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Review

Biobased natural deep eutectic system as versatile solvents: Structure, interaction and advanced applications

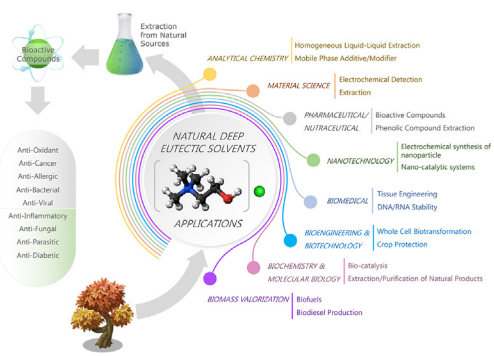
Zeba Usmani [a,b,1], Minaxi Sharma [c,1], Manikant Tripathi [d,1], Tiit Lukk [b], Yevgen Karpichev [b], Nicholas Gathergood [e], Brahma N. Singh [f], Vijay Kumar Thakur [g], Meisam Tabatabaei [h,i], Vijai K. Gupta [g,*]

[a] Department of Applied Biology, University of Science and Technology, Meghalaya 793101, India
[b] Department of Chemistry and Biotechnology, Tallinn University of Technology, 12618 Tallinn, Estonia
[c] Haute Ecole Provinciale de Hainaut-Condorcet, 7800 ATH, Belgium
[d] Biotechnology Program, Dr. Rammanohar Lohia Avadh University, Ayodhya, Uttar Pradesh 224001, India
[e] School of Chemistry, University of Lincoln, Joseph Banks Laboratories, Green Lane, Lincoln, Lincolnshire LN6 7DL, UK
[f] Herbal Nanobiotechnology Lab, Pharmacology Division, CSIR-National Botanical Research Institute, Lucknow-226001, Uttar Pradesh, India
[g] Biorefining and Advanced Materials Research Center, SRUC, Kings Buildings, West Mains Road, Edinburgh EH9 3JG, UK
[h] Higher Institution Centre of Excellence (HICoE), Institute of Tropical Aquaculture and Fisheries (AKUATROP), Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia
[i] Department of Biomaterials, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Chennai 600 077, India

HIGHLIGHTS

- The biobased natural deep eutectic system (NADES) is used as versatile solvents.
- NADES are mixtures of natural constituents, eco-friendly and highly biocompatible.
- They have key role in biological systems, usage in green & sustainable chemistry.
- Presented recent progress in sustainable chem-bio-pharma applications of NADES

GRAPHICAL ABSTRACT



Abbreviations: API, active pharmaceutical ingredient; AuNPs, gold nanoparticles; BGlc, betaine:glucose; BOD, biological oxygen demand; [BMIm][BF_4], 1-butyl-3-methylimidazolium tetrafluoroborate; CBT, Closed Bottle Test; CCO, channel catfish ovary cell lines; ChOX, choline chloride:oxalic acid; ChCl, choline chloride; ChSol, choline chloride:sorbitol; ChXylol, choline chloride:xylol; CLV, clavulanic acid; ChU, choline chloride:urea; COD, chemical oxygen demand; DDS, drug delivery systems; DES, deep eutectic solvents; DMSO, dimethyl sulfonate; EAC, N,N-diethyl ethanol ammonium chloride; EC_{50}, effective concentration of the drug which gives half maximal response; EG, ethylene glycol; EMLA, eutectic mixture of local anaesthetic; ER, endoplasmic reticulum; [$EtNH_3$][NO_3], ethyl ammonium nitrate salt; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; HEK-293, human embryonic kidney cell line; HeLa, Henrietta Lacks cell line; HOSEY, heteronuclear Overhauser spectroscopy; IL, ionic liquids; IMP, invalid metabolic panacea; MA, malic acid; aMMP-9, matrix metalloprotease-9; MCF-7, Michigan Cancer Foundation-7 cell line; MITI, Ministry of International Trade and Industry; MP, melting point; MWCNT, multi-walled carbon nanotubes; NADES, natural deep eutectic solvents; NMR, nuclear magnetic resonance spectroscopy; NOSEY, nuclear Overhauser effect spectroscopy; OECD, Organization of Economic Cooperation and Development; ORAC, oxygen radical absorbance capacity; REACH, registration, evaluation, authorization and restriction of chemicals; SWCNT, single-walled carbon nanotubes; $scCO_2$, supercritical carbon dioxide; TEM, Transmission electron microscopy; THEDES, therapeutic deep eutectic solvents; ThOD, theoretical oxygen demand; U, urea; WHO, World Health Organization.

* Corresponding author.
E-mail addresses: vijai.gupta@sruc.ac.uk vijaifzd@gmail.com (V.K. Gupta).

[1] Equal contribution.

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A R T I C L E I N F O

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A B S T R A C T

The increasing emphasis on the development of green replacements to traditional organic solvents and ionic liquids (ILs) can be attributed to the rising concerns over human health and detrimental impacts of conventional solvents towards the environment. A new generation of solvents inspired by nature and extracted from plant bioresources has evolved over the last few years, and are referred to as natural deep eutectic solvents (NADES). NADES are mixtures of natural constituents like sugars, polyalcohols, sugar-based alcohols, amino acids and organic acids. Interest in NADES has exponentially grown over the last eight years, which is evident from an upsurge in the number of research projects undertaken. NADES are highly biocompatible as they can be biosynthesized and metabolized by nearly all living organisms. These solvents pose several noteworthy advantages, such as easy synthesis, tuneable physico-chemical properties, low toxicity, high biodegradability, solute sustainability and stabilization and low melting point. Research on the applicability of NADES in diverse areas is gaining momentum, which includes as - media for chemical and enzymatic reactions; extraction media for essential oils; anti-inflammatory and antimicrobial agent; extraction of bioactive composites; as chromatographic media; preservatives for labile compounds and in drug synthesis. This review gives a complete overview of the properties, biodegradability and toxicity of NADES which we propose can assist in further knowledge generation on their significance in biological systems and usage in green and sustainable chemistry. Information on applications of NADES in biomedical, therapeutic and pharma-biotechnology fields is also highlighted in the current article along with the recent progress and future perspectives in novel applications of NADES.

Contents

1. Introduction

The growing awareness towards environmental impacts has impelled research and development on 'green extraction' as an alternate and preferable process (Radosevic et al., 2016). Innovation and blueprint of extraction processes, which propounds on ideal utilization of solvents, energy and resources form the basis of green extraction. Thus, a substantial amount of research is being focused towards designing novel, environmentally-friendly, naturally derived and tunable solvents which serve several biosustainable purposes (Bubalo et al., 2015). Developing environmentally sustainable industrial chemicals requires the nexus of green chemistry and ecotoxicology, and represents a momentous synergistic challenge. Comprehension of this challenge is possible by expanding the standard descriptive knowledge of the behaviour of these chemicals in the environment.

Natural deep eutectic solvents (NADES) are derived from bio-based sources, a subset of deep eutectic solvents (DES) which are synthesized from chemicals independent of their feedstock source. These NADES liquid supermolecules are combinations of economically viable and readily available constituents: innocuous quaternary salts of ammonium salts (viz. choline chloride (ChCl) or betaine), hydrogen bond acceptors (HBA) and naturally derived uncharged hydrogen bond donors (HBD) (i.e. amines, sugars, acids and alcohols) (Halder et al., 2019). Characterization of

NADES using nuclear magnetic resonance (NMR) spectroscopy revealed that water plays a major role in their formation (Dai et al., 2015). Naturally derived NADES and bio-based ILs owing to their chemical diversity, biodegradability and toxicity profile, are suitable for pharmacology applications. As the ingredients of NADES are abundantly present, they play a central physiological role as a third category of polar liquid medium in the living cells (Dai et al., 2013a; Choi et al., 2011).

NADES can be regarded as 'designer solvents' owing to several configurational possibilities for tailoring their physical and chemical attributes to adapt to diverse applications (Graphical abstract) (Paiva et al., 2014; Dannie van Osch et al., 2019). These promising sustainable media exhibit a broad range of polarity, very low volatility, sub-0 °C liquid state, high solubilization strength for an extensive array of compounds, high stabilization activity for natural products and excellent extraction property (Dai et al., 2014). High biodegradability, low toxicity, sustainability, low cost and easy synthesis are other major advantages of NADES (Dannie van Osch et al., 2019). The discovery of these low-toxic solvent alternatives to water has far-reaching consequences for the currently held views on plant physiology and biochemistry. NADES are safe solvents which exhibit great opportunities in the area of cosmetics, food technology, drug-delivery techniques, pharmacological industries and bone-therapy scaffolds (Bubalo et al., 2015; Dai et al., 2013a; Paiva et al., 2014). NADES properties have also drawn attention from the research community in substituting ILs with NADES as the solvents for extraction (Craveiro et al., 2016), as biocatalysts (Carriazo et al., 2012), as active pharmaceutical ingredients (APIs) (Craveiro et al., 2016) and in several other chemical conversions.

The cytotoxicity of a wide variety of NADES was found to be low when compared against imidazolium ILs (Paiva et al., 2014). Ahmadi et al. (2018) assessed the cytotoxicity of choline-chloride (ChCl) on human HEK-293 cells. The stabilizing activity of NADES in the extraction of phenolic composites indicates its usability in the production of plant extracts for human usage (Paiva et al., 2014; Dai et al., 2013b). NADES can also assist in the purification of fuels, isolation and recovery of target compounds, and development of the selective analytical methodology for pre-treatment of samples (Pena-Pereira and Namiesnik, 2014). Radosevic et al. (2016) studied phenolic compounds from grape skin extracts using NADES for biomass valorization. NADES have played unique roles as anhydrous media for DNA processing (Zhao and Qu, 2013). These guanine-enriched nucleic acids make four-stranded structures of G-quadruplex. They have attracted tremendous interest in various fields like supramolecular chemistry, medicinal chemistry and nanoscience.

NADES are used extensively as enzymatic reactions media (Durand et al., 2013), in biological transformations (Gutierrez et al., 2010), biomass valorization (Xia et al., 2014) and biological pigment stabilization (Dai et al., 2014). NADES can assist in the transportation of poorly soluble compounds, storage and biosynthesis (Dai et al., 2013b; Vanda et al., 2018). Lores et al. (2017) reported that the combination of NADES along with ultrasonic energy led to the development of a green method for protein solubilization. Mouden et al. (2017) kickstarted the utilization of NADES in the field of eco-friendly crop protection. Dai et al. (2015) explored NADES-water mixture to understand the physico-chemical characteristics and solubilizing potential of two sparsely soluble complexes in water to ascertain the function of water and to assist in designing NADES for specific applications. However, NADES possess some drawbacks due to their high viscosity, e.g. (200–500 mm^2 s^1 at 40 °C), which is a significant issue leading to some practical difficulties like mass transfer hindrance during extractions and inefficient solvent transfer processes (Dai et al., 2013a).

This review is a comprehensive article focusing on the analysis of recently available relevant information on plant-derived NADES and their chemical structures, physical properties and sustainable applications across diverse fields. The article also highlights the limitations in the application of NADES in certain fields and possible ways to overcome these roadblocks. Extensive case studies related to biodegradation and toxicity of NADES are also a highpoint of this review. An in-depth interpretation of structures and physico-chemical characteristics of NADES may help in identifying convenient methods to modify NADES for health-associated usages, in the life-sciences arena, biomedicinal usages and pharmaceutical industries. The review brings forward the future perspectives of NADES in order to discover their novel applications to subsequently replace ILs and other conventional organic solvents.

1.1. Origin and evolution of NADES

The incessant search for sustainable, cost-effective and environmentally safe solvents that could be used in several biochemical and chemical processes has been a major initiative. ILs were considered as greener substitutes to traditional organic solvents owing to their outstanding thermal and chemical stabilities (or inertness), low melting point (MP) and very low vapor pressures (Natalia et al., 2020). ILs achieved high visibility owing to their tailored polarity and selectivity for various applications like enzymatic or chemical reactions. However, their biodegradability and biological toxicity were often questioned by researchers (Natalia et al., 2020). DES are a different kind of solvents having phase behaviour and physical properties similar to ILs (Halder et al., 2019). They are the combinations of eutectic mixtures with a MP much lower when compared to its specific components, often attributed to the formation of intermolecular hydrogen bonds. Several attempts were made to synthesize ILs and DES using quaternary ammonium salt mixtures (Abbott et al., 2003) through a variety of carboxylic acids and amides (Abbott et al., 2004). This was further expanded to ChCl with alcohols (Gorke et al., 2008), and urea with organic acids and amides (Gore et al., 2011). DES however, had the edge over ILs due to their easy synthesis and frequently at a much lower cost. However, higher MP of several DES proved to be a hindrance to their utility as green solvents especially around room temperatures. This resulted in limiting the application of DES to electrical chemistry (Jhong et al., 2009), organic reactions (Gore et al., 2011), organic extractions (Abbott et al., 2009) and enzymatic reactions (Gorke et al., 2008). However, in the case of biodegradability and toxicity studies, comparatively many ILs suffer from higher toxicity which limited the scope of their applications in pharmaceutical and food industries (Zhao et al., 2007).

The concept of NADES came into existence as a result of the occurrence of a few natural eutectic mixtures and miscellany of redundant metabolites in the natural resources (Choi et al., 2011). A timeline showing the evolution of NADES and their growing application over the years is presented in Fig. 1 highlighting landmark events in the realm of green chemistry. Plant constituents in NADES, for instance, have been referred to as 'biosynthetically primordial metabolites' and are produced naturally in the living organisms. These metabolites are hypothesized to play an important function in the plant physiological systems. Quercetin is a perfect example of NADES that is produced in large quantities in various plant species and is documented as an invalid metabolic panacea (IMP) present in the form of glycosides (Bisson et al., 2016). Certain natural products, referred to as lipophilic metabolites, can also be produced in substantial quantities naturally.

NADES can attain a broad set of polarities ranging from hydrophilic to lipophilic metabolites (Liu et al., 2018). NADES can be derived from natural metabolites like sugars, amino acids and choline that act as primary components (Choi et al., 2011). Even from an early phase of their discovery, NADES have exhibited various applications due to their sustainability, non-toxicity and ecologically friendly compared to DES and ILs (Paiva et al., 2014; Yang, 2018). Still, the demarcation between the DES and NADES is quite blur. Few eutectic combinations synthesized from naturally derived compounds, like ChCl or glucose, can be considered both as the NADES and DES. The abundantly available natural metabolites are an ideal resource of NADES and DES because of their chemistry, biological degradability, and pharmaceutically tolerable toxicity profiles.

