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A brief review on eutectic mixture and its role in pharmaceutical field

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ABSTRACT



Eutectic mixture (EM) is as a mixture of more than one substance that does not interact individually to create a new entity but in a particular ratio that exhibits a lower range of melting point than it had in individual. EM should be formulated in such a way that it should have major advantages in pharmaceutical industries. EM can be a mixture of Active Pharmaceutical Ingredients (APIs), or different ratios of APIs and excipients, or various excipients. Deep eutectic solvents containing APIs (API-DES) considered as an innovative approach to form different APIs in the liquid state. This new approach of liquid form is versatile and plays an important role in drug delivery. The selection of ideal hydrogen bond-donor (HBD) and hydrogen bond-acceptor (HBA) is an essential parameter. Ionic liquids (IL), derivatives of deep eutectic solvents (DES) have got much attention since it can replace harmful organic solvent by their extraordinary properties. Therapeutic deep eutectic solvents (THEDESS) are considered to be an exceptional option in the advancement of biomedicine. This can be utilized for improvising drug solubility, bioavailability as well as drug permeation through the skin. Natural deep eutectic solvent (NADES) can be considered as an alternate option, replacing harsh solvents. It has special characteristics of better biodegradability and biocompatibility. These NADES mainly used to separate and purification of natural compounds. This review focuses on the eutectic mixture and its application in the area of drug delivery systems, and pharmaceutical and pharmacological fields.

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INTRODUCTION

The eutectic formation is defined as “an isothermal, reversible reaction between two (or more) solid phases during the heating of a system, as a result

of which a single liquid phase is produced” (Zhang *et al.*, 2012). The word ‘eutectic’ is taken from the Greek word called eutectos, which means low melting or easily fused. Eutectic mixture (EM) is defined as a mixture of more than one substance that does not interact individually to create a new entity but in a particular ratio that exhibits a lower range of melting point than it had in individual. Deep eutectic solvents derivatives (DESDs) and Deep eutectic solvents (DESS) have low toxicity characteristics. As well as it increases drug solubility, bioavailability and permeability. Thus, it plays a significant role in drug delivery (Mbous *et al.*, 2017). The new generation of (DESS) eutectic mixture currently gained attention as it is a less costly alternative to organic solvents and also overcomes the limitation of ionic liquids (ILs). The reason behind the less melting point of EM is delocalization of

charge from the bond between the halide anion and hydrogen bond donor (Mbous *et al.*, 2017). DES and ILs have important characteristics like very less vapor pressure, negligible volatility in room temperature and more thermal stability. Recently some anions and cations associated with ILs exhibited high toxicity and poor biodegradability which limits the use of ILs. (Abbott *et al.*, 2001). DESs are widely used in the field of purity extraction and separation. DESs have been used as an additive in the extraction and separation process of polysaccharide and other bioactive compounds from natural products. In other cases DESs have also been used to modify some materials like silica for improving the extraction and separation process. A therapeutic deep eutectic solvent (THDES) enhances transdermal drug delivery. Ibuprofen-based THEDESs are widely reported for the enhancement of drug penetration through the skin membrane. The use of terpenes mainly menthol is preferred as it is an effective permeation enhancer. To enhance the transdermal permeation of local anesthetic drugs like lidocaine and prilocaine EM of these drugs have been used widely. Trade name of these formulations termed as EMLAs (Stott *et al.*, 1998).

Ionic liquids (ILs)

ILs are fluid containing ions, and generally are in a liquid state at a temperature below 100 °C. Previously studies were performed to distinguish classical molten salts and ILs. Now ILs are considered as a solvent that consists only ions (Dai *et al.*, 2013). In recent days researchers modified the design of ILs by merging an organic cation like imidazolium-based cations with a wide range of anions like Cl, BF₄⁻, PF₆⁻, and NTf₂⁻, which turned into a novel class of solvents. Chloroaluminate based ionic liquids was developed initially. But it has limitations it will undergo rapid hydrolysis on moisture contact. This limitation was overcome by more stable metal halides like ZnCl₂ and formed ideal eutectic based ionic liquids. This generation of ILs forms bulky ions like chloroaluminate or chlorozincate which makes ILs liquid in less temperature also. (Smith *et al.*, 2014). The second generation of ionic liquids are made up of discrete ions, not like the first generations containing EM of complex ion. Use of more hydrophobic anions like trifluoromethanesulfonate, tris- (trifluoromethanesulphonyl)methide [(CF₃SO₂)C⁻] and bis- (trifluoromethanesulphonyl) imide [(CF₃SO₂)₂N⁻]. These have some advantages like broad electrochemical windows, allows. The ILs can be categorized into two groups which are as follows. One in which ILs are formed from EM of metal halides like AlCl₃ and some organic salts which are generally nitrogen-

based and contain halide anions. And another one which contains anions like PF₆ or bis- (trifluoromethanesulphonyl) imide (Beyersdorff *et al.*, 2008).

