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Formulation Approaches for Deep Eutectic Solvents Solubilized APIs

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ABSTRACT

Increasing the efficacy of currently available medications is one of the pharmaceutical industry's main objectives. It is far simpler to develop current medications or enhance their efficacy than to create novel therapeutic candidates. This can be accomplished by altering deep eutectic solvents are prepared for solubility in the formulation techniques improvements made to different Active Pharmaceutical Ingredients (APIs).

Usually, to modify DES, compounds having hazardous profiles that were previously well-known determined. DESs are thought to function as solubilization carriers. The evolution Organic solvents such as ethanol and acetone ethers are typically needed for soluble medicines.

The melting of APIs is improved as a result. Along with improving the solubility of currently available medications, DESs also has a number of other uses.

Keywords- solubility enhancement, deep eutectic solvent, polymorphism, effectiveness of drug delivery, dermal and transdermal, drug and delivery.

I. INTRODUCTION

Improving the effectiveness of existing medicines is one of the major goals of the pharmaceutical industry [1]. Instead of developing new high-availability drugs, which require new clinical trials, there are undeniable guarantees and benefits in developing therapies that have been tried and tested. [2] To improve their drug performance, drugs may undergo increasing changes, such as modification of drug form and composition, testing of new compounds, and the use of different doses or novel administration routes. One of the features with a large roof of development is hydrophilicity; about 40% of the drugs are approved and about 90% of the drugs being developed do not dissolve in water, leading to low availability and saturation [3]. In particular Biopharmaceutics Classification System II (BCS Class II) materials, with low melting and high availability, the availability of performance-enhancing properties can be improved by increasing melting point and dissolving of the drug in the intestinal fluid [4]. Although many methods are reported in documents [5], improved drug solubility and drug availability remain one of the most challenging aspects of drug development, especially in oral drug delivery systems. To improve oral availability, solid distribution has been used as one of the most effective methods [6]. This is defined as a family of scale forms in which the active ingredient of the drug (API) is distributed to an inert biological matrix prepared by dissolving or dissolving evaporation methods [6]. The first drug in its dosage and the amount of absorption was greatly improved using a robust distribution process dating back to the 1960s when Sekiguchi and Obi [7] studied the absorption difference between sulfathiazole and its eutectic and urea mixture. Following this pioneering work, and aimed at developing melting and soluble API profiles, some studies reported on eutectic compounds and deep eutectic solvents (DES) containing active pharmaceutical ingredients (APIs) [8,9]. The naming of the development of drug effectiveness has been hampered by the common use of robust API forms, which are often associated with physical and chemical instability in their final scales [10]. These concerns may be due to their polymorphism and the impairment and oral administration of drugs in

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humans, thus correcting drug availability [11]. One way to overcome these problems is to change the APIs into liquid. Generally, in solid forms, liquids show high solubility in water since the energy barrier associated with the fusion enthalpy is disturbed, providing a superior therapeutic response [12]. However, the implementation of APIs in the liquid form must ensure the safety, efficacy, and stability of the final drug product. One example demonstrating the development of liquid forms of the API is its conversion into ionic fluids, anionic compounds, and/or active cationic compounds (API-ILs) [13 - 15]. The first report on API-IL described the synthesis of ranitidine docusate, a dark red liquid with a glass temperature of −12 ° C, which can prevent the conversion of ranitidine's polymorphic [16]. Additional API-IL, which includes lidocaine and docusate as ions, has also been reported [17]. For their benefits, an increasing number of report API-ILs have emerged over the years, described as a novel strategy to improve drug treatment and delivery[18,19]. However, the difficulty of using IL as a liquid chemical is the new APIs that transmit to their lesser toxic profiles, highly dependent on the structure of IL. This fact has delayed their acceptance in pharmacological and medical settings [13]. Therefore, the development of alternative processes that may be used in the pharmaceutical industry should be followed. In this field, eutectic alloys and deep eutectic solvents (DES) have emerged as useful other ways to install APIs, to know and produce new liquid forms of APIs, and to improve their availability.

DES is usually modified by combining molecules with toxic profiles already well established and by whom the use of drug applications has already been well received. These compounds allow for the passage of in vitro and in vivo studies and appropriately reduced the high E-factor associated with the pharmaceutical industry [13]. Moreover, too above IL, the preparation of DES requires only a mixture of at least two types, namely a hydrogen-bond donor (HBD) and hydrogen-bond (HBA) receiver, without the chemical reaction that occurs. DES is a eutectic compound that deviates from the behavior of the thermodynamic solid-liquid phase, i. e. a mixture of innocence compounds where the temperature of the eutectic point is lower than the ideal liquid mixture (Figure 1) [20,21]. And power the hydrogen-bond interaction between the HBD and HBA types that make up DES is responsible for the reduction of melting the temperature to the point where the mixture can be liquid in the room or at a person's body temperature [22]. DES, unlike IL, is a compound, not a pure chemical, and can be a better solution for ions and not just synthetic liquids by ionic species [21]. Preparation for DES usually involves a simple combination of at least two parts, usually less stimulating and moderate heat [23]. Importantly, the temperature at which the mixture is placed should be taken care of it is controlled to prevent decay of the individual components that make up the DES [24]. Since there is no chemical reaction is involved in the preparation process (reflects 100% of the atomic economy and enters within a single Green Principles of Chemistry), and there is no product structure [25]. Therefore, their purity depends solely on the purity of each material and the avoidance of degrading products. That being said, the poison of the final mixture should be carefully tested because the major differences from the individual may be observed [26 - 28]. Further triumph of cytotoxicity concerns related to DES, especially when considering their human use, a study of natural DES (NADES) recently expanded [29]. Also, because it is possible to combine a large number of HBD at once HBA, NADES can be considered as highly chemical compounds that are highly developed in pharmaceutical and pharmaceutical applications. [30,31]. Thus, DES comprising an API as HBD or HBA variants or as a liquid chemical to improve the flexibility of targeted APIs has been studied.

DESs as carriers for solubilization:

Chemicals require a solvent to aid in performance and function in the transport of goods [32]. Water is the most abundant a commonly used and highly desirable used vehicle for medical products [33]. However, the development of solubility of soluble drugs usually requires the use of organic solvents such as ethanol, acetone, or ethers. Therefore, improving the melting of APIs, more securely it is still a challenge. A significant increase in melting can be is achieved through the use of many hazardous co-solvents, e.g. sorbitol, glycerol, propylene glycol, and polyethylene glycol, among others [34]. However, melting enhancements the achievement is not as promising as seen with DES. Deep eutectics solvents have been studied as widely as other solvents of the melting of APIs, especially the structure of topics [23]. Promising results in dissolving solids in water drugs in DES have been reported, as summarized in Table 1. For example, the dissolution of ibuprofen in a potential solution may be increased by propylene glycol and polyethylene glycol (PEG 300) as co-solvents receiving 193-fold enhancements and 700, respectively [34]. However, the melting of ibuprofen can increase by more than 5,400 times in DES, were compared with its solubility in water [35]. Other non-inflammatory drugs (NSAIDs), such as naproxen and ketoprofen, and analgesics such as acetaminophen, are additional examples of the drugs investigated in this see [35,36]. Li and co-workers [37] showed melting enhancers of itraconazole, piroxicam, lidocaine, and itraconazole of 6700-, 430-, 28-, and 6400, respectively, compared to their melting in water, using DES based on choline chloride (ChCl) and glycolic acid (molar ratio 1: 2). 53,600 itraconazole solvent enhancement doubled by adding a third, oxalic acid, to this DES, to a molar ratio of 1: 1.6: 0.4, also reported [37]. The NADES made of menthol: camphor (1: 1 molar ratio) also proven as a biocompatible solvent for ibuprofen, allowing to achieve a melting point of