1.2. NADES - missing link between cellular metabolism and plant physiology

There was a worldwide notion that all enzyme-mediated reactions and biosynthesis processes occurring in the living organisms are generally composed of water and lipids. The question which comes to mind: Is it possible to control biosynthetic processing and transportation in a lipid or an all

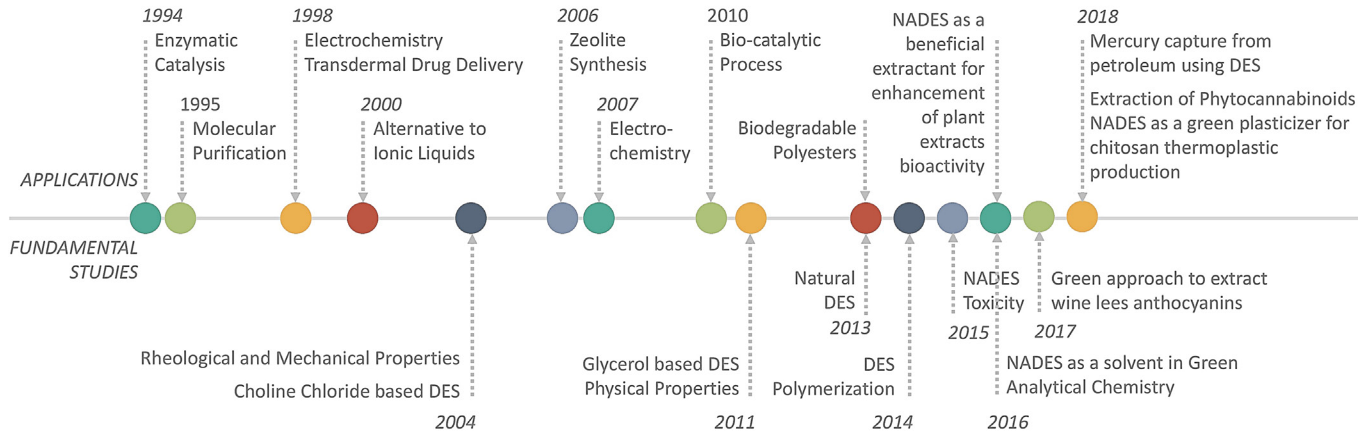

Fig. 1. Timeline depicting the evolution of deep eutectic solvents, natural deep eutectic solvents and their applications; DES: deep eutectic solvents; NADES: natural deep eutectic solvents.

aqueous media in plants that can control a broad range of primary and secondary metabolites? Cells, in general, are composed of lipid membranes and water as two immiscible liquid phases. Cells constitute several complexes of midway polarity having elevated concentrations which do not get dissolved in the water or lipid phase. Thus, a question about the biosynthesis and storage of these compounds must be considered. It was a general assumption that enzyme-mediated biosynthesis reactions take place in water. This again raises the question of why the substrates and respective products are weakly soluble in water?

It was hypothesized that living organisms possess an alternative media of water and the lipids but in case if solely these two media exists, several biological processes occurring in all living organisms (for instance survival during drought stresses and cold circumstances) would be very difficult to explain (Abbott et al., 2009). The hypothesis came into light because several potential ingredients of DES were observed in identical quantities in NMR-dependent metabolomics (of several types of organisms and cells) (Dai et al., 2013a). NMR spectrum of nectar further revealed that the composition of this secretion is closely analogous to a NADES composition. Honey also shows similarity in configuration to NADES (Dai et al., 2013a). The components of NADES were found in microorganisms, lichen and *Selaginella* species such as Mexican moss. Similar components were also reported in the seeds of barley during the periods of dormancy. In fact, several studies have revealed an increase in primary metabolites in plants like *Arabidopsis* due to the shortage of water. Dai et al., 2013a reported that NADES in nature can behave as an alternate liquid phase for water to aid biological synthesis, storing of less water-soluble particles and protecting living organisms from cold (i.e. cryoprotectants in plants) and drought stresses. Analogous to synthesized IL applications, life forms also utilize a third liquid media as a substitute to lipids and water. This idea was further strengthened from the fact that several primary plant metabolites turn into liquid on mixing in a particular ratio, proving the fact that NADES were indeed derived from nature. To confirm the theory of NADES to be the third liquid state in the living organisms, solubilization levels of few natural substances were measured (Choi et al., 2011). The experiment, however, showed that solubilization of flavonoid rutin in several NADES was about 50 to 100 folds greater compared to water. Also, ginkgolide B and paclitaxel, which are entirely insoluble in water exhibited greater solubilities of 0.81 mg/mL and 5.85 mg/mL correspondingly, in glucose-ChCl. Albumin, lignin and cellulose macromolecules, amylase and DNA (obtained from male salmon) also showed higher solubility in the NADES. Intracellular presence of NADES elucidates the biochemical processes, like storage and transport of compounds (especially one which are often tough to solubilize), storage and biological synthesis (Choi et al., 2011). Nearly 100 stable NADES configurations were synthesized by mixing two or more compounds like organic acids, sugars, derivatives of choline and amino acids in a variety of ratios (Dai et al., 2013a). Liu et al. (2018) found that several combinations of solid compounds abundantly present in plants viz., organic acids, amino acids and sugars (Wen et al., 2015; Radosevic et al., 2018) (Fig. 1S, Supplementary file) becomes liquid under particular conditions. They verified >60 mixtures of solids screened can form liquids. The presence of hydrogen bonds intramolecularly in NADES resulted in the significant decrease of MP causing liquefaction of solids. The melting point temperature of eutectic mixes is much below its individual constituents and exists as fluid at room temperature (Mouden et al., 2017). Several metabolites could be 10–100 times more dissolved in the recently revealed liquids compared to water (Liu et al., 2018).

NADES are considered as a replacement medium for water in plants and other organisms as depicted in Fig. 2S (Supplementary file). This has given answers to several biological questions regarding how does organism interact with hydrophobic or lipophilic metabolites? How can seeds survive germination and drought conditions? And how plants overcome cold and dry conditions? NADES play an important function during the survival of living organisms like cactus, lichen, plants, prokaryotes in extreme cold or drought conditions. During drought condition, NADES in plants strongly retains water. Thus, plants synthesize NADES for protection and storage of bioactive compounds. It was also observed that laccase could entirely dissolve in NADES. However, it was inactive, but on the addition of water, the enzyme showed activity. Thus, due to this NADES can act as cryoprotectants, aid in germination and drought resistance (Choi et al., 2011). Most of the cryoprotectants constitute various forms of NADES (Mustafa et al., 2011). Kovacs et al. (2011) stated that tolerance towards freezing in *Triticum aestivum* was dependent on the proline content. NADES have further exhibited the role of stabilization of phenolic compounds in safflower (Dai et al., 2014).

Another phenomenon of 'glass formation' in plants can be the result of NADES formation constituting choline, proline, organic acids and sugars, and can be seen in the metabolome through NMR. There may be a variety of NADES in each cellular component adjusted to the sort of proteins and compounds which needs to be preserved by being dissolved in NADES (Choi et al., 2011). When the tissue metabolome of barley seeds (*Hordeum vulgare*) was analysed, major constituents like choline and sucrose formed NADES admixed in the ratio of 1:1 (Choi et al., 2011). During stress situations of extremely high or low temperature, cells of the living organisms may subsist by NADES formation during which the metabolites, enzymes and membranes persist as stable. While water is greatly retained, freezing is prevented due to low MP of DES. Maple syrup of *Acer* spp. majorly comprises of sucrose along with some quantities of sugars constituting malic acid and glycerol (Fig. 3S, Supplementary file). All mixtures of these components exist as liquid despite evaporation of all the residual water. Most stable composition of glycerol and malic acid was at a mixing ratio of 1:1. Metabolites of *Cleome hasselorna* nectar exist as a liquid despite freeze-drying which depicted that it generally constitutes sugars (Choi et al., 2011). Pandey et al. (2010) found an increase in proline content of *Selaginella bryopteris* plant due to a decrease in the level of sucrose concentration.

The stabilization of enzymes can be attributed to the hydrogen bond formation with surface residues. Several enzymes such as esterases (Gorke et al., 2008), epoxide hydrolases (Lindberg et al., 2010), α-chymotrypsin (Maugeri et al., 2013), and lipases (Durand et al., 2013; Zhao et al., 2013) were known to exhibit high activity and stability. Although the role of NADES in their biosynthetic pathway still needs to be explored. It is also believed that constituents forming eutectic mixtures show a considerable decline in the thermodynamic activity so the molecules resulting in the formation of this liquid phase gets interconnected through a tri-dimensional system. These interactions occur through intra- and inter-molecular hydrogen bonding which maintain open regions for the solubilization of the solutes. Therefore, proteins, macromolecules or the metals which get associated with these molecules get highly solubilized. It is thus hypothesized that NADES formation occurs not only in different organelles but can also be attached to cellular membranes or aggregates of proteins thus acting as storage media for proteins (Fig. 4S, Supplementary file) (Lores et al., 2017). These hypotheses still need to be proved for a better understanding of biological sciences.

1.3. Advantages of NADES over ILs and organic solvents

ILs are basically salts that exist as fluids at room temperature and are formed through ionic bonds, while DES are combinations of solid constituents which transition to liquid state due to huge depression in the MP and charge delocalization caused by hydrogen bonding. The positive and negatively charged ions in many of the ILs studied remain separated in order to decrease the interactive forces amongst them and delay crystallization, dropping the MP and resulting in the liquid state at room temperature (Abbott et al., 2004). NADES, however are mixtures of natural constituents which interact through hydrogen bonding. However, for solvents to hold a place in the discipline of green chemistry they must fulfil essential conditions of biodegradability, low toxicity, reusability, sustainability, availability and economic viability. A solvent passing such assessment satisfactorily is generally regarded as 'green' medium.

First samples of DES were synthesized by mixing of quaternary ammonium salts as the HBA with HBD, like alcohols, organic acids or urea. These components formed complexes through halide anion of quaternary salts of ammonium. The physical characteristics of DES and ILs are similar, but DES are superior in some aspects as they are often more economical, lower toxicity, sustainable, and easily synthesized (Jhong et al., 2009). Still, the safety of these compounds needs additional investigation as some DES have been observed to be harmful to the living organisms (Wen et al., 2015; Hayyan et al., 2013a). DES showed many improvements over the negative aspects of ILs, though apprehensions related to its safety existed which resulted in a shift towards the natural sources in the quest for alternative constituents. Novel ILs were prepared using natural components like choline along with the organic acids (Fukaya et al., 2007). Room temperature ILs constituting amino acids like histidine, threonine, glycine, alanine and phenylalanine and choline from the feedstocks have also been synthesized (Moriel et al., 2010). The chemical reaction involved Knoevenagel condensation of benzaldehyde with the active methylene compounds which were observed to - proceed well at room temperatures (Moriel et al., 2010).

NADES differ from DES, in their synthesis and constituents, in terms of low transition temperature complexes. The water level in NADES hugely influences the physico-chemical characteristics of NADES (Vanda et al., 2018). NADES exhibits insignificant toxicity level but should be tested before its application in nutraceuticals and pharmaceuticals. Phytotoxicity tests performed on NADES have shown their non-toxic nature towards seed germination (Radosevic et al., 2015). Some tailor-made NADES were tested for toxicity towards the human cell lines (MCF-7 and HeLa) and were observed to have low cytotoxicity, thus acting as beneficial candidates in pharmaceutical industries (Radosevic et al., 2016). The application of NADES has evolved from being initially used as extraction media for secondary metabolites from plants in pharma and food-based enterprises. Dai et al. (2014) used NADES for safflower extraction and observed much higher yield compared to ethanol and water.

NADES possess an exceptional potential for substituting the conventional organic solvents which exhibit high volatility and toxicity by the release of volatile organic compounds in the environment (Dai et al., 2013a). Ability of NADES to extract bioactive natural compounds is associated with polarity, viscosity, pH and H-bonding. NADES enhances the extractability of phenolic acids by hydrogen bonding interactions with each other. NADES hold a significant function in case of nutraceuticals and functional food products, as they can deliver multiple possibilities of combining molecules resulting in tailor-designed solvents for the extraction of solutes having diverse properties (Sut et al., 2016; Bakirtzi et al., 2016). As NADES are derivatives of natural resources and possess food-grade property, the extracts attained from NADES can directly be utilized for human consumption, eliminating the need for costly purification downstream steps (Paiva et al., 2014).

Thus, NADES during their evolution from the ILs and DES acquired all the useful properties and diverse applications along with fulfilling the guidelines of green chemistry.

1.4. Classification of plant-based NADES

NADES are derived from the metabolites, which can naturally exist in all kinds of organisms and cells (Dai et al., 2013a). The common NADES constituents include organic acids (viz. lactic acid, citric acid, malic acid), sugars (fructose, glucose, galactose, maltose, saccharose), ChCl and urea. Various mixtures of NADES are observed to be stable liquids. NADES, in general, are classified into different groups: (a) Derivatives from ChCl, (b) derivatives from organic acids (c) sugar mixtures and (d) other combination. Major combinations constitute ChCl with different metabolites amongst which lactic acid has received maximum attention of researchers being admixed in several ratios (1:1, 1:2, 1:3, 1:4, 1:5, 1:9, 2:1 and 3:1). Choline chloride (ChCl) is a vital nutrient which is biodegradable, non-toxic and often referred to as vitamin B4 (Espino et al., 2016).

NADES are divided into 5 major classes depending upon their constituents: (i) ionic, synthesized by an acid and a base; (ii) neutral along with the acids, consisting of sugars or polyalcohols and organic acid; (iii) neutral along with the bases, comprising sugars, polyalcohols and organic bases; (iv) amino acids, comprising NADES synthesized of amino acids along with sugars or organic acids; and (v) neutral, consisting of only sugars or sugars and other polyalcohols. NADES can generate a network of complexes by widespread hydrogen bonding as observed through NMR studies. The classification of NADES/DES based on intermolecular interactions and the major constituents in it (ionic bonds, hydrogen bonds, polar interactions) are presented in Table 1.

