

The melting point of two components, solid A and solid B, strongly depends upon their reciprocal interaction: when considering a binary mixture of solid A + solid B, the difference in the freezing point at the eutectic composition compared to that of a theoretical ideal mixture which is directly proportional to the interaction between the two single components solid A and solid B. The stronger the interaction, the larger will be the depression of the mixture melting point [13]. This effect is schematically shown in the phase diagram presented in figure 1.

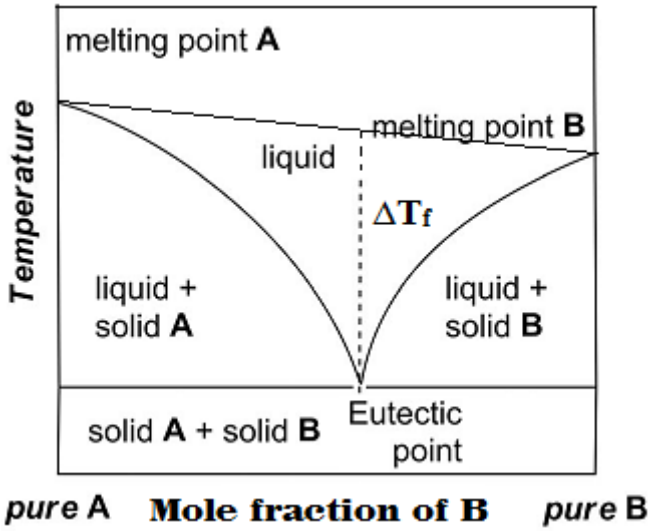

Figure 1. Eutectic formation phase diagram for two solid compounds, A and B, form a simple eutectic with no new compound formation.

2.1.1. Deep eutectic solvent (DES).

In 1884, the British physicist Frederick Guthrie coined the term eutectic, derived from the Greek ευτηκτος, which means “easy (or lowest than an individual) liquefaction” [14]. A DES is a new class of solvents [15]. It is defined as a mixture of two or more compounds that are typically solid at room temperature, but when combined at a particular molar ratio, changes into liquid at room temperature [16]. DESs were easily synthesized by mixing two naturally occurring components, namely hydrogen bond acceptor (HBA), such as quaternary ammonium halide salts, phosphonium halide salts, and metal chloride, and hydrogen bond donors (HBD) such as carboxylic acids, alcohols, amides, carbohydrates and metal chloride which associated to each other through hydrogen bond interaction [17].

Complexation between HBD and HAD results in charge delocalization which makes the DESs with large, non-symmetric ions, and it has low lattice energy and results in low melting points compared to an individual substance [18]. The extensive hydrogen-bonded network is responsible for the mixture's reduced melting point compared to those of the individual components [19]. DESs are composite solvents with a melting point considerably lower (>50 °C) than what would be expected for the pure component melting points of their constituents [20].

Liquid and liquid interactions in the liquid mixture are a lot more complicated than a pure liquid due to the possibility of better solvation and liquid-liquid interactions. Consequently, DESs can be used as solvents in a combination of dual or triple solvents to increase the effectiveness of processes and encourage solvents' physical and chemical properties [21]. For the pharmaceutical field, the eutectic system has been applied for many

purposes, such as increasing drug solubility, permeation, and absorption or applying as oil phase in emulsion system [22]. ES's advantages are that it's less toxic, inexpensive, eco-friendly, and non-flammable [23].

2.1.1.1. Classification of DESs.

Depending upon the nature of the complexing agent Abbott and co-workers classified DESs into four types, as shown in table 1.

Table 1. Classification of DESs.

Type	HBD and HBA
I	Organic salt + metal salt
II	Organic salt + metal salt hydrate
III	Organic salt + hydrogen-bond donor
IV	Metal salt + hydrogen-bond donor

2.1.1.2. Pathway of DES.

From 1994 to now, the pathway of eutectic solvents (ES) [8] is shown in table 2.

Table 2. Pathway of different DESs.

Year	Pathway of ES
1994	The substrate for enzymatic reactions/synthesis
1995	Separation and purification of molecular mixtures
1998	Usage of enzymatic reactions/synthesis in larger applications and novel industrial development
2003	Replacement to ILs
2006	Ionothermal analysis of zeolites
2007	In the field of electrochemistry
2010	Biocatalytic process
2012	Enzyme catalysis and whole-cell biocatalysis process
2013	NADES
2015	Hydrophobic DESs

2.1.1.3. Preparation of DES.

Usually, DESs can be prepared by any one of the following techniques that appeared in table 3. Commonly, DESs are prepared by mixing the components in a mortar and pestle by trituration method. This method is useful when the composition of DES ingredient is in equal amounts. If the blended mixture is hazy i.e., unclear then the obtained hazy liquid can be placed into a magnetic stirrer and allowed to rotate for a few minutes to hr without applying any heat until a clear liquid was obtained.

Table 3. Preparation of DESs by different methods

Technique/Method	Procedure	Endpoint
Mortar and pestle	Mix two components in mortar and pestle	Until formation of clear liquid
Mixing in magnetic stirrer without heat	Mix two components in a magnetic stirrer without heat	Until formation of clear liquid
Mixing in magnetic stirrer with slight/more heat	Mix two components in a magnetic stirrer with slight/more heat	Until formation of clear liquid
Freezing	Mix the component and freeze it	Until formation of clear liquid
Vacuum evaporating	Highly viscous sugar-based DESs are difficult to stir. This problem can be overcome by adding extra water into the mixture. Then evaporate the water at 323 K using a rotary flash evaporator. Keep the obtained DESs in a desiccator containing silica gel until uniform weight is attained	-

There is no need to apply heat to obtain a clear DES for components in equal proportion. If the ratio of any one component is kept constant and the other component ratio is increased, even mixing for a long time without heating results in no formation of clear DES. At that condition, if the temperature is increased (slight to more) depending upon the ratio, it results in a formation of clear DESs. DESs can also be made using the freezing process, which involves mixing the ingredients and freezing them to produce a transparent liquid. The vacuum-evaporating method can also be used to prepare DES. It is difficult to stir highly viscous sugar-based DESs; however, this problem can be solved by adding water to the mixture. The water in the DESs can then be vaporized using a rotary flash evaporator at 323K/49.85°C using a vacuum-evaporating process [24].