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40.4 ± 8.8 µg/mL (vs. 9.81 ±2.71 µg/mL in the water at the same temperature) [38]. A better understanding of DES resolution skills was provided by the conceptual approach to the resolution of lidocaine to ChCl: lactic acid and β-alanine: lactic acid (1: 1) [39]. The reported results indicate the effective solution of lidocaine by solvents indicated due to the combination of hydrogen bonding and the indirect contact of Van der Waals. Predicted the melting of lidocaine in these solvents was the largest order of higher than water and can be compared to that obtained by IL, which is why it is a competitive platform for APIs to solve. In addition to the melting point, DES is also back reported as promising chemical development chemicals API stability. It is known that many APIs in various ways and unstable in aqueous solution, for example, for many ester-containing drugs, like aspirin, you get hydrolysis when it is stored for a long time in water [40]. Recently, DES was highlighted for its stability the ability to improve when used to process APIs. In one study, hydrolysis of aspirin into salicylic and acetic acid acids in DES ChCl: 1,2-propanediol was 8.2 times there is a water solution [35]. Beta mix: urea too increases the stability of β-lactam antibiotics, namely imipenem and clavulanic acid, by 7 and 2.5, respectively, were compared to their powerful solutions [41]. Therefore, DES may be designed to improve both the melting and the stability of the target tree. Defined features are essential to maximizing API availability. Appropriately, in the pioneering work in Fergana Blab / c mice and colleagues [42], in which the pharmacokinetic studies of rutin are dissolved in proline: glutamic acid DES was performed; reported improvements to oral ingestion of the intended drug. By comparing the administration of rutin solution in water with the same rutin formation in DES, change in t-max (peak time) was noted, i.e. 15 min vs 60 min, with no changes to the absorption rate. Surprisingly, a significant difference in C-max (high focus) and AUC (lower curve area) found, revealing an increase in the availability of rutin-related findings in the construction of DES by almost 100% compared to its behaviors in water solution. The proline: malic acid: lactic acid: a mixture of water, in molar proportions 1: 0.2: 0.3: 0.5, and leads to an increase (12 times) in melting of berberine, known for its anti-diabetic properties, while also which led to an eight-fold increase in its focus on blood [43].

Among the DES studied, compounds for ChCl have been available highly tested for processing APIs. This practice is associated with the fact that these DES are already well documented in the literature, and ChCl is a powerful and safe HBA type and a cost-effective combination [37]. Without significant results on the development of solubility, the use of ChCl and HBDs with toxic levels, such as glycolic acid or oxalic acid (Table 1), may have been a major problem in the use of these compounds as solvent media for pharmaceutical production. In this sense, DES components should be carefully selected, to cytotoxicity was assessed for this purpose.

Table 1: Reported solubility improvements of APIs in DES solvents at room temperature.

API	Solubility in H2O (mg-mL−1)	DES (molar ratio HBA-HBD)	Solubility in DES (mg.ml-1)	Reference No.
Aspirin	7.03±0.03	ChCl:1,2-propanediol (1:2)	202.00±3.15	[12]
Acetaminophen	19.95 ± 0.12	ChCl:1,2-propanediol (1:2)	324.00±4.23	[12]
Ibuprofen	0.07±0.00	Campq1hor: menthol (1:1)	282.11±6.67	[13]
Itraconazole	<0.001±0.00	ChCl: glycolic acid: oxalic acid (1:1.6:0:4)	383.40±4.03	[12]
Lidocaine	3.63±0.00	ChCl: glycolic acid: oxalic acid (1:1.7:0.3)	295.00±6.80	[11]
Ketoprofen	0.34±0.00	ChCl: Levulinic acid (1:2)	329.10±4.42	[11]
Naproxen	0.06±0.00	ChCl:1,2-propanediol (1:2)	45.26±1.24	[12]

Applications of DESs in drug delivery fields:

To achieve the treatment results you want; APIs must be well accessible and especially accessible to the operating sites. However, moving APIs from the administrative area to the workplace is not often disrupted by poor biopharmaceutical properties such as low solubility in body fluids, low penetration through the membrane of biology, chemical instability, and rapid body formation as well physical elimination (Emani et al. 2018). To address the issues mentioned, the APIs are developed as a variety of drug delivery systems such as solid distribution (Serajuddin 1999), cocrystals (Emani et al. 2019), and polymeric delivery systems (Kumari et al. 2010). In the program in the next section, we try to briefly look at the potential of DESs to improve drug delivery.

Designing polymeric drug delivery systems through DES:

Polymeric agents improve the effectiveness of drug delivery by controlling the release, providing cell-targeted delivery of tissue, and protection from damage (Tibbitt et al. 2016). Naturally (Yang et al. 2015), semi-synthetic (Qi et al. 2015), and synthetic (Englert et al. 2018; Selselehjonban et al. 2019) polymers used to design DDS. Still, there are survivors' challenges in raw compounding, use, and proper loading of polymeric

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carrier drugs. Over the past decade, DES has emerged as a separate resource for performance integration materials such as nanomaterials (Chen F et al. 2013), metal-organic structures (Zhang J et al.2009), and biocompatible compliant polymers (Sánchez-Leija et al. 2014; Pradeep Kumar et al. 2018), as an enzymatic reaction (Durand E. et al. 2012). DES can provide green media for the polymerization reaction occurs when DES can act as a solvent, monomer, or reaction included. With the use of DES, integration is possible in mild conditions (low temperatures, compatible media). Also, the discovery of many non-toxic compounds makes it possible it is possible to measure DES properties and provide a configuration for each response. Therefore, biocompatible and environmentally friendly integration methods can be developed (del Monte et al. 2014). Some excellent reviews have been published in DESs applications such as responsive media for the integration of different types of building materials (Carrizo et al. 2012; del Monte et al.2014; Alonso et al. 2016; Motta-Morales et al. 2018).

API-DES formulations:

From a historical point of view, the first use of API-DES in the field of drug delivery it has been reported in the delivery of the leading and extreme articles. 1889, Jules-Aristide Benaim found that phenol, cocaine hydrochloride, and menthol in equal amounts form a room temperature fluid and I used a synthetic liquid mixture for topical anesthesia (Fiala et al. 2010). Later, in 1984, lidocaine and prilocaine were reported to form a 1: 1 eutectic mixture at a melting point of 18 ° C (Borodin, Nyquist-Mayer, Wads ten, et al. 1984). Thereafter, these API-DES are formulated as an oil in a water emulsion (Figure 1) called EMLA®. (Eutectic integration for Local Anaesthetics) cream and as a result approved by the FDA for local anesthesia in 1992 (Nyquist-Mayer et al. 1986; Ehrenfeld et al. 2002). Analgesic effects of emulsions API-DES-based formulations are higher than prilocaine or isolated lidocaine (Gujrat et al. 1994). EMLA®cream is still the most widely used anesthetic. Similarly, line, an aerosol delivery form containing a compound similar to lidocaine - eutectic prilocaine (Fortuin ™) Accepted manuscript approved for use in the treatment of premature ejaculation in the European Union in 2016 (Porst and Burris 2017). These marketed examples highlight the great potential of API-DES in the area of drug delivery in skin centers and body transfusions.