2. Structure and biosynthesis of NADES

Various NMR spectroscopy studies on NADES lead to identifying intermolecular interactions associated with the presence of hydrogen bonds in NADES. Abbott et al. (2004) used heteronuclear Overhauser spectroscopy (HOSEY) to report about cross association amongst choline fluoride, fluoride ion and protons from urea. In another study, Mele et al. (2003) disclosed the intra- and inter-molecular interactions amongst 1-*N*-butyl-3-methylimidazolium tetrafluoroborate molecules observed using nuclear Overhauser proton-proton spectroscopy (NOESY). The spectra obtained from HOSEY of 1,2-propanediol-ChCl-H_2O (PCH) indicated a signal confirming the proton presence over the methyl group of 1,2-propanediol showing interaction through methylene and methyl carbon of ChCl (Fig. 2). The NOSEY spectrum of PCH showed a strong interaction between the protons present on the hydroxyl group from 1,2-propanediol, ChCl and H_2O, suggesting the presence of hydrogen bonds between the hydroxyl groups (Fig. 2). Interactions like these were found in malic acid, proline and water. NMR studies have also suggested that water plays a significant role in defining the NADES structure.

Table 1
Categorization of natural deep eutectic solvents (NADES) and deep eutectic solvents (DES) on the basis of chemical interactions.

Intermolecular forces between the compounds	Hydrogen bond interactions	Ionic interactions	Polar interactions	References
NADES classes	Sugar:sugar	Amino acid:carboxylic acid	Amino acid:sugars	(Radosevic et al., 2016; Dai et al., 2013a; Choi et al., 2011;
	Urea:sugar	Organic cation:carboxylic acid	Organic cation:sugar	Paiva et al., 2014; Craveiro et al., 2016; Lores et al., 2017;
	Carboxylic acid:sugar	Metal carboxylate salt:carboxylic acid	Metal carboxylate salt:sugar	Abbott et al., 2004; Espino et al., 2016; Wei et al., 2015a;
	Carboxylic acid:carboxylic acid		Organic cation:urea	Wei et al., 2015b; Dai et al., 2016; Mbous et al., 2017;
DES classes	Urea:hydroxy cpd	Organic cation:inorganic metal salt	Inorganic metal salt:sugar	Wikene et al., 2017)
	Carboxylic acid:hydroxy cpd		Organic cation:amide	
	Polyol:hydroxy cpd		Organic cation:hydroxy cpd	

The stability of NADES is significantly impacted by the ratio of its constituents, thus determining its longevity in the liquid phase. For instance, in case of mixtures of sugars-ChCl, glucose:ChCl (2:5) is stable while, in ratios of 1:1, 1:4, 2:1, although a pure liquid may be synthesized by intermixing there will be a steady formation of crystals. A single chloride ion can make two hydrogen bonds along with the two hydroxyl groups of sugars, which can be seen in the combination of carboxylic acid and chlorine chloride (Abbott et al., 2004). The ratio of 1:1 is the most suitable combination. Most of the constituents such as amino acid-organic acid, alcohol-organic acid, sugar/sugar were considered to be the root of complex formation of solids resulting in liquids, comprising a supramolecular structure.

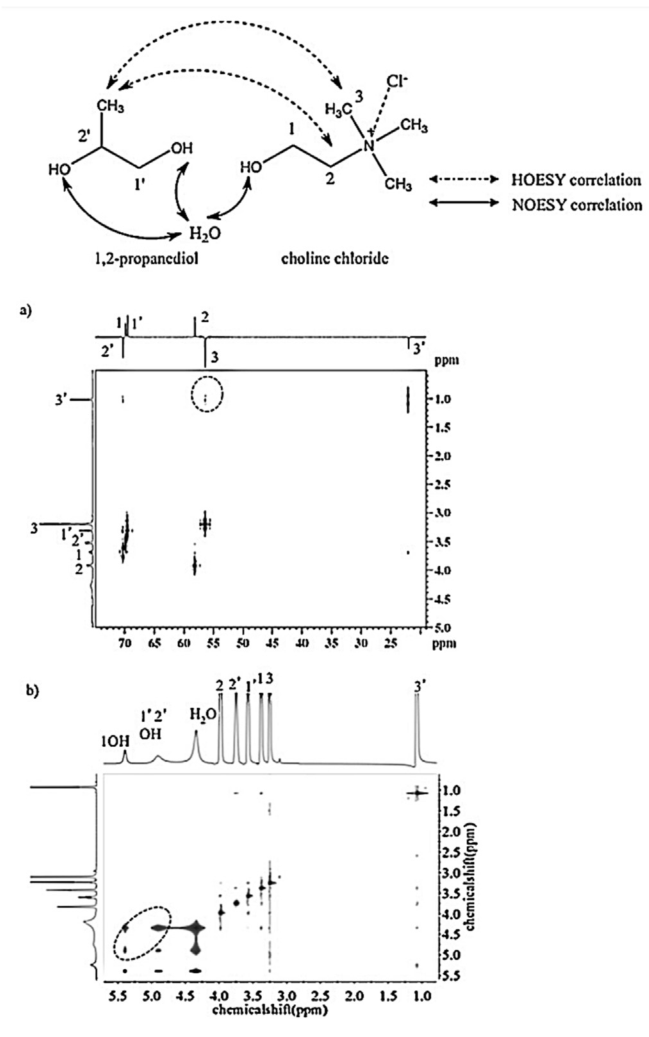

Fig. 2. Two-dimensional spectrum of 1, 2-propanediol:choline chloride:water (mixing ratio 1:1:1) (a) heteronuclear Overhauser spectroscopy (HOSEY) (b) proton-proton nuclear Overhauser enhancement spectroscopy (NOSEY).
(Reprinted with permission of Analytica Chimica Acta, Elsevier Publication; Dai et al., 2013a).

The number of HBD or HBA, spatial assembly of related groups and positioning of bonds holds a significant role in the synthesis and stability of NADES. Depending upon liquids structure, the occurrence of an extra carboxyl group may result in the development of several hydrogen bonds, hence enhancing the liquids' stability. Organic acids and the sugars combinations comprise of one carboxylic group, e.g. acetic acid or several carboxylic groups, e.g., citric acid, which acts as stable liquids on combining with different types of sugars (Durand et al., 2016). Hydroxyl groups and their three-dimensional structure have a pronounced impact on synthesis and stabilization of the hydrogen bonds. The liquid obtained with glucose, ChCl and water in the molar combinations of 2:5:5 forms a liquid phase at ambient temperature and maintains its form even below room temperatures (Durand et al., 2016). These examples are in agreement with the theory of the importance of the NADES in nature with respect to the dehydration of several living organisms forming NADES after the evaporation of water.

The addition of water to the NADES brings in additional impacts, such as reduction of temperature and synthesis time and further decreasing the viscosity. The ratio in which to admix water with NADES varies a lot in order to obtain liquid stabilization at the room temperature (Dai et al., 2015). Several NADES have water present at levels around 0.2, which is quite less compared to the molar percentage of the water in individual NADES, signifying the difficulty of water to evaporate from NADES. Thus, for instance, solubilization capacity of NADES could be designed by changing the water level resulting in greater solubilization of secondary compounds like carthamin, rutin and cinnamic acid (Dai et al., 2013c).

2.1. Synthesis of NADES

NADES are synthesized in the laboratory by three methods (Espino et al., 2016) (i) constituents of NADES are mixed in the bottle using a stirrer, covered with the cap and heated in a water bath at 50–90 °C. The mixture is agitated until a clear solution appears (30–90 min) (Dai et al., 2015; Bosiljkova et al., 2017) or, by the conditions followed by Abbott et al. (2003), heating and stirring at a temperature of 80 °C (Dai et al., 2013a; Wei et al., 2015a; Wei et al., 2015b), (ii) evaporation method: constituents are solubilized in water and are evaporated using a rotary evaporator (Dai et al., 2013a; Espino et al., 2016), liquid attained was placed in a desiccator comprising silica gel till a persistent weight is attained, and (iii) freeze-drying method: it is dependent on desiccating of aqueous solutions of particular constituents (2–24 h) in a freezer (Gutierrez et al., 2010). These procedures have been successfully used in the synthesis of NADES and various chemical usages were projected. The amount of work and time demanded by these synthesis procedures vary widely with respect to the green characteristics of these solvents. Thus, the advancement of new techniques for the synthesis of NADES is essential.

In order to align with the principles of green chemistry, there should be a consistent assessment of the optimization of energy consumption in the chemical process. The scientific community is taking note of a few non-traditional methods for the synthesis of NADES. Wei et al., 2015b described the microwave irradiation method to be an effective means for the development of a green and environmentally safe process. Microwave radiation is a highly important method because of several advantages like short reaction times, milder reaction conditions and high yields (Wei et al., 2015b). These techniques are also easy, cheap, green and traditional method. However, very few articles related to the use of the microwave for NADES preparation are reported.

Paiva et al. (2014), evaluated the green chemistry metrics of NADES and emphasized on the simple synthesis process of NADES involving HBD and HBA (Fig. 5S, Supplementary file). Their synthesis of NADES is a green process because even the water used in the preparation can be recovered through evaporation and condensation. Neither it leads to the generation of waste, nor does it produce harmful by-products. Sustainability of NADES in the environment can further be assessed by evaluation of an E-factor that is described as the ratio of total waste generated by the total product quantity. For NADES, the factor of 0 is theoretically achievable. In addition, the atom economy is 100 %. A 100 % value of carbon efficiency is also assumed for the process. Different mixtures of NADES derived from natural products prepared by vacuum evaporation, freeze-drying and heating and stirring method have been described in Table 1S (Supplementary file).

Choi et al. (2011) discovered that several prime metabolites in solid-state can become liquid on being mixed under particular conditions. They verified this with various mixtures of cellular constituents like alcohols, sugars, choline derivatives, amino acids and organic acids. Thus, different mixtures of these constituents were observed to form liquids. About 100 combinations of NADES were developed constituting metabolites present in all types of organisms and cells (for more Refer Table 1S, Supplementary file).

NADES can be categorized into different groups: (a) sugar-constituting NADES with amino acids, (b) sugar constituting NADES with acids (c) sugars constituting NADES with bases, and (d) ILs, constituting an acid and a base. Different sorts of sugars and the organic acid mixture may form liquids like malic acid and citric acid and fructose + glucose + sucrose (Choi et al., 2011). Other combinations of two or more constituents can also form clear liquids like glucose + sorbitol + malic acid and ChCl + proline + malic acid. Such multiple-constituent combinations can be quite similar to NADES observed in the plants and comprise a combination of these metabolites.

3. Properties of NADES

NADES are an emerging class of designer solvents and are low-transition temperature mixtures (Choi et al., 2011). NADES constituting two or more components bound together by hydrogen bonds are characterized by MP lower compared to each of its constituents (Craveiro et al., 2016; Liu et al., 2018). They exhibit properties of non-flammability, very low vapor pressure, biocompatibility, biodegradability, low-toxicity (Dai et al., 2014; Xin et al., 2017) and their compatibility with water (Mulia et al., 2015). These solvents involve simple synthesis which is not associated with waste generation and are broadly utilized in enzyme catalysis (Hadj-Kali et al., 2015), electrochemistry (Jones et al., 2006) material preparation (Jablonsky et al., 2015), synthesis of polymer (Wikene et al., 2015) and separation processes (Hayyan et al., 2015). Several important characteristics and properties of NADES are discussed in Tables 2S and 3S (Supplementary files).

3.1. Renewable properties of NADES and its reusability

NADES are natural derivatives and thus, can easily be biosynthesized and metabolized by all the living organisms. In contrast most of the traditional organic solvents and ILs, they are highly 'biocompatible'. The behaviour of low toxicity and biodegradability in NADES prevents hazards posed to the environment. NADES are functional solvents and possess the ability to be recycled and reused (Fig. 6S, Supplementary file). Several recovery techniques like chromatography involving anion-exchange and counter-current separation, antisolvents, back-extraction and supercritical carbon dioxide have been used for this objective (Dai et al., 2013b; Liu et al., 2016). Dai et al. (2016) reported that NADES dilution would not influence its chromatographic behaviour which establishes that separation of a particular constituent and NADES recycling can occur concurrently. The restored NADES quality can be analysed quantitatively by mass spectroscopy, infrared spectroscopy and NMR techniques (Liu et al., 2016). Sometimes during recovery, the setup may require reconfiguration by supplementing with specific quantities of certain constituents. This property of reusability or renewability of NADES can decrease the total cost of NADES applications (Liu et al., 2018).

3.2. Biodegradability

Biodegradation is a crucial aspect to determine the design of safer and green chemicals. Biodegradation is the 10th guideline of green chemistry and is important with respect to green chemistry and NADES studies (Sudheer et al., 2018). The research related to biodegradation has been categorized into the five following terms (Jordan and Gathergood, 2015): (1) 'primary biodegradation' which involves breakdown of a particular compound due to conversion of a structural component, such as ester bond hydrolysis; (2) 'readily biodegradable' which refers to biodegradation of a compound to a specific percentage (60 %) within a given frame of time; (3) 'inherently biodegradable' which refers to a compound that shows at least 20 % biodegradation, then possibility of degrading it further is assumed, (4) 'ultimate biodegradability' which implies the entire breakdown of a compound, and, (5) 'mineralization' refers to degradation of a compound into smaller molecules which are bioavailable to the plants (OECD, 2006).

Organization of Economic Cooperation and Development (OECD) and the International Organization for Standardization (ISO) have also implemented several biodegradation testing strategies which are followed by researchers (OECD, 1992; Raba et al., 2018a). Testing stratagem given by OECD is (i) Examining of aerobic biological degradation to evaluate whether the compound is 'readily biodegradable'; (2) if the readily biodegradability test is not passed, then chemical may be tested by the other simulations (optimized aerobic conditions showing settings similar to that of sewage treatment plant) to regulate biodegradability, and, (3) potentially biodegradable nature of compounds can also be determined under anaerobic conditions (OECD, 2006). General pathways followed for predicting biodegradation process are bio-oxidation, fatty acid oxidation and hydrolysis of liable bonds, like the esters or amides succeeded by the β oxidation (Jordan and Gathergood, 2015).

