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Published in:
Industrial and Engineering Chemistry Process Design and Development

DOI:
10.1021/acs.iecr.3c00410

First published: 17/05/2023

Document Version
Publisher's PDF, also known as Version of record

I&EC research
Industrial & Engineering Chemistry Research
pubs.acs.org/IECR
Review

Deep Eutectic Solvents toward the Detection and Extraction of Neurotransmitters: An Emerging Paradigm for Biomedical Applications

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Cite This: https://doi.org/10.1021/acs.iecr.3c00410
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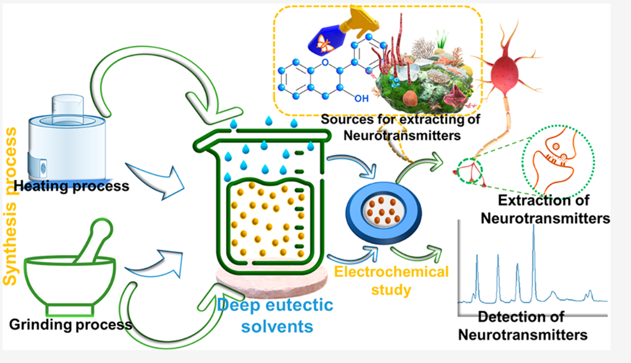
ABSTRACT: Neurotransmitters (NTs), the chemical messengers crucial for the proper functioning of the human brain, have some specific concentration within the human physiological system. Any fluctuations in their concentration may cause several neuronal diseases and disorders. Therefore, the requirement for fast and effective diagnosis to regulate and manage human cerebral diseases or conditions is surging swiftly. NTs can be extracted from natural products. The researchers have developed new protocols to improve the sensors' sensing ability and eco-friendly nature. Deep eutectic solvents (DESs) have gained popularity as "green solvents" in sustainable chemistry. DESs provide a greater range of a potential window that helps in the enhanced electrocatalytic performance of the sensor and more inertness which helps in the corrosion protection of electrodes, ultimately giving better sensitivity and durability to the system. In addition, DESs provide facile electrodeposition of different materials on working electrodes, which is a prime prerequisite in electrocatalytic sensors. Here, in this review, the application of DESs as green solvents in detecting and extracting NTs is described in detail for the first time. We cover the available online articles up **to December 2022** for the extraction and monitoring of NTs. Finally, we have concluded the topic with future prospects in this field.



1. INTRODUCTION

Neurotransmitters (NTs) are chemical messengers of the brain that transform the information between different neurons to the behavioral and physiological states of the human neural network.[1] Neurological processes such as sleep, learning, mood, concentration, appetite, and other cognitive functions are directly governed by neurotransmitters (NTs).[2] Specific concentration to each NT is required for the proper functioning of the human brain. Any fluctuation in their concentration can cause neuronal disorders such as traumatic brain injury[3] and cerebral meningitis.[4] Epinephrine, norepinephrine, glutamate, serotonin, and acetylcholine are excitatory NTs, while γ-aminobutyric acid is considered inhibitory NTs and dopamine (DA) is considered to exhibit both excitatory and inhibitory functions.[5] A disturbance in the concentration of NTs can cause severe neuropsychiatric diseases such as Parkinson's, Schizophrenia, Alzheimer's, and epilepsy.[6]

Therefore, an early stage diagnosis of NTs is required to avoid risk factors. Various methods, such as electrochemical,[7] positron-emission tomography,[8] optical,[9] and microdialysis,[10] are available for sensing NTs. However, several organic and inorganic solvents are utilized in these sensing techniques that have detrimental impacts on the environment. In addition to the neurophysiological importance of NTs, these analytes can also be regarded as the most attractive drug candidates because of numerous biological activities involving therapeutic strategies.[11] Hence, the extraction of NTs from natural products has great importance. Most of the techniques involved in extracting NTs utilized conventional solvents, threatening the environment.

One of the significant steps to ensure sustainable development in all areas of human activity is the replacement of harmful chemicals with eco-friendly ones.[12] This effort has led to new solvent types, such as DESs[13] and switchable hydrophilicity solvents.[14] This review article discusses the importance and utilization of DESs in monitoring and extracting NTs. In 2003, Abbott et al.[15] introduced DESs utilized as alternatives to room temperature ionic liquids and nonaqueous solvents. DESs are formed by combining a

Special Issue: Vivek Ranade Festschrift

Received: February 14, 2023
Revised: April 27, 2023
Accepted: May 4, 2023

hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) in a specific mole ratio and possess high thermal and chemical stability, low toxicity, melting points, and high biodegradability, which found great interest in the diverse field.[16] The evolutionary development of DESs with time is listed in Figure 1.[17]

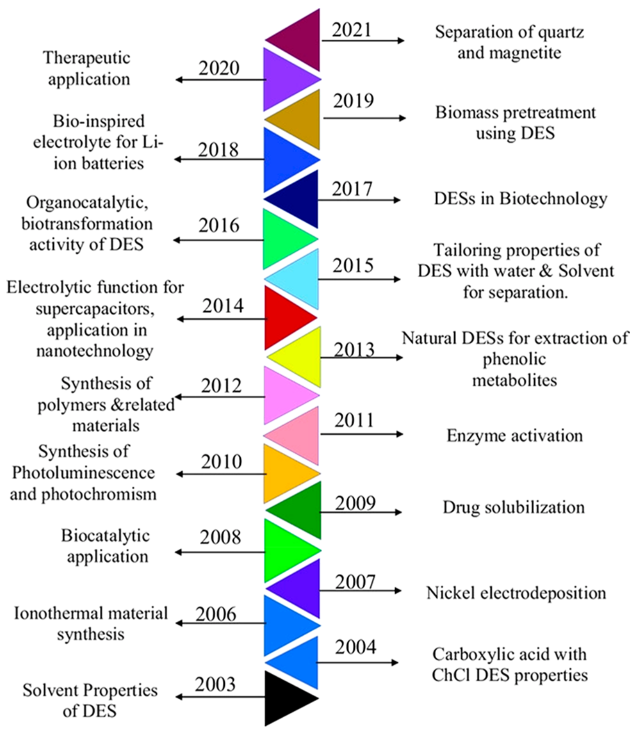


Figure 1. Evolutionary development of DESs with time. Reprinted with permission from ref 17. Copyright 2021 John Wiley and Sons.