EM or ES can be formulated between (a) a pair of naturally occurring excipients said to be NADES [25], (b) between APIs and excipients or between at least two APIs called therapeutic DES [26] (c) incorporating any polymers to the ES known as polymeric DES [23].

2.1.2. Natural deep eutectic solvents (NADES).

NADESs is an attractive sort of DESs. When DES is prepared from neutral, acidic, or basic ingredients that are obtained naturally, are said to be NADES. It has been used to alternate organic solvents in various fields [27]. NADES comprising natural compounds, such as organic acids, amino acids, and sugars, have been recently developed for possible application in the natural product field [28]. The NADESs are obtained by mixing HBA (usually choline chloride (CHCl), lactic acid, betaine hydrochloride, tetrabutylammonium chloride, trioctyl ammonium chloride) and HBD (generally natural plant-based organic species, such as amino acids, carboxylic acids, sugars, and sugar alcohols) in a specific molar ratio at different temperatures [29]. Even though only at the beginning stage, studies on NADESs have started to bud with exponential growth, showing attractiveness and shows potential for use in various areas [30]. NADESs non-volatile below atmospheric conditions, are chemically and thermally stable, non-flammable, and have great dissolvable properties for several organic compounds [28]. The high viscosity of most DES at room temperature limits their application as extraction solvents. To overcome these drawbacks, NADES were introduced. NADES can be prepared in a large number of combinations [8]. Few compounds isolated with NADESs are shown in table 4.

Table 4. Compounds isolated with NADESs

Compound	From	NADES			Year	Ref
		HBD	HBA	Highest extraction composition		
Anthocyanins	Molina *(Luma chequen*)	CHCl, citric acid, glucose, glycerol, lactic acid, and tartaric acid		Lactic acid:Glucose (8:1)	2021	[28]
Phenolic Compounds (phenol and flavonoids)	Chokeberry (*Aronia melanocarpa*)	CHCl	D-(-) fructose, D(+) glucose, lactic acid, and urea	CHCl:Fructose	2020	[30]
Flavonoids	Buckwheat sprouts	CHCl	1,2-propanediol, 1,4-butanediol, acetamide, ethylene glycol, glycerol, melonic acid, oxalic acid, triethylene glycol, and urea,	CHCl:Acetamide	2019	[31]
Polyphenol	Orange peel	Glycerol and ethylene glycol	CHCl	CHCl:Ethylene Glycol (1:4)	2018	[32]
Vanillin	Vanilla pods	Combination of 1,2-propanediol, betaine, betaine, CHCl, citric acid, D-		Lactic acid: 1,2-propanediol (1:1)	2017	[33]

Compound	From	NADES			Year	Ref
		HBD	HBA	Highest extraction composition		
		fructose, D-glucose monohydrate, glycerol, lactic acid, lactic acid, L-serine, malic acid, sucrose, water, and β-alanine,				
Polyphenols	Thyme, Oregano, Greek sage and Sage	Lactic acid	Ammonium acetate, CHCl, glycine, L-alanine, nicotinamide, sodium acetate, and β-Cyclodextrin	Lactic acid:Nicotinamide with β-Cyclodextrin	2017	[34]
Polyphenolic compounds	Dittany, Fennel, Marjoram, Mint and Sage	Lactic acid	Ammonium acetate, CHCl, glycine, sodium acetate, and water	Lactic acid:Glycine:Water (3:1:3)	2016	[35]
Polyphenolic compounds	Virgin olive oil	CHCl	1,2-propanediol, 1,4-butanediol, glycerol, lactic acid, malonic acid, sucrose, urea, and xylitol	CHCl :Xylitol (2:1) and CHCl :1,2-propanediol (1:1)	2016	[36]
Rutin	*Sophora japonica*	CHCl	1,4-butanediol, acetamide, citric acid, D-sorbitol, ethylene glycol, fructose, glucose, glycerol, levulinic acid, malic acid, malonic acid, maltose, oxalic acid, p-toluenesulfonic acid, sucrose, tartaric acid, triethylene glycol, urea, xylitol, and xylose	CHCl:Triethylene glycol (1:4) containing 20% water	2015	[37]
Rotenone (Isoflavanoid)	*Derris* species roots *(Derris elliptica and Derris malaccensis)*	CHCl	1,4-butanediol	CHCl:1, 4-butanediol (1:5) with acetonitrile	2015	[22]

2.1.3. Therapeutic deep eutectic system (THEDES).

THEDES is a type of DES having API as one of its components [20]. THEDES is defined as a mixture of two components, one of which is an API, at a specific molar composition, become liquid at room temperature [38]. In the pharmaceutical field, the eutectic system has been used in many proposes. The liquid solution obtained from a eutectic mixture has been applied for some drugs to increase solubility, permeation, and absorption or used as oil phase in the emulsion system [39]. The eutectic mixture can be prepared by synthetic polymers and natural polymers like urea-based (proline–urea), sugar and organic acid-based (citric acid–glucose), organic acid and amino acids-based (malic acid, glutamic acid, lactic acid, etc.), CHCl-based, etc. [40]. THEDES formed with few eutectic forming components, and the drug is shown in table 5.

Table 5. THEDES prepared with eutectic forming component and drug.

