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Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review

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Corresponding Author:	Marcello Locatelli Gabriele d'Annunzio University of Chieti and Pescara Chieti, ITALY
First Author:	Fotouh R. Mansour
Order of Authors:	Fotouh R. Mansour
	Alaa Bedair
	Mahmoud Hamed
	Galal Magdy
	Imran Ali
	Marcello Locatelli
Abstract:	Natural deep eutectic solvents (NADES) have gained significant attention as green solvents due to their unique properties, such as high solubility, low volatility, low toxicity, and tunability. Liquid phase microextraction (LPME) is a sample preparation technique that plays a crucial role in analytical chemistry, and the use of NADES as extraction solvents in LPME offers numerous benefits compared to traditional solvents. NADES can effectively extract bioactive compounds from natural sources without damaging their structure and activity. They can also serve as solvents and catalysts in organic reactions, enhancing the bioavailability of natural compounds. In addition, NADES can be utilized as mobile or stationary phases in chromatographic techniques for separating and analyzing natural compounds. The review highlights the efficiency of NADES in terms of extraction ability, analyte stabilization capacity, and detection compatibility. Moreover, the availability of their components, ease of preparation, low toxicity, cost-effectiveness, and biodegradability make NADES attractive for researchers in the field of analytical chemistry. The applications of NADES in LPME contribute to the principles of green analytical chemistry and green sample preparation by providing a sustainable and environmentally friendly approach to sample preparation. A comprehensive overview of the applications of NADES in liquid phase microextraction is provided, emphasizing their potential for advancing green practices in analytical chemistry.

Prof. Marcello Locatelli
University "G. d'Annunzio" of Chieti-Pescara,
Dept. of Pharmacy, Build B level 2, Via dei Vestini 31, 66100
Chieti (CH), Italy
E-mail: marcello.locatelli@unich.it

Dear Editor,

Please find enclosed the revised manuscript "***Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review***" submitted to the **Microchemical Journal** as a review article.

We are very grateful to the Editor and Reviewers for their suggestions. All were accepted and reported in the revised version.

Changes were highlighted in yellow in order to better evaluate the improvements following the suggestions.

We hope that in the present form the paper fulfil with Journal high quality.

The submitted manuscript matches the journal's scopes. We hope that our manuscript will receive favorable peer reviews and subsequent publication in your esteemed journal.

Full name	Institutional address	Email address
Fotouh R. Mansour	Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Tanta University, Tanta 31111, Egypt	fotouhrashed@pharm.tanta.edu.eg
Alaa Bedair	Department of Analytical Chemistry, Faculty of Pharmacy, University of Sadat City, Sadat City 32958, Egypt	alaa.m.bedair@gmail.com
Mahmoud Hamed	Pharmaceutical Chemistry Department, Faculty of Pharmacy, Misr International University, Km 28 Ismailia Road, Cairo 44971, Egypt	mhaboaisha@gmail.com
Galal Magdy	Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh 33511, Egypt	galal_magdy@pharm.kfs.edu.eg
Imran Ali	Department of Chemistry, Jamia Millia Islamia (Central University), Jamia Nagar, New Delhi 110025, India	drimran.chiral@gmail.com
Marcello Locatelli	Department of Pharmacy, University "G. d'Annunzio" of Chieti-Pescara, Chieti, 66100, Italy	marcello.locatelli@unich.it

Sincerely,

Prof. Marcello Locatelli
Department of Pharmacy, University "G. d'Annunzio" of Chieti-Pescara, Via dei Vestini 31, 66100 Chieti, Italy E-mail: marcello.locatelli@unich.it

Proposed Reviewers:

1. **Prof. Dr. Victoria Samanidou**; Aristotle University of Thessaloniki, Department of Chemistry, Laboratory of Analytical Chemistry, Greece; samanidu@chem.auth.gr
2. **Prof. Dr. Abuzar Kabir**; International Forensic Research Institute, Department of Chemistry and Biochemistry, Florida International University, Miami, USA, akabir@fiu.edu
3. **Prof. Dr. Halil I. Ulusoy**; Department of Analytical Chemistry, Faculty of Pharmacy, Cumhuriyet University, Sivas, Turkey; hiulusoy@yahoo.com
4. **Prof. Dr. Sibel A. Ozkan**; Ankara University, Faculty of Pharmacy, Ankara, Turkey; ozkan@pharmacy.ankara.edu.tr

Dear Prof. Justyna Płotka-Wasylka;

(Editor, Microchemical Journal)

Thank you for the review of our manuscript (MICROC-D-23-05391R1) entitled "**Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review**". We have deeply considered the referees' comments and made the suggested changes to the best of our ability. These revisions are highlighted in the manuscript and are summarized below:

Comment	**Response**
Reviewer #1	
The authors made the requested changes. Therefore, I recommend that the article be accepted.	We are truly grateful to the Reviewer for the final evaluation and for considering this review publishable in the Journal
Reviewer #2	
	We are truly grateful to the Reviewer for the final evaluation and for considering this review publishable in the Journal
LPME again appears in the abstract without mentioning full form. Though it is given in the list of abbreviations, abstract is meant to be stand alone.	Liquid phase microextraction has been defined in the abstract at its first mention (**Line 32**).
Not convinced with the re-framed statements 227-31. "Besides" is not required here.	We have removed "Besides" from the re-framed statements as suggested (Line 230)
Reviewer # 3	
As stated in the first review, the main drawback of the MS is the citation of improper references and the lack of the appropriate ones, that is a sufficient argument to reject the submission (citation of the relevant references is an essential part of a review work). The entire text and tables are full of references to deep eutectic solvents (DES), not to natural deep eutectic solvents (NADES). [104, 120, 123, 124, 125, 126, 127, 129, 131, 132, 133, 134, 135, 136 …….] An excellent review on the use of deep eutectic solvents (including some NADES) in liquid-phase microextraction was carried out by Santos et al in 2022 (Trends in analytical Chemistry, doi:10.1016/j.trac.2021.116478.), as the authors point out in line 108.	Although we agree with the reviewer that citing improper references and lacking the appropriate ones is a sufficient argument to reject a submission, we assure that this is not the case with our submission, also because the criticisms that were highlighted in the first submission were revised in R1 version following the Reviewer suggestions. In particular, in the first round of evaluation, Reviewer 3 had reported "The main drawback of the MS is the citation of improper references and the lack of the appropriate ones". This point has been extensively revised in the R1 version, as per the uploaded R1 files. He/She had made no mention of the fact that "The entire text and tables are full of references to deep eutectic solvents (DES), not to natural deep eutectic solvents (NADES). [104, 120, 123, 124, 125, 126, 127 , 129, 131, 132, 133, 134, 135, 136 …….]. An **excellent review on the use of deep eutectic solvents (including some NADES)** in