Various nanocomposites have been utilized for sensing NTs because of their solid hybrid connection and synergistic effect with redox relationships, enhancing their electrocatalytic performance.[18] These nanocomposites can be synthesized by utilization of DESs due to their crucial features like adjustable physiochemical properties, biodegradability, and cost-effectiveness that modulate and tailor the growth of nanocomposites.[19] DESs can be utilized as a reactant, precursor, solvent, and shape-controlling agent to fabricate nanocomposites. Some studies show that materials prepared with the help of DESs exhibit better performance than materials prepared in conventional aqueous solutions. For instance, the $CeO_2-Co(OH)_2$-based sensor was developed in L-proline/$Ce(NO_3)_3 \cdot 6H_2O$ DES. The synthesized material acquired more prominent oxidase-like activity than materials prepared in aqueous solutions. This nanocomposite acts as a sensor for detecting acetylcholinesterase and studying the irreversible inhibitor activity.[20] There is a need to explore the utilization of DESs in monitoring the activity and extraction of NTs.

As far as we know, no review article provides critical information regarding the potential effectiveness of DESs as environmentally friendly solvents in the field of NTs. It is the first review which includes information related to DESs for extraction and determination of NTs. We discuss the types, synthetic processes, and properties of DESs. Furthermore, applications of DESs in detecting NTs, followed by their extraction, are described. Herein, we provide future scenarios of DESs in neurosensors as only a few NTs are detected and extracted using these green solvents.

2. IMPORTANCE OF DESS IN NEUROSENSING

Up to the present time, DESs have discovered numerous applications within analytical chemistry, for example, in the extraction of NTs from intricate liquid and solid media,[21] as a conversion environment for nanomaterials,[22] toward elution into disseminative solid-phase removals, and as a mobile-phase changer within chromatography.[23] They have also been used to extract bioactive combinations,[24] such as flavonoids, phenolic acids, polyphenols, saponins, and anthraquinones, from different biological origins.[25,26] Additionally, DESs can solubilize multiple other mixtures, like drugs, metal oxides, and carbon dioxide.[27]

Herein, DESs may occupy an essential part as solvents, extractive agents, and other utilizations, for example, the selective sanctification of effluents. DESs have been utilized in analytical techniques, but the recognition approaches used up until now have been chromatographic or spectroscopic. The attraction has been established in changing electrode shells in DESs as a region of synthesis techniques for electrochemical sensors and biosensors with various characteristics, Figure 2.[28] Similarly, as happens in ionic liquid,[29] the explanation is that the different surface morphologies, approximated to the aqueous media, will prepare access through the analyte to the sensor medium in another form, and the unique surface design may confer distinctly, hopefully, improved, sensing effects.

3. TYPES AND SYNTHESIS OF DEEP EUTECTIC SOLVENTS

3.1. Types of DESs.

DESs are categorized within four kinds (I–IV) based upon the general formulation $Cat^+ X^- zY$, where Cat^+ usually represents phosphonium, ammonium, or sulfonic, and X means Lewis's base. At the same time, Y is a Lewis/Bronsted acid, and the quantity of Y particles interacting through the analogue's anion is represented by z.[30] Type I utilizes nonhydrated metal salts, while hydrated metal hydrides are used in the type II DES system. The type III DES system is a mixture of quaternary ammonium salts and common HBDs like carboxylic acids and amines. In contrast, the type IV DES system involves a combination of hydrogen bond donors with metal halides.[31] Quaternary ammonium and imidazolium cations with choline, such as [ChCl, $HOC_2H_4N^+(CH_3)_3Cl^-$], are the most widely studied systems due to their cost-effectiveness on large-scale use. Few halide salts and HBDs that are utilized in the production of DESs are illustrated in Figure 3. Some common examples of type I eutectic solvents comprise chloroaluminate/imidazolium salt, various metal halides such as $FeCl_2$, CuCl, LiCl, $SnCl_2$, $ZnCl_2$, and $CdCl_2$.[32] These nonhydrated metal halides have limitations, such as low melting point for the formation of type I eutectics. Still, by using hydrated metal halides and choline, the scope of DESs can be improved, which are type II solvents. Cost-effectiveness and insensitivity toward moisture make hydrated metal halides useful in large-scale industrial production feasible. Much focus has been attracted toward type III DESs because of their capability to solvate a broad series of transition metal species. Nonetheless, some reported DESs do not fall into these four types. Consequently, type V DESs were proposed by

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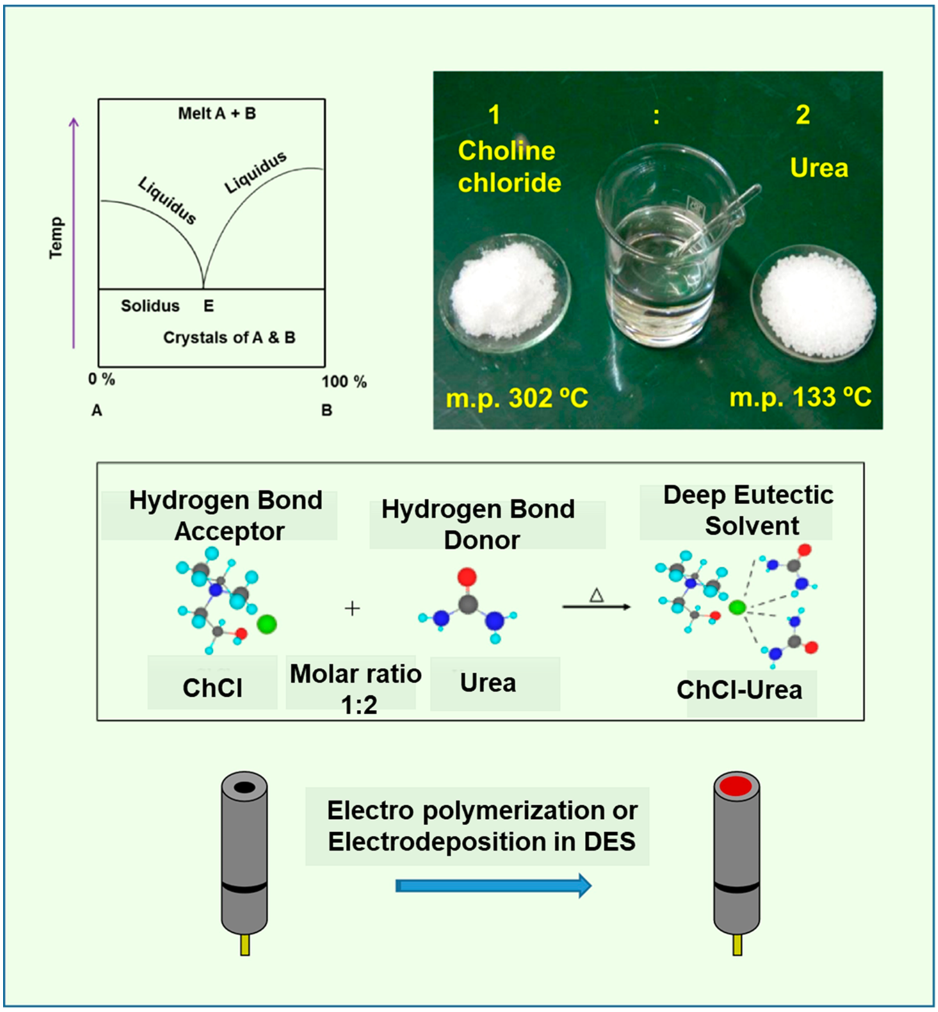