3.2.1. Biodegradation tests: standardized

As per the OECD, the standardized methods for biodegradation of NADES/DES are Closed Bottle Test (OECD 301D) (OECD, 1992; Raba et al., 2018a; Raba et al., 2018b) and Respirometry Manometric test (OECD 301F) (Wen et al., 2015). These tests provide biodegradation data to whether the compound is readily biodegradable or not. The DES may be classified as readily biodegradable, inherently biodegradable, ultimately biodegradable and mineralizable depending upon the percentage of biodegradation and test performed. Biodegradation studies hold importance in assessing the damage to the environment caused due to anthropogenic pollutants. Environmental risk assessment is necessary for appropriate legislation of the novel compounds through REACH.

A compound is considered to be readily biodegradable if 60 % of the substance degrades after a duration of 28 days as per the OECD guidelines. 301D and 301F standard biodegradation tests are conducted to evaluate the theoretical oxygen demand (ThOD) and biological oxygen consumption. Theoretical oxygen demand refers to the quantity of oxygen needed to break down the substance into the final products of oxidation. Sodium acetate can act as a reference compound for the biodegradation tests. Cholinium chloride, which is an important constituent of many NADES is considered to be readily biodegradable since it qualifies the criteria of OECD (MITI-I tests) involving measurements of biological oxygen demand (BOD). This compound attained 93 % degradation within 14 days of the CBT (OECD, 1992).

3.2.2. Reported cases on biodegradation of NADES

Wen et al. (2015) assessed biodegradability of NADES comprising of ChCl and choline acetate as salts and urea, ethylene glycol (EG), glycerol and acetamide as HBD combined in mixing ratios of 1:2, 1:1 and 2:1. They compared these DES with the conventional IL, 1-butyl-3-methylimidazolium tetrafluoroborate [BMIm][BF_4]. The biodegradation values were measured by the CBT. Amongst DES tested, ChCl + urea and ChCl + acetamide were found to show ready biodegradability (>60 %) while the others screened presented a biodegradability lower than the pass limits.

Radosevic et al. (2015) assessed the biodegradability of similar compounds, i.e., ChCl constituting NADES. Choline chloride (ChCl) constituting NADES along with glycerol, glucose and oxalic acid as HBD were assessed for biodegradability by means of microorganisms from wastewater treatment plant (WWTP) using the CBT. They observed all these DES be readily biodegradable with values such as 96 % biodegradation for ChCl + glycerol and 68 % for ChCl + oxalic acid (OA). ChCl and Glycerol (1:1) achieved 84 % biodegradation after 7 days of the test and 60 % biodegradation was achieved for ChCl:OA after 14 days. They put forward the explanation that such high degrees of DES biodegradation could be attributed to the components constituted by them. As per OECD criteria (MITI-I Test; BOD measurements), ChCl is readily biodegradable denoting 93 % biodegradation within 14 days. However, this study showed contrasting results compared to Wen et al. (2015) This could be attributed to the differences in reaction conditions used, different DES concentration (100 mg/L as per Radosevic et al. (2015)) and 4 mg/L used by Wen et al. (2015) and differences in the source of wastewater microorganisms.

Zhao et al. (2015) also observed the biodegradation of 20 choline constituting NADES synthesized from ChCl and HBD like acids, sugars or alcohols with combinations such as ChCl and EG (1:2), ChCl and levulinic acid (1:2), ChCl and glycerol (1:2), ChCl and citric acid (1:1), ChCl and tartaric acid (2:1), ChCl and oxalic acid (1:1) exhibiting percentage biodegradation values as 81.9, 74.2, 95.9, 81.6, 84.6 and 73.4 %, respectively. They observed that biodegradation trends were: Amine based ~ sugar-based NADES > alcohol-based NADES > acid-based NADES biodegradation in the range 97.1 % to 69.3 % were observed. They further observed that their biodegradability was higher during the first 14 days compared to the next 14 days. The biodegradation values of all the NADES used in this study were observed to be greater than traditional imidazolium and pyridinium ILs. Use of cholinium cations in ILs, however, improves their biodegradability. Radosevic et al. (2015) and Zhao et al. (2015) in their study have encouraged a change of interest away from traditional pyridinium and imidazolium ILs towards NADES constituting components derived from natural sources like sugars, organic acids, alcohols and amines. It has been observed that only a few readily biodegradable traditional ILs with longer alkyl chains were observed and this is in part due to extremely high microbial toxicity because of the lipophilic characteristics. ILs having smaller alkyl side chains were significantly less toxic but had lower biodegradability values (Bubalo et al., 2014), with the exception of some imidazolium octyl examples. However, the conflict between biodegradability and toxicity was not observed for cholinium compounds (Zhao et al., 2015) for which good biodegradability was correlated with low toxicity.

Juneidi et al. (2015) assessed the biodegradability of various classes of NADES constituting *N*, *N*-diethyl ethanol ammonium chloride (EAC) and ChCl as salts with HBD in molar ratios of: ChCl + EG (1:2); ChCl + glycerol (1:2); ChCl + U (1:2); EAC + EG (1:2); EAC + glycerol (1:2); EAC + MA (1:1); EAC + zinc nitrate (1:1); EAC + zinc chloride (1:2). They observed that biodegradability was above 60 % for all verified NADES in water, and was referred to be 'readily biodegradable'. Maximum biodegradability was observed by ChCl:glycerol-NADES aqueous solution (91 %) followed by ChCl:urea (85 %). Lower values of biodegradation were obtained with EAC:malic acid aqueous-DES solution (61 %). ChCl based NADES were observed to be more biodegradable (77–91 %) compared to EAC-based except for EAC:zinc nitrate-NADES aqueous solution (80 %). HBD like urea, glycerol and EG were further accountable to biodegradation than malic acid and zinc chloride. They elucidated that biodegradation level of NADES could be accounted to salts of ammonium and HBD which forms NADES. The results were consistent with the study performed by Henkel and Ga (2001) in which 92 % biodegradation was observed after 30 days for glycerol. Moreover, the BOD_5/COD ratio obtained was 0.86 and was higher than 0.5, it portrays ready biodegradability of glycerol.

Ford et al. (2010) specified that occurrence of the carbon atoms in methyl groups in the ChCl may be beneficial for biodegradation compared to the ethyl groups in EAC (C_2H_5). Biodegradation levels can be enhanced with the presence of the hydroxyl group as observed for different ILs (Craveiro et al., 2016). Glycerol exhibited higher levels of biodegradation owing to the existence of three hydroxyl groups (ChCl:glycerol 91 %; ethyl acetate:glycerol 74 %) in comparison to EG having two hydroxyl groups (ChCl:EG 77 % ethyl acetate:EG 70 % respectively) (Radosevic et al., 2015). Greater biodegradability was also exhibited by ChCl:urea (85 %) which may be attributed to excellent biodegradability of amide and carboxylic acid groups. The results were consistent with the occurrence of carboxylate groups or hydrolysable bonds like esters and amides which enhances aerobic biodegradation values. Lower biodegradation of ChCl: malic acid was due to its acidity after addition of mineral medium (pH: 4.14) which does not favour the environment for the growth of all types of microorganisms.

Researchers such as Juneidi et al. (2015), Radosevic et al. (2015) and Zhao et al. (2015) have characterized NADES/DES as readily biodegradable in nature. This further encourages a transition from conventional imidazolium and pyridinium ILs to NADES derived from the natural metabolites like sugars, alcohols, amines and organic acids.

3.3. Toxicity

NADES constitute components basically of natural origin which are less harmful and mostly non-toxic. However, several studies have been conducted to determine hazard associated along with these solvents (Wen et al., 2015; Radosevic et al., 2015; Hayyan et al., 2015). These tests were performed to explain their possible usage in the pharmaceutical industry. Emphasis should be laid on whether the synergy effect between two molecules leads to higher toxicity compared to individual components (Paiva et al., 2014). NADES have not shown any inhibitory impact on the growth of *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Toxicity and cytotoxicity of phosphonium based NADES towards *Artemia salina* larvae and several bacteria were studied. It was observed that aquatic organisms have shown to be susceptible to the NADES and its toxicity was quite greater than that of the individual constituents. NADES based on phosphonium has shown a greater inhibitory effect in comparison to the ChCl constituting NADES. It gives them the potency of producing antibacterial products (Hayyan et al., 2013a, b).

3.3.1. Reported cases on toxicity tests of NADES/DES

Morrison et al. (2009) explored the applicability of DES as vehicles of drug solubilization in case of oral medicating of rats through initial developmental pharmacological researches. They used DES for this process having pharmaceutically acceptable constituents. These DES surpassed the datasheets of material safety denoting that toxicity in case of rats has LD50 values for malonic acid, ChCl and urea as 1310 mg/kg, 3400 mg/kg and 8471 mg/kg, respectively. However, their hypothesis did not consider the prospect of the synergetic outcome of coalescing the mixtures of DES. They did not account for the synergistic effect of combining two constituents, agents or factors which was observed to be higher than the total individual constituents. Their research included an assessment of the toxicity profile of DES used in the experiment. Toxicity of DES on the Gram-positive bacteria (like *B. subtilis* and *S. aureus*) and Gram-negative bacteria (e.g. *P. aeruginosa* and *E. coli*) were determined. These bacteria are most extensively used microorganisms to examine the toxic behaviour of several chemicals (Fu et al., 2013).

Cytotoxicity assay for the brine shrimp is regarded as a suitable analysis for primary determination of cytotoxicity, mycotoxins recognition, pesticides, trace metals and examining of dental constituents. These tests can further be determined by anti-tumour activity and evaluating the toxicity of cell-line. Cell toxicity by NADES was also examined towards *Artemia salina* (*A. salina*) leech (larvae of brine shrimp) (Manilal et al., 2009). In a study, NADES comprising ChCl and four HBD (EG, glycerine, urea and triethylene glycol) were carefully chosen based on their possible applications as observed in several reports (Lindberg et al., 2010; Morrison et al., 2009; Rimsza and Corrales, 2012). Their study stated that all the NADES analysed showed no inhibition towards the bacteria. This finding was consistent with other researches performed earlier (Wu et al., 2012). Their outcomes further depicted that cytotoxicity was observed on brine shrimp due to these DES.

Hayyan et al., 2013a assessed the toxicity of phosphonium constituting DES comprising three HBD like EG, glycerine and triethylene glycol using two Gram (+) and Gram (−) bacteria. They observed that the toxicity of examined DES was higher than their singular component. These DES posed a noxious impact on the bacteria demonstrating their probable use as antibacterial agents. These authors first identified the parameters for toxicity studies which include – conformation, viscosity and DES concentration. The authors concluded that the toxic effect was greater in the case of the eutectic mixture compared to each constituent of DES. This property promoted the role of DES as antibacterial agents.

Cytotoxicity studies on *A. salina* leeches found them to be highly prone towards DES toxicity (Hayyan et al., 2013a). They were quite resilient towards toxicity of the aqueous solutions in case of DES constituents. The longevity of *A. salina* is quite limited wherein the cells did not live >4.05 min in case of ChCl:urea, 2.58 min in ChCl:triethylene glycol, 10.13 min in ChCl:EG and 5.32 min in ChCl:glucose DES. Several explanations were proposed to account for the cytotoxicity of brine shrimps like oxygen loss, growth inhibition because of high DES viscosity. The chemical behaviour of constituents (HBD, mixing ratio, type of salt) of DES influence its temperature, content of water and viscosity. Hydrogen bond formation amongst the salt anion and HBD not only affects the physical characteristics of pure constituents but also influences chemical construction of the compound (Zhang et al., 2012).

Toxicity experiments were performed by Radosevic et al. (2015) by seeding channel catfish ovary (CCO) and breast cancer cell lines (MCF-7) cells in a 96-well plate having a density of 5×10^4 cells in each well using 100 mL of the media. DES components were applied to the cells. Incubation of the samples was performed overnight for 72 h, in which the minimal examined concentrations varied from 1 mg/L to 2000 mg/L. 10 mL of the tetrazolium salt WST-1 was injected before exposure to every well and further incubation of the samples were performed for 4 h. A microplate reader was used for measuring absorbance at 450 nm. Viability of the cells was represented as the percentage of treated cells with the control. Values of EC_{50} are referred to as the concentration of the examined compounds which will result in a reduction of 50 % of growth which is evaluated by dose-response curves by equations of most suited trend lines. They used light microscopy to detect morphological transformations on exposure to DES. Thus, CCO cells were seeded in a Petri plate with 6-wells and were subjected to EC_{50} concentration or the maximum examined concentration (200 mg/ L). They found that toxicity of DES may be due to one constituent or both the constituents of eutectic solvents. The results obtained in these studies highlighted the fact that most of the DES have higher toxicity compared to their constituents (Radosevic et al., 2015). The reason behind the cytotoxicity due to the HBD and salt leading to synergistic effects was confirmed by several experiments.

Hayyan et al. (2016) conducted the toxicity studies by evaluating NADES such as ChCl + fructose (molar ratio-2:1) [NADES I] and ChCl + glucose (ratio-2:1) [NADES II] and a DES:*N*, *N*-diethyl ethanol ammonium chloride (DEAC) and triethylene glycol (TEG) (mixing ratio: 1:3) [DES 1] by means of cancer cell lines of human. The cytotoxicity results depicted the following direction: NADES2 < NADES1 < DES1, based on their EC_{50} values. They thus delivered proofs that the NADES studied show less toxicity compared to DES. Their results further strengthen the significance of the factors mentioned in unravelling mechanism of cytotoxicity. Their studies also established that the uptake of glucose and fructose may activate an upsurge in the preparation of the end products of advanced glycation method and consequently, synthesis of reactive oxygen species (ROS).

Mbous et al. (2017) observed the effects of DES (1) (prepared by 1:3 molar ratio of DEAC and TEG) and NADES (prepared by mixing 2:1 mixing ratio of ChCl and fructose (1) and 2:1 molar ratio of ChCl and glucose (2)) on HelaS3, A375, AGS, and WRL-68 cell line. EC_{50} values were determined to assess the toxicity towards cell lines. They observed there were lethal effects of these NADES on cell lines. Their results showed no consistent growth in their morphology or shape. There was a huge effect on the cell union and abundant dead cells were observed in the necrotic stage. They further verified the membrane permeability by treating the DES with EC_{50} concentrations and incubating them for 24 h in 5 % CO_2 at 37 °C. A dead cell green dye was used to observe whether the plasma membrane of the cells cooperated. The capture cell images revealed that NADES have the capacity to perforate the membranes. DES were observed to be more damaging than NADES depending upon the fluorescence of DES1-treated cells. The differences may be due to the intricate connections between the mixtures and the cell membrane. Fructose based NADES was observed to exhibit higher toxicity (across all the cell lines) when compared to the glucose counterpart.