Eutectic forming ingredients/drug	Drug	Obtained benefits	Year	References
Menthol	Stearic acid, myristic acid, and lauric acid	Wound curing	2019	[41]
Ascorbic acid and CHCl	Dexamethasone	Increase in solubility, diffusion and permeability	2018	[42]
CHCl and menthol	Acetylsalicylic acid, benzoic acid and phenylacetic acid	Dissolution enhancement and antibacterial activity	2016	[20]
Lidocaine	Tetracaine	Local anesthetic action	2008	[43]
Menthol	Ibuprofen	To enhance the rectal bioavailability of ibuprofen.	2004	[44]
Poly(ethylene glycol)	Fenofibrate	Dissolution improvement	2003	[45]

Eutectic forming ingredients/drug	Drug	Obtained benefits	Year	References
Menthol	Ubiquinone	To overcome the drawbacks like low solubility and irreversible precipitation of Ubiquinone	2002	[46]
Terpene binary mixtures (*p*-cymene, D-limonene, thymol, 1,8-cineole, menthol, menthone)	Ibuprofen	Increase in transdermal permeation	1998	[47]

2.1.4. Polymeric deep eutectic solvent (PODES).

Any polymer dissolved into the prepared eutectic mixture then it is said to be PODES. Various polymers can be used to dissolve in the vehicle to prepare the polymeric eutectic system. Different physical properties like viscosity and rheology of the selected polymeric eutectic system will be evaluated. The obtained lowest viscosity liquid eutectic will be/can be used as a vehicle in the study. The drug release (immediate or sustained) from the formulations developed with polymeric liquid eutectic depends on the polymer's nature [48]. The advantage of this type of DES is cheaper to produce due to the lower cost of the raw materials, less toxic, and often biodegradable. The disadvantage of the DES is the high viscosity, and the solid-state of most DES at room temperature restricts their application as extraction solvents [7]. PODESs formed with few eutectic forming components, drug, and polymer are shown in table 6.

Table 6. PODES prepared with the eutectic forming component, drug, and polymers.

Eutectic forming compound	Polymer used	Drug	Year	References
Menthol:Camphor (1:1)	Eudragit EPO, Eudragit L100, Eudragit RLPO, Eudragit RSPO, and Eudragit S100	Aspirin, Azithromycin, Chloramphenicol, Clotrimazole, Diclofenac sodium, Ibuprofen, Indomethacin, Nevirapine, Paracetamol, and Piroxicam,	2012	[48]
Menthol:Camphor (1:1 and 1:2)	Eudragit RL-100	Ibuprofen	2019	[49]

3. Classification of DES Based on Water Solubility

Depends upon the water solubility DESs can be classified into hydrophilic DESs and hydrophobic DESs [50].

3.1. Hydrophilic DES.

Initially, research in DES paid much attention to hydrophilic DESs [51]. Due to their hydrogen bonding ability, DESs are generally hydrophilic and dissolve easily in an aqueous environment [52]. Since 2001 more than 1800 articles were published related to DES; most of them are related to hydrophilic DES [53]. Hydrophilic DESs are applied in many fields, including solvents or catalysts for chemical reactions, electrochemistry, pharmaceuticals, and separation process. Most DESs proposed in the reported articles were the hydrophilic DESs, which were not stable in water [54]. The main drawback of hydrophilic DES is only polar compounds can able to separate [53]. Hydrophilic DES unstable in water has been also reported [55]. In general, the density of hydrophilic DESs is higher when compared to water at room temperature, but increase in temperature results in a decrease in viscosity [56].

3.2. Hydrophobic DES.

For the past five years, hydrophobic DESs have emerged as an alternative extractive media capable of extracting non-polar organic and inorganic molecules from aqueous

environments. The water-immiscible solvent was applied to extract water-insoluble volatile organic compounds, which reported a high extraction yield and efficiency [53].

The concept of hydrophobic DES (HDES) was introduced by Osch and co-workers [52] in 2015 when they combined diverse quaternary ammonium salts (QAS) with decanoic acid (DecA). Osch and his co-workers worked on the first hydrophobic DESs consisting of fatty acid and a quaternary ammonium salt. DecA is chosen as HBD for its high hydrophobic behavior in combination with 6 quaternary ammonium salts were chosen as HBA, namely tetrabutylammonium chloride (N_{4444}-Cl), methyltrioctylammonium chloride (N_{8881}-Cl), tetraheptylammonium chloride (N_{7777}-Cl), tetraoctylammonium chloride (N_{8888}-Cl), methyltrioctylammonium bromide (N_{8881}-Br) and tetraoctylammonium bromide (N_{8888}-Br). With the help of these hydrophobic DESs they successfully evaluated the recovery of volatile fatty acids from dilute aqueous solutions.

Florindo *et al.* [57] and his research team focused on developing hydrophobic DESs, as inexpensive extractants for removing four neonicotinoids (imidacloprid, acetamiprid, nitenpyram, and thiamethoxam) from dilute wastewater by liquid-liquid extraction method. They used two families of DESs, one based on natural neutral ingredients (DL-menthol and natural organic acids) and the other based on quaternary ammonium salts (N_{4444}Cl) and organic acids (acetic acid, levulinic acid, pyruvic acid, butyric acid, hexanoic acid, octanoic acid, decanoic acid, and dodecanoic acid) were used in their studies. They concluded that DL-menthol:octanoic acid is normally the most appropriate DES for removing pesticides from wastewater. The solvation properties of hydrophobic DES are favorable for both non-polar and polar compounds. It has also been shown to be effective in the extraction of organic and inorganic compounds [55].

Bioactive components like polyprenyl acetates, artemisinin, and neonicotinoids can be extracted with Hydrophobic DESs [58]. Yousefi *et al.* and his team [59] evaluated Carboxylic acid-Tetra-*n*-butyl ammonium bromide (TBAB) as hydrophobic DESs in microextraction methods based on solidification of floating drop (SFD). Hydrophobic DESs are suitable alternatives to common organic solvents and hydrophilic DESs in extraction processes. Polycyclic aromatic hydrocarbons (PAHs) are among the major environmental pollutants found in all environmental matrices such as water, soil, and atmosphere. They have attracted much attention due to their toxic, mutagenic, and carcinogenic properties. PAHs are a non-polar or lipid-soluble nature, and they have low water solubility. In this work, TBAB acts as a hydrogen bond acceptor, and oleic acid, decanoic acid, octanoic acid, propionic acid, acrylic acid, acetic acid, and butyric acid in a 1:2 mol ratio act as hydrogen bond donors. Among all, the TBAB/2decanoic acid DES possessed the desirable properties as an extraction solvent in SFD, such as good hydrophobicity and proper freezing or melting point near room temperature (15–20°C). They proved that carboxylic acid-based DESs could be suitable extractants for SFD-based liquid-phase microextraction methods. Dispersive liquid-liquid microextraction solidification of DES can be a powerful, fast, facile, environmentally compatible, and cheap method for the trace analysis of PAHs in water samples.