Figure 2. Principles after Type III eutectic solvents, demonstrated with relining (choline chloride (ChCl) and urea), and their usefulness in changing the configuration and surface of modifier sheets upon electrodes through electropolymerization or electrodeposition. Reprinted with permission from ref 28. Copyright 2018 Elsevier.

Abranches and his co-workers comprising nonionic species like menthol and thymol.[33]

3.2. Synthesis of DESs. Heating and grinding methods are generally employed for the synthesis of DESs. DESs are readily prepared by mixing an appropriate number of solid substances, such as Lewis/Bronsted bases and acids, in a container where one component behaves as a HBD while the other acts as an HBA; heat this mixture and stir until a colorless liquid is obtained as showcased in Figure 4. By utilizing ultrasounds and microwaves, the experimental procedure can be speeded up.[34,35] This synthesis method is environmentally friendly because solvents can be synthesized without producing any waste and emissions, and all initial atoms are comprised in the final mixture. For instance, Omar, K.A. and R. Sadeghi synthesized a pyrogallol-based DES by mixing the appropriate amount of suitable solids and pyrogallol, heating at 60 °C, and stirring with a magnetic stirrer at 300 rpm where pyrogallol acts as the hydrogen bond donor.[36] In one case, a 1:2 molar proportion of ChCl and pyrogallol was utilized by the authors for the formation of the DES, which showed a glass transition temperature of −50.9 °C measured with differential scanning calorimetry.

4. PROPERTIES OF DEEP EUTECTIC SOLVENTS

Depending on certain factors such as molecular size and chemical composition of quaternary ammonium compounds and HBDs, their molar ratio, and temperature, the properties of DESs can be easily changed, which makes this system highly flexible. The remarkable physiochemical properties of DESs, such as lower vapor pressure and volatility, thermal and chemical stability, etc., make them attractive in the solvents to be designed for specific applications.[37] Very high viscosity (usually ≫100 cP at 298 K) is the fascinating property of DESs that is highly advantageous in various areas of polymer synthesis. The high viscosity is due to the lower mobility of free species resulting from the extensive hydrogen bond formation during the production of DESs. In this section, various physiochemical characteristics of DESs are discussed.[38]

4.1. Phase Behavior. DESs are mixtures of more than one pure compound instead of a single combination. Therefore, they are generally represented by solid−liquid phase diagrams where the eutectic point shows the minimum melting point temperature and the composition of both compounds in the case of the binary mixture, as displayed in Figure 5.[39] DESs are called "deep" because their melting point is lower compared to ideal eutectic temperature, which cannot be differentiated from other mixtures. So, all types of combinations are not

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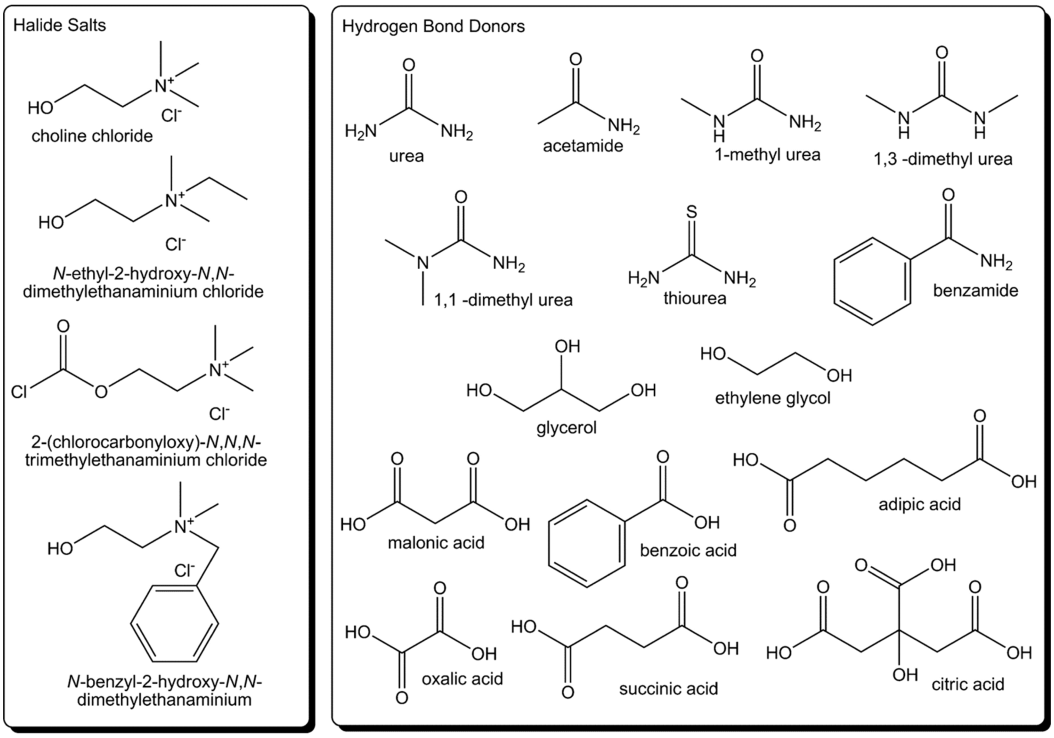

Figure 3. Assemblies of a few halide salts and HBDs are utilized in the production of DESs. Reprinted with permission from ref 32. Copyright 2014 American Chemical Society.