Examples have encouraged researchers to experiment with eutectic design alternative delivery methods. API-DES can improve transdermal intake of propranolol, testosterone, ibuprofen, itraconazole, and development capacity of conformers (such as menthol), melting point melting, and increased membrane solubility (Stott Paul W. et al. 1998; Fiala et al. 2010). Indeed, the oil-rich (API-DES) category contains a high concentration of drugs that acts as a pool and thus can provide a great driving force for the proliferation of drug molecules on the skin (Nyquist-Mayer et al. 1986). For example, the formation of API-DES for testosterone, lipophilic molecule, containing menthol, a known permeation enhancer, at a molar ratio of 4: 1 led to severe stress point testosterone from 153.7 to 39.9 ° C there is an aqueous solution of testosterone. Increased permeation is dependent on improvement in the dissolution of testosterone in a hydroalcoholic car and the reduction of SC-blocking properties is approx. menthol (Kaplun-Frischoff and Touitou 1997). Despite these promising results, there are still many unanswered questions about API-DESs type, physicochemical stability, compliance with materials, and the formation of this liquid as an acceptable final form. The formation of the Hydrogen bond between API and conformer is considered the driving force of melting point melting and formation of API-DES. Theoretically, API-DES formation is possible with a large number of pharmaceutical molecules that support hydrogen bond or quaternary ammonium salt (Abbott et al. 2017). However, so far the availability of API-DES has been performed primarily with the test function of a mixture of different APIs and conformers in different ratings. Recently, Wollert et al (Wollert et al. 2019) developed thermodynamic modeling to predict the eutectic formation and eutectic temperature of the API / conformer eutectic system. Melting points, melting of enthalpies, and coefficients of thermodynamic API activity and conformer were used to create predictions. Predictions made for a11 combination of three APIs and six conformers. Predicted eutectic naming and eutectic temperatures in good agreement with test data showing the effectiveness of the proposed model for rapid API-DES design. Of course, there is plenty of room for this progress in developing strategic strategies to guide the integration process API-DES and eligibility options for a given application. It will also be interesting to see whether it is possible to properly configure API-DES architecture by changing partners. The chemical structure of the molecule remains unaffected when a rigid API is converted to an error liquid API-DES. This can be of great help to API-DES from drug development as well-controlled decisions because drug properties can be changed outside the building API change. However, there are no regulatory authority guidelines. The answer to the question of whether regulatory agencies treat API-DES as new chemicals organizations that need advanced medical and toxicology courses or see it as new make-up? it is important. The answer could have a profound effect on industry interest regarding research in API-DES.

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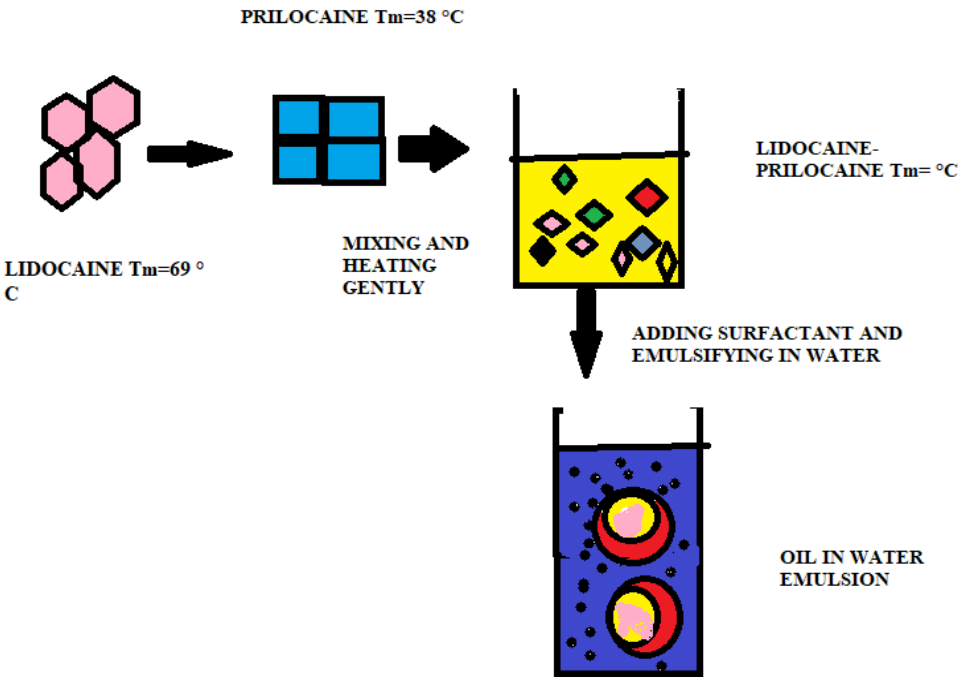

Figure 1: Schematic presentation of the preparation of oil in water emulsion based on a deep eutectic mixture of lidocaine and prilocaine.

Table 2: API-DESs reported for transdermal delivery applications

S.No.	API	Conformer	Mole Ratio	Tm of API	Tm of conformer	Tm/Tg of API-DES	Reference
1.	Ibuprofen	Menthol	3:7	76	41	19	(Stott P. W. et al. 1998)
2.	Ibuprofen	Methyl nicotinate	1:1(w/w)	76	41	**a**	(Wolfson et al. 2000)
3.	Itraconazole	Phenol	1:1	168	39	< 0	(Park et al. 2012)
4.	Lidocaine	Camphor	1:1(w/w)	68	175	33	(Gala et al. 2015)
5.	Lidocaine	Tetracaine	1:1(w/w)	68	41	30	(Gala et al. 2015)
6.	Lidocaine	Decanoic acid	1:1	68	32	-61	(Bica et al. 2011)
7.	Lidocaine	Hexanoic acid	1:1	68	-3	-56	(Bica et al. 2011)
8.	Lidocaine	Linoleic acid	1:1	68	-5	-71	(Bica et al. 2011)
9.	Lidocaine	Oleic acid	1:1	68	13	-47	(Bica et al. 2011)
10.	Lidocaine	Stearic acid	1:1	68	69	43	(Bica et al. 2011)
11.	Lidocaine	Ibuprofen	1:1	68	76	-27	(Wang H et al. 2014)
12.	Lidocaine	Menthol	3:7(w/w)	68	41	26	(Kang et al. 2000)
13.	Lidocaine	Phenyl salicylate	3:2	68	41	18	(Lozenges et al. 2010)
14.	Lidocaine	Prilocaine	1:1	68	38	18	(Borodin, Nyquist-Mayer, Broberg, et al. 1984)
15.	Paeonol	Menthol	------	- 52	41	**a**	(Wang W et al. 2017)
16.	Propranolol	Capric acid	3.5:6.5(w/w)	92	32	15	(Stott et al. 2001)
17.	Propranolol	Lauric acid	3:7 (w/w)	92	43	16	(Stott et al. 2001)
18.	Testosterone	Menthol	1:4	154	41	39	(Kaplun-Frischoff and Touitou 1997)

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DES as transdermal delivery vehicles:

Another exciting area of research is using DES as carriers / incoming vehicles to increase capacity in drug delivery systems in pest control centers. In this world, the Mitragotri group (Zakrewsky et al. 2014) compiled a list of ionic fluid and DES and investigated their cytotoxicity, skin irritation, antimicrobial effects on bacterial biofilm, and delivery of antibiotics on the skin. Excellent results obtained with choline - geranate (1: 2) DES. This DES showed the lowest toxicity of epithelial cells, skin thinner, excellent antimicrobial activity against bacterial biofilms, and very effective in improving the delivery of hydrophilic molecule model. For example, skin fullness of cefadroxil, hydrophilic an antibiotic with a log P of 0.4, was developed 5 times when dissolved in choline - granite (1: 2) compared to a powerful herbal remedy. The process of strengthening the power supply was so proposed removal of lipids from SC. The results show that choline - grantee (1: 2) can be a promising carrier for the delivery of skin antibiotics to eliminate biofilm-associated diseases. Biological macromolecules such as proteins and peptides have very low transdermal availability due to their large size (Benson and Namjoshi 2008). Encouraged by low toxicity, low irritability, and good infiltration enhancing choline-granite (1: 2) hydrophilic-detected properties antibiotics, the Mitragotri team continued to investigate the effectiveness of DES in the development of protein richness in the skin. The research team (Banerjee et al. 2017) studied the skin of ex vivo entry of serum albumin (MW: ≈66 kDa), ovalbumin (MW: ≈45 kDa), and insulin (MW: 5.8 kDa) dissolved in choline - granite (1: 2). DES significantly improved skin the penetration of these macromolecules also worked better than most commonly used chemicals access enhancements; diethylene glycol monomethyl ether and ethanol.