	liquid-phase microextraction was carried out by Santos et al in 2022 (Trends in analytical Chemistry, doi:10.1016/j.trac.2021.116478.), as the authors point out in line 108". It almost seems that "a little at a time" wants to take time (or prevent this work from being published), especially considering that NaDES are a particular category of DES (AS WRITTEN BY THE SAME REVIEWER IN THIS EVALUATION) and often the boundary between the 2 "classes" is very thin. In this case, we would like to highlight that the mentioned references refer to the preparation of DES from: 1- ChCl: phenol [104, 120, 123-127, 129, 133, 134, 136] 2- ChCl:p-cresol [131] 3- ChCl: Maltose [132] The materials used for the preparation are natural. Therefore, DES in such cases can be classified as NADES. Herein, we provide references as proof for considering ChCl, phenol, and maltose as natural compounds available in nature: **ChCl** 10.1016/j.lwt.2023.114595 10.1021/acssuschemeng.2c01976 10.3390/molecules25071619 **Phenol** 10.1177/074823378700300407 https://etheses.whiterose.ac.uk/29929/1/Zeolite%20Catalysts%20for%20Water%20Treatment%20Catalytic%20Wet%20Peroxide%20Oxidation%20%28CWPO%29%20of%20Phenol.pdf 10.1080/03067319.2020.1738412 10.1177/07482337870030040 **p-Cresol** 10.1007/978-3-319-26932-0_48 10.1046/j.0269-283x.2001.00297.x **Maltose**

	10.1016/j.seppur.2023.123271 10.25083/rbl/26.5/2936.2941 10.1111/tpj.15246 In light of what has just been reported, and the extremely positive evaluations of the other 3 Reviewers (two specified the acceptance for publication and the third asked for 2 minimal revisions of the text), we do not understand why this Reviewer (net of further corrections and clarifications) remains in a clearly opposite position. However, once again we want to satisfy the Reviewer's requests and in light of what has highlighted and to avoid confusion, we believe that by changing the title of the review to "Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review" (where the term "natural" is placed in brackets to indicate this subtle subdivision) may be a good compromise that satisfies the Reviewer.
Reviewer # 4	
Accept	We are truly grateful to the Reviewer for the final evaluation and for considering this review publishable in the Journal

We hope the changes that have been made were appropriate and the manuscript can now be accepted for publication. Please address all correspondence to the author indicated below.

Best regards,

Highlights

1. NADES offer greener alternatives for liquid phase microextraction
2. HF-LPME technique benefits from NADES' environmental friendliness
3. Automation advancements improve efficiency of NADES-based extraction
4. Potential limitation in the utilization of NADES