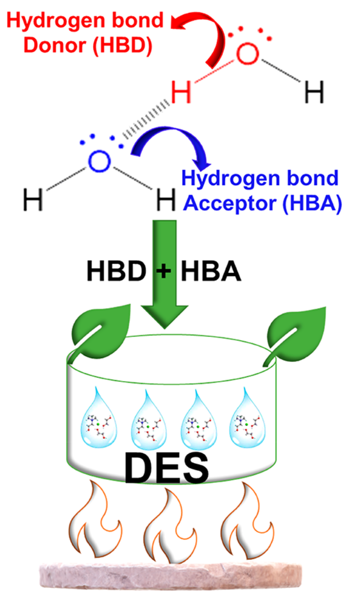

Figure 4. Graphical representation of DESs via heating and grinding methods.

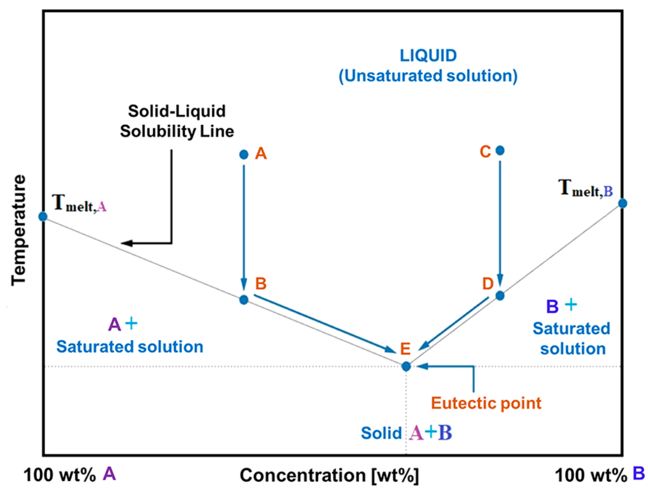

Figure 5. Prototypical binary phase graph for eutectic combinations. Intercalation of **A** in **B** (or vice versa) hinders the natural crystallization trends of the other segment, and the consequent combinations partake in a noticeable excavation into the melting point. DESs pursue this same broad direction but display abruptly deep pits. Reprinted with permission from ref 39. Copyright 2021 American Chemical Society.

considered to be DESs; only those mixtures with low melting points compared to individual compounds are known as DESs.[40] The eutectic composition indicates the composition at which the lowest melting point takes place. Moreover, at operating temperature, DESs should be liquid even if it needs a dissimilar design than a eutectic one. So, a phase diagram is necessary to determine the ideal solubility curve; one must know the melting characteristics of pure compounds.

At slightly different compositions, the characteristics and dynamics of DESs can transformation radically, so for industrial applications, analyzing their characteristics is advantageous. Specific designs and binary phase diagrams of individual DESs are mainly present to date, which further attracts the focus of researchers to obtain phase diagrams, composition and temperature range of DESs, and their yielding information to design DESs for specific applications.[39]

4.2. Role of Viscosity and Ionic Conductivity. Viscosity is another significant characteristic of DESs and is highly studied for forming materials. Mostly DESs have high viscosity nearly equal to or greater than 100 mPa·s. Extensive hydrogen bonding between the components of DESs is the main reason

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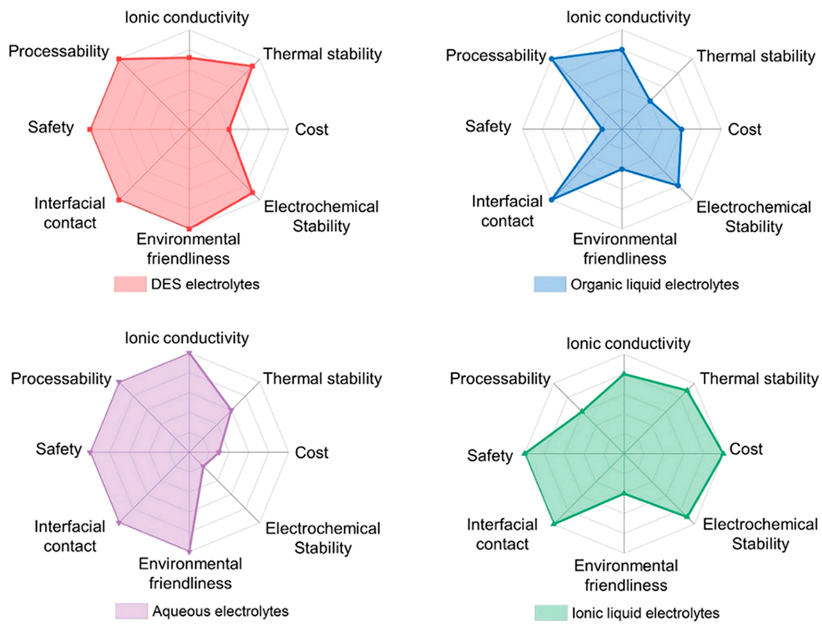

Figure 6. Comparison of different characteristics of DESs with other electrolytes. Reprinted with permission from ref 46. Copyright 2021 John Wiley and Sons.

for the higher viscosity of these solvents. Electrostatic interactions and small empty volumes also contribute toward the high viscosity of DESs.[34,39] The length of the alkyl chain also affects viscosities; longer chains have a higher viscosity than shorter chains. So, larger anions, e.g., Br^-, are shown high viscosities compared to smaller anions, e.g., Cl^-.[41] These high viscosities of DESs can hinder sensors' electrochemical performance as it reduces ions' ionic mobility. Further, mass transfer between phases is hindered by high viscosities, which cause issues with extraction processes.