SC spectroscopy studies have suggested that choline-granite (1: 2) improves infiltration through the release of SC lipids. In a further step, the authors investigated in vivo blood glucose reduction of insulin-soluble insulin secretion - granite (1: 2) into nondiabetic skin mice (Figure 2). When insulin is depleted in DES it leads to a reduction of 25 and 40% blood glucose for 2 and 4 h, respectively, compared with a significant decrease in blood sugar Level with insulin dissolved in phosphate buffer. Galfridian is a water-free polyphenolic flavonoid with anti-oxidant, antiregulatory, and skin-lightening properties. Liu et al (Liu C et al. 2017) used a menthol-camphor (1: 1) DES as a fuel category (vehicle) for oil development in water nanoemulsion of this drug. Menthol and Camphor have been reported to be non-toxic, inefficient, and effective transdermal penetration enhancers (Sapra et al. 2008). These natural terpenes form an invisible DES in water with hydrophobic properties. The menthol-camphor DES can act as an infusion enhancer and solvent for the transfer of non-soluble chemicals. The authors compare the discovery of eutectic-based anti pension with nanoemulsion synthetic and isopropyl myristate and the aqueous solution of the drug. Isopropyl myristate is a widely used lipophilic vehicle to enhance penetration into transdermal delivery (U-Engelbrecht et al. 2012). The melting of guardian in DES was almost double higher than its solubility in isopropyl myristate. More importantly, in vitro skin the discovery of eutectic-based nanoemulsion was almost 3 and 7 times higher than that isopropyl myristate-based nanoemulsion and the aqueous solution of the drug, respectively. Accepted manuscript Although DES can eliminate solvents it has a wide variety of chemical properties but unlike IL analogs, the number of published works using DESs as solvent/vehicle delivery drug delivery is rare at this time. We predict that additional data will be produced soon with the introduction of new DES, especially hydrophobic ones. DES can be used as double-acting solvents in this area. Take advantage of a large number of possible combinations, the researcher may choose a DES-based vehicle with desired features such as wound healing, existing, strengthening penetration, or antimicrobial, depending on the condition.

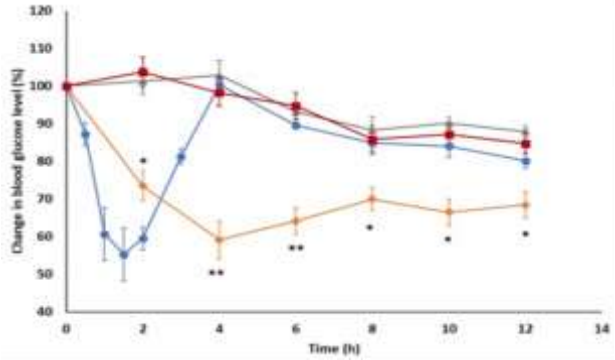

Figure 2: Percentage change in blood glucose level and time after various administration formation in baseless mice. Topical use of choline - granite (1: 2) (CAGE) alone (0 U kg – 1 insulin, green triangles); insulin in the buffer (Insulin-PBS, 10 U mL-1 as 25 U kg – 1 bodyweight, red squares); insulin in choline - germinate (1: 2) (10 U mL-1 in total 25 U kg – 1 bodyweight, blue circles); and underground insulin injection (1 U kg – 1 insulin, magenta converted triangles) made. This figure has been changed with permission from (Banerjee et al. 2017). Copyright (2017) Wiley-VCH.

Application of DESs in dermal and transdermal drug and delivery:

Drug delivery to the skin offers different benefits than other management methods. The benefits are non-invasive, better patient compliance, pre-systemic avoidance **of** intestinal and hepatic metabolism, low side effects, direct access to the indicated or diseased area, and the potential for continuous and controlled delivery (Brown et al. 2006). A major challenge in the development of delivery systems for the treatment of

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skin diseases (topical or leather delivery) or skin delivery system (incompatible delivery) low skin penetration (Alvarez-Román et al. 2003).

The human skin has its important barrier properties to protect the organs from external toxins entering and reducing water loss. Stratum corneum (SC), a non-living, outer layer of skin, in particular, prevents the entry of multiple APIs (Prausnitz et al. 2004). Only a limited number of drugs contain low molecular weight (<500 Da) and good lipophilicity (Log P = 1-3), which can work effectively penetrated imperfect skin (Naik et al. 2000). Therefore, proper approval enhancement techniques should be used for hydrophilic drugs and macromolecules. Accepted manuscript Various techniques such as chemical penetration enhancers (Pham et al. 2016), physiological approaches (Nanda et al. 2006), and vesicular carriers (Dubey et al. 2006) have been investigated for improvement. skin access APIs. These tactics are mainly based on disrupting the SC bar or altering lipid formation. Toxicity and skin irritation of chemicals and diseases, burns, and scars associated with physiological processes require the introduction of effective functioning as well-advanced improvement methods (Karanda and Mitragotri 2009; Banerjee et al. 2017).

Due to the low toxicity and the liquid at room temperature, there have been eutectic compounds investigations into drug and drug trafficking applications are being investigated. For these purposes, some researchers focus on converting solid APIs into API-DESs (room temperature) by the appropriate ports are used and some have used DES as an API carrier.

DES incorporation in (bio)polymers for drug delivery:

In recent years the emergence of drug delivery strategies has been observed, including both modifications to conventional methods and the design of new devices [81]. Polymers play an important role in this evolution, by giving controlled release of therapies in chronic doses long periods, cyclic rate, and directional (or responsive) release of both hydrophilic and hydrophobic drugs. In addition to API-DES that contains APIs to improve medical efficacy, API-DES can also be used for the development of regulated delivery systems such as polymer production monomers. Their use in polymer-based systems was originally introduced in poly (octane diol-co-citrate) compounds. elastomers use a mixture of 1, 8-octane diol and lidocaine, and citric acid as a second precursor of the polymer [82]. The revision of the drug delivery system allowed the authors to conclude that DES performs a triple action, providing an API in drug release, it acts as a necessary monomer to prepare elastomers and to do as is done media for polymerization. However, this approach is still controversial, because in DES 'polymerization DES' concept is that damaged by a decrease of 1, 8-octane diol per citric acid. However, using the power of DES to do polymerize, novel systems are suggested using the former polymerization (FP) techniques include acrylic acid and lidocaine [48]. Acrylic acid: lidocaine and methacrylic acid: lidocaine reported as API-DES in a triple role, after which polymerization can provide a controlled release of lidocaine. Or targeted API-DES shows performance monomers, the polymerizing monomer co-former does not respond chemically with an API. These mixtures initially liquid at room temperature and have all the usual DES requirements; however, when the same polymerization is performed, the concept of DES is lost due to the construction of a wooden delivery system with an API embedded in a polymeric matrix. The beauty of the delivery of drug delivery plans in one step that the chance of reduction or loss of drug activity by processing is reduced. Also, the simple texture of monomer viscosities as well the prevalence of DES through HBD deception and the molar scale of the composite favors the achievement of FPs has the highest conversion of monomers (90-100%) [48]. Without the power of FP, in future studies, improvement polymerization efficiency is almost 100% important to avoid the presence of free radicals. In addition to their application for the development of polymer delivery systems for polymer, DES has proven to be so. it is beneficial for the use and disposal of biopolymer, as demonstrated by agar [83], chitin [84], and cellulose [85]. Given their well-matched and usable character after the elimination of biopolymers, compounds containing DES can be used directly as delivery systems [86]. The oldest API-DES learning program delivery is associated with EMLA®, for sale or cream, or in the form of a patch [87]. In the latter case, a single dose EMLA® unit is included in the cellulose absorption disc. Although EMLA® patches have been developed and highlighted with their simple plan, they seem to have the same effect as a cream to relieve short-term pain [88]. An important improvement in the level of analgesia. The combination of lidocaine and prilocaine used in EMLA® has been studied in the construction of a local delivery system in the periodontal sac [89]. Cellulose-related as ethyl- (hydroxyethyl) cellulose (EHEC) and hydrophobically modified EHEC evaluated as potential transport systems for delivery of anesthesia mixture, indicating preservative drug discharge above at least 1 h [89]. Interaction between converted cellulose polymers and cationic and ionic surfactants, namely myristoyl-choline bromide and sodium dodecyl sulfate (SDS), were determined when API-DES were absent and present. One of the most interesting things about mixed worker / EHEC systems increase viscosity when the increasing temperature. This behavior allows you to manage the API in a low-level polymer system that is strong in physical contact.

The data received indicated that it was possible to do so a heat-sensitive system where small amounts of API-DES can be installed without significantly interfering with gelation polymer performance. However, even if it is caused by heat increased viscosity

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is advantageous, the use of these surfactants associated with toxicological and carcinogenic effects [90]. API-DES can only be used in biopolymer-based applications for their therapeutic action and polymerizable character however and as promoters of porosity in critical sugar consumption. an example is shown with anti-inflammatory API-DES menthol: ibuprofen (3: 1 molar ratio) [44]. This submission the system was developed for polymeric insertion compound (made of starch and poly-ε-caprolactone (SPCL)) via API-DES, after excessive CO2 (scCO2) processing. This debugging process with API-DES allows for porous detection matrix installed API target. Aquatic API-DES contributes to significant changes in the integration of polymer particles, which lead to high surface area and bonding (Figure 3). In vitro dissolution studies are shown similar termination profiles between pure ibuprofen and liquid form with menthol; however, ibuprofen has been introduced rapid discharge rate from polymeric abstract pregnant.

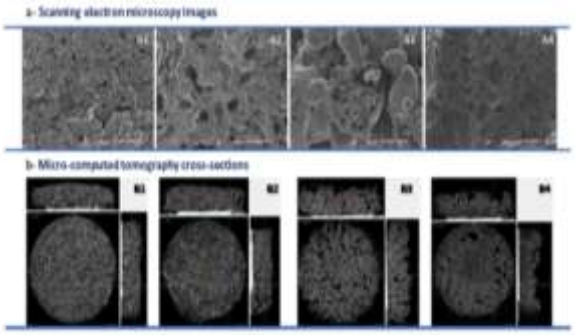

Figure 3: SEM images and micro-CT images of SPCL (B1), SPCL + ibuprofen (B2); SPCL + 10% API-DES (B3), and SPCL + 20% API-DES (B4) (Reproduced with permission from [44])

API-DES rather than its pristine method. Such a fact emphasizes the benefits of using API-DES and biopolymer programs for modifying/modify the release profile of the APIs. Other than that, full implementation of this strategy must continue to improve. A lot more recently, the same combination of polymeric and a similar approach based on scCO2 sintering, could have been improved a controlled drug delivery system with DES-based on ChCl and ascorbic acid, in which the dissolution of dexamethasone increased by multiple orders of magnitude [91]. Recently, a system based on the dissolution of gelatine has been studied API-DES delivery. Often in previous studies in this area, which aim to be presented with current and extreme topics, Mano's work as well colleagues [92] focused on oral drug formulation delivery system. Fast-melting delivery systems will dissolve or disperse in the mouth quickly, without the need for water help with swallowing. These programs usually enable a faster start of action with a significant increase in drug availability compared with conventional oral management programs. For this purpose in mind, a mixture of ChCl: mantellic acid is used as an API-DES model to test the strength of these compounds incorporation into gelatine nanofibers produced by electrospinning. Manufactured, low-cost, perishable nanofibers environment and antibacterial activity, introduced a fast-acting drug remove the profile. Cytotoxicity studies have shown that gelatine fibers Apart from showing the rapid deterioration of the model tree and what is evidence of the potential of electrospinning nanofibers for amplification oral discovery, this should be examined in detail, taking into account pharmacokinetic parameters to confirm the benefits of these programs are more than programs that contain a solid API form. its polymorphs have a profound effect on the chemical composition and therapeutic efficacy of a particular drug. Besides, strong drugs show low melting in water, and thus decrease the availability of bioavailability, there are similar types of water. To overcome these obstacles, water forms novels APIs in the form of API-DES proposed and investigated and stands for new the approach that the pharmaceutical industry should consider. API-DES, created by APIs as components of DES itself or the use of DES to integrate APIs, defined. DES does not need to be constructed of just two types, and both routes are connected since the dissolution of DI-directed API leads to the installation of the API in DES itself. However, both approaches can lead to improved melting, therapeutic action, and stability of target API, while avoiding the original polymorphism drug. Also, API-DES can be built with many variations of chemicals, and thus is designed to have a specific specification as well improved therapeutic action, including those with a dual effect, and by including input enhancements. Some advances in systems based on therapeutic polymers updated API-DES delivery, emphasizing potential and new inventions introduced by API-DES with unadulterated character. This particular type of API-DES can be used three times action, which means by providing a drug release API, which acts as monomer itself and as a synthetic media for polymerization. These programs offer new drug delivery options and are representative a step forward in developing new drug delivery systems. Although there are some promising first results in this regard strategy and examples of potential use, more research is still needed to fully understand it and the management of these drug delivery systems.