Dandan Ge *et al.* [60] used DL-menthol and decanoic acid at different ratios as a hydrophobic DES to extract parabens in water. They have collected water samples from different sources like tap, river, lake, and wastewater in Kunming, China. From the collected water sample, they analyzed different parabens contents like methylparaben, ethylparaben, propylparaben, and butylparaben by the proposed method. They concluded that they

successfully determined four parabens in environmental water samples with acceptable recoveries by their proposed method.

Qu *et al.* [54] prepared five hydrophilic and three hydrophobic DES for the microextraction of sulfonamides in water samples. Five hydrophilic DESs were prepared with Choline chloride: Phenol (1:1), Choline chloride:Catechol (1:1 and 1:2), Choline chloride:Resorcinol (1:1 and 1:2). Three hydrophobic DESs were prepared with Choline Chloride:*o*-cresol, Choline Chloride:*m*-cresol, and Choline Chloride:*p*-cresol (1:2). Compared with the performance of five hydrophilic DESs in the water phase, the three hydrophobic DESs were more suitable for application in dispersive liquid-liquid microextraction to determine sulfonamides in the water sample. Their results revealed that three hydrophobic DESs showed commendable performance for extraction of sulfonamides in water samples.

Osch *et al.* [52] identified and characterized terpenes-based DES for extracting riboflavin from water. They identified 17 new hydrophobic DESs by testing 507 combinations of solid components. The maximum extraction of riboflavin (81.1%) from water was attained with the Decanoic acid:Lidocaine (2:1).

Verma and Banerjee [55] worked in the extraction of lower alcohols (ethanol/propanol/butanol) from the aqueous phase with the help of a new, natural, hydrophobic DES based on DL-menthol (hydrogen bond acceptor (HBA) and palmitic acid (hydrogen bond donor (HBD) with different ratios. The recovered 1-butanol using DES was found to be lower than the conventional solvent, i.e., mesitylene.

Raja Sekharan *et al.* [49] and his team formulated Ibuprofen-loaded emulsion from the hydrophobic eutectic solvent prepared from Camphor and Menthol. Their work concluded that Ibuprofen emulsion was successfully formulated with Eudragit RL 100 in an eutectic mixture.

4. Applications of DESs

4.1. DES in transdermal delivery.

Stott *et al.* [47] have done a study on enhanced permeation of ibuprofen drug through transdermal delivery with the help of terpene eutectic system. A different range of ibuprofen:terpene binary mixtures were melted together, cooled, and recrystallized. The melting points of these systems were found to be 32°C for Ibuprofen:thymol (40:60 % w/w), -13°C for Ibuprofen:1,8-cineole (40:60 % w/w) and 76°C for Ibuprofen alone. DSC and FT-IR analysis were used to determine the nature of the interaction. FT-IR studies indicated that only the terpenes which formed hydrogen bonds with ibuprofen produced eutectic systems. Their study concluded that ibuprofen forms eutectic systems with certain terpene penetration enhancers. The terpene is able to interact with ibuprofen and disrupt the hydrogen-bonded dimmers, the resultant melting point depression of the formulation correlated with a significant increase in transdermal flux.

4.2. DES in a cream formulation.

Zuń *et al.* [61] formulated fluconazole cream with the help of salicylic acid–menthol and benzocaine–menthol as a eutectic mixture and evaluated for their physical properties. The formulated creams were subjected to physical tests such as spreadability, slip, and tenacity tests. Further, it was evaluated for their rheological properties. The fluconazole creams with eutectic mixtures had better physical properties when compared to the formulations formulated without an eutectic mixture.

Ohzeki *et al.* [43] prepared a local anesthetic cream from a Lidocaine-Tetracaine eutectic mixture for the clinical treatment of postherpetic neuralgia. They prepared Lidocaine-Tetracaine (LT cream) and Lidocaine-Prilocaine (LP cream) using the same base. The release rate of lidocaine from the formulated creams was examined using a cellulose ester membrane. The release rate of lidocaine from LT cream was similar to that of LP cream. The release rate of tetracaine was slightly slower than that of lidocaine in LT cream, reflecting the larger molecular size of tetracaine. With the help of Yucatan micropig skin, they examined the penetration rate. The penetration rate of lidocaine was similar between LT and LP creams. Infiltration anesthesia action examined in guinea pigs indicated that the difference between the two creams was statistically insignificant. Their study suggests the equivalence of the LT and LP creams as a local anesthetic for clinical use either in the easy formulation or in the low-cost formulation.

4.3. DES in emulsion formulation.

To eliminate the oil or oil combination and antioxidant molecule from the emulsions, a very attractive but less expensive alternative/replacement is the utilization of eutectic liquid made from eutectic forming excipients in the oil phase to prepare an oil-in-water emulsion. Since the developed emulsions contain water and emulsifier molecules, they do not have the oil or oil combination. It can conveniently be termed as oil-less emulsions. Tamilvanan *et al.* [62], with his co-researchers, formulated oil-less emulsion containing coriander seed powder in eutectic solvent prepared with camphor and menthol and tween 80 as a surfactant. They concluded that the potential of coriander-based oil-less emulsion in topical therapeutic use is very certain.

Biswal *et al.* [63] formulated and evaluated microemulsion-based topical hydrogels containing lornoxicam. Eutectic mixture of camphor and menthol was used as oily phase (maximum 10%), solvent for lornoxicam, and also it acts as a powerful penetration enhancer. Tween 80, ethanol and Carbopol 934p, HPMC K-15M, and Xanthan gum were selected as a surfactant, co-surfactant, and hydrogel thickening agent, respectively. They obtained the concentration range of oil phase, surfactant, and co-surfactant for formulating microemulsion with ternary phase diagrams. The formulated hydrogel thickened microemulsions were characterized for pH, viscosity, spreadability, *in vitro* drug transport study with excised rat skins, and *in-vivo* anti-inflammatory activity. Their results showed that the content of microemulsion-based hydrogel components had a significant effect on their physical, rheological, and *in vitro* drug release characteristics.