However, some DESs have lower viscosities than organic solvents.[42] Also, by the proper proportion of water, the viscosities of DESs can be decreased. Still, the amount of water content is crucial for reliable and accurate performance because it can change the polarity and surface tension of the solvent with the addition of water content. For instance, in an experiment with 30% water content in ChCl:glycerol, maximum extraction efficiency for DA was obtained.[43] The viscous behavior of DESs is generally expressed in terms of the *Arrhenius* equation in the case when the temperature range is narrow. At the same time, over a wide range of temperatures, the viscosities are measured by Vogel−Fulcher−Tammann (VFT) equations,[44] as in eqs 1 and 2

$$\eta_{Arrehenius} = Ae^{E/RT} \quad (1)$$

where R, E, and A represent molar gas constant, activation energy, and a prefactor and

$$\eta_{\mathrm{VFT}} = Ae^{B/(T-T_0)} \quad (2)$$

where B is a fitting parameter, A is the preexponential factor, and T_0 is the ideal glass-transition temperature. With the differences in the viscosities of the same DESs, for instance, for 1:1 ChCl:urea at 40 °C, viscosity was 202 mPa·s vs 2142 mPa·s, while for the 1:2 ratio of the same salt at 30 °C, viscosity was 152 mPa·s vs 527.28 mPa·s, which can be attributed to the synthesis method, experimental conditions, and impurities.[42]

The property which quantifies the flow or conduction of current and ions by the ionic conduction mechanism is known as ionic conductivity. Conductivity is inversely related to viscosity, so, owing to high viscosities, most DESs have lower ionic conductivity.[39]

4.3. Surface Tension. Studies revealed that DESs have higher surface tension than organic solvents and are comparable with imidazolium-based ionic liquids.[45] Figure 6 showcases the comparison of different properties of DESs with other electrolytes.[46] Organic liquid electrolytes are favorably explosive and unstable, whereas aqueous media suffer from a thin ESW. Due to the inherently more ionic conductivity, better metal-salt solubility, good electrochemical constancy, and nonflammability, ILs suit nicely with maximum battery chemistry. Inappropriately, their applied applications are overwhelmed with high costs and problems in practice and being poisonous. On the other hand, DES-based electrolytes have earned a growing awareness with different rechargeable batteries because they are nontoxic and affordable and have the worth of ILs.

Surface tension is one of the critical DES physical effects. Its evaluation is required to determine industrial-associated issues and design new partition machineries. Understanding these effects delivers significant details of the molecular impact upon the intensity of relations within the combination. Also, surface tension is essential in innovation and mass transfer operations like condensation, absorption split, and withdrawal.[47]

Numerous techniques have been proposed toward the projection of surface tension. Between them, the experimental directions suggested by Macleod are a straightforward process. This approach represents the temperature-self-governing connection amid surface tension and density of the liquid, eq 3:[48]

$$\frac{\sigma 1}{4} = k\rho \quad (3)$$

Here, σ is the surface tension, ρ is the density, and k is a constant which is not temperature dependent.

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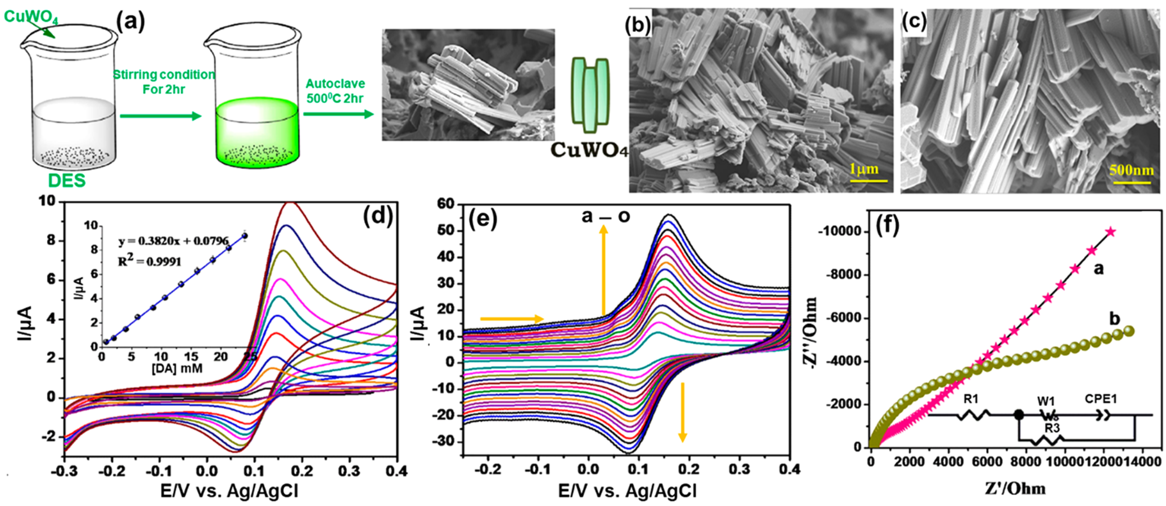

Figure 7. Graphical representation of the $CuWO_4$ nanorods' sensor (**a**); fast electron SEM images of $CuWO_4$ nanorods (**b, c**); CV images at a sweep rate of 50 mV/s for different concentrations of DA and 0.1 mM DA at a sweep rate of 10−300 mV/s (**d, e**); electrochemical impedance spectra (**f**). Reprinted with permission from ref 60. Copyright 2022 Elsevier.

Generally, the surface tension of a liquid reduces as the temperature rises, and the increased temperature increases the kinetic energy, which in turn reduces intermolecular magnetic interactions. Therefore, the "cohesive force of surface tension" falls. Additionally, the surface tension of the liquid evolves to zero at the critical temperature (T_c). Suppose the T_c of the liquid is comprehended. In that case, the liquid surface tension at dissimilar temperatures may be assessed utilizing the Othmer equation (eq 4). With this equation, the surface tension at one temperature may be defined from a reference surface tension at another temperature.

$$\sigma(T) = \frac{\sigma_{ref}(T_c - T)(T_c - T_{ref})11}{9} \quad (4)$$

Here, σ_{ref} is the reference surface tension, T_{ref} is the reference temperature, and T_c is the critical temperature.