Radosevic et al. (2018) explored the effect of ten different NADES to several species of bacteria such as *S. typhimurium*, *E. coli*, *P. aeruginosa*, *P. mirabilis* and *S. aureus* and the yeast *C. albicans* and on human cell lines such as HEK293T, MCF-7 and HeLa (Fig. 7S, Supplementary file). They determined the antioxidative behaviour of the given NADES using radical oxygen absorbance capacity method. They also reported that NADES comprising citric acid showed the maximum growth inhibition for citrate:glucose:glycine (22–83 mm) and citrate:fructose:glycine (28–81 mm) referring them to be potential antimicrobial agents. Their results were conformant with the previous publications indicating that NADES comprising organic acids exhibit greater antimicrobial action in comparison to the amine, alcohol, and sugar-based NADES. Zhao et al. (2015) and Wikene et al. (2017) stated that insertion of an extra hydroxyl group to the organic acids as HBD in DES enhances its antibacterial nature. Their toxicity results showed that maximum inhibitory impact was noticed for ChOX acid in tumour HeLa and MCF-7 cells and (EC_{50} of 330.90 and 558.98 mg/L, correspondingly), however, the impact on HEK293T cells (EC_{50} > 2.000 mg/L) was several degrees greater in comparison to the tumour cells. These findings were showing similar results as per the study conducted by Radosevic et al. (2018). They observed that all tested microorganisms had relatively high sensitivity towards the tested NADES. They further reported that NADES with single constituents might have antibacterial activity only in case of acids. They further reported the antioxidant activity of NADES using the oxygen radical absorbance capacity (ORAC) method. They observed that ChXylol, ChSol and ChU showed no antioxidative behaviour and they cannot serve as radical scavengers. The trend for ORAC values of the other NADES was as follows: Betaine:malic acid:glycerol > citrate:proline > ChCl:OX > betaine:glycerol ≈ citrate:glucose:glycerol ≈ Citrate:fructose:glycerol.

Macario et al. (2018) unravelled the ecological toxicity of DES through the toxicity theory of the mixture. They evaluated the toxicological profiles of DES depending upon $[N_{1111}]Cl$, $[N_{2222}]Cl$ and $[N_{3333}]Cl$ as HBA in association with HBD like EG and 1-propanol via the Microtox Acute Toxicity Test (Fig. 8S, Supplementary file). Different concentrations and independent activity concentration addition and independent action were used for toxicity predictions. Various toxicity studies have attributed the lower toxicity of NADES when compared against DES and IL, to their preparation from primary natural metabolites. A list of different types of toxicity case studies of DES/NADES performed on model organisms and cell lines are presented in Table 4S (Supplementary file).

4. Sustainable chemical-biological-pharmaceutical-medical applications of NADES

4.1. NADES in sustainable chemistry

The world today demands sustainable chemistry to facilitate new methods or bring about enhancement of the existing ones. This sustainability approach contributes to evolutionary advancement in the arena of science and technology dealing with health, environment and industry. NADES follow all the green chemistry guidelines and present various opportunities in diverse fields of synthesis, extraction, biocatalysis, gas separations, materials science, electrochemistry and nanotechnology (Fig. 3). NADES being the tailored solvents may be used as safe, green and sustainable extraction media. Better knowledge about physico-chemical characteristics of NADES, intermolecular forces amid NADES and targets and their effectiveness and selectivity, solubilization, stabilization, dispersion and adsorption are essential to explore the diversity in NADES applications. A few remarkable applications of NADES in promoting sustainable chemistry are discussed in the following sub-sections.

4.1.1. In pharma industries as drug development

Pharmaceutical industries are rising at a fast rate worldwide; thus, this growth promotes a considerable increase in research and development for generating novel drugs for better health propagation. Pharmaceuticals need a solvent for the processing and transportation of drug materials (World Health Organization, 2007). Generally, water is considered to be the most suitable and desirable vehicle for pharma-based products (Villiers, 2009). However, for enhancement of solubilities of water-soluble drugs, organic solvents like ether, ethanol or esters are required. Thus, proper media is required to improve the solubilization of the APIs. Park et al., 2012a reported that an enhancement in solubility can be attained by using various benign co-solvents like EG, glycerol, propylene glycol and polyethylene glycol. Though, these were not as effective as in the case of NADES, which are globally considered to be the alternative solvents for solubilization of API's (Smith et al., 2014). Lu et al. (2016) compared solubilities of aspirin in water [7.03 mg/mL] and ChCl:1, 2 propanediol in the ratio of 1:2 [202 mg/mL] and observed it to be much higher in NADES at the same room temperature. ChCl:1, 2 propanediol (1:2) was found to be a promising solvent for acetaminophen compared to water. Li and Lee (2016) have reported that the solubility of lidocaine was increased to 295.40 mg/mL in case of NADES constituting ChCl + glycolic acid + oxalic acid in mixing ratio of 1:1.7:0.3 compared to that in water (3.63 mg/mL). This may be attributed to both the Van der Waal forces and hydrogen bonding amongst API and solvent have resulted in its high solubilization (Pedro et al., 2019). They also mentioned higher solubility of APIs such as piroxicam (3.10 mg/mL), itraconazole (53.60 mg/mL) and posaconazole (88.40 mg/mL) in NADES than that of water. Lu et al. (2016) observed that solubility of ibuprofen was enhanced by 5400-fold in DES constituting tetrapropyl ammonium bromide:1, 2 propanediol. The solubility of rutin was also increased in NADES comprising ChCl:proline (3:1) (Faggian et al., 2016). Solubilities of analgesics such as acetaminophen and anti-inflammatory drugs like ketoprofen and naproxen were also found to increase in NADES compared to water. Further examples include lidocaine solubilization in β-alanine + lactic acid in mixing ratio of 1:1 and similarly for ChCl + lactic acid (1:1). Table 5S (Supplementary file) depicts the differences in the solubilities of APIs in water and diverse NADES solvents.

NADES have shown their virtue as probable solvents in enhancing the chemical stability of APIs. Several of the APIs such as ester constituting pharma products are not stable in the aqueous solution and are decomposed by different pathways (Blessy et al., 2014). NADES are known to develop stability during the solubilization of APIs. A mixture of betaine and urea was observed to increase stabilization of β-lactam antibiotics specifically clavulanic acid (2.5-fold) and imipenem (7-fold) compared to that in water (Olivares et al., 2018). Similarly, hydrolysis of aspirin into its breakdown products: acetic acid and salicylic acid was much lower in ChCl:propanediol compared to the aqueous solution (8.2 times higher) (Olivares et al., 2018). NADES, thus hold a promising role in the stability and solubility of a specific drug/API.

Faggian et al. (2016) performed ground-breaking research using Balb mice. They conducted pharmacokinetic studies on rutin solubility in the solvent, proline:glutamic acid and observed an increase in oral absorption of the specific API. A variation in the maximum time was observed without any changes in the rate of absorption on comparing the dispensation of rutin in water (15 min) than that of NADES (60 min) used. A distinct variation in the values of area under the curve and maximum concentration were also observed, indicating an upsurge in the relative biological availability of rutin in NADES compared to the aqueous solvent. Sut et al. (2017) observed an enhancement in the solubilization (12 times) of berberine in NADES comprising proline:malic acid:lactic acid:water in mixing ratios of 1:0.2:0.3:0.5. An 8-fold rise of its concentration in blood as a solvent was also reported in the study (Sut et al., 2017). The class of ChCl constituting NADES is considered to best solvents for APIs solubilization. This is supported by the fact that ChCl is a strong hydrogen bond acceptor and is safer and greener compound (Li and Lee, 2016). In contrast, ChCl when combined with HBD like oxalic or glycolic acid does not behave as good solubilization solvents for pharmaceutical drugs. Thus, constituents of NADES should be sensibly selected for solubilization taking into account their toxicity properties.

The selection of the correct formulation of API-NADES is essential for the successful production of pharmaceutical drugs (Fig. 9S, Supplementary file). The solubility of API can be further increased on being converted into a liquid state by formation of NADES constituting the target API (API-DES). NADES exhibit therapeutic properties due to the presence of API in their constitution. APIs either act as HBD or HBA during making a formulation with NADES. Suitable HBD and HBA should be chosen as it holds an important function for the API-DES formulations for pharmaceutical uses.

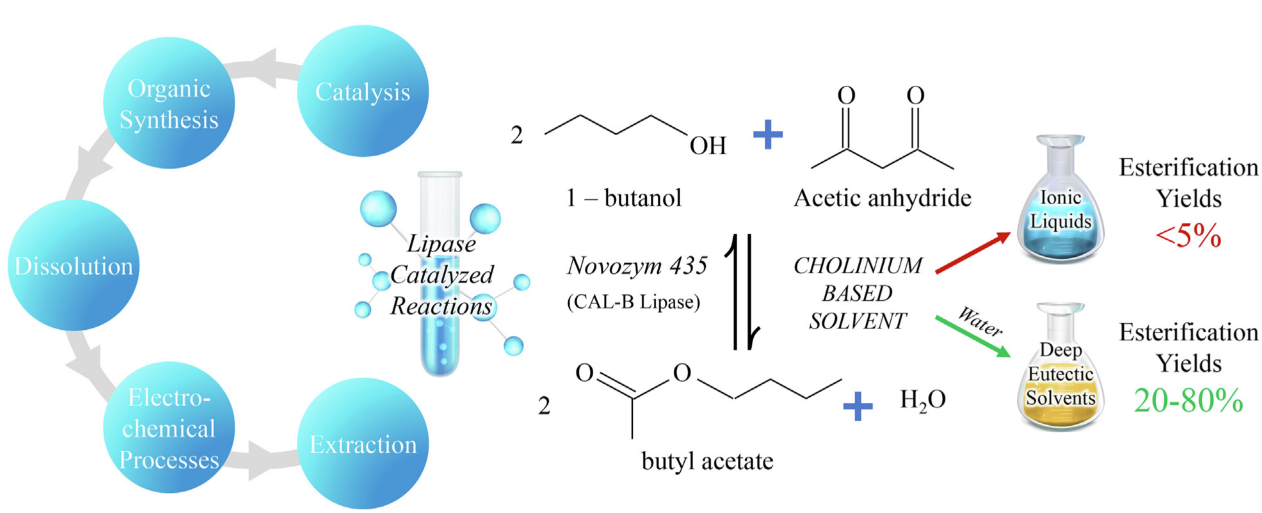

Fig. 3. Relevance of natural deep eutectic solvents in sustainable chemistry.

Synthesis of an API-NADES formulation can occur by several other ways like permeation enhancers (Tarate and Bansal, 2015) or by metabolites (Abbott et al., 2017). Different APIs can also combine to form NADES of the liquid state (Abbott et al., 2017; Berton et al., 2017).

In combined form, they exhibit a polymerizable property, thus involving sufficient regulation of the delivery profile. API mostly acts as HBD as they generally constitute carboxylic acid, alcohols and amines (Abbott et al., 2017). Combination of API-NADES is a promising approach as it includes two active constituents in the same formulation, thus preventing polymorphism in case of formation of liquid (Abbott et al., 2017). An anaesthetic cream referred to as Eutectic mixture of local anaesthetic (EMLA) used in cases of transdermal delivery is considered to be the oldest and most promising eutectic mixture in field of 'drug solubilization approaches'. It constituted lidocaine and prilocaine and was first eutectic mixture to be commercialized and patented (Pedro et al., 2019). Though, due to its several side effects, various other mixtures like lidocaine:tetracaine and lidocaine:procaine were developed which were also liquids at room temperature. A very recent development in pharma industries: resulting in the eutectic mixture derived from lidocaine and ibuprofen was discovered. The anaesthetic effects in this mixture were quite faster (pharmacological effect 10 min) and stronger on comparing with the commercial EMLA Pharmacological effect: 1 h 30 min. After this discovery, a new level of API-NADES mixtures was prepared; thus, constituting per meation enhancers. These mixtures can be applied topically and transdermally. Menthol is a commonly used permeation enhancer for transdermal delivery. Duarte et al. (2017) reported that menthol gets combined with ibuprofen, coenzyme Q10 (Nazzal et al., 2002), paeonol and aspirin (Aroso et al., 2016), leading to a liquid formation at human body temperature.

The fatty acids were also considered to be an important attribute of API-DES formulations. A mixture of palmitic and lauric acids along with lidocaine and ibuprofen forming a liquid was first of the fatty acids known for transdermal delivery purposes (Nazzal et al., 2002; Benessam et al., 2013). These API-DES generally show melting temperatures below the temperature of the human body. Park et al., 2012a stated about the role of API-NADES in case of topical application. The antifungal liquid mixture enhances the drug concentration for topical use along with preventing recrystallization (Park et al., 2012b). Thus, the API-NADES combinations not only increase the oral availability of drugs but also promote the production of a different delivery system to overcome erratic absorption and insufficient plasma concentrations of the drugs (Pedro et al., 2019). However, future studies related to their dissolution rate, drug solubility and bioavailability should be taken into account (Park et al., 2012b).

Polymers possess an imperative function in the evolution of the drug delivery systems as they result in the regulated release of therapeutic drugs in constant doses for longer durations, are tuneable, have cyclical dosage and discharge equally the hydrophilic and hydrophobic drugs. NADES can also be employed for developing regulated delivery schemes as monomers for the production of polymers. Production of the poly(octanediol-*co*-citrate) elastomers comprising a combination of citric acid, lidocaine and 1,8-octanediol is a polymer-depended precursor (Serrano et al., 2012). NADES have further proven their worth in dissolution and processing of biopolymers for instance in case of cellulose (Lynam et al., 2017), agar (Sousa et al., 2015), chitin (Sharma et al., 2013). Mano et al. (2017) discovered the advancement of oral drug delivery systems. These rapid- dissolution delivery systems fragments in the mouth deprived of the need of water. ChCl:mandelic acid combination can be utilized as an API-DES complex to assess the ability of NADES combinations to get condensed in gelatine nanofibers shaped by the electrospinning method. Nanofibers, thus obtained were economical, biodegradable along with antibacterial action, presenting a rapid release of drug profile. These display no toxic effects on cell proliferation. However, such drug delivery systems should be further assessed with respect to pharmacokinetic characteristics to give them an edge over solid APIs.