Shen *et al.* [64] enhanced intestinal absorption of daidzein by making it in a microemulsion formulation with the help of Borneol/Menthol eutectic mixture (25:75). They formulated their microemulsion, which consists of ethyl oleate (oil), Cremophor RH40 (surfactant), PEG400 (co-surfactant), and water. A pharmacokinetic study in rats was conducted by orally administering borneol:menthol eutectic solvents or daidzein suspension at a measured quantity of 10 mg/kg. The relative bioavailability of borneol:menthol eutectic solvents and microemulsions was increased by approximately 1.5-fold and 3.65 times, correspondingly compared with a daidzein suspension. They concluded that a borneol/menthol eutectic mixture could increase the absorption of daidzein, but the mechanism of the increase in absorption was still uncleared.

4.4. DES Emulsion to nanosuspension.

Phaechamud and Tuntarawongsa [65] transformed ibuprofen eutectic emulsion to nanosuspension with solvent evaporation and ultrasonication technique. They first formulated the emulsion with the help of an eutectic mixture [camphor:menthol (1:1)] and tween 20 as an emulsifying agent. The emulsion prepared with eutectic solvent was mixed in a homogenizer for 2 min and then with the help of probe ultrasonicator sonicated for 2 min. Then, 25-mL emulsion was diluted to 125 mL with a dilution medium (12.5 gm of glucose in water) to prevent water loss before conversion. For two days, they evaporated the diluted emulsion continuously under a laminar airflow hood with the help of a hot plate stirrer at 45°C and 200 rpm. Finally, the volume of the formulated suspension was adjusted to 25 mL with distilled water and further sonicated with a probe ultrasonicator. They successfully achieved the conversion mechanism.*4.5. To stabilize the API.*

Olivares *et al.* prepared a NADES consist of betaine and urea (1:1.5 molar) on a water bath at 60°C. β-lactam antibiotics like Clavulanic acid and Imipenem monohydrate was incorporated into the above to make it stable. β-lactam antibiotics, once dissolved in aqueous solvents, have stability for about four to eight hours when stored at room temperature. Clavulanic acid and Imipenem monohydrate was completely dissolved in the betaine and urea (1:1.5 molar) NADES. The NADES were characterized with FT-IR, ^{1}H and ^{13}C NMR. Results showed that the obtained solvent has a microstructure mainly based on hydrogen bonding interactions, and water addition strongly affects its dynamic. Microbiological studies showed that antibacterial activity at day seven was significantly decreased for both Clavulanic acid and Imipenem monohydrate when dissolved in water, while no change in their antibacterial properties was observed when antibiotics were dissolved in betaine and urea [66].

Funding

This research received no external funding..

Acknowledgments

The access to scientific literature and lab facility to perform the stability studies are provided jointly by Vinayaka Mission's College of Pharmacy, Salem, and Sankaralingam Bhuvaneswari College of Pharmacy, Sivakasi.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Solvents. Available at https://www.chemicalsafetyfacts.org/solvents/ [accessed March 9, 2020].
2. Occupational safety and health solvents and the workplace. OSH Brief No. 5. Available at https://www.ilo.org/wcmsp5/groups/public/---americas/---ro-lima/---sro-port_of_spain/documents/presentation/wcms_250196.pdf
3. Davis, S.J. *Deep eutectic solvents derived from inorganic salts*. University of Leicester. Thesis. **2015.**
4. Pass, G.; Sutcliffe, H. Chemistry in non-aqueous solvents. In: *Practical Inorganic Chemistry*. Springer, Dordrecht, **1974;** pp. 122-132, https://doi.org/10.1007/978-94-017-2744-0_13.
5. Morgan, C.M. Investigating eutectic mixtures for poorly soluble compounds. KU ScholarWorks. Thesis. **2014**.