Screening for Natural deep eutectic solvents enhanced rutin solubility:

The experimental procedure was performed to identify deep natural eutectic solutions capable of resolving rutin more strongly than the solvents described above. For this purpose, 16 new acids and two new amino acids were added to the pool of chemicals used during validation, which resulted in a total depth of 126 eutectic solvents. The process described in the section Model construction and verification ^ done in all these Natural deep eutectic solvents their composition was determined by considering their outstanding forms of ionic and by performing corresponding response time calculations. The design works very well plans are presented in Table

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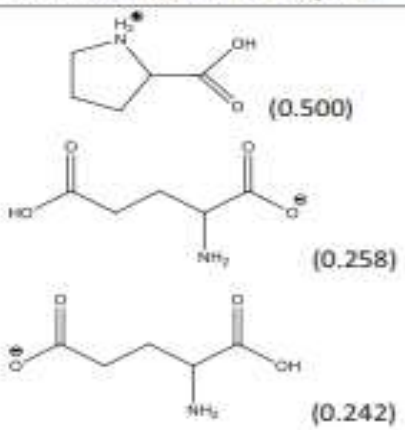
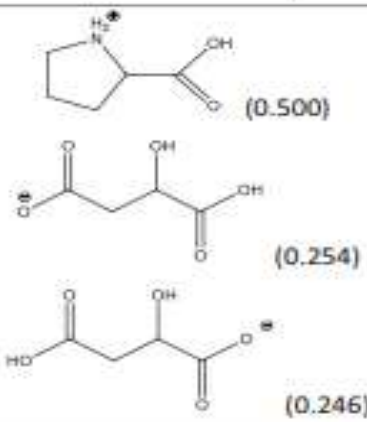
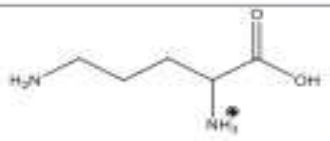
4. A detailed description of all NADES considered for this project is provided in Table S1 of ESM. Original NADES set the sections were expanded systematically, allows for the analysis of the relationship between the structure and performance in the new NADES. Carboxylic acids all contained two groups of carboxyl separated by an adaptive series of various lengths containing hydroxyl or amino substances. Found number, positions, and the types of functional groups that have significant influences on the performance of the NADES studied. Indeed, various standards were observed due to the melting of rutin estimated using the return line provided in no of computer-generated work with endless mixing, New NADES results are shown that ten programs performed better than the best index one. It is interesting to note that it is 2,3-di amino succinic acid he was involved in the four programs, and proline was involved in six programs. Indeed, the depth of nature of the eutectic solvent comprising both of these compounds were found to be the best NADES solution for rutin; its solubility was rated as high as 5.25 mg / mL, representing a 130% increase in rutin termination compared in the system of proline - glutamic acid. Two more NADES with a much higher solubility of rutin than the solvent chemicals tested were 2,4-di amino glutaric acid - proline (4.78 mg / mL, 111% increase), 4-amino-3 hydroxy glutamic acid - proline (4.21 mg/ml, 86% increase), and aspartic acid - proline (4.06 mg / mL, 80% increase). It should also be noted that these NADES pass through water by the dissolution of rutin 34- to 44 (reference value: 120 μg / ml). Among the amino acids studied, those with a heterocyclic structure are highly proven effective, as they were included in nine of the ten programs with very high rutin solutions. Activate the structure of carboxylic acid to improve the absorption of rutin including variations in the length of the main chain and active groups present in acid. As indicated in the figure.

Table 3: Dominant types of amino acids and organic acids in deep natural eutectic solvents used to validate the built model

No	NADES	Dominant forms in the system
1	Glutamic acid - Proline	 (0.500) (0.258) (0.242)
2	Malic acid - Proline	 (0.500) (0.254) (0.246)
3	Malic acid - Ornithine	 (0.241)

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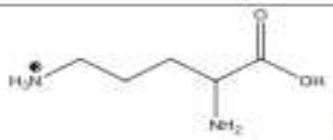
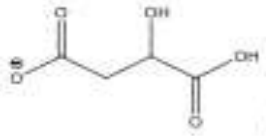
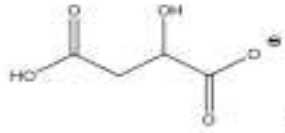
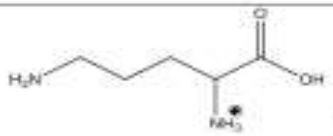
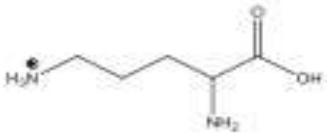
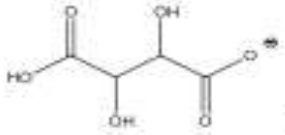
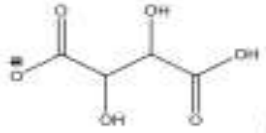
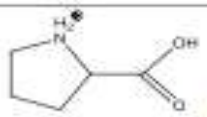
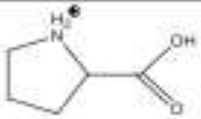
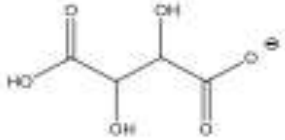
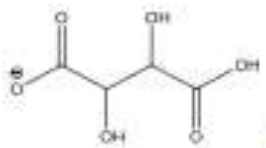
		 (0.259)  (0.252)  (0.248)
4	Tartaric acid - Ornithine	 (0.243)  (0.257)  (0.249)  (0.251)
		 (0.500)
5	Tartaric acid - Proline	 (0.500)  (0.248)  (0.252)

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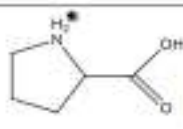
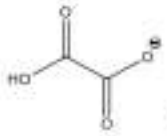
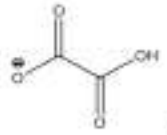
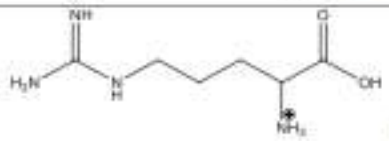
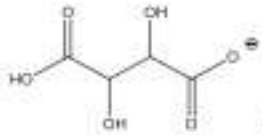
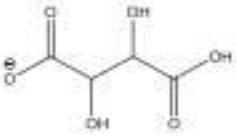
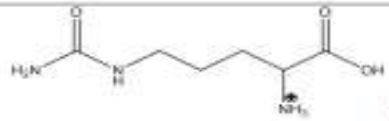
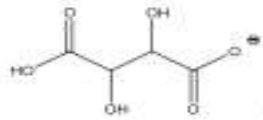
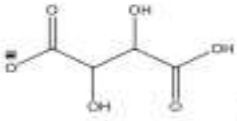
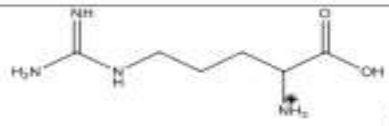
6	Oxalic acid - Proline	 (0.500)  (0.247)  (0.253)
7	Tartaric acid - Arginine	 (0.500)  (0.248)  (0.252)
8	Tartaric acid - Citrulline	 (0.500)  (0.244)  (0.256)
9	Oxalic acid - Arginine	 (0.500)

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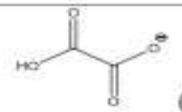
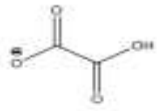
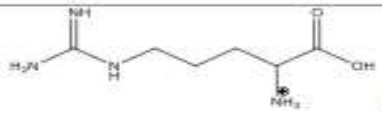
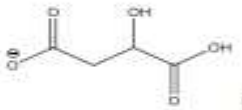
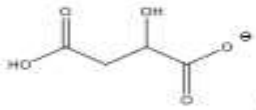
		 (0.244)  (0.256)
10	Malic acid - Arginine	 (0.500)  (0.252)  (0.248)
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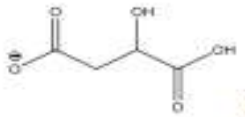
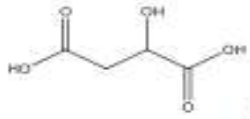
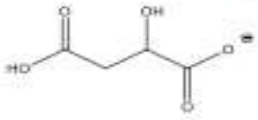
11	Malic acid - Citrulline	 (0.317)  (0.183)  (0.270)  (0.183)  (0.038)