Figure 1

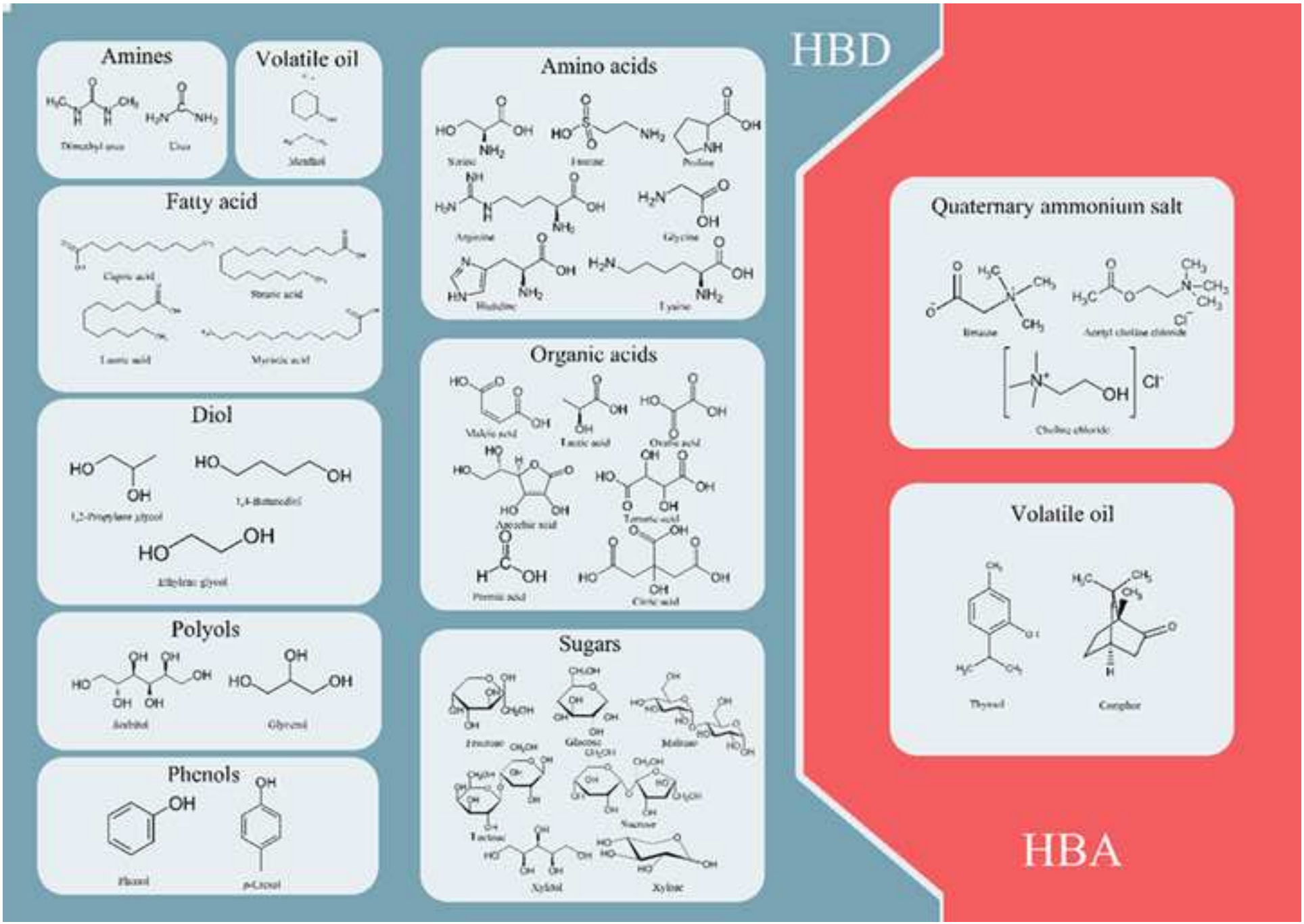


Figure 2

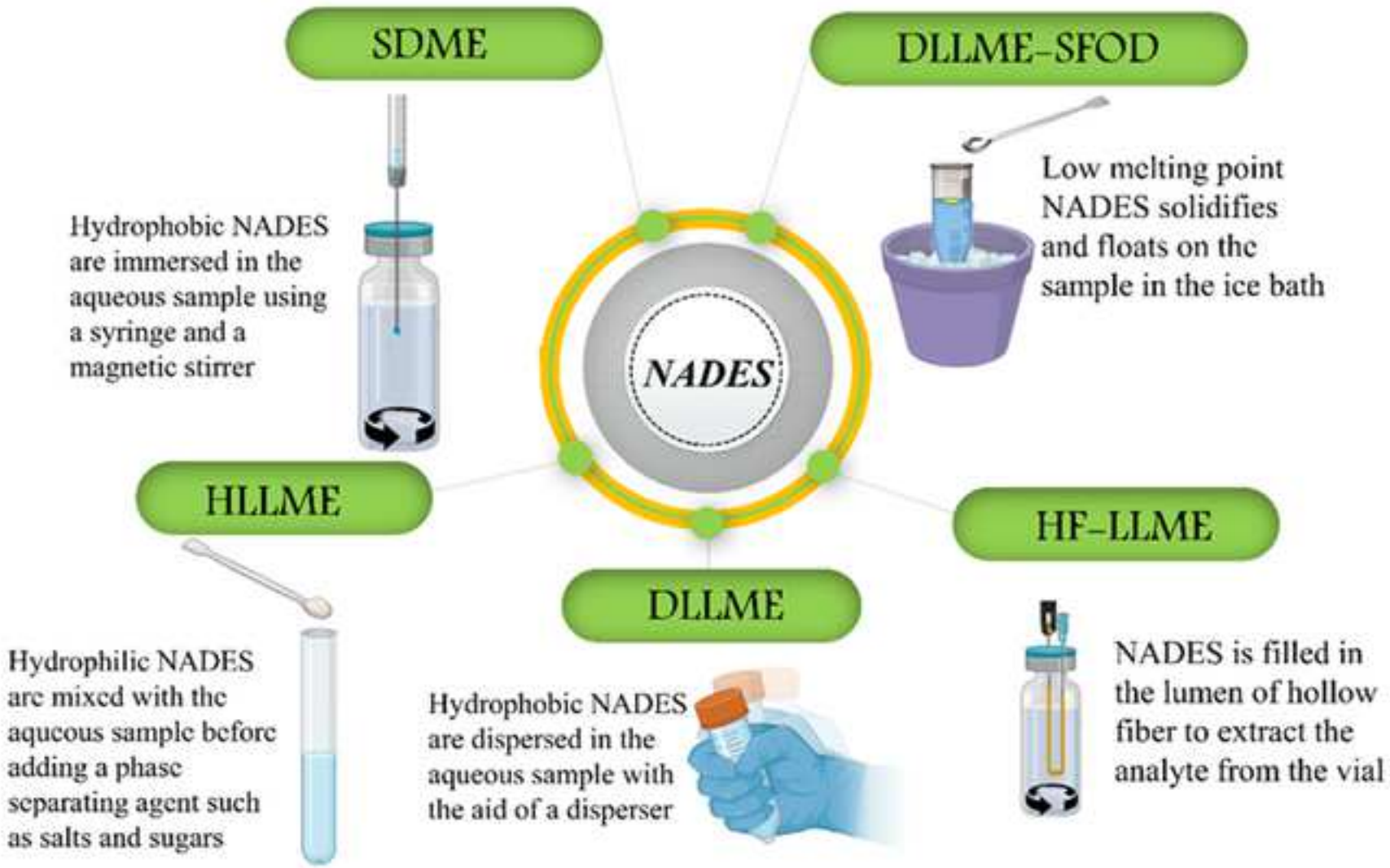


Figure 3

Click here to access/download;Figure;NADES - Figure 3 - R1.tif

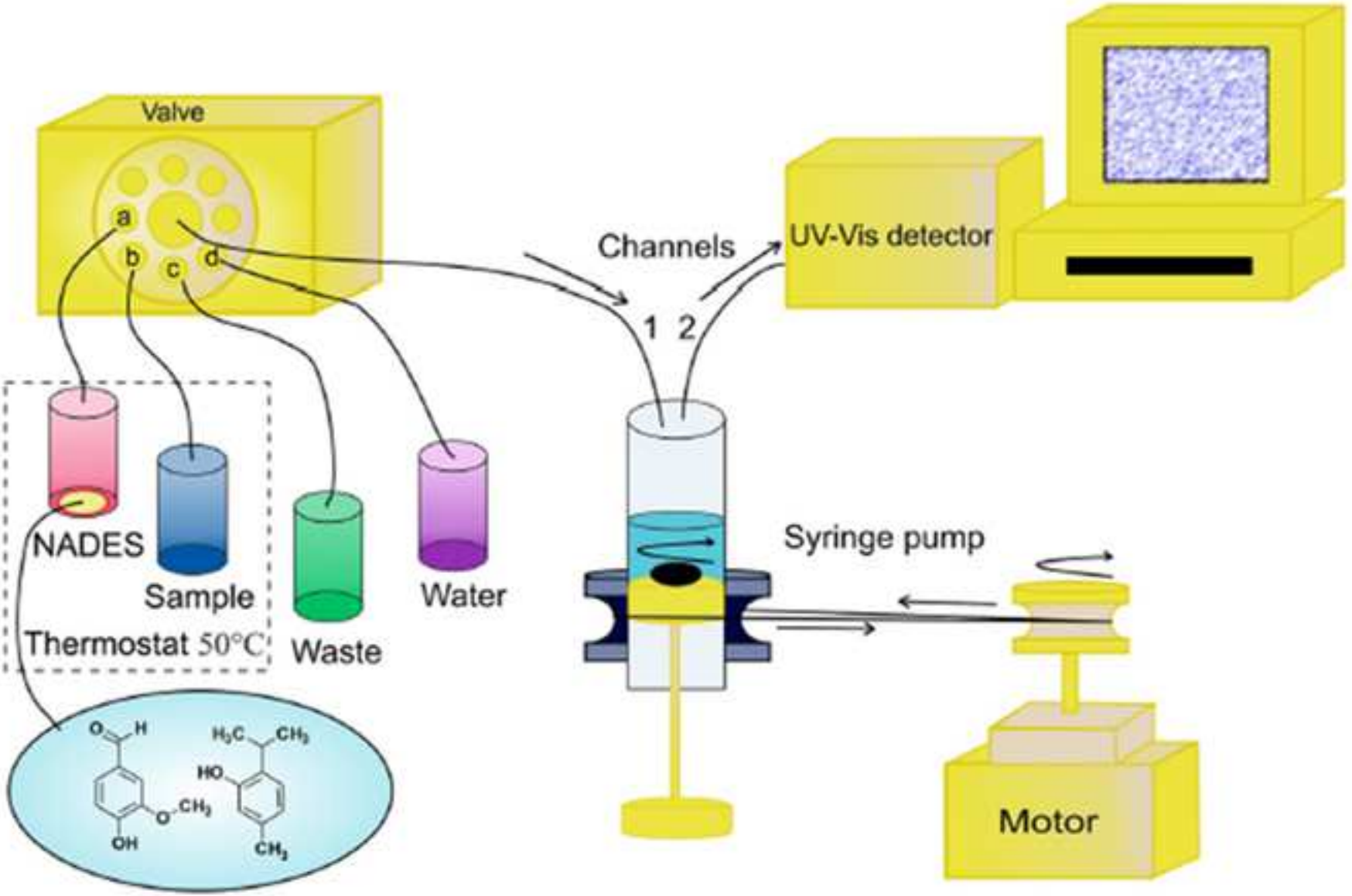
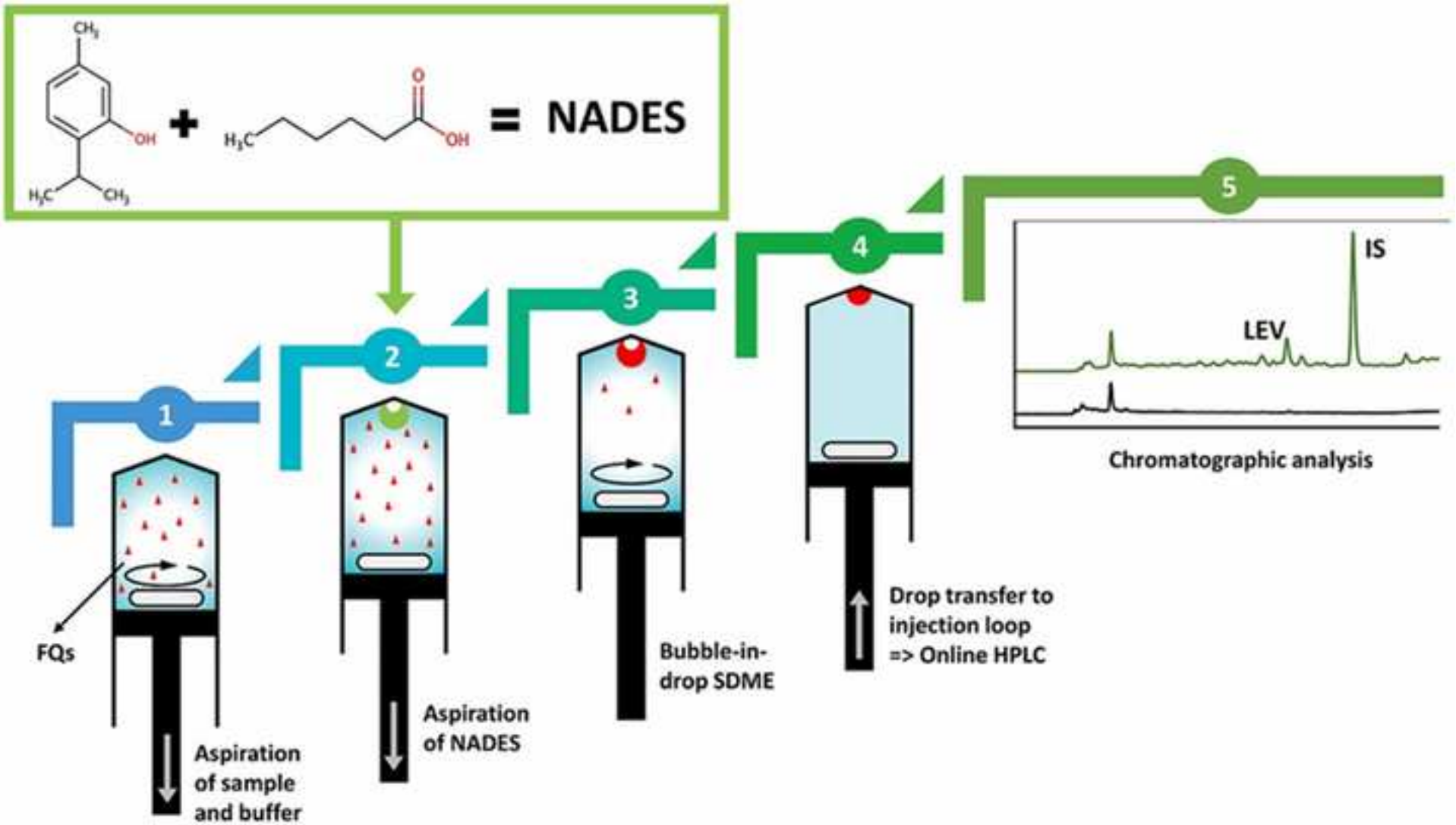
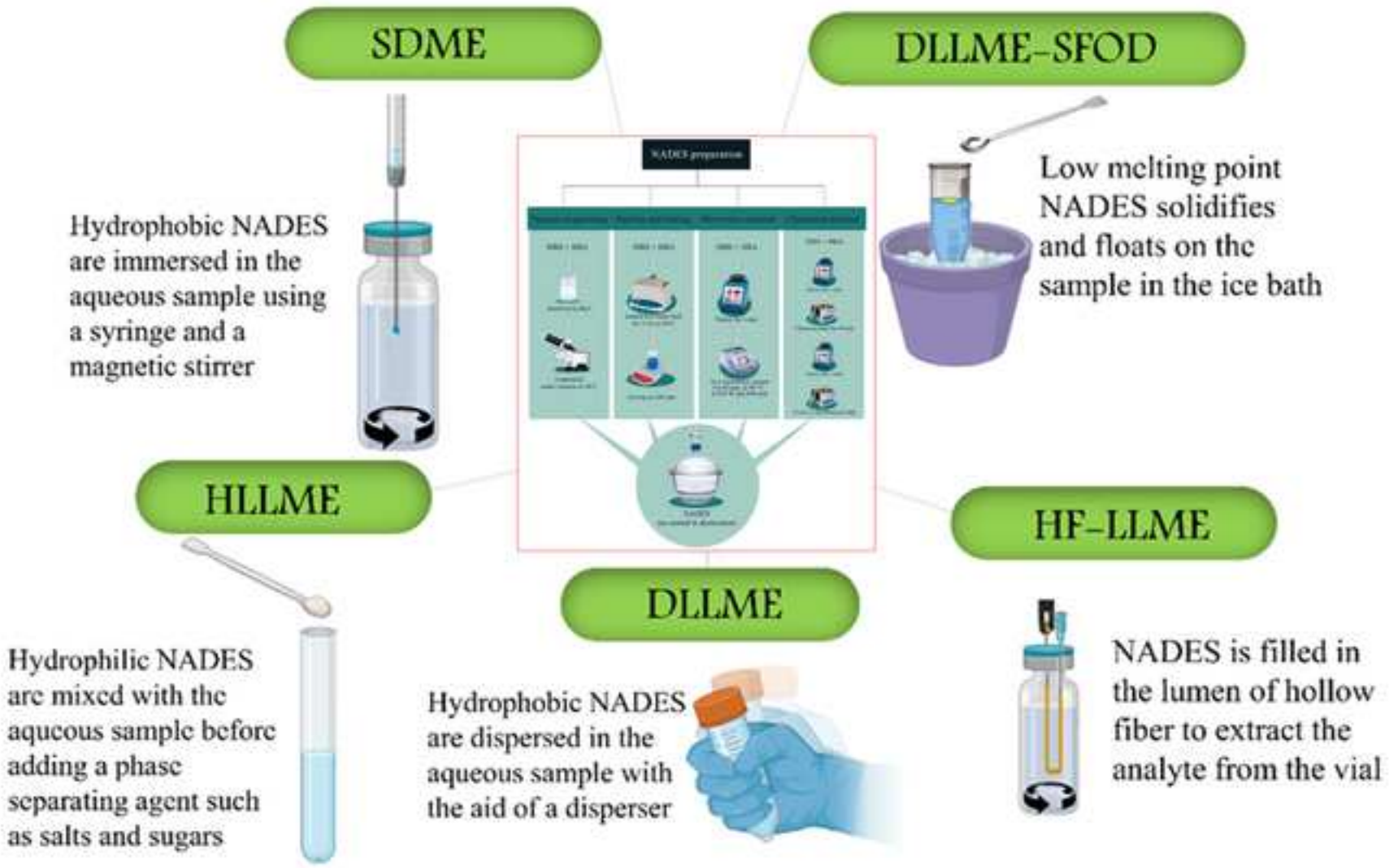