6. Holliday, A.K.; Massey, A.G. Chapter I-The nature and scope of inorganic non-aqueous solvents. In: *Non-Aqueous Solvents in Inorganic Chemistry*. The Commonwealth and International Library: Chemistry Division, Pergamon Press, London, **1965**; pp. 1-6, https://doi.org/10.1016/C2013-0-01906-8.
7. Lozowski, D. *Supercritical CO_2: A green solvent. By Chemical Engineering.* **2010**.
8. Owczarek, K.; Szczepańska, N.; Płotka-Wasylka, J.; Rutkowska, M.; Shyshchak, O.; Bratychak, M.; Namieśnik, J. Natural Deep Eutectic Solvents in Extraction Process. *Chemistry & Chemical Technology* **2016**, *10*, 601-606, https://doi.org/10.23939/chcht10.04si.601.
9. O'Neil, N.J.; Scott, S.; Relph, R.; Ponnusamy, E. Approaches to Incorporating Green Chemistry and Safety into Laboratory Culture. *Journal of Chemical Education* **2021**, *98*, 84-91, https://doi.org/10.1021/acs.jchemed.0c00134.
10. O'Neil, N.J.; Scott, S.; Relph, R.; Ponnusamy, E. Approaches to Incorporating Green Chemistry and Safety into Laboratory Culture. *Journal of Chemical Education* **2021**, *98*, 84-91, https://doi.org/10.3389/fchem.2020.00450.
11. Yilmaz, E.; Soylak, M. Chapter 5 - Type of green solvents used in separation and preconcentration methods. In: *New Generation Green Solvents for Separation and Preconcentration of Organic and Inorganic Species.* Editor(s): Soylak, M.; Yilmaz, E.; Elsevier: **2020**; pp. 214, https://doi.org/10.1016/B978-0-12-818569-8.00005-X.
12. Doble, M.; Kruthiventi, A.K. Chapter 5 - Alternate Solvents. In: *Green Chemistry and Engineering.* Editor(s): Doble M., Kruthiventi AK., Academic Press: **2007**; pp 93-104, https://doi.org/10.1016/B978-012372532-5/50006-7.
13. Phaechamud, T.; Tuntarawongsa, S.; Charoensuksai, P. Evaporation Behavior and Characterization of Eutectic Solvent and Ibuprofen Eutectic Solution. *AAPS PharmSciTech* **2016**, *17*, 1213-1220, https://doi.org/10.1208/s12249-015-0459-x.
14. Martins, M.A.R.; Pinho, S.P.; Coutinho, J.A.P. Insights into the Nature of Eutectic and Deep Eutectic Mixtures. *Journal of Solution Chemistry* **2019**, *48*, 962-982, https://doi.org/10.1007/s10953-018-0793-1.
15. Bernasconi, R.; Panzeri, G.; Accogli, A.; Liberale, F.; Nobili, L.; Magagnin, L. Chapter 11-Electrodeposition from Deep Eutectic Solvents. Progress and Developments in Ionic Liquids. Handy, S. IntechOpen, **2017**; pp. 236, http://dx.doi.org/10.5772/64935.
16. Dai, Y.; van Spronsen, J.; Witkamp, G.-J.; Verpoorte, R.; Choi, Y.H. Ionic Liquids and Deep Eutectic Solvents in Natural Products Research: Mixtures of Solids as Extraction Solvents. *Journal of Natural Products* **2013**, *76*, 2162-2173, https://doi.org/10.1021/np400051w.
17. Smink, D.; Juan, A.; Schuur, B.; Kersten, S.R.A. Understanding the Role of Choline Chloride in Deep Eutectic Solvents Used for Biomass Delignification. *Industrial & Engineering Chemistry Research* **2019**, *58*, 16348-16357, https://doi.org/10.1021/acs.iecr.9b03588.
18. Smith, E.L.; Abbott, A.P.; Ryder, K.S. Deep Eutectic Solvents (DESs) and Their Applications. *Chemical Reviews* **2014**, *114*, 11060-11082, https://doi.org/10.1021/cr300162p.
19. Mamashli, F.; Badraghi, J.; Delavari, B.; Sabbaghian, M.; Hosseini, M.; Saboury, A.A. Evaluation of Versatile Peroxidase's Activity and Conformation in the Presence of a Hydrated Urea Based Deep Eutectic Solvent. *Journal of Solution Chemistry* **2019**, *48*, 689-701, https://doi.org/10.1007/s10953-019-00881-3.
20. Aroso, I.M.; Silva, J.C.; Mano, F.; Ferreira, A.S.D.; Dionísio, M.; Sá-Nogueira, I.; Barreiros, S.; Reis, R.L.; Paiva, A.; Duarte, A.R.C. Dissolution enhancement of active pharmaceutical ingredients by therapeutic deep eutectic systems. *European Journal of Pharmaceutics and Biopharmaceutics* **2016**, *98*, 57-66, https://doi.org/10.1016/j.ejpb.2015.11.002.
21. Mirzaei, M.; Khorshahi, H.; Tebyanian, H.; Moradi, R.S.; Rastegar, M.; Panahi, S.; Sariri, R.; Latifi, A.M. The effect of deep eutectic solvents as co-solvent on organophosphorus hydrolase targeting engineering enzyme-catalyzed. *Biointerface Research in Applied Chemistry* **2020**, *10*, 6488-6497, https://doi.org/10.33263/BRIAC105.64886497.
22. Othman, Z.S.; Hassan, N.H.; Zubairi, S.I. Alcohol based-deep eutectic solvent (DES) as an alternative green additive to increase rotenone yield. *AIP Conference Proceedings* **2015**, *1678*, https://doi.org/10.1063/1.4931283.
23. Tuntarawongsa, S.; Phaechamud, T. Polymeric Eutectic System. *Advanced Materials Research* **2012,** *528*, 180-183, https://doi.org/10.4028/www.scientific.net/AMR.528.180.
24. Kalhor, P.; Ghandi, K. Deep Eutectic Solvents for Pretreatment, Extraction, and Catalysis of Biomass and Food Waste. *Molecules* **2019**, *24*, https://doi.org/10.3390/molecules24224012.
25. Shikov, A.N.; Kosman, V.M.; Flissyuk, E.V.; Smekhova, I.E.; Elameen, A.; Pozharitskaya, O.N. Natural Deep Eutectic Solvents for the Extraction of Phenyletanes and Phenylpropanoids of Rhodiola rosea L. *Molecules* **2020**, *25*, https://doi.org/10.3390/molecules25081826.
26. Santos, F.; P.S. Leitão, M.I.; C. Duarte, A.R. Properties of Therapeutic Deep Eutectic Solvents of l-Arginine and Ethambutol for Tuberculosis Treatment. *Molecules* **2019**, *24*, https://doi.org/10.3390/molecules24010055.
27. Yue, Y.; Huang, Q.; Fu, Y.; Chang, J. A quick selection of natural deep eutectic solvents for the extraction of chlorogenic acid from herba artemisiae scopariae. *RSC Advances* **2020**, *10*, 23403-23409, https://doi.org/10.1039/D0RA03786A.