Deep Eutectic Solvent (DES)

Past few years, ILs has been in a limelight but because of its some limitations like poor biodegradability, biocompatibility, and sustainability, the “green” identity of ILs is in a questionable state. To overcome those limitations deep eutectic solvents (DESs), as an equivalent of ILs, have been introduced in the year 2003. DESs are in a liquid state at room temperature and have wide freezing point depression. So, DES is considered as an ideal potential substitute for common ILs. (Juneidi *et al.*, 2015). Deep eutectic solvents vary from Ionic liquids in two specific ways, i.e., the process of chemical their chemical formation and starting material sources. Complexation between a hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) or halide salt, because of these bonds a supramolecular structure has been shown by the deep eutectic (Mbous *et al.*, 2017).

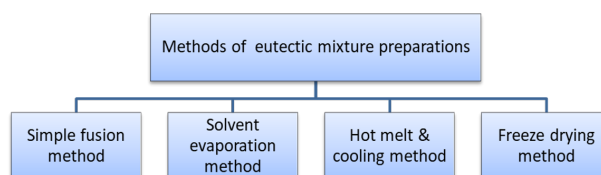


Figure 1: Common methods of preparation of eutectic mixture

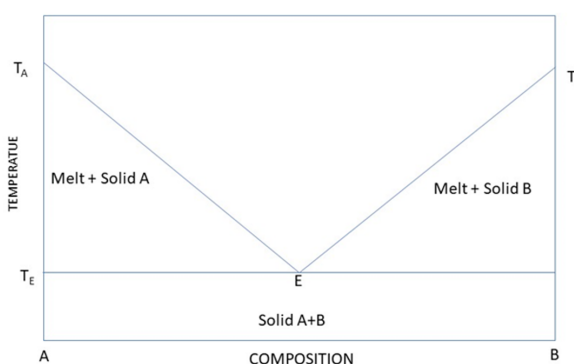


Figure 2: Binary phase diagram of Simple eutectic mixture

Types of DES (deep eutectic solvents)

In below the Table 1 categories of DES were discussed by a formula Cat+X-zY; in which Cat⁺ indicates the cations of various salts like phosphonium, sulfonium, ammonium X⁻ represents the halide anion of the salt, z be the number of molecules of

Table 1: Categories and general formula of DES

Category	General Formula	Term
I(choline based)	Cat+X-zMClx	M: Sn, Zn, Al, Fe,Al, In,Ga,
II(betaine based)	Cat+X-zMClx• yH2O	M: Co, Cr, Cu, Fe, Ni
III(quaternary ammonium based)	Cat+X-zRZ	Z: COOH,CONH2, OH
IV(metal salt based)	MClx + RZ = MClx-1 +• RZ + MClx+1	M: Al, Zn Z: OH, CONH2

Table 2: solubility study report of various drugs with different composition

S.no	DES derivatives	Drug	Solubility (mg/ml)
1	ChCl:glycolic acid	Itraconazole	6.70
2	ChCl:glycolic acid	Piroxicam	3.10
3	ChCl:glycolic acid	Lidocaine	295.40
4	ChCl:glycolic acid	Posaconazole	88.40
5	ChCl:maleic acid	Curcumin	0.0667
6	ChCl:maleic acid	Griseofulvin0.002	0.002
7	ChCl:maleic acid	Benzoic acid	18.0
8	ChCl:maleic acid	Itraconazole	1.20
9	ChCl:1,2-propanediol	naproxen	45.29
10	ChCl:1,2-propanediol	Acetaminophen	324.00
11	ChCl:1,2-propanediol	aspirin	202.00
12	ChCl:levulinic acid	Ketoprofen	329.10
13	Glucose:sucrose	Curumin	0.05211

acid. And Y indicates Lewis or Brønsted acid (Hou *et al.*, 2013). Choline chloride (ChCl) is broadly used for the development of DESs since it is biodegradable, cheap and non-toxic. This can form DESs very rapidly by combining with safe hydrogen bond donors like renewable polyols (such as carbohydrates, glycerol), urea, renewable carboxylic acid (such as citric acid, oxalic acid, amino acids, succinic acids). DESs can be made from both ionic and non-ionic species (Abbott *et al.*, 2004).