Figure 4



Declaration of interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review

Fotouh R. Mansour[1*], Alaa Bedair[2], Mahmoud Hamed[3], Galal Magdy[4], Imran Ali[5], Marcello Locatelli* [6]

[1] *Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Tanta University, Tanta 31111, Egypt*
[2] *Department of Analytical Chemistry, Faculty of Pharmacy, University of Sadat City, Sadat City 32958, Egypt*
[3] *Pharmaceutical Chemistry Department, Faculty of Pharmacy, Misr International University, Km 28 Ismailia Road, Cairo 44971, Egypt*
[4] *Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh 33511, Egypt*
[5] *Department of Chemistry, Jamia Millia Islamia (Central University), Jamia Nagar, New Delhi 110025, India*
[6] *Department of Pharmacy, University "G. d'Annunzio" of Chieti-Pescara, Chieti, 66100, Italy*

*** Corresponding authors**

Prof. **Marcello Locatelli**; Department of Pharmacy, University "G. d'Annunzio" of Chieti-Pescara, Via dei Vestini 31, 66100 Chieti, Italy E-mail: marcello.locatelli@unich.it

Prof. **Fotouh R. Mansour**; Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Elgeish Street, the medical campus of Tanta University, Tanta, Egypt 31111. E-mail: fotouhrashed@pharm.tanta.edu.eg

List of abbreviation:

NADES: Natural deep eutectic solvents,
LPME: liquid phase microextraction,
GAC: Green Analytical Chemistry,
GSP: Green Sample Preparation,
BIONPs: bismuth oxide nanoparticles,
HBD: hydrogen bond donner,
HBA: hydrogen bond acceptor,
DSC: Differential scanning calorimetry,
TGA: thermogravimetric analysis,
LPME: liquid-phase microextraction,
DLLME: dispersive liquid-liquid microextraction,
HF–LPME: hollow fiber–LPME,
EF: enrichment factor,
HF-MMLLE: hollow fiber-microporous membrane liquid-liquid microextraction,
SALLME: salt-assisted LLME,
SULLME: sugar-assisted LLME,
SDME: Single-drop microextraction,
HS-SDME: headspace SDME,
DLLME-SFOD: dispersive liquid-liquid microextraction based on solidification of floating organic droplet,

Abstract

Natural deep eutectic solvents (NADES) have gained significant attention as green solvents due to their unique properties, such as high solubility, low volatility, low toxicity, and tunability. Liquid phase microextraction (LPME) is a sample preparation technique that plays a crucial role in analytical chemistry, and the use of NADES as extraction solvents in LPME offers numerous benefits compared to traditional solvents. NADES can effectively extract bioactive compounds from natural sources without damaging their structure and activity. They can also serve as solvents and catalysts in organic reactions, enhancing the bioavailability of natural compounds. In addition, NADES can be utilized as mobile or stationary phases in chromatographic techniques for separating and analyzing natural compounds. The review highlights the efficiency of NADES in terms of extraction ability, analyte stabilization capacity, and detection compatibility. Moreover, the availability of their components, ease of preparation, low toxicity, cost-effectiveness, and biodegradability make NADES attractive for researchers in the field of analytical chemistry. The applications of NADES in LPME contribute to the principles of green analytical chemistry and green sample preparation by providing a sustainable and environmentally friendly approach to sample preparation. A comprehensive overview of the applications of NADES in liquid phase microextraction is provided, emphasizing their potential for advancing green practices in analytical chemistry.

Keywords

Natural deep eutectic solvents; Microextraction; Sample preparation; Analytical chemistry; NADES; Green analytical chemistry

1. Introduction

There is a growing interest in the development of new solvents and procedures that are safer for both analysts and the environment [1,2]. This is related to the fact that current organic solvents are highly hazardous, easily vaporized, and combustible. This shift aligns with the principles of green analytical chemistry (GAC) and green sample preparation (GSP) [3–5], which aim to create sustainable solvents, particularly for sample preparation [6,7], a process that can generate significant amounts of waste [8–10]. Natural deep eutectic solvents (NADES) are a novel class of green solvents that captured significant interest in recent years for their potential applications in the domain of research related to natural products. (**Fig. S1)** illustrates the upward trend of NADES publications recently [11].