28. Velásquez, P.; Bustos, D.; Montenegro, G.; Giordano, A. Ultrasound-Assisted Extraction of Anthocyanins Using Natural Deep Eutectic Solvents and Their Incorporation in Edible Films. *Molecules* **2021**, *26*, 984. https://doi.org/10.3390/molecules26040984.
29. Altunay, N.; Elik, A.; Gürkan, R. Natural deep eutectic solvent-based ultrasound-assisted-microextraction for extraction, pre-concentration and analysis of methylmercury and total mercury in fish and environmental waters by spectrophotometry. *Food Additives & Contaminants: Part A* **2019**, *36*, 1079-1097, https://doi.org/10.1080/19440049.2019.1619939.
30. Islamčević Razboršek, M.; Ivanović, M.; Krajnc, P.; Kolar, M. Choline Chloride Based Natural Deep Eutectic Solvents as Extraction Media for Extracting Phenolic Compounds from Chokeberry (Aronia melanocarpa). *Molecules* **2020**, *25*, https://doi.org/10.3390/molecules25071619.
31. Mansur, A.R.; Song, N.-E.; Jang, H.W.; Lim, T.-G.; Yoo, M.; Nam, T.G. Optimizing the ultrasound-assisted deep eutectic solvent extraction of flavonoids in common buckwheat sprouts. *Food Chemistry* **2019**, *293*, 438-445, https://doi.org/10.1016/j.foodchem.2019.05.003.
32. [Ozturk, B.; Parkinson, C.; Gonzalez-Miquel, M. Extraction of polyphenolic antioxidants from orange peel waste using deep eutectic solvents. *Separation and Purification Technology* **2018**, *206*, 1-13, https://doi.org/10.1016/j.seppur.2018.05.052.
33. González, C.G.; Mustafa, N.R.; Wilson, E.G.; Verpoorte, R.; Choi, Y.H. Application of natural deep eutectic solvents for the "green"extraction of vanillin from vanilla pods. *Flavour and Fragrance Journal* **2018**, *33*, 91-96, https://doi.org/10.1002/ffj.3425.
34. Georgantzi, C.; Lioliou, A.E.; Paterakis, N.; Makris, D.P. Combination of Lactic Acid-Based Deep Eutectic Solvents (DES) with β-Cyclodextrin: Performance Screening Using Ultrasound-Assisted Extraction of Polyphenols from Selected Native Greek Medicinal Plants. *Agronomy* **2017**, *7*, https://doi.org/10.3390/agronomy7030054.
35. Bakirtzi, C.; Triantafyllidou, K.; Makris, D.P. Novel lactic acid-based natural deep eutectic solvents: Efficiency in the ultrasound-assisted extraction of antioxidant polyphenols from common native Greek medicinal plants. *Journal of Applied Research on Medicinal and Aromatic Plants* **2016**, *3*, 120-127, http://dx.doi.org/10.1016/j.jarmap.2016.03.003.
36. García, A.; Rodríguez-Juan, E.; Rodríguez-Gutiérrez, G.; Rios, J.J.; Fernández-Bolaños, J. Extraction of phenolic compounds from virgin olive oil by deep eutectic solvents (DESs). *Food Chemistry* **2016**, *197*, 554-561, https://doi.org/10.1016/j.foodchem.2015.10.131.
37. Zhao, B.Y.; Xu, P.; Yang, F.X.; Wu, H.; Zong, M.H.; Lou, W.Y. Biocompatible Deep Eutectic Solvents Based on Choline Chloride: Characterization and Application to the Extraction of Rutin from *Sophora japonica*. *ACS Sustainable Chemistry & Engineering* **2015**; *3*, 2746–2755. doi:10.1021/acssuschemeng.5b00619
38. Duarte, A.R.C.; Ferreira, A.S.D.; Barreiros, S.; Cabrita, E.; Reis, R.L.; Paiva, A. A comparison between pure active pharmaceutical ingredients and therapeutic deep eutectic solvents: Solubility and permeability studies. *European Journal of Pharmaceutics and Biopharmaceutics* **2017**, *114*, 296-304, https://doi.org/10.1016/j.ejpb.2017.02.003.
39. Tuntarawongsa, S.; Phaechamud, T. Menthol, Borneol, Camphor and WS-3 Eutectic Mixture. *Advanced Materials Research* **2012**, *506*, 355-358, https://doi.org/10.4028/www.scientific.net/AMR.506.355.
40. Gala, U.; Chuong, M.C.; Varanasi, R.; Chauhan, H. Characterization and Comparison of Lidocaine-Tetracaine and Lidocaine-Camphor Eutectic Mixtures Based on Their Crystallization and Hydrogen-Bonding Abilities. *AAPS PharmSciTech* **2015**, *16*, 528-536, https://doi.org/10.1208/s12249-014-0242-4.
41. Silva, J.M.; Pereira, C.V.; Mano, F.; Silva, E.; Castro, V.I.B.; Sá-Nogueira, I.; Reis, R.L.; Paiva, A.; Matias, A.A.; Duarte, A.R.C. Therapeutic Role of Deep Eutectic Solvents Based on Menthol and Saturated Fatty Acids on Wound Healing. *ACS Applied Bio Materials* **2019**, *2*, 4346-4355, https://doi.org/10.1021/acsabm.9b00598.
42. Silva, J.; Reis, R.; Paiva, A.; Duarte, A. Design of functional therapeutic deep eutectic solvents based on choline chloride and ascorbic acid. *ACS Sustainable Chemistry & Engineering* **2018,** *6*, 10355-10363. https://doi:10.1021/acssuschemeng.8b01687
43. Ohzeki, K.; Kitahara, M.; Suzuki, N.; Taguchi, K.; Yamazaki, Y.; Akiyama, S.; Takahashi, K.; Kanzaki, Y. Local Anesthetic Cream Prepared from Lidocaine-Tetracaine Eutectic Mixture. *Yakugaku Zasshi* **2008**, *128*, 611-616, https://doi.org/10.1248/yakushi.128.611.
44. Yong, C.S.; Oh, Y.-K.; Jung, S.H.; Rhee, J.-D.; Kim, H.-D.; Kim, C.-K.; Choi, H.-G. Preparation of ibuprofen-loaded liquid suppository using eutectic mixture system with menthol. *European Journal of Pharmaceutical Sciences* **2004**, *23*, 347-353, https://doi.org/10.1016/j.ejps.2004.08.008.
45. Law, D.; Wang, W.; Schmitt, E.A.; Qiu, Y.; Krill, S.L.; Fort, J.J. Properties of Rapidly Dissolving Eutectic Mixtures of Poly(ethylene glycol) and Fenofibrate:The Eutectic Microstructure. *Journal of Pharmaceutical Sciences* **2003**, *92*, 505-515, https://doi.org/10.1002/jps.10324.
46. Nazzal, S.; Smalyukh, I.I.; Lavrentovich, O.D.; Khan, M.A. Preparation and in vitro characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation. *International Journal of Pharmaceutics* **2002**, *235*, 247-265, https://doi.org/10.1016/s0378-5173(02)00003-0.