5. DESS AS A GREEN SOLVENT FOR THE DETECTION AND EXTRACTION OF NEUROTRANSMITTERS (NTS)

In sensors or biosensors, the surfaces of electrodes have been modified with DESs. As a part of the preparation methods, the various properties of DESs are explained in the above section. Various nanomaterials have been synthesized in DESs, such as Au-SiO_2 for sensing glucose in human serum,[49] Pd/Ag hollow structure for the detection of hydrazine,[50] carbon nanotube-based sensor for sensing dichlorvos,[51] and many more. Further, DESs are used to separate and extract various bioactive compounds from natural products. For instance, saponins or flavonoids,[52] pesticides,[53] plant and animal proteins,[54] and alkaloids[26] are extracted from plants using DESs. The extraction of other bioactive compounds, such as NTs, remains to be explored. Only a few NTs have been removed, which we will describe further in this article.

5.1. DESs for the Detection of Neurotransmitters. Detection of NTs is crucial due to their importance in the physiological system of living beings. DESs being green and sustainable solvents are utilized in synthetic processes of various nanomaterials modified on several working electrodes for sensing applications of NTs. The detection of several NTs using DESs is described in this section.

5.1.1. DESs in Sensing of Dopamine. Dopamine (DA) is an NT that circulates in mammalian central nervous systems to reduce transmission among the brain and neurons. The fundamental principle of sensing DA involves detecting DA release and its subsequent effects on the activity of neurons. DA is synthesized in specific areas of the brain and released from neurons in response to various stimuli, such as rewarding experiences or drugs of abuse. Once released, DA interacts with specific receptors on target neurons, leading to changes in their activity.

One of the most common methods for sensing DA is using electrochemical sensors, such as fast-scan cyclic voltammetry (FSCV) or amperometry. These sensors measure the changes in electrical current that occur when dopamine is oxidized at an electrode surface. By measuring the changes in current over time, researchers can determine the concentration of DA in a given brain region.[55] Another method for sensing DA is through positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). These imaging techniques allow researchers to visualize the distribution of DA in the brain and to monitor changes in DA release in response to specific stimuli or drugs.

Overall, the fundamental principle of sensing DA involves detecting its release and subsequent effects on neuronal activity through electrochemical sensors or imaging techniques.[56] These methods have provided important insights into the role of DA in normal brain function and various neurological and psychiatric disorders.

In the medical area, DA is issued intravenously to treat low blood pressure and low cardiac results and cut down the flow of organs induced through shock, trauma, and septicemia.[57] A substantial quantitative decision of DA is essential in clinical research. Chang et al.[58] proposed polymelamine in DESs for electrocatalytic detection of DA. Polymelamine showed tremendous sensing ability when prepared with DESs as compared to conventional electrolytes. This polymelamine-DES was incorporated with a multiwalled carbon nanotube (MWCNT) on a glassy carbon electrode (GCE) (polymelamine-DES/MWCNT/GCE) for selective detection of the DA with the interference of uric acid (UA). The authors observed a limit of detection of 288 nM within a linear range of 1 μM-1

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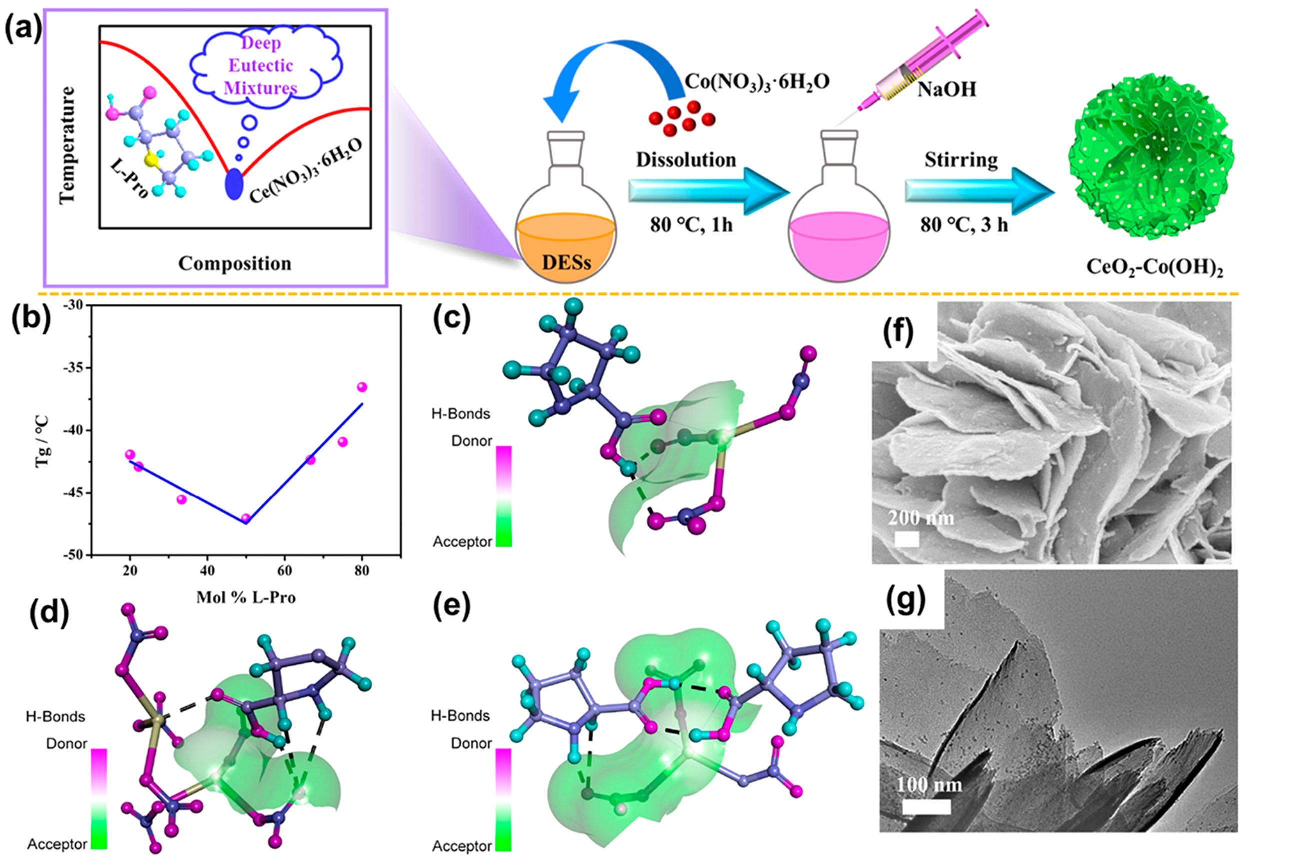