The term "NADES" was coined by Choi et al [12] in 2011. NADES are formed by mixing a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) of natural origin (**Fig. 1)** [13] to form a liquid mixture at room temperature or below [14]. The robust hydrogen bonding interactions between the components lower the melting point of the mixture and drive the formation of NADES. For this reasons, NADES have several unique properties that make them attractive as green solvents. Some of these properties are high solubility, low volatility, low toxicity and tunability. Also, they can dissolve a wide range of compounds, such as proteins, lipids, nucleic acids, metal ions and organic pollutants and bismuth oxide nanoparticles (BIONPs) that are not soluble in water [15–18]. NADES have very low vapor pressure, which reduces the risk of evaporation [19–21]. These solvents are derived from biodegradable compounds, which minimize the environmental and health impacts of solvent use and disposal [22]. Additionally, they can be tailored to suit different applications by changing the type and ratio of the components, which affects the viscosity, polarity, acidity and conductivity of the solvent [23].

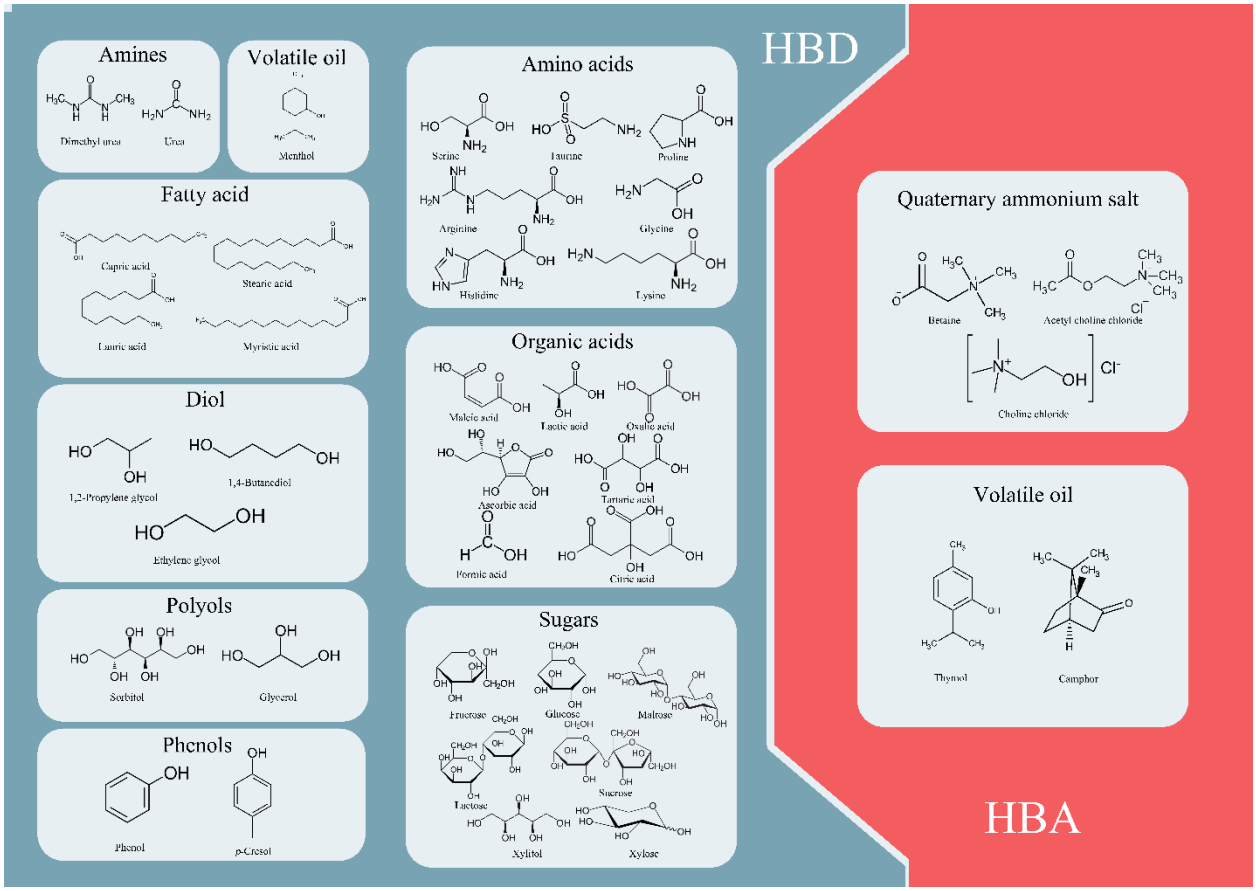


Fig. 1. Names and structures of the most common hydrogen bond donners and acceptors involved in NADES preparation.

NADES have been used for various applications in different fields, such as extraction, synthesis, separation, electrochemistry and bioavailability enhancement [24]. They are also able to extract bioactive compounds from natural sources [25], such as plants, algae and fungi, without damaging their structure and activity [26]. NADES can also act as both solvents and catalysts for organic reactions, such as esterification, transesterification and aldol condensation [27–30]. They can improve the bioavailability of natural compounds by increasing their solubility, stability, permeability, and absorption in biological systems [31]. By creating complexes or micelles [32–34] with poorly water-soluble drugs, NADES can increase their solubility and bioavailability [35]. They can also serve as carriers or adjuvants for various drug delivery systems like nanoparticles, liposomes, or hydrogels. Additionally, NADES can regulate the absorption and release of drugs by modifying their phase behavior or viscosity [36]. These solvents could also be used as antibacterial and antifungal agents [37].

In the field of analytical chemistry, NADES can separate mixtures of compounds based on their solubility and affinity to the solvent as mobile phases or stationary phases in

chromatographic techniques for separating natural compounds [38–41]. They are also presented as a green alternative in analytical chemistry, showing high extraction ability [42], analyte stabilization capacity [31], and detection compatibility [43] [44]. These advantages make NADES suitable solvent for LPME, which is principally considered green due to the huge reduction in solvent and sample consumption. So, finding the most suitable solvent took massive effort along the years [45]. One major advantage, besides the previously mentioned benefits, is their high polarity, which allows them to dissolve a wide range of substances that are typically insoluble in conventional solvents such as cellulose [46].

Several review articles on the microextraction techniques utilizing deep eutectic solvents can be found. Makoś et al. provided an article concentrating in hydrophobic deep eutectic solvents in different microextraction techniques [47]. Nakhle et al. focused on microextraction methods employing deep eutectic solvents as extraction solvents, and exploring the impact of these solvents' properties on extraction efficiency [48]. Andrade et al. presented an overview on the utilization of deep eutectic solvents for the analysis of biological matrices, with a particular emphasis on urine, blood, plasma, and oral fluid. The focus was placed on microextraction techniques, highlighting the various analytical features [49]. Santos et al. explored the application of deep eutectic solvents in LPME and their significant contributions to the field of green chemistry [50]. To the best of our knowledge, this is the first review article to highlight the applications of NADESs in liquid phase microextraction.