NADES possess beneficial properties like anti-cancerous, anti-oxidant, anti-allergic, anti-bacterial (Fig. 10S, Supplementary file), anti-viral, anti-inflammatory, anti-fungal, anti-parasitic and anti-diabetic. Some of the pharmaceutical applications of NADES such as antioxidant, anti-tumourous and anti-inflammatory properties are itemized in Table 6S (Supplementary file). Thus, NADES exhibits three prime functions in the pharmaceutical industries (i) rendering the API for release of the drug (ii) as a monomer for the synthesis of elastomers (iii) and play the function of a synthetic media for polymerization. However, this strategy is under controversy as the concept of NADES gets compromised during polymerization, owing to the condensation reactions such as citric acid with 1,8-octanediol. Though, several new systems related to the polymerization behaviour of NADES have been developed for example involving lidocaine and acrylic acids by frontal polymerization (Mota-Morales et al., 2013).

4.1.2. In nanotechnology

The role of NADES in nanotechnology came into knowledge during 2008 involving the use of DES synthesized by the molar mixtures of ChCl and urea. The carbon nanomaterials like single- and multi-walled carbon nanotubes and graphene hold a lot of importance in this area. This biobased solvent class was used for chemical synthesis of the gold nanoparticles without surfactants in the reaction medium. Several pieces of research were performed based on the usage of DES in nanotechnology (Table 2). Several patents have been filed connected to the role of DES in nanotechnology. Fig. 4 depicts the various functions of NADES in nanotechnology. Nanomaterial productions were studied with respect to 6 aspects: electrodeposition of films, metal combined with organic frameworks, assembly of colloids, porous carbons based on hierarchy, as well as DNA and RNA designs.

Nanoparticles generally tend to naturally aggregate with each other (Saidur et al., 2011) which may thus restrict their benign characteristics necessary for usages such as the ability to absorb specific compounds. Moreover, this results in difficulty in modifying the process to achieve its application in the field of sensors and biosensors. NADES can thus overcome this issue and are considered to be convenient media for splitting and dispersing of nanomaterials. DES is often the preferred choice for nanoparticles synthesis owing to their good dispersibility, thermal stability, large ionic conductivity, huge electrochemical window. Wagle et al. (2014) have reviewed 'designer solvents' NADES for their applications in the production of different nanomaterials. NADES can direct the chemistry at the nano-scale and acts as a template, metal or carbon source, and also as a reactant in the production of nanomaterial.

DES holds a significant function in controlling the morphology of nanoparticles. The tendency of agglomeration of nanoparticles is a huge restriction in its application. It results in a decrease in the surface in terms of lower chemical and catalytic behaviour of particles and a reduction in the bulk volume. However, the stability of these nanoparticles can be enhanced with the help of surfactants, which prevents the agglomeration of nanoparticles by forming a protective covering around its surface (Janiak, 2014). NADES can act as suitable media during initial steps of nanomaterials synthesis, thus replacing the conventional surfactants (Polo-Luque et al., 2013). They also prevent clustering of nanomaterials. DES were utilized extensively as effective dispersants during nanoproducts synthesis along with influencing their size, shape and morphology (Oh and Lee, 2014; Javadian et al., 2013). They can split small scale structures into nanoscale by functioning as a dispersion solvent (Table 7S, Supplementary file). Though the reported cases of NADES in the dispersion of nanomaterials are fewer compared to that of ILs.

Mondal et al. (2014) in their study observed the property of NADES for the solubilization of DNA in the testes of Salmon. The procedure involved the use of ferric oxide (Fe_3O_4) nanoparticles and performed protonation of the layered sheets of di-titanate (H_2-Ti_2O_5-H_2O) as the mediators of functionalization in the medium of DES constituting ChCl and EG (1:2 molar ratio). Subsequently, a hybrid substance presenting both the antibacterial and magnetic properties was obtained. The DES was then again recycled and reutilized for the solubilization process. The stabilized DNA obtained in this process was used in the areas of biosensing and biomedics.

NADES also exhibit an important role in exfoliation of the nanomaterials. The microstructures of nanomaterials are a cluster of particles in nanosize. Nevertheless, they stay bound together to make large structures. The

Table 2
Applications of natural deep eutectic solvents in the field of nanotechnology.

S. no.	NADES/DES	Mixing ratio	Function	References
1.	Choline chloride:malonic acid	1:1	Media for chemical synthesis of nanoparticles	(Oh and Lee, 2014)
2.	Choline chloride:tris (hydroxymethyl)-propane	1:1	As a dispersion media	(Maka et al., 2014)
3.	Choline chloride:zinc chloride	1:1	Nano-confinement	(Chen et al., 2009)
4.	Choline chloride:thiourea	1:2	As a media for chemically synthesizing nanoparticles	(Mukesh et al., 2014)
5.	Choline chloride:gallic acid:glycerol	1:0.25:0.25	Synthesis of nanoparticles chemically	(Shahidi et al., 2014)
6.	Choline chloride:urea	1:2	Deposition of nanoparticles	(Guo et al., 2014; Wei et al., 2013; Bock et al., 2013)
			As nanostructure sensor	(Zheng et al., 2014b)
			As production media in sputter deposition method to create nanoparticles	(Raghuwanshi et al., 2014a; Raghuwanshi et al., 2014b)
			Media for synthesis of nanoparticles chemically	(Zheng et al., 2014b; Chen et al., 2013; Huang et al., 2012; Lu et al., 2014)
			Exfoliation Dispersion	(Boulos et al., 2013)
7.	Choline chloride:1,3 diethyl urea	1:2	Media for synthesis of nanoparticles chemically	(Sheng et al., 2012)
8.	Choline chloride:acrylic acid	1.3:1 1.6:1 2.0:1 2.3:1	Media for synthesis of nanoparticles chemically	(Gu et al., 2011)
9.	Choline chloride:chromium chloride (hexahydrate)	1:2	Nanoparticle deposition Nanodroplet embedded in the microstructure	(Wright et al., 2012)
10.	Choline chloride:para toluene sulfonic acid	1:1	Chemical synthesis media for production of nanoparticles	(Gutierrez et al., 2011)
11.	Choline chloride:ethylene glycol	1:2	Nanoparticle deposition	(Gu et al., 2011; Zhang et al., 2015; Renjith et al., 2014; Cai et al., 2013a, b)
12.	Choline chloride:tri hydroxy-methyl propane	1:1	Dispersion media	(Maka et al., 2014)
13.	Citric acid:diethyl urea	1:1.5	Noncatalytic assembly	(Lu et al., 2014)

graphite is several layered graphene sheets of higher dimensions. It was reported that on rolling a graphene layer a single-walled carbon nanotube (SWCNT) is formed while, to form seamless cylinders multi graphene layers are formed leading to multi-walled carbon nanotubes (MWCNTs) (Rao and Govindaraj, 2011). Boulos et al. (2013) have described the transition of human hair into functional nanomaterial obtained with the help of ChCl: urea (2:1). It was observed by SEM that before the treatment, a typical hair of 50 μm diameter was observed along with 5 μm of cuticle cells concealing the surface of the hair. Hair, after the treatment with DES, was found to have 13 cuticle cells exfoliated from the hair. On examining by Transmission electron microscopy (TEM), huge numbers of small particles having granular morphology were observed, that are mostly melanin pigment of hair cells. TEM images further confirmed the fact that macrofibrils nano-rods existence (200 nm diameter) is attributed to the unravelling of the cells of the cortex into the nano-structural constituents due to the role of NADES in protein denaturation.

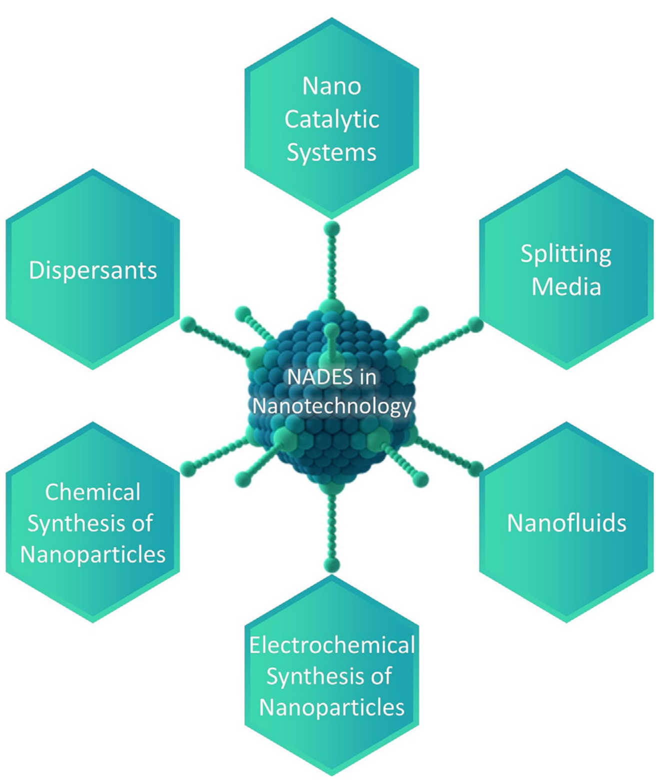

Fig. 4. Various roles of natural deep eutectic solvents in the field of nanoscience.

NADES are further considered to be directing agents of morphology and thus holds a vital role in influencing size, shape and morphological composition of the nanomaterials. Gutierrez et al. (2011) stated the application of NADES comprising, ChCl and *para*-toluene sulfonic acid (mixing ratio, 1:1) to form a porous carbon. NADES can be utilized as a medium and a catalyst for condensation of furfuryl alcohol. It can further be used in the carbonization method to generate various spongy carbon monoliths, involving MWCNTs. NADES thus can act as the 'morphology-shaping agent' for formed carbon and are further accountable for creating microporous network throughout polycondensation along with acting as particle stabilizer (Lloyd et al., 2013). ChCl and malonic acid constituting NADES as a media for facilitating reactions were reported by Oh and Lee (2014) to act as a structure shaping agent to prepare extremely monodispersed microparticles of gold. The product obtained had well-described diameters and could sustain different reductive conditions. Three-dimensional network of nanostructures (90 °C) and different structures obtained at different temperatures was an attribute of huge dependency of NADES on temperature.

NADES can also be applied as electrolytes in the electrochemical system like batteries, solar cells, actuators, capacitors and fuel cells but studies reporting this are very few. A study was performed by Zheng et al., 2014a using an acetate buffer mixture and NADES constituting, ChCl:urea in mixing ratio 1:2 as an electrolyte for quercetin sensing electrochemically. They observed a good linear relationship for the peak oxidation current and strength (9.95×10^{-7} to 4.76×10^{-5} mol/L) of quercetin in the electrolyte. Use of NADES as in electrochemical field is a quite cheap and economical process.

Lu et al. (2014) developed an effective reusable nano-catalytic procedure for preparation of imidazo [1, 2-a] pyridines. Citric acid and dimethyl urea (1:1.5) were used as a eutectic solvent and it resulted in attaining of an optimum catalytic activity. Three basic constituents' aldehydes, aminopyridine and alkynes of different types were used as reactants.

Copper salts were used accompanied by variable metallic oxides nanoparticles to test the efficiency of the catalyst. Citric acid:dimethyl urea-$CuFeO_2$ nanoparticles were selected depending upon the greatest yield of 95 %. NADES along with recovering catalyst nanoparticles also function as a catalyst due to its acidity.

NADES are green solvents and can also synthesize several nanomaterials. They play several functions as a solvent and the precursor during the same time. It depends on the sort of nanomaterial produced, type of DES, reaction method, composition and conditions. ChCl:urea based NADES are generally utilized for the chemical synthesis of nanomaterials.

NADES also participates in the electrodeposition of nanomaterials. Great solubilization of the metal oxides, hydroxides and salts in the NADES delivers them huge eminence over the traditional electrolytes depending upon the organic solvents or aqueous solutions (Smith et al., 2014). NADES were used worldwide to make nanoparticles through the electrochemical process, which holds applications in generating magnetic attributes of materials, corrosion resilient functionalized surfaces photoactive semiconductors, and building important units of the electrical industries. Examples of DES as successful electrolytes are depicted in Table 8S (Supplementary file). ChCl:urea constituting DES was the foremost and common electrolyte used in the electrodeposition of platinum and palladium. ChCl:EG comprising NADES were used for electrodeposition of Ni nanostructure.

There are various efficient techniques for manufacturing of nanoparticles for instance, microwave mediated synthesis, physical vapor deposition, and chemical synthesis. The synthesis and evolution of gold nanoparticles on environment-friendly NADES (DES; ChCl and urea) was studied by Raghuwanshi et al. (2014a). These particles were formed in NADES by utilizing a soft sputtering and low energy deposition method under hygienic settings in the vacuum chamber. Self-assemblage of the gold nanoparticles (AuNPs) into the study was attributed to the templating behaviour of NADES in combination with equilibrium amongst particular physical communication forces between AuNPs.

Thus, NADES depict great adaptability in diverse reaction processes. They serve a platform for several reactions like polymerization, precipitation, condensation, reduction, oxidation and ion thermal reactions. Nanomaterials synthesized ionothermally using NADES exhibit applications in a wide range of arenas. They may regulate the morphology, shape and size of nanoparticles which is an important attribute to attain advanced applications. Moreover, they are economical, greener, safe and suitable alternatives for the traditional solvents in the field of nanotechnology. Several researchers have also reported about effective recycling of NADES after utilizing them as a media for dispersion and preparation of the nanoparticles and the nanocomposites (Mota-Morales et al., 2013; Mukesh et al., 2014; Lu et al., 2014; Gutierrez et al., 2011; Mondal et al., 2014). Although synthesis of nanostructured catalysts using DES needs to be further explored with regards to adjustment of their synthesis conditions. The environmental impacts of NADES used in the synthesis of nanoparticles, and during their discharge should also be taken into account. NADES can also be synthesized in nano-size with several fascinating properties but research related to it is still in progress when compared with the ILs which have achieved great advances in the field of nanotechnology.