Figure 8. (a) Graphical illustration of the preparation process of CeO_2−$Co(OH)_2$ nanosheets utilizing a DES; (b) glass-transition temperature of a DES, (c-e) 3-D structures with 1:1, 1:2, and 2:1 ratios of L-proline and $Ce(NO_3)_3$, respectively); (f, g) SEM and TEM images of prepared nanosheets. Reprinted with permission from ref 20. Copyright 2022 American Chemical Society.

mM. An electrochemical sensor based upon pristine/La-doped magnesium titanate ceramics utilizing a 1:2 DES mixture of ChCl and urea to detect DA was fabricated.[59]

The synthesized sensor showed a detection limit of 1.32 μM within a linear range of 5−50 μM. The $CuWO_4$/GCE-based electrochemical system was prepared in a DES. The DES was prepared with ethylene glycol and ChCl in a 1:1 ratio. $CuWO_4$ was synthesized using the grinding method, and then this powdered $CuWO_4$ was dissolved in 60 mL of the DES. Finally, the mixture was kept at 180 °C in a muffle furnace. The sensor showed a detection limit of 24 nm within a linear range of 6.0×10^{-7} to 26×10^{-5} M and a sensitivity of 9.48 $\mu A\ \mu M^{-1}\ cm^{-2}$. Graphical representation of the obtained sensor is showcased in Figure 7(**a**); fast electron SEM images of $CuWO_4$ nanorods are shown in Figure 7(**b, c**); CV images at a sweep rate of 50 mV/s for diverse concentrations of DA and 0.1 mM DA on a sweep rate of 10−300 mV/s are shown in Figure 7(**d, e**); electrochemical impedance spectra are shown in Figure 7(**f**).[60]

5.1.2. DESs in the Sensing of Acetylcholine. Acetylcholine (ACh) is an NT that plays a vital role in the nervous system, particularly in transmitting signals between nerve cells and muscle cells. The fundamental principle of sensing ACh involves the interaction of the NT with specific receptors on the surface of cells, which triggers a series of biochemical events that result in the transmission of nerve impulses.[61] ACh receptors are classified into two types: nicotinic and muscarinic receptors. Nicotinic receptors are ionotropic, meaning that they directly control the flow of ions into and out of the cell.[62] These receptors are typically found at the neuromuscular junction, where they mediate the effects of acetylcholine on skeletal muscle. Nicotinic receptors are also found in the brain and other parts of the nervous system. On the other hand, muscarinic receptors are metabotropic receptors, meaning that they indirectly control the flow of ions into and out of the cell by activating intracellular signaling pathways. These receptors are typically found in the brain, heart, and smooth muscle.

When ACh is released from the presynaptic terminal of a nerve cell, it diffuses across the synaptic cleft and binds to its receptors on the postsynaptic cell.[63] This binding triggers a conformational change in the receptor protein, which allows ions to flow into or out of the cell, depending on the receptor type. The influx of ions into the cell generates an electrical signal, which propagates down the length of the cell and triggers the release of NTs from the presynaptic terminal, thus multiplying the signal to the next neuron in the pathway.[64] In summary, the fundamental principle of sensing ACh involves the interaction of the NT with specific receptors on the surface of cells, which triggers a series of biochemical events that result in the transmission of nerve impulses.

DESs are suitable green solvents toward the extraction of mixtures from natural consequences. As there need to be more details about DESs, investigation is required to understand better the relations and complicated nature of DES arrangements and their relevancy for extraction of biologically active mixtures from plant substances. Silva and Brett fabricated a biosensor utilizing a DES as a solvent for the detection of ACh in synthetic samples of urine. A DES was prepared using a 1:2 molar proportion of ChCl and ethylene glycol. The

https://doi.org/10.1021/acs.iecr.3c00410
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Table 1. Summary of DESs Used in Synthetic Processes of Several Sensors to Detect NTs

Composition of DES	Limit of detection	Linear range	Sensitivity	Detected analyte	ref
Glycol:ChCl in 1:1 ratio	24 nM	6.0×10^{-7}−26×10^{-5} M	9.48 μA μM^{-1} cm^{-2}	DA	60
ChCl:urea in 1:2 ratio	1.32 μM	5−50 μM	-	DA	45
-	288 nM	1 μM-1 mM	1.19 μA μM^{-1} cm^{-2}	DA	58
ChCl:urea in 1:1 ratio	0.11 μM	1−300 μM	124 μA μM^{-1} cm^{-2}	DA	67
ChCl:urea in 1:2 ratio	1.3 μM	5−180 μM	1.46 ± 0.13 mA cm^{-2} mM^{-1}	DA	68
ChCl:urea in 1:2 ratio	28.6 ± 0.2 μM	-	32.49 ± 0.37 μA mM^{-1} cm^{-2}	DA	69
ChCl:urea in 1:2 ratio	0.1980 μM	100−1200 μM	0.044 μA μM^{-1} cm^{-2}	DA	70
ChCl:ethylene glycol in 1:2 ratio	1.06 μM	2.5−60 μM	600 μA cm^{-2} M^{-1}	ACh	65
L-proline:$Ce(NO_3)_3$ in 1:1 ratio	-	0.2−20 mU/mL	-	AChE	20

chronoamperometry technique was utilized to investigate the performance of the as-prepared biosensor, which reveals that it exhibited a sensitivity of 600 μA cm^{-2} M^{-1} and a low limit of detection of 1.06 μM within a linear range from 2.5 to 60 μM.[65] The authors also compared this performance with other sensors and found that this sensor showed better performance; for instance, it showed higher sensitivity, nearly six times in comparison to the sensor developed by Moreira et al.[66] The enzyme that helps ACh maintain its average level is known as acetylcholinesterase (AChE), as it hydrolyzes ACh into thiocholine and acetic acid. A sensor based on CeO_2−$Co(OH)_2$ nanosheets was prepared for the detection of AChE. The sensor was synthesized in a DES, designed by mixing 0.02 mol of L-proline and $Ce(NO_3)_3 \cdot 6H_2O$ in a round-bottom flask and heated at 60 °C.[20] Figure 8(**a**) represents the graphical presentation of the preparation process of CeO_2−$Co(OH)_2$ nanosheets utilizing a DES; Figure 8(**b**) represents glass-transition temperature of a DES; Figure 8(**c-e**) represents 3-D structures with 1:1, 1:2, and 2:1 ratios of L-proline and $Ce(NO_3)_3$, respectively; Figure 8(**f, g**) represents SEM and TEM images of prepared nanosheets. This sensor showed high sensitivity within the linear range of 0.2−20 mU/mL.