Natural deep eutectic solvents (NADES)

Various plant constituents have been recognized as functionally active and can be considered as a source. New green solvent made by green chemistry plays a key role in this field. However ILs and DESs capable enough to replace the harmful organic solvents and is used in numerous chemical process like synthesis and extraction of various compounds. In some recent studies, it has been found that abundant primary metabolites from plant sources change their state from solid to liquid on mixing in the appropriate ratio (Dai *et al.*, 2013). The idea of NADES has been proposed because of diversity in natural metabolites which can be used as a source and result in the formation of the nat-

ural eutectic mixture. The most important functional groups of NADES are hydroxyl groups, carboxylic acid groups and carbonyl groups. These groups inside the NADES matrix forms hydrogen bonding and adjust the physicochemical environment (Dai *et al.*, 2013). Phenolic acids, Chalcones, anthocyanins are the major natural product groups. Lactic acid, choline chloride, and 1, 2- propanediol are the most frequently used in NADES. These solvents are more viscous than organic solvents in suitable temperature (Duan *et al.*, 2016).

Therapeutic deep Eutectic solvent (THEDES)

Recently these EM solvents are formed as drug-based or API based DESs, which shows pharmacological effectiveness. THEDES has been defined as a mixture of dual components among one it should be an API. These components will be in a liquid state at room temperature at a particular molar composition. (Duarte *et al.*, 2017). THEDES development has gained interest from researches in current days because of their boosting characteristics like an increase in drug solubility and bioavailability as well as increases skin permeation in the transdermal drug delivery system. (Duarte *et al.*, 2017; Aroso *et al.*, 2016, 2015). Methods of preparation

of eutectic mixture was given in Figure 1 (Liu *et al.*, 2018) and the basic phase diagram was given in Figure 2 (Smith *et al.*, 2014).

T_A – Melting point temperature of solid A; T_B – Melting point temperature of solid B; T_E – eutectic melting point temperature

Application of eutectic system

For topical formulations DES has been broadly reported as the best alternative option for solubilization of APIs as well as poorly water-soluble drugs. Among all the studies ChCl-based mixtures have been found the most suitable ones to solubilize APIs. ChCl is preferred as it's a strong and safe HBA species with less cost. Solvents like glycolic acid and oxalic acid are not useful as solvent media since it creates patent problems in the execution of the mixtures for preparation of pharmaceutical formulations. (Pedro *et al.*, 2019). Among all the derivatives of ChCl some are well accepted as carriers for enhancement of drug permeation, solubility, and bioavailability. Some of these derivatives are ChCl:malonic acid (1:1), ChCl:urea (1:3), ChCl:glycolic (Morrison *et al.*, 2009). In the following Table 2 (Zainal-Abidin *et al.*, 2019) solubility of different DES, derivatives have discussed

In recent studies role of DES as a promising solvent has been reported which can improve the stability when used for solubilization of APIs as many solvents are not stable in many solutions specially in aqueous solutions. ChCl:1,2-propanediol has increased the solubility and stability in one hydrolysis study of aspirin in acetic acid and salicylic acid (Lu *et al.*, 2016). Few more study examples include few antibiotics such as imipenem and clavulanic acid uses betaine: urea mixture 7 folds and 2.5-fold, respectively which enhances the solubility and stability. Menthol and capric acid mixture increase the solubility of mometasone furoate and fluconazole and considered to be a productive mixture. Hydrogen bond has been formed between the drugs by menthol and capric acid. (Al-Akayleh *et al.*, 2019). THEDES system is the most simple and effective way to improve the bioavailability of APIs by altering the state from solid to liquid. (Duarte *et al.*, 2017).

Permeation Applications

The main barrier for transdermal drug delivery is the permeation through the skin. The long-term strategy to overcome this limitation is the use of penetration enhancers which will interact with skin constituents (Kasting *et al.*, 1987). Terpenes are considered as the best enhancer as it shows high percutaneous penetration as well as a reversible

effect on the lipids of stratum corneum and less irritation rate. Menthol and camphor are generally used terpenes as enhancer. Menthol is one of the most promising non-irritant and non-lethal transdermal enhancers as it increases the smoothness of the lipid bilayer. (Kang *et al.*, 2000). In some studies it has been shown the permeation of lidocaine has increased as menthol has suppressed the melting point range of lidocaine and formed a eutectic melt system (Akhter and Barry, 1985). Numerous studies reported that camphor and menthol can form eutectic fluids in a wide range of ratios which can enhance the permeation of topical formulations. In the literature the eutectic mixtures between ibuprofen and seven terpene permeation enhancers has been reported. Studies have been performed to see the impact of lowering the melting point on transdermal drug delivery (Gordon *et al.*, 1984).