2. Preparation and characterization of NADES

NADES are prepared by blending specific natural metabolites at specific molar ratios to create a clear liquid at room temperature. Common components of NADES include amino acids, sugars, organic acids, choline salts, essential oil ingredients, and inorganic salts [51–53]. The preparation techniques include thermal mixing, vacuum evaporation, ultrasound-based methods, and microwave-based methods. In the thermal mixing method, two components are heated and stirred with or without a predetermined amount of water to obtain a clear liquid [44,54–60]. Vacuum evaporation involves heating the NADES components under reduced pressure to remove excess water [44,54]. Ultrasound-based methods utilize ultrasonic waves to create cavitation and facilitate the formation of NADES [61]. Microwave-based methods use microwave energy to induce molecular agitation and collisions between the components [62,63].

The characterization of NADES involves several analytical techniques. Nuclear magnetic resonance (NMR) [23,64], Fourier transform infrared spectroscopy (FTIR)[23], Raman

spectroscopy [65,66], and mass spectrometry (MS) [67] are also used to determine the chemical composition of NADES. NMR, in combination with FTIR, helps identify the constituents and purity of components [68,69]. FTIR can also be employed to determine NADES' structures [70,71] while thermogravimetric analysis and differential scanning calorimetry are used to assess density, thermal features, and stability [44,72]. Density and viscosity measurements provide important physical property information for designing processes and evaluating solvent suitability and to determine the best ratio between HBD and HBA [73–75].

3. Application of NADESs in liquid phase microextraction

Despite obvious developments in analytical science and technology, sample preparation remains the bottleneck of all analytical procedures. Miniaturizing the analytical scale and/or using safer alternatives instead of hazardous solvents can be used to mitigate the negative environmental effect of analytical procedures [76,77]. Both hydrophilic and hydrophobic NADES have been employed in different modes of LPME, as shown in (**Fig. 2)**. In this section, the role of NADES in liquid phase microextraction approaches are discussed in details.

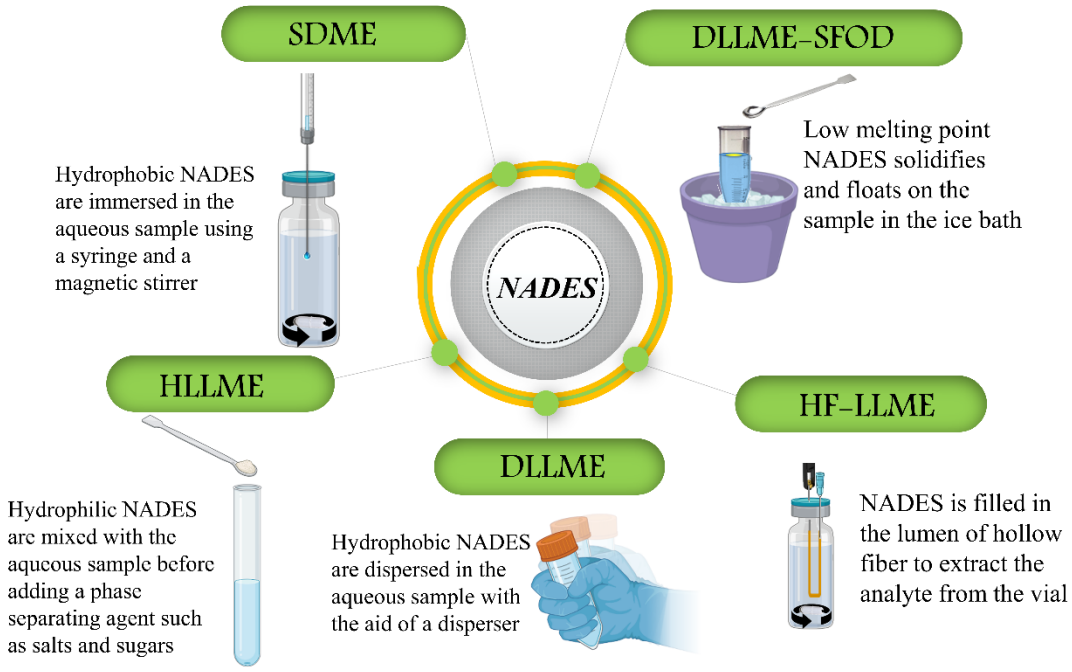


Fig. 2: Modes on LPME in which NADESs were employed

3.1. Applications of NADES in HF–LPME

Sample preparation trends tend to minimize the amount of organic solvent and extraction time. The liquid-phase microextraction (LPME) approach offers an alternative to typical preparation procedures [78]. There are different modes of LPME including dispersive liquid-liquid

microextraction (DLLME) [79], single drop microextraction (SDME) [80], and hollow fiber–LPME (HF–LPME) [81]. Among these techniques, the HF-LPME has distinct benefits such as low cost, high preconcentration factor, low solvent consumption, and environmental friendliness. The HF-LPME technique is based on the use of different materials such as porous polypropylene hollow fiber, polyvinylidene difluoride, or PTFE, which first extract analytes from an aqueous sample as the donor phase and then back-extract them into the acceptor phase situated in the HF lumen [82]. Organic solvents are often used in the HF-LPME technique, but they have various drawbacks, including volatility, toxicity, instability, and deleterious effects on laboratory workers. Nia et al [83] prepared amino acids hydrophobic NADES in two phase HF-LPME. In this application, NADES was prepared by mixing amino acids (as an HBA) with lactic acid (as an HBD) using a hollow fiber's supported liquid membrane. The lumens were impregnated with extremely stable NADESs (serine: lactic acid). The developed method was successfully applied to extract caffeic acid from green tea, tomato samples and coffee. The enrichment factor was in the range of 418–438. Morelli et al. [84] investigated both hydrophilic and hydrophobic NADESs hollow fiber-microporous membrane liquid-liquid microextraction (HF-MMLLE). The best NADES was composed from thymol and camphor. Selected NADESs were introduced into the porous polypropylene membrane for 10 minutes, substituting widely used solvents (for example, hexane and octanol). The developed method was successfully applied and verified for 11 emergent contaminants from various classes, demonstrating the method's adaptability.