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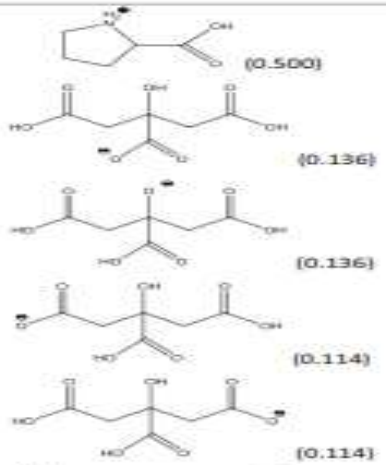
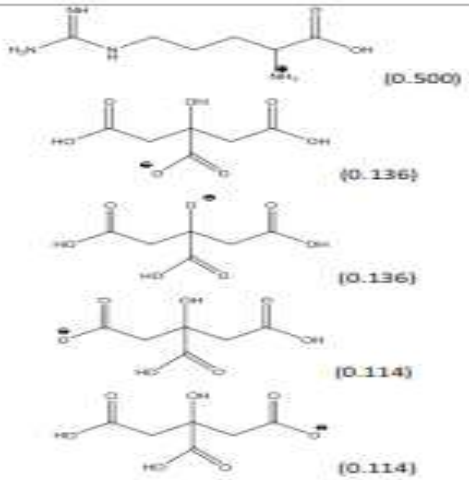
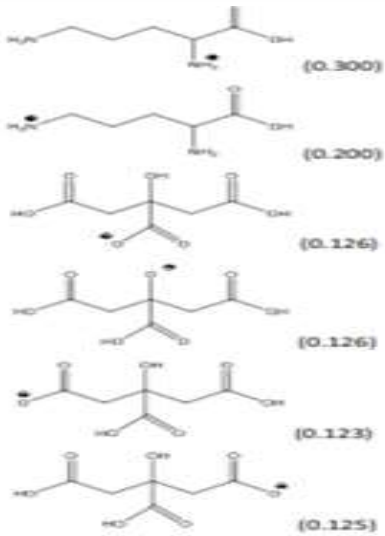
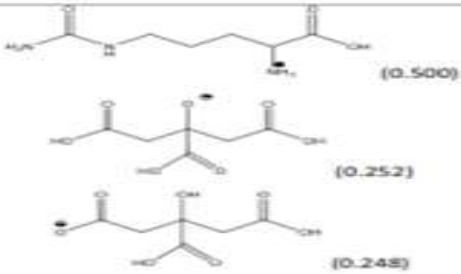
12	Citric acid - Proline	 (0.500) (0.136) (0.136) (0.114) (0.114)
13	Citric acid - Arginine	 (0.500) (0.136) (0.136) (0.114) (0.114)
14	Citric acid - Ornithine	 (0.300) (0.200) (0.126) (0.126) (0.123) (0.125)
15	Citric acid - Citrulline	 (0.500) (0.252) (0.248)

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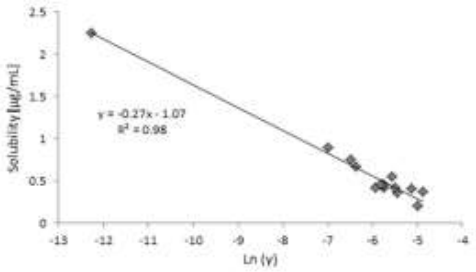

Figure 4: The correlation of the computed activity coefficients at infinite dilution with the solubility of rutin in different natural deep eutectic solvents

The molar fractions given in parentheses were used for computation of activity coefficients at infinite dilution of f Rutin in the mixtures expressing a mixture of rutin in NADES containing proline and different carboxylic acids, the highest concentration (approximately 5.00 mg / mL) was obtained carboxylic acids had two amino groups attached to them their chains. Placing one of the NH2 groups with the hydroxyl group reduced rutin melting, just as it does remove one group of amino acids, which resulted in melting of around 2.00 mg / mL. Carboxylic acids externally any amino groups linked to the chain are visible with low rutin melting. Those acids contained one of them or two hydroxyl groups as stimulants or did not resource at all; in those cases, the melting of rutin was around 1.00 mg / mL or less. And positions currently, the length of a large chain of carboxylic acid and affect the melting of rutin, because all the acids studied, he had two carboxyl groups containing some methylene groups between them. The high melting point of rutin was obtained by acids contained in a large double chain methylene group. The ability to dissolve rutin carboxylic acids with groups attached to amino acids is understandable. Rutin is weak acid due to the proton contribution from phenolic groups bound to the fragrant ring, to ChemAxon [93], the lowest pKa value of rutin is approximately 6.4. We would expect the presence of basic institutions in components of the solution combination will help direct the stimulation of heteromolecular contacts and enhance solubility. Of course, amino acids provide such basic sites. However, the acid components in NADES are also thought to contain amino groups, enhances the possible association with rutin. Also, the carboxylic acid is an important factor since then affects the breakdown of basic amino acid structures. It is, therefore, reasonable to expect that these two factors are important because of choosing the best NADES parts to resolve rutin. Unfortunately, for replacement carboxylic acids, there are inconsistent trends between the ability to break down carboxylic acid groups and the protonation potential of amino groups linked to a chain. This can be detected by examining the micro acidities of the targeted institutions. Except that it has nothing to do with it test data, estimated values may still be useful for the context above. For this purpose, ChemAxon properties [93] are used to calculate pKa values, and the detailed results are as follows collected in ESM. Finally, quality trends can be imported from this data. It is very clear that the extension of the aliphatic chain reduces dicarboxylic acid and that the addition of hydroxyl or amino groups increases the acidity of the ingredient. Besides, amino acids play a very important role because they are so important to increase the carboxylic acid content. Also, amino groups behave differently depending on their nature. These two results are collected but not required included. However, an interesting trend shows the influence of the formation of NADES on the solubility of Rutin can be added. Indeed, there is a connection between acid element carboxylic acid dependent on proline containing NADES and melting of rutin in that NADES. The corresponding structure of this merger, which means that the basic elements of a series of carboxylic acids, high solubility rutin. Therefore, any further testing should take into account the factors listed above, as the substances that promote rutin degradation are the higher acid content of the carboxylic acid component NADES and a large number of basic institutions. Also, the amino acid composition of NADES should contain compounds as basic as possible.

Hansen solubility parameters (HSP):

Proper selection of solvent is important for drug performance in the medical field. One of the predictive and selective methods of solvent is the use of Hansen solubility (HSP) parameters. The concept of melting parameter, δ, was introduced by Hildebrand and Scott, who suggested that parts with the same values may be obscure [23]. The melting point of an object is a square root of the energy of vaporization, ΔE, divided by its molar volume, V:

$$\delta_2 = EcOh/V$$

The expression “Like dissolves like” is the result of the fact that if it is very similar to the melting points of two objects, the height will be melted between them. Charles Hansen established that melting the partial parameter depends on three types of interaction: distribution potential, polar interaction, and hydrogen bond [24,35].

δt_2

II. CHARACTERIZATION

Fourier transform infrared spectroscopy (FT-IR)

The prepared DESDs were characterized using a DRS (Model: 8400-S-Shimadzu) FT-IR spectrometer with a 2 cm1 resolution and 45 scans in the range 4000–400 cm1 by employing a NaCl optical window at room temperature.29a

Kinematic viscosity (ᵛ)

The kinematic(ᵛ)viscosities of all four DESDs were prepared scanned using a well-designed Cannon Ubbelohde. The viscometer is vertical in the water bath (Model: 14 L-SS, Equiptron, India). A digital electronic stopwatch with a resolution of 0.01 s was used to

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measure the travel time (in seconds) of the sample. At least three measurements were made for each sample, and their standard value was taken into account kinematic viscosity calculation (ᵛ). The uncertainty in n and temperature was estimated to be 0.004 CST and 0.02 K, respectively.