4.1.3. In nutraceuticals

Health-stimulating products viz. pharmaceuticals, nutraceuticals, and food additives attained via solvent extraction of from the plants are prevalent. Nonetheless, there are two chief concerns regarding them: bioavailability of the product and safety of the solvent. NADES present a safer and preferred choice because of their recognized low toxicity.

NADES constitute natural compounds and have great applications in the area of natural products. They are formed by hydrogen bond interactions and are chemically, thermally very stable along with great solvation properties (Dai et al., 2015; Durand et al., 2016; Gutierrez et al., 2009). Several bioactive compounds possess low solubilization in water and the ethanol mixes. This could be a major drawback in food industries which rely on the extraction of nutraceutical constituents and food supplements (Wikene et al., 2017; Xin et al., 2017; Gertrudes et al., 2017). NADES, however, are considered to be ideal alternative solvents for the extraction procedures in the food and cosmetics industries. Method illustration for extraction of bioactive compounds using NADES is presented in Fig. 5. They are green, have high safety and are environmentally sustainable (Wikene et al., 2017; Durand et al., 2016).

Hayyan et al. (2012) stated that NADES can even act as ingredients in functional food and nutraceuticals. They deliver the potential of combining with different molecules and resulting in the synthesis of designer solvents employable in nutraceutical-based industries. NADES can be utilized in solubilization and extraction of solutes with varying properties owing to the presence of different constituents (Paiva et al., 2014; Dai et al., 2013b; Durand et al., 2016; Gutierrez et al., 2009). Hayyan et al., 2013a and Hayyan et al. (2016) performed studies to enhance the bioavailability of berberine using NADES. They selected three different mixtures such as urea, malic and lactic acid and proline depending on their solubilization activities towards berberine. These were administered orally to the mice and were linked with the aqueous suspension. The concentrations of blood in

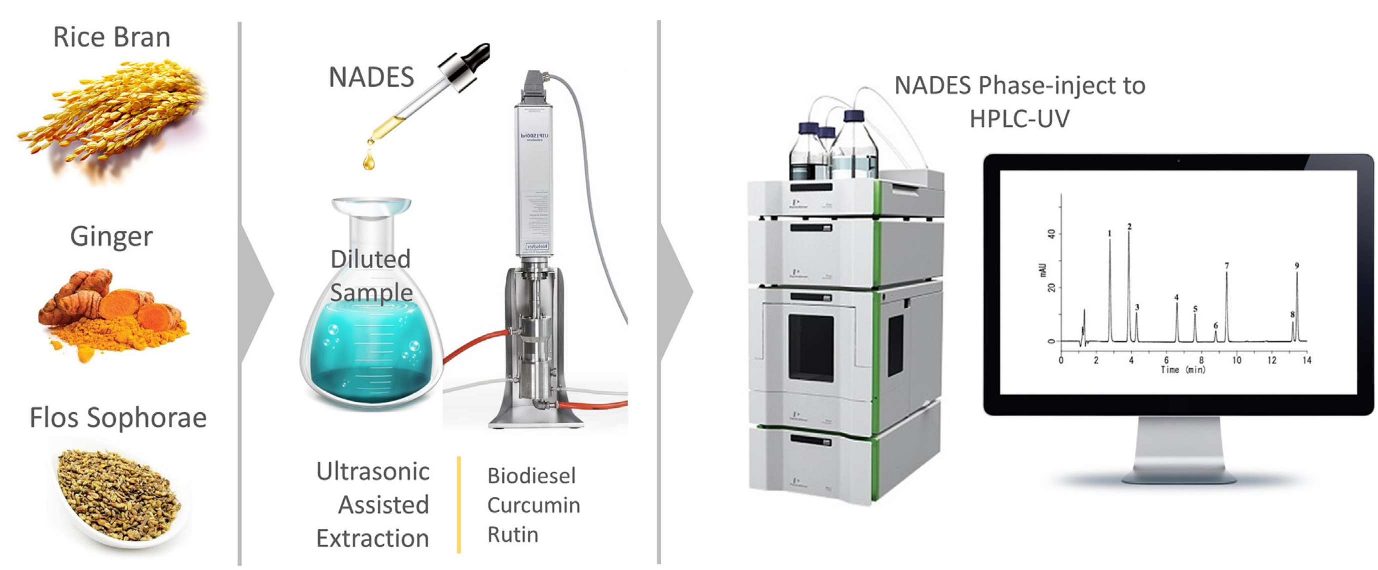

Fig. 5. Method of extraction of bioactive substances with the help of natural deep eutectic solvents.

mice were checked through the High Performance Liquid Chromatography methods and function of NADES as adsorption enhancers were established (Faggian et al., 2016).

NADES as solvents were also screened by Sut et al. (2016) in the case of alkaloid berberine. They administered the solutions of NADES-berberine to mice orally. These researches have highlighted the ability of NADES as solubilization and formulation agent for enhancing adsorption of less biologically available natural substances.

High solubilization activity and low toxicity of NADES have resulted in their applications in pharmaceutical formulations. 1, 2-propanediol + ChCl + H_2O (molar ratio, 1:1:1), a substitute of dimethyl sulfoxide (DMSO) was used for dissolution of the sparingly soluble salsalate in case of In vitro assays by means of the brown cell adipocytes. Durand et al. (2017) reported about the inhibition of the activity of polyphenolic compounds by the reactive oxygen species on being formulated with 1,2-propanediol, ChCl and H_2O in a ratio of 1:1:1 in cell lines of fibroplast. Thus, the antioxidant activity of the polyphenolic compounds was enhanced considerably. Mbous et al. (2017) reported that this may be attributed to the increase in permeation ability of membranes or function optimization in the intracellular medium by unknown pathways. Shamseddin et al. (2017) in a recent investigation observed an increase in hermetic action of resveratrol (antioxidant and anti-inflammatory) by the decline in the activity of matrix metalloprotease-9 (aMMP-9) on being expressed with, 1, 2-propanediol:ChCl:H_2O. These studies will promote the feasibility of using NADES in nutraceuticals and pharmaceutical formulations. However, NADES physical and chemical properties, thermodynamic and pharmacokinetic properties further need to be explored for its oral administration as drugs.

4.1.4. In dissolution of lignocellulosic biomass

Biomass in the form of lignocellulosic materials can be sustainable sources of feedstock for fuel and biochemical production (Gandam et al., 2022; Usmani et al., 2021). However, lignin forms a natural barrier against enzymatic hydrolysis of biomass through its complex structure and non-specific bonding with enzymes. Thus, pre-treatment is an essential step in the production of ethanol from cellulose derived from lignocellulosic biomass to breakdown the complex molecular structure of cellulose as well as the removal of lignin (delignification). A plethora of pre-treatment processes has been developed for delignification of biomass (Usmani et al., 2022), with varying rates of success and challenges. Biomass pre-treatment using NADES overcomes many of the hurdles often associated with conventional solvents and, such as high toxicity, biodegradability, biocompatibility, recyclability, sustainability, and prohibitive cost. Utilization of NADES in the pretreatment of woody biomass (Alvarez-Vasco et al., 2016) and lignocellulosic biomass (wheat and rice straw) (Kumar et al., 2016) has proven to exhibit its high specificity towards lignin solubility. Additionally, NADES have received great attention due to their interaction with water.

NADES formed by mixing lactic acid and ChCl as the HBD and HBA, respectively, have been effectively utilized for the pre-treatment of lignocellulosic biomass, partly because of milder conditions required during the extraction process and the high quality of extracted lignin and cellulose (Mamilla et al., 2019; Li et al., 2018). The delignification and cellulose yield using NADES can vary widely depending on the type of lignocellulosic biomass and its source (Table 9S). For instance, the delignification of wheat straw using NADES prepared by mixing lactic acid and ChCl in the molar ratio 9:1 with reaction temperature ranging from 60 to 90 °C resulted in residual lignin of ~14.6 % (Jablonsky et al., 2015); corncob, 93.1 % (Zhang et al., 2016); Kraft pulp (hardwood), 37.8 % (Jablonsky et al., 2018); apple residues, 62 % and potato peels, 33 % (Procentese et al., 2018). Smink et al. (2019) found that Cl^- ions in ChCl were the prime reactant during the pulping and conversion of Eucalyptus chips. Procentese et al. (2018) also observed that inhibitors, such as furfural and hydroxymethyl furfural, concentration were below 0.015 g L^{-1} whereas, coumaric, ferulic and gallic acid concentrations were below detectable values (0.1 g L^{-1}). These concentrations were much below the threshold values that could limit the enzymatic hydrolysis and subsequent saccharification. Thus, pre-treatment using NADES eliminates the additional step of detoxification.

Biomass recalcitrance is primarily caused by the cross-linked polymeric structure formed between lignin and hemicellulose through strong hydrogen bonds and covalent bonding network with functional groups such as found in phenyl glycosides, benzyl ethers and benzyl esters (Yongzhuang et al., 2017). NADES can hydrolyse these links by disrupting the bonds between lignin and hemicellulose and develop new hydrogen bonds between the Cl^- ions from the NADES and OH^- groups in the lignin and hemicellulose. But the hemicellulose removal is highly dependent on the reaction processing conditions. For instance, ChCl:urea (1:2), a weakly basic NADES, when applied at 120 °C for 12 h was only able to remove ~20 % hemicellulose from Kraft lignin. On the other hand, ChCl:oxalic acid (2:1), a strongly acidic NADES, was able to hydrolyse 95.8 % hemicellulose at 120 °C in 4 h (Hou et al., 2017).

4.2. Role of NADES in biological systems

The application of NADES in the field of life sciences was explored by numerous researchers (Dai et al., 2013a; Dai et al., 2014). As NADES are derived from natural products, they exhibit excellent properties such as high biodegradability, no toxicity, sustainability and low cost. These characteristics of NADES have opened avenues for its application in health-related fields, foods and cosmetics. In biological systems, NADES offer various applications: media for the enzymatic reactions (Choi et al., 2011), biotransformations (Gutierrez et al., 2010), extraction procedures (Paiva et al., 2014; Dai et al., 2013b), DNA dissolution (Dai et al., 2013a), natural pigments stabilization (Dai et al., 2014), and biomass valorization (Francisco et al., 2012).

4.2.1. In biomedicines

NADES are extensively utilized in the biomedical field owing to their low-toxicity, versatility and biodegradability. NADES can enhance solubilization, permeation and absorption and also bring about the dissolution of drugs. NADES with biomedical properties were developed using ibuprofen, menthol, and camphor by Tuntarawongsa and Phaechamud (2012). In comparison to water, NADES can highly solubilize drugs at a much faster rate. NADES on combining with bioactive substances like menthol, ibuprofen, mandelic acid, natural and biodegradable polymers along with supercritical carbon dioxide (SC-CO_2) are considered to be suitable alternatives for various biomedical usages like bone therapy scaffolds and production of drug delivery systems (Abbott et al., 2004). NADES when mixed with biopolymers generates an ideal path for delivering the therapeutic drug. Further doping of biopolymer to polymer SC-CO_2, foam is produced, where the polymer permeability enhances the surface area. The polymer can achieve the desired shape using a template.

In a recent study, Olivares et al. (2018) used NADES constituting betaine and urea as the solvent to evaluate the stabilities of clavulanic acid (CLV) and imipenem (IMP) and also assessed their anti-microbial by determining the minimum inhibitory concentration. They observed enhanced stabilization of the β-lactam antibiotic IMP (7-fold) and CLV (2.5-fold) on using NADES as solvent compared to that in aqueous solution. Microbiological tests further revealed that the antibacterial activity at day 7 was considerably reduced both for CLV and IMP in aqueous solution while no antibacterial activities were observed in blood urea (BU). Enhanced stabilization in BU might be attributed to the inert behaviour of NADES and high energetic restraint which supports antibiotics to attain a further steady conformation. The statistical analysis of the results supports the possible usage of BU in the prevention of β-lactam antibiotics degradation.

NADES thus exhibit efficient biomedicinal applications owing to their natural constituents and biocompatibility. They assist in the extraction of various bioactive substances from the natural resources which hold biomedical usages. For some authors, NADES present as a greener generation of the ILs due to their pseudo ionic fluid state and as ILs, they can be designed to achieve required physico-chemical characteristics (Dai et al., 2015). The work reported on the application of NADES in biomedicines, drug delivery and extraction of bioactive compounds are summarized in Tables 3 and 4.

4.2.2. In clinical therapy

DES family exhibits several advantages in clinical therapy due to low cost, easy synthesis, negligible vapor pressure and non-flammable nature (Dai et al., 2014; Smith et al., 2014). Stott et al. (1998) observed the role of DES in transdermal devices also known for their role in the dissolution of model drugs by enhancing permeation, solubility and absorption (Aroso et al., 2016). These DES were called as 'Therapeutic deep eutectic solvents' (THEDES) as their system constitutes an API. Fig. 11S (Supplementary file) depicts, the formulation of ChCl and ascorbic acid yielding Dexamethasone with therapeutic effects. Developing a new, highly efficient and specific release dosage is an urgent necessity of the society to enhance the low solubility of drugs, their bioavailability, and evading heavy dosage. THEDES have acquired a lot of momentum and consideration owing to the great solubility power for an extensive variety of mixtures and high stabilization (Aroso et al., 2016; Wang et al., 2014). Various NADES are being used successfully in healthcare all over the world. They enhance the bioavailability of APIs which is an important challenge in the field of clinical therapy. APIs can be either formulated with DES or can be solubilized by DES thus, forming a eutectic constituent.

Aroso et al. (2016) have reported the coupling of THEDES along with a polymeric substance to bring out new opportunities for the generation of novel pharmaceutical schemes. They also performed doping of polymers with the THEDES, thus exposing it to a mix of $scCO_2$ which is a foaming or sintering method which occurs owing to the plasticizing attributes of the THEDES. Thus, the polymeric matrices have greater permeability and are feasible substitutes for the drug delivery processes. Several examples of THEDES are eutectic mixtures like acetylsalicylic acid, benzoic acid and antiseptic APIs. APIs can further form mixtures with quaternary ammonium salts (e.g. ChCl and terpenes such as thymol or menthol). This demonstrates their possibility to obtain wide variety and tunability of THEDES. They mediate the controlled release of the drug which in turn is a highly efficient system. APIs in form of THEDES have various advantages with respect to their pharmaceutical applications such as enhancing its solubility. API bioavailability increases, resulting in a lower dosage of therapeutic compounds required. This can lead to benefits like fewer side effects, better patient-compliance and a more economical process.