Different compositions of DESs that are utilized for synthesizing various sensors for detecting DA and ACh with sensitivity, detection limit, and linear range of sensors are summarized in Table 1.

5.2. DESs for the Extraction of Neurotransmitters.

DESs are a solvent system that has gained attention in recent years for its potential as an alternative to conventional organic solvents in various chemical and biological applications, including the extraction of neurotransmitters. A DES is formed by mixing two or more components, usually an HBD and an HBA, with a eutectic point at a temperature below their melting points. The unique properties of DESs make them attractive for use in the extraction of NTs. First, DESs are environmentally friendly and have low toxicity compared to conventional organic solvents, which makes them safer to handle and dispose of.[71] Second, DESs have a tunable nature, which means that they can be customized to suit the specific properties of the NT being extracted, resulting in higher extraction efficiency and selectivity.[72]

Several studies have shown that a DES can effectively extract various NTs, including dopamine, serotonin, and gamma-aminobutyric acid (GABA).[73] For example, a study[74] demonstrated the potential of a ChCl-based DES for extracting dopamine from brain tissue samples. The study found that a DES showed a higher extraction efficiency and selectivity for dopamine than traditional organic solvents such as methanol and acetonitrile. Another study showed the effectiveness of a DES in extracting serotonin from human plasma samples.[75] The study found that a DES composed of ChCl and glycerol had a higher extraction efficiency and selectivity for serotonin than other solvents such as methanol and acetonitrile.

Despite the potential benefits of DESs, their use in the extraction of NTs is still in its early stages, and more research is needed to understand their capabilities and limitations fully.[76] Additionally, DESs are still relatively expensive compared to conventional solvents, which may limit their widespread use in research and industrial applications.[77] In summary, DESs are a promising alternative to traditional organic solvents for extracting NTs due to their unique properties, such as low toxicity, tunability, and high selectivity. However, further research is needed to explore their potential fully and to make them more economically feasible for widespread use.

DESs are emerging as an alternative solvent to classical organic solvents for extracting and separating various bioactive compounds with several purposes, such as obtaining raw materials, separation and purification techniques, etc. NTs can also be separated from natural products by utilizing DESs. The most common procedure for the extraction of NTs involves water[78] and methanol[79] as a solvent. The extraction through these traditional solvents is highly efficient but threatens the environment because of toxicity, flammability, and volatility.[80] It is essential to develop eco-friendly methods to extract NTs. DESs can be measured as a greener alternative for the extraction of NTs. We briefly explain the importance of DESs in the extraction process of NTs, although very little information has been available to extract NTs using DESs until now. Briefly, to remove epinephrine, norepinephrine, and DA, Fe_3O_4@MIL-100 (Fe) core−shell grafted with pyrocatechol was fabricated by Khezeli and Daneshfar.[81] DESs were prepared by mixing ChCl with urea/ethylene glycol/glycerol in a 1:2 molar ratio. The obtained sorption capacities were 70.48 mg/g for epinephrine, 73.26 mg/g for norepinephrine, and 75.57 mg/g for DA. The recovery rates were more than 91% with a detection limit of 0.26, 0.36, and 0.22 μ/L, respectively, within the linear range from 1 to 300 μ/L.

DESs containing ChCl and glycerol in a 1:2 molar proportion with 30% water were utilized to extract DA from *Portulaca oleracea* L.[43] About 2.96 mg of DA was extracted from 1 g of plant material when the temperature was 58 °C, and the solid−liquid ratio was 40 mg/mL. The authors compared their work with previously applied methods for extracting DA from different parts of the plants with traditional organic solvents. They found that extraction by using DESs showed higher yield in min., compared to other solvents.

6. CONCLUSION AND FUTURE PROSPECTS

In conclusion, DESs have shown great potential as a novel class of solvents for detecting and extracting NTs. DESs have unique

https://doi.org/10.1021/acs.iecr.3c00410
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properties such as low toxicity, low volatility, and high solubility, making them attractive for extracting and detecting NTs. The use of DESs combined with various techniques, such as electrochemical and spectroscopic methods, has shown promising results in detecting NTs. Moreover, DESs extract NTs from biological samples, such as blood and urine.

To achieve the goal of green and sustainable chemistry, there is a quest for green solvents. DESs contribute considerably to attaining the goal of sustainability and can be considered the most investigated solvents. DESs have many applications, such as in energy storage devices and biosensing. The facile preparation and nontoxic nature of DESs ensure the future with their economic viability and sustainability. Some reports have been studied, which revealed that the physiological properties of DESs are majorly affected by HBDs, and the performance of sensors is also affected by the combination of HBD-HBA. The varieties of HBD and HBA systems still need to be explored. We explore the utilization of DESs in specific applications related to NTs. Owing to the importance of NTs in the physiochemical functioning of human beings, this review article delivers a wide-ranging outline of the performance of DESs in detecting and extracting NTs. Although DESs have detected only DA and acetylcholine, only a few experiments were performed for the extractions of NTs. NTs such as serotonin, epinephrine, norepinephrine, and γ-aminobutyric acid are as crucial as DA and acetylcholine for the neurophysical activities of humans. Therefore, DESs must be utilized for the sensing of these NTs. Our understanding of DESs in neurosensing is still in its infancy. It can improve future studies by understanding the mechanism of DESs in separating and monitoring NTs. This will make the analysis more robust and systematic in neurosensing and separation and enable logical selection for a particular application. Overall, DESs provide a promising avenue for developing new and efficient techniques for detecting and extracting NTs, which could have significant implications for the diagnosis and treatment of neurological disorders. Further research is needed to explore the full potential of DESs in this field and to optimize their use for practical applications.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the support from the Department of Chemistry and Research & Development Cell of Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala, Haryana, India.

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