Biocidal assay The Kirby Bauer method was employed to evaluate the antimicrobial performance i.e., the toxicity of the DESDs against the tested microorganisms.28

Cytotoxicity assays

The proliferation of HeLa cells was tested in the presence of the prepared DESDs according to a protocol reported in the literature.28,29

Genotoxicity

Test For the DNA fragmentation study, the HeLa cells were cultivated and incubated for 24 h (same procedure as in the cytotoxicity test). An□er seeding the cells, the culture plates were treated with the DESDs (at two different concentrations 50 mL and 200 mL). Fluorouracil and mitomycin C (100 mL) were used as positive controls. An□er extraction, 20 mL DNA from each sample along with ethidium bromide stain was loaded in a gel, and UV light was used to visualize the plate. DNA from the control and DESD-treated HeLa cells was assessed to understand whether solvents have any effect on the integrity of DNA. Here, the agarose gel electrophoresis □findings displayed a smear for the treated group.17

Drug solubility

The most popular shake-□ask method was employed for the drug solubility experiment. Here, 25 mg of LDC was solubilized in 1 mL of each DESD by stirring at room temperature and then, placed in a temperature-controlled water bath for 2 days to attain equilibrium. Later, the sample solutions were □altered (0.45 mm, Millipore, MA) before they attained the maximum solubility of LDC in DESDs. The clear solutions were then assayed using a double beam spectrophotometer (ModelShimadzu, Japan) to measure the absorbance spectra, which depict drug solubilization.30.

Computational study

The HOMO–LUMO frontier orbital compositions were obtained at the theoretical level using the semi-empirical method with the basis set 3-21 G via the open-source code: Gaussian 09W calculation window using the Gauss View 5.0.9 so□ware package.28a,29

Challenges and limitations of DES:

In previous sections, we briefly reviewed the use of DES remedies. However, the choice as liquid chemicals or pharmaceutical industry materials, DES they have to compete with current systems for the delivery of natural drugs and chemicals. Upcoming section, discussions will be conducted to investigate some of the key challenges and limitations standing in the way of DES drug applications.

a) Cost-

Without a doubt, the cost is a major factor to consider for commercial DES use. To our knowledge, the commercial potential of DESs has not been investigated yet. As the field maturity, studies need to be done in the technical and economic analysis of DES. For now, category, it seems that the cost of the original materials and the method of assembling are the largest providers in the form of DES commercial applications (Chen L et al. 2014). Many DES parts are expensive, some of which are often used in pharmaceutical programs as emitters. For example, choline chloride, a common component of DESs, is produced internally megaton scales at low cost (Jablonský et al. 2019). From a preparatory perspective, accepted manuscript DES has a simple and easy-to-measure production method. So, one person can think that maybe not all but at least some DES can be as expensive as the normal environment solutions (Cruz et al. 2017). Besides, if DES is considered part of the drug delivery system, the benefits of a prepared structure can exceed the highest cost.

b) Structure and classifications-

The structure determines the function. Although recently some studies have focused on it DES resolution frameworks are growing (Zahn 2017; McDonald et al. 2018) but the question of what is the liquid structure of DES currently remains largely unanswered. Shortage insufficient structural details and makes it difficult to establish a generally accepted one Definition and classification of DES. We need to know more about the structure of the liquid, powerful integration, and DES cell experience to establish structural and material relationships and logical design designed for DES.

c) High viscosity-

Generally, due to strong hydrogen networks, DES has 100-1000 times viscosities there are common water and liquid chemicals (Tang and Row 2013a). High viscosity is the limit a feature of DESs applications and can cause problems in drug performance such as handling, mixing, and filling. Therefore, techniques are needed to reduce viscosity to a suitable level. Among other things, the viscosity of DES can be affected by temperatures and the presence of a third like water. Increasing the temperature leads to a sharp decrease in viscosity. For example, the viscosity of choline chloride-urea (1: 2) was reduced from 1100 to 200 cP when the temperature was increased from 20 to 40 ° C (Abbott et al. 2003). Studies have shown that the addition of small amounts of water, up to 10%, in DES can significantly reduce their viscosity while maintaining their solvency capacity. For example, 10% water addition Choline chloride-urea (1: 2) DES lowers viscosity to 1/550 of its actual value (Guajardo et al. 2017).

d) Hygroscopicity-

Hygroscopicity is the tendency of an object to take water vapor from the surrounding air (Newman et al. 2008). In general, the water spell may increase, where there is a crystal an object is converted into a liquid

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because natural water can easily dissolve in an unclean liquid state (Balk et al.2015). Thanks to their large hydrogen-bonding networks as well hydrophilic environment, most DES are hygroscopic and the best moisture emissions from air reported some of them (Hammond et al. 2017). For example, choline chloride-urea (1: 2) can absorb about 4% of water after exposure to 24 h at a relative humidity of 64% and 20◦C (Zhao H et al. 2011). Other studies have shown that DES is derived from choline chloride and carboxylic acids absorb 10-20% water when stored for 30 days in contact with air (Florindo et al 2014). The presence of water can significantly affect the structure and physicochemical properties of DESs (Dai et al. 2015). The introduction of water can significantly reduce the viscosity of DES (Yadav and Pandey 2014). Polarity and DES 'ability to solve solutes are also affected properties (I Pandey no Pandey 2014). As mentioned earlier, the presence of water, or low prices, could cause significant changes in the solvency capacity of DESs. Moreover, it is predictable that the chemical stability of DES and the installed API will reduce DES pollution with water. For these reasons, it is important to check the hygroscopicity of DES and its water content should be carefully monitored and controlled.

III. CONCLUSIONS

Eutectic and DES combinations represent a competitive platform for this to improve the therapeutic action and delivery of APIs. They do not only show the high potency of other solvents of APIs but are also able to incorporate APIs into their design. Both of these approaches lead to reduced melting and availability, as well as drug stability. Moreover, it is amazing improved melting of various APIs and improved pharmacokinetics suggest the potential use of DES in many drug delivery systems as alternatives to common solvents and other enhancement methods. Even if other DES involving non-toxic substances are reported in the literature, be very careful a selection of DES items should be made. In general, in ILs, there is still a severe lack of knowledge in molecular-level processes that address the high solubilization power of DES. Therefore, serious efforts must be made to close this gap. Results in this field will allow for the correct format of DES for targeted applications, to avoid trial and error methods. In the same line, it has always been a challenge to predict which mixtures and what molar measurements will appear in the API-DES. An important collection of their solid-liquid phase drawings and associated data construction and buildings are still needed, especially to allow to easily distinguish DES from other eutectic compounds. Besides, there is a lack of knowledge about drug release, cytotoxicity, and API-DES medical action. Future progress should include detection of bioavailability, melting, skin penetration, and irritation tests, e.g., and testing of various permeation providers. Shortly, a different chemical compound will create expected DES, which led to unlimited options for make-up. The study of the novel will allow you to understand the role of API such as HBD or HBA in full DES functionality. In addition to the use of biopolymers to install APIDs for controlled delivery purposes, the opportunity to use the API-DES with the characters used stands out. However, more research is still needed it is necessary to make a complete understanding and interpretation of these drug delivery systems.

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DATA AVAILABILITY STATEMENT

All of the data supporting the findings of the presented study are available for corresponding author on request.

DECLARATIONS

Conflict of interest:

The authors declare that they have no conflict of interest.

Ethical approval:

The manuscript has not been published or submitted to another journal, nor is it under review.

Supplementary File

None.

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