Separation of natural compounds

Normally because of the ability of high dissolving power DES and ILs mainly used in purification and extraction of few compounds. The ILs have more extraction efficacy of natural products and the metabolites. ILs dissolves the biomass fully and facilitates the metabolites in the skin. This nature significantly increases the extraction yield and the extraction efficiency of a wide range of natural metabolites. ILs is appropriate solvents for natural products as it has high extraction efficiency on a broad spectrum of metabolites as well as the selection of certain compounds. They can dissolve the biomass and influence the release of metabolites inside the cell. (Bica *et al.*, 2011). These solvents have very little vapor pressure which helps in the direct distillation process and separations of volatile oils. DESs, are the novel eco-friendly solvent, widely used in chromatography for separations of compounds from nature as the source (Roehrer *et al.*, 1434).

Drug delivery Application

The formulations contain less melting point mixture along with permeation enhancer drug can easily disrupt the skin structure and improves the penetration of the drug through skin layers. Selection of right permeation enhancers along with drug synergize the enhancing property. A huge number of studies are going on to encourage the transport of drugs through skin barrier which was brought by EMLA[®]. Moreover dual capacity DES like API- DES containing enhancers focuses on topical and transdermal drug delivery (Pedro *et al.*, 2019). With this concept various marketed formulations have been prepared which for example a cream made up of a eutectic mixture of local anesthetics, containing

2.5% prilocaine and 2.5% lidocaine (Friedman *et al.*, 2001). Delivery of the drug glabridin by the transdermal way can be achieved by the nanoemulsion formulation containing EM of camphor and menthol. (Liu *et al.*, 2017). Numerous monoterpenes like menthol, cineole, menthone, pulegone, carvone and terpineol were involved in an ex vivo study on rodent skin to see their impact in permeation enhancement of zidovudine drug across the skin. Some studies were performed to see the activity of the system such as saturation solubility determination of the drug, partition coefficient determination between stratum corneum and vehicle. As well as the initiation energy required to diffuse through the skin in both the presence and absence of terpenes. Results showed was in this order cineole > menthol > menthonepulegonecarvone > terpineol > carvone > vehiclewater. EM of sulfathiazole and urea is directed by mouth. The blood level of sulfathiazole arrives at the greatest sooner and the measure of absorbed and excreted increases. There is little uncertainty that diversity must be attributed to the way that microcrystalline suspension of sulfathiazole is all the more effectively formed in the intestine and rate of solution increases after administration of eutectic structure. (Sekiguchi *et al.*, 1964). Menthol can create EM with cholesteryl oleate, ceramides and testosterone. The delivery of peptide and protein to the systemic circulation through the transdermal route is nearly impossible because of low permeability. The bioavailability of the protein like ovalbumin, bovine serum albumin and insulin can be done by deep eutectic solvent choline and geranate(CAGE). Few DES has pharmaceutical activities like antibacterial, anti-viral, and anti-cancer activities. Further examination and information are expected to come soon (Mbous *et al.*, 2017).

CONCLUSIONS

DES and EM are considered as the most efficient and competitive stage to enhance the therapeutic efficacy of drugs and helps in the delivery of various APIs. These can act as an ideal alternative to harsh solvents and it can also incorporate many APIs. These approaches will improve the stability, solubility and bioavailability of the drugs. The eutectic strategy has many beneficial applications in pharmaceutical fields, as it is potential enough to enhance drug dissolution profile as well as acts as a synthesis medium for drug carries in topical delivery and microemulsion. ILs have been developed to avoid the polymorphism of drugs by altering them to liquid form. DES does not need the reaction steps of synthesis which are needed by ILs. The limitation of this strategy is the mechanism of the drugs

incorporated in the eutectic system still not clearly explained. The eutectic point forms a new identity and the behaviors and physicochemical properties will differ from the original one. There is still less information available regarding comparative studies by avoiding any conflict of interest and uncertain results from various research groups. Though these hold a promising field in the pharmaceutical industry and commercialized novel APIs and can be served as an alternative solvent. But thorough studies are still required and the evaluation studies are still in demand.

Conflict of Interest

None.

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