NADES have further established their role in antibacterial photodynamic therapy (Fig. 12S, Supplementary file). This therapy uses light, a photosensitive chemical and molecular oxygen for preventing bacterial infections to cause cell death. Wikene et al. (2017) have observed photosensitizers like curcumin (hydrophobic in nature) (Wikene et al., 2015), which is a natural THEDES. Curcumin can considerably enhance phytotoxicity towards the bacterial cells on combining with NADES. Thus, THEDES are known to be the most remarkable and versatile sustainable solvents in the area of clinical therapy, opening doors for various novel applications.

4.2.3. As a nanocarrier for drug delivery

Currently, about 40 % of the pharmaceutical solid drugs have poor water solubility that results in low permeation and less bioavailability (Kalepu and Nekkanti, 2015). Moreover, the efficiency of the drug is weak due to the poor solubility or degradation through intestine enzymes or internal metabolic activates, and the drug is economically expensive (in part due to larger doses required) and also can lead to worse side effects (Barbas et al., 2010). Hence, pharmaceutical researchers have focused on the development of drug delivery strategies to increase the efficiency of the existing drug by enhancing the solubility and permeation rather than the discovery of new drugs. For instance, the application of NADES (camphor or menthol based) improves the solubility of API - ibuprofen (Lu et al., 2016). The combination of the glycolic and oxalic acid has enhanced the solubility of itaconazole, piroxicam, posaconazole and lidocaine (Li and Lee, 2016). The application of levulinic acid has improved the solubility of ketoprofen (Lu et al., 2016). Proline/glycine is known to trigger the solubility of rutin (Faggian et al., 2016). Moreover, the combinations of

Table 3
Application of natural deep eutectic solvents in biomedical application and drug delivery.

NADES	Polymer	Drug/gene	Composite	Application	References
Citric acid	Poly(ethylene glycol)	Microdiol	Poly(1,8-octanediol citrate) (POC) and poly (1,12-dodecanediol citrate) (PDDC)	Cardiovascular tissue engineering	(Yang et al., 2005)
Citric acid	Poly(ethylene glycol)	Macrodiol	Poly(1,8-octanediol-co-citrate)	Cardiovascular tissue engineering	(Yang et al., 2006)
Citric acid	Poly(ethylene glycol) 1,8-octanediol	–	Elastomer poly(1,8-octanediol-citrate) (POC)-hydroxyapatite	Orthopedic implants	(Qiu et al., 2006)
Citric acid	Poly(tetrafluoro-ethylene) (PTFE) 1,8-octanediol	–	Poly(1,8-octanediol citrate)	Cartilage tissue engineering	(Kang et al., 2006)
Citric acid	1,8 Octanediol	–	Poly(1,8-octanediol-co-citrate) elastomeric thin films	Bladder regeneration	(Sharma et al., 2010)
L-cysteine/citric acid	PEG; 1,8-octanediol	–	PEG, citric acid, and amino acid. (BPLP-PEG-amino acid)	Bio imagining	(Yang et al., 2009)
Citric acid	1,8-Octanediol	Luciferase and GFP mixed (pEGFPLuc: 5.7 kb) pEGFP-C2: 4.7 kb; pNGVL1: 5.7 kb	Citric acid-based polyester elastomers	Gene delivery	(Zhang et al., 2009)
Citric acid,	1,8-Octanediol, and *N*, *N′*-bis(2-hydroxyethyl) ethylenediamine		Poly(diol citrate) elastomers	Nitric oxide release	(Zhao et al., 2010)
Citric acid	Poly(ethylene glycol)	Macrodiol	Biodegradable shape-memory elastomers	Drug-release	(Serrano et al., 2011)
Citric acid	1,8-Octanediol	ChCl (DES-C), tetraethylammonium Bromide (DES-T), hexadecyltrimethyl-ammonium bromide (DES-H), or methyl-triphenylphosphonium bromide (DES-M)	Poly(octanediol-co-citrate)	Antibacterial activity	(Garcia-Arguelles et al., 2013)

DES: deep eutectic solvents; PEG: polyethylene glycol; PDDC: poly 1,12-dodecanediol citrate; PTFE: poly tetrafluoroethylene; ChCl: choline chloride.

Table 4
Natural deep eutectic solvents role in extraction of natural products.

NADES in extraction	Molar ratio	Source of extraction	Bioactive compounds	References
Choline chloride:glycerol	1:1	*Fagopyrum tataricumhul*	Rutin	(Huang et al., 2017)
Choline chloride:glycerol	1:2	*Phyllanthus flexuosus*	Diterpenoid	(Xu et al., 2016)
Choline chloride-1,3-butanediol	1:2	*Lonicerae japonicae*	Phenolic acids	(Peng et al., 2016)
Choline chloride:D-(þ)-glucose	5:2	*Mentha piperita*	Volatile monoterpene compounds	(Jeong et al., 2018)
Choline chloride:oxalic acid	1:1	Grapes skin	Phenol extraction	(Bubalo et al., 2016)
Choline chloride:urea heated until homogeneous colourless liquid formed	0.69:1	Pineapple leaf and kapok fiber	Lignocellulosic fibers	(Draman et al., 2016)
Choline chloride:lactic acid	1:2	*Lippia citriodora*	Phenolic compounds	(Ivanovic et al., 2018)
Choline chloride-lactic acid	1:9	Rice straw	Lignin and xylan	(Kumar et al., 2018)
Lactic acid:glucose:water	6:1:6	Virgin olive oil	Phenol extraction	(Paradiso et al., 2016)
	5:1:1	*Larrea divaricata*	Phenolic compounds and alkaloids	(Gomez et al., 2018)
Glycerol:proline:sucrose (1:1:1), 20 % water (w/w)	1:1:1	*Ginkgo biloba*	Ginkgolides phenolics acid	(Khezeli et al., 2016)
LGH:water	6:1:6	Extraction from extra virgin oil	Phenolic compounds extraction	(Paradiso et al., 2016)
LGH	5:1	By-products from agro-food industries	Extraction of phenolic compounds	(Fernandez et al., 2018)
Acetylcholine chloride:lactic acid	2:1	Fruits vegetables and spices	Flavonoids	(Bajkacz and Adamek, 2017)

LGH: lactic acid, glucose and water.

NADES with API have increased the drug release by oral or topical or transdermal applications. The combinations for example, are (NADES:API ratio) menthol:CoQ10 (Nazzal et al., 2002), lauric acid:CoQ10 (2:1) (Tarate and Bansal, 2015), lauric acid:ibuprofen (5:2) (Berton et al., 2017), phenol: itraconazole (20:3), camphor:lidocaine (1:1) (Gala et al., 2014), menthol: paeonol (6:4) (Wang et al., 2017), aspirin:adiphenine (1:2), aspirin:ranitidine(1:2) (Abbott et al., 2017). Thus, application of naturally derived NADES can increase the drug delivery and bioavailability through increasing the solubility and permeation.

Recent developments in the nanomedicine and polymer chemistry have enabled the innovations in drug delivery systems (DDS) that increases the stability and targeted release of drug in the pathological site without causing the side effect to normal cells (Pradeepkumar et al., 2018). There are several types of biopolymers utilized in the development of DDS including the chitosan, alginate, cellulose, xanthan gum, etc. (Patra et al., 2018) However, the therapeutic potency of the drug carriers depends upon the design, formulation, and properties of the nanomaterials. The combination of NADES with biopolymers can enhance therapeutic efficiency through targeted release. The growth of NADES based THEDES has increased the permeation and penetration of the drugs. Moreover, the API are solids with low solubility, reduced bioavailability and deprived polymorphism (Datta and Grant, 2004), therefore, the combination of the NADES would enhance the therapeutic efficiency of the drug without affecting the pharmaceutical activity by improving the physical properties such as compaction behaviour, solubility and bioavailability (Clarke et al., 2012). The NADES based nanocarriers have the most promising advantages in sustained release of the drugs, fewer side effects, prolonged activity over the conventional DDS (Prausnitz and Langer, 2008; Aroso et al., 2015). For example, the lidocaine-1,8-octanediol-citric acid loaded in elastomers poly(octanediol-*co*-citrate) triggers the high capacity of the drug-elution (Fig. 13S, Supplementary file). Although it enhances the API release and acts as polymerizing media, it has the disadvantage that the condensation occurs with 1,8-octanediol-citric acid (Serrano et al., 2012). To overcome this, a new formulation has been developed for the delivery of lidocaine hydrochloride either methacrylic acids or acrylic acids with the lidocaine, which increases the polymerization and triggers the controlled release (Sanchez-Leija et al., 2014).

The bacterial pathogens and infections are a major concern in causing a significant impact on human life survival. Recently, the routine use of various antibiotics increased the multi-drug resistance of pathogens. Hence the development of the novel biodegradable antibacterial coating agents incorporated with polymeric elastomer is essential (Carriazo et al., 2012). For instance, the antibacterial compounds loaded citric acids based poly (octanediol-co-citrate) elastomer (Fig. 14S, Supplementary file) have enhanced delivery of the antibacterial agents resulting in augmented antibacterial activity (Garcia-Arguelles et al., 2013). The citric acids (NADES) based novel polyester elastomers are applied in the tissue engineering of bone, cardiovascular, bladder and cartilage (Sharma et al., 2010; Serrano et al., 2011; Zeimaran et al., 2017), and other biomedical applications such as gene delivery, bio-imagining and regulated drug discharge (Yang et al., 2009; Zhang et al., 2009).

Thus, the NADES based media have enabled the fabrication of the drug that is adequately soluble towards drug release in targeted organs. For instance, a current study has shown that the application of folic acids constituting DES mediated doxorubicin-loaded DES@FA-g-β-alanine-co-PCL enhances the sustainable drug release in a targeted location (Pradeepkumar et al., 2018).

5. Limitations and future perspectives in the application of NADES

NADES were discovered by scientists in an attempt to direct focus on the negative impacts of traditional organic solvent on the environment. NADES are promising with excellent properties of simple synthesis, eco-friendly with low toxicity, efficient extraction abilities and economical value. Though they possess a great role in extraction procedures, their use is often compared with that of the ILs. There is a dearth of information regarding the usage of NADES in the separation process. Their role as modifiers for background electrolyte in capillary electrophoresis should be further investigated. Some limitations were observed in the conventional NADES due to their high viscosity, similar to that of ILs and DES which results in several problems like slow transfer of mass in dissolutions and extractions and time utilizing solvent transfer processes. As NADES constitute polar constituents, their application is limited to hydrophilic complexes and can extract polar metabolites only. Thus, non-polar NADES should be synthesized to extend their applications.

Moreover, to apply NADES in large scale industries, it becomes difficult to manipulate processes with non-volatile and extremely viscous solutions of pure complexes. To extract pure compounds from the extracts of NADES, it is important to discover new methods for elimination of the solvent as evaporation is not possible. Due to their tailor-made properties, they possess huge potential to adapt the interaction amongst the target analytes and to overcome such practical problems mentioned above. More research should be promoted using NADES to overcome its limited applications compared to that of solely NADES. The contribution of NADES in the field of nanotechnology still needs to be persuaded as the information is limited compared to that for ILs, which are pioneers in the field of green solvents in nanoscience. Research should be performed on different mixtures of NADES and task specificity should be investigated rather than focusing only on the most prevalent DES studied. Thus, the full potential of NADES is still yet to be explored.

Extensive studies related to the complex nature and interactions of NADES compositions should be promoted for their better understanding. These results will be beneficial as NADES are considered to be selective chemicals that can destroy abnormal cells such as tumour cells and shows no destruction towards normal cells. Evaluating the noxiousness for human and animal cell lines is necessary for further application-based researches on NADES. Investigation of whether NADES can be used as potential future alternative drugs in radiotherapy and chemotherapy will be a key breakthrough in the field of science. NADES are already being utilized in DNA solubilization and antibiotics stabilization, which is a major achievement in this field. Future studies should concentrate on evaluating elementary toxicological parameters for standardized biotests of diverse trophic stages, synthesizing less harmful materials into safe and non-toxic substances, determine toxicity for standardized cell lines to develop awareness, operational methods and their application in pharmaceutical and medical fields and to develop degradation methods for removal of substances through enzymatic oxidation.

6. Conclusions

Solvents are crucial for industries and experimental division of natural sciences. Major problems associated with the application of ILs can include difficulty in their synthesis, steep costs, lower biodegradation rates and high toxicity concerns. NADES, a subset of DES, in turn, are easier to prepare, biodegradable and shows low toxicity. As per the properties of NADES, they are selective towards a wide range of solvents even challenging ones with an intermediate polarity that often cannot dissolve easily. Their very low vapor pressure prevents evaporation losses, and high biodegradability ensures their safe discharge in the environment and low toxic nature promotes their use in nutraceuticals and food industries. NADES offer great usages in pharmaceuticals, nanotechnology, biotechnology and clinical therapy. Applications of NADES are, however, restricted to several organic reactions, extractions, electrochemistry and enzymatic responses that comprise a minor fraction of ILs universality. Extensive studies should be performed to acquire information as much as possible regarding these types of solvents. The biodegradability studies of NADES will help in evolving new and varied applications of these solvents. To successfully use a particular NADES in a certain application, their impacts on the environment should be thoroughly studied. The rational use of NADES may thus render many benefits to society and the environment.

CRediT authorship contribution statement

Zeba Usmani: Writing - original draft; Review & editing. Minaxi Sharma: Writing - original draft; Review & editing. Manikant Tripathi: Writing - original draft; Review & editing. Tiit Lukk: Review & editing. Yevgen Karpichev: Review & editing. Nicholas Gathergood: Review & editing. Brahma N. Singh: Review & editing. Vijay Kumar Thakur: Review & editing. Meisam Tabatabaei: Review & editing. Vijai K. Gupta: Conceptualization, Writing - review & editing, Supervision.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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