Pharmaceutical Sciences, 2022, 28(4), 492-495
doi:10.34172/PS.2022.31
https://ps.tbzmed.ac.ir/

Editorial

Natural Deep Eutectic Solvents (NADES)- Progress in Polymer Synthesis and Pharmaceutical Application

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Article History: Received: 29 June 2022 Accepted: 7 July 2022 ePublished: 17 July 2022

Over the past century, organic synthesis, through the development of novel pharmaceuticals, has led to a revolution in medical care. On the other hand, this practice has created some concerns as it can adversely impact the environment.[1] The so-called natural deep eutectic solvents (NADES), known as eco-friendly solvents, are identified as a potential solution to this environmental issue.[2] This topic is the most crucial as half of the reagents in the synthesis processes are solvents, and they contribute to high waste, and pollution.[3]

The concept of green chemistry, firstly conceptualized in 1991 by Paul Anastas and Roger Garrett, and later termed by Joe Breen, is not new in the pharmaceutical industry. The design of sustainable chemicals and chemical processes is considered a central topic to control environmental hazards and pollution. This is because the regulatory requirements for the purity of pharmaceuticals lead to the generation of more waste and by-products, per kilogram of the product, than in other industrial productions. Therefore, many pharmaceutical industries, in the last two decades, have tried to adopt green approaches for the development and manufacturing of drugs.[1,3-6] Green chemistry, to reduce manufacturing costs and waste products, and decrease resource consumption, has been considered. Many opportunities for greener methods have been given by solvents.[7,8]

Most of the organic solvents are toxic, harmful, and environmentally damaging, resulting in major industrial waste and concern for their disposal. Besides, their recovery and reuse are often associated with complex procedures and expensive treatments. In this frame, the replacement of petroleum-based solvents with eco-friendly alternatives can be beneficial and achieved through the use of green/sustainable solvents, aqueous solvents, supercritical carbon dioxide assisted approach, the gas expanded solvents, ionic liquids assisted approach, and solvent-free processing.[9-11] Ionic liquids, due to their unique physicochemical properties, are considered attractive "green" recyclable alternatives to volatile, toxic, hazardous, and highly flammable organic solvents.[12] As a subclass of ionic liquid, NADES meet the "green" criteria, and thus they have drawn great attention from the scientific community.[13,14] NADES (Figure 1) consist of a mixture of hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs), exhibiting lower melting temperatures than their components separately. Low cost, easy preparation, biodegradability, stability at high temperatures, non-flammability, and sustainability are several advantages of NADES.[13,15,16]

Figure 2 presents the evolution of NADES, over years, for pharmaceutical applications starting from the eutectic mixture to the replacement of ionic liquid solvents, and the formation of the therapeutic deep eutectic system (THEDES).[17,18]

Since the introduction of NADES, in 2011, by Choi *et*

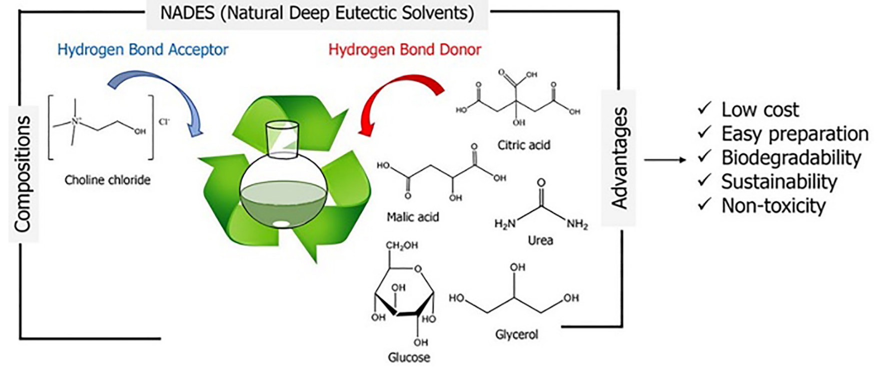

Figure 1. Composition and advantages of NADES.