47. Stott, P.W.; Williams, A.C.; Barry, B.W. Transdermal delivery from eutectic systems: enhanced permeation of a model drug, ibuprofen. *Journal of Controlled Release* **1998**, *50*, 297-308, https://doi.org/10.1016/s0168-3659(97)00153-3.
48. Tuntarawongsa, S.; Phaechamud, T. Polymeric eutectic drug delivery system. *Journal of Metals, Materials and Minerals* **2012**, *22*.
49. Raja Sekharan, T.; Tamilvanan, S.; Rajadurai, S.; Mohammed, I.S.; Kavipriya, K. Development of Ibuprofen-loaded emulsion from eutectic mixture and Eudragit RL 100. *PharmaTutor* **2019**, *7*, 7-13; http://dx.doi.org/10.29161/PT.v7.i7.2019.7.
50. Ma, Y.; Wang, Q.; Zhu, T. Comparison of hydrophilic and hydrophobic deep eutectic solvents for pretreatment determination of sulfonamides from aqueous environments. *Analytical Methods* **2019**, *11*, 5901-5909. https://doi.org/10.1039/c9ay02244a.
51. van Osch, D.J.G.P.; Zubeir, L.F.; van den Bruinhorst, A.; Rocha, M.A.A.; Kroon, M.C. Hydrophobic deep eutectic solvents as water-immiscible extractants. *Green Chemistry* **2015**, *17*, 4518-4521, https://doi.org/10.1039/C5GC01451D.
52. van Osch, D.J.G.P.; Dietz, C.H.J.T.; van Spronsen, J.; Kroon, M.C.; Gallucci, F.; van Sint Annaland, M.; Tuinier, R. A Search for Natural Hydrophobic Deep Eutectic Solvents Based on Natural Components. *ACS Sustainable Chemistry & Engineering* **2019**, *7*, 2933-2942, https://doi.org/10.1021/acssuschemeng.8b03520.
53. Dwamena, A.K. Recent Advances in Hydrophobic Deep Eutectic Solvents for Extraction. *Separations* **2019**, *6*, https://doi.org/10.3390/separations6010009.
54. Qu, Q.; Lv, Y.; Liu, L.; Row, K.H.; Zhu, T. Synthesis and characterization of deep eutectic solvents (five hydrophilic and three hydrophobic), and hydrophobic application for microextraction of environmental water samples. *Analytical and Bioanalytical Chemistry* **2019**, *411*, 7489-7498, https://doi.org/10.1007/s00216-019-02143-z.
55. Verma, R.; Banerjee, T. Palmitic-Acid-Based Hydrophobic Deep Eutectic Solvents for the Extraction of Lower Alcohols from Aqueous Media: Liquid–Liquid Equilibria Measurements, Validation and Process Economics. *Global Challenges* **2019**, *3*, https://doi.org/10.1002/gch2.201900024.
56. Lee, J.; Jung, D.; Park, K. Hydrophobic deep eutectic solvents for the extraction of organic and inorganic analytes from aqueous environments. *TrAC Trends in Analytical Chemistry* **2019**, *118*, 853-868, https://doi.org/10.1016/j.trac.2019.07.008.
57. Florindo, C.; Branco, L.C.; Marrucho, I.M. Development of hydrophobic deep eutectic solvents for extraction of pesticides from aqueous environments. *Fluid Phase Equilibria* **2017**, *448*, 135-142, https://doi.org/10.1016/j.fluid.2017.04.002.
58. Cao, J.; Chen, L.; Li, M.; Cao, F.; Zhao, L.; Su, E. Two-phase systems developed with hydrophilic and hydrophobic deep eutectic solvents for simultaneously extracting various bioactive compounds with different polarities. *Green Chemistry* **2018**, *20*, 1879-1886, https://doi.org/10.1039/C7GC03820H.
59. Yousefi, S.M.; Shemirani, F.; Ghorbanian, S.A. Hydrophobic Deep Eutectic Solvents in Developing Microextraction Methods Based on Solidification of Floating Drop: Application to the Trace HPLC/FLD Determination of PAHs. *Chromatographia* **2018**, *81*, 1201-1211, https://doi.org/10.1007/s10337-018-3548-7.
60. Ge, D.; Wang, Y.; Jianga, Q.; Daia, E. A deep eutectic solvent as an extraction solvent to separate and preconcentrate parabens in water samples using in situ liquid-liquid microextraction. *J Braz Chem Soc* **2019**, *30*, 1203-1210, https://doi.org/10.21577/0103-5053.20190014.
61. ZuŃ, M.; Wojciechowska, K.; Dwornicka, D.; Poleszak, E. The influence of the eutectic mixtures: Salicylic acid - menthol and benzocaine - menthol on physical properties of the creams with fluconazole. *Current Issues in Pharmacy and Medical Sciences* **2013**, *26*, 457-460, https://doi.org/10.12923/j.2084-980X/26.4/a.24.
62. Tamilvanan, T.; Gill, S.; Kaur, I.; Rahman, S.N.R.; Pawde, D.M.; Katari, O.; Hmingthansanga, V.; Raja Sekharan, T. Candidiasis management: current status of allopathic drugs and utility of coriander-based oil-less emulsions. *Letters in Applied NanoBioScience* **2019**, *8*, 586-590, https://doi.org/10.33263/LIANBS83.586590.
63. Biswal, B.; Karna, N.; Nayak, J.; Joshi, V. Formulation and evaluation of microemulsion based topical hydrogel containing lornoxicam. *Journal of Applied Pharmaceutical Science* **2014**, *4*, 077-084, https://doi.org/10.7324/JAPS.2014.41214.
64. Shen, Q.; Li, X.; Li, W.; Zhao, X. Enhanced Intestinal Absorption of Daidzein by Borneol/Menthol Eutectic Mixture and Microemulsion. *AAPS PharmSciTech* **2011**, *12*, 1044-1049, https://doi.org/10.1208/s12249-011-9672-4.
65. Phaechamud, T.; Tuntarawongsa, S. Transformation of eutectic emulsion to nanosuspension fabricating with solvent evaporation and ultrasonication technique. *Int J Nanomedicine* **2016**, *11*, 2855–2865, https://doi.org/10.2147/IJN.S108355.
66. Olivares, B.; Martínez, F.; Rivas, L.; Calderón, C.; M. Munita, J.; R. Campodonico, P. A Natural Deep Eutectic Solvent Formulated to Stabilize β-Lactam Antibiotics. *Scientific Reports* **2018**, *8*, https://doi.org/10.1038/s41598-018-33148-w.