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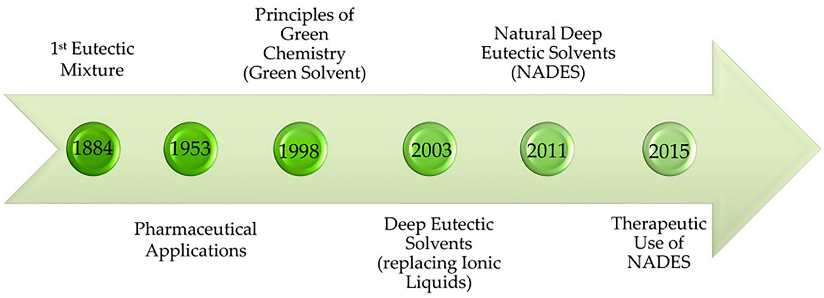

Figure 2. The timeline of NADES evolution for pharmaceutical applications.

al.[19], their important role in cellular metabolism has been investigated, unveiling many questions in the biochemistry of cells and organisms. NADES, as a greener alternative to conventional solvents, are widely applied as extracting solvents through two mechanisms of action such as direct action interacting with target compounds through hydrogen bonding, and indirect action damaging the cell wall.[13] NADES have been indicated as a green solvent for the extraction of various bioactive compounds such as hydroxytyrosol from olive fruits (proving its antioxidant and anti-bacterial abilities),[20] chlorogenic acid,[21-22] antioxidants[23] from the plants with many numerous biological activities, etc.

Further, NADES can be considered substantial solvents for enzymatic reactions, and synthetic organic chemistry.[19] Duarte *et al.*[24] demonstrated the efficiency of THEDES (therapeutic deep eutectic solvents) to enhance the bioavailability and pharmacokinetics of the active pharmaceutical ingredients. To optimize the therapeutic effects of the drug, and minimize its adverse effects, various delivery strategies have been developed. Jeliński *et al.*[25] presented NADES as a new media to achieve a desired therapeutic effect by enhancing the solubility and bioavailability of curcumin, a polyphenol with anti-oxidant, anti-inflammatory, anti-microbial, anti-diabetic activities, etc. NADES are also used to enhance the solubility of resveratrol (increasing its capacity to inhibit the activity of matrix metalloproteinases, which have a key role in the development of various diseases),[26] acetaminophen (a poorly water-soluble drug),[27] dexamethasone (increasing its antioxidant properties),[28] etc. Further, Olivares et al.[29] showed the NADES influence on the anti-bacterial effectiveness of beta-lactam antibiotics.

Gutiérrez *et al.*,[30] through a theoretical approach, confirmed the deep eutectic solvents (DES) as suitable vectors for the delivery of anesthetic active pharmaceutical ingredients (bupivacaine, prilocaine, and procaine). Mano *et al.*[31] used NADES to synthesize the functionalized electrospun fibers which are of great interest for biomedical applications.

In addition to several studies previously reported, NADES are not yet extensively studied in polymer science, probably because of their newness.[16] Pradeepkumar *et al.*[32] developed 5-fluorouracil (5-FU) NADES-poly 2-hydroxyethyl methacrylate (HEMA) to effectively treat cancer over a prolonged period of drug release. The improvement of the biological activities of therapeutic agents, mostly drugs, has been observed through the development of polymeric materials with a remarkable encapsulation efficiency.[33,34] Cyclodextrin (CD)-based polymers, due to their various features, have been considered a nanomedicine strategy to overcome the challenge issues of the drug delivery.[33,35] CD-based polymers have been synthesized using organic solvents or toxic reactants, and widely applied in many fields such as pharmacy, chemistry, agriculture, gene delivery, biomedicine, biotechnology, food, cosmetics, biocatalysis, etc.[36] Therefore recently, NADES, acting as a solvent and as a reactive media, have been reported as an approach to synthesizing novel beta-cyclodextrin (β-CD) -based polymers.[37]

To sum up, the discovery of NADES has stirred up a lot of the research community, starting from their use as extracting solvent to their assistance in polymer synthesis, showing a good platform for the delivery of therapeutic agents.

Such advances in dissemination and investments in the significance of green chemistry, with NADES as the principal representative, are extraordinarily important for the process of future improvements since they can influence the pharmaceutical analyses, the health of patients and employees, and the environmental sustainability.[38] Therefore, there is no doubt that the application of NADES will further grow in the near future.[39] It will also give the appropriate attention to the technical green chemistry evolution that has not been attained in comparison to the green chemistry philosophy.[5] This collection provides a platform for interdisciplinary research of NADES in pharmaceutical applications.

Author Contributions

The manuscript was written by CC, GH, PB and FT and approving the final version for submitting in journal.

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