Analytical method automation, commonly employed to minimize reagent and sample usage, is a highly effective tool for integrating all stages of necessary analytical procedures onto a single manifold while minimizing human and environmental hazards. Shakirova et al. [85] developed an automated liquid-liquid microextraction process for determining sulfonamides (sulfamethoxazole, sulfamethazine, and sulfapyridine) in urine samples utilizing NADES. The extraction of sulfonamides was based on the synthesis of colored Schiff bases in the presence of vanillin, which served as a derivatization reagent as well as a precursor of NADES (an extractant). Thymol was utilized in this process as both a medium for Schiff base synthesis and a second precursor of the NADES. Mass spectrometry verified the production of the Schiff bases. The microextraction method was automated using the Lab-In-Syringe approach as indicated in (**Fig. 3)**.

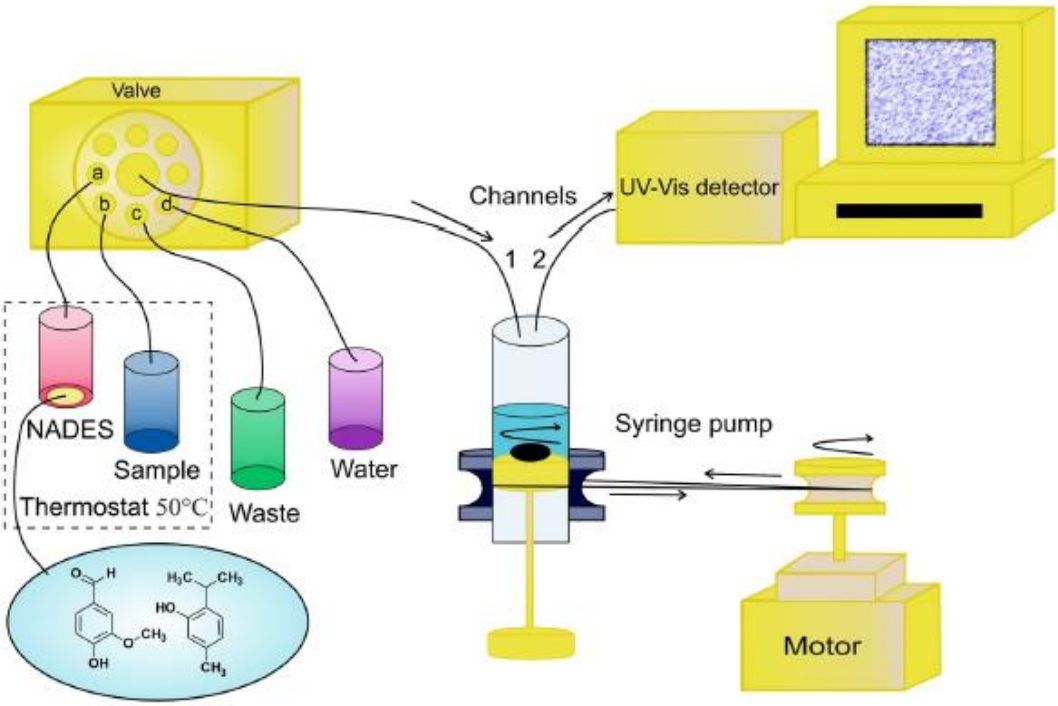


Fig. 3: manifold for the determination of sulfonamides in urine samples with permission from [85].

The developed approach had enough sensitivity to determine the concentration of sulfonamides at therapeutic levels. In addition to that, this method was ecologically benign, providing full automation with a sample throughput of six samples/h.

3.2. Applications of NADES in DLLME

DLLME is a miniaturized sample preparation process used in many analytical chemistry applications [86,87]. In this mode, an immiscible organic solvent is used with an organic disperser, the two solvents are combined. The organic extractant is dispersed as tiny droplets by manual shaking resulting in a homogeneous hazy solution. DLMME has several benefits over other sample preparation approaches in terms of simplicity, affordability, convenience of use, and speed. However, the right selection of dispersing and extracting solvents (µL scale) is quite difficult [88]. The pioneers of DLLME mode (Rezaee et al. [89]) developed this mode as a modification of LLME in an attempt to boost the recovery rate in LLME. DLLME results in extending the contact surface between the extractant and the sample, and this dispersion procedure greatly increases extraction kinetics. The sample is then centrifuged to separate the extractant and break up the emulsion. It worth mentioning that dispersion could be achieved by using a disperser solvent or by using external mechanical force such as manual shaking,

vortex agitation, magnetic stirrer power, ultrasonic power, and microwave irradiation. Traditional DLLME procedures use hazardous halogenated organic solvents such as chloroform, carbon tetrachloride, and chlorobenzene, which can be harmful to human health and the environment. In addition to using long chain alcohols as extractant and hazardous dispersers such as acetonitrile (ACN), methanol, acetone, tetrahydrofuran (THF), ethanol. Therefore, one of the GAC principles that should be adopted in method development is the replacement of harmful solvents with more benign ones. As a result, more environmentally friendly NADESs have recently been offered as a sustainable alternative in DLLME [90]. In general, NADES is made up of two or more natural components (HBD and HBA) blended in a certain ratio to generate a homogeneous mixture with a eutectic point at a lower temperature than the separate substances. The most common components used in synthesis of NADESs are monoterpenes (menthol, thymol, and camphor) [91–102]. These solvents are biodegradable, less hazardous, widely accessible, and simple to make. Monoterpenes such as are considered an ideal choice of extractant because of their poor water solubility [103]. In general, hydrophobic NADESs were used as extractants in DLLME mode however, hydrophilic NADESs could be used as a disperser in the same mode. As reported in Table 1, the use of NADESs in DLLME was successfully applied for the extraction of different analytes from different matrices including water [102], biological samples [104], foods [105], beverages [94] and personal care products [93].

220 **Table 1:** Application of NADES in DLLME

Analyte	Sample	Sample volume (mL)	NADES component	Dispersion mode	Extractant volume (µL)	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Tetracyclines	Water	5	[ChCl]: [thymol]: [nonanoic acid]	Air assisted DLLME	400	HPLC/UV	18.2-500	≤11.2	[102]
Warfarin	Biological samples	10	Borneol: decanoic acid	Air assisted DLLME	60	HPLC/UV	5–500	<5.87	[104]
Vanadium	Food stuff	2	ChCl: phenol	Ultrasound assisted DLLME	1000	Electrothermal atomic absorption spectrometry (ETAAS)	N/A	3.4%	[106]
Tert-Butylhydroquinone	Soybean Oils	0.2 g	ChCl: sesamol	Ultrasound assisted DLLME	400	HPLC/UV	5-500 mg/kg	<2.3%	[107]
NSAIDs	Water and milk samples	10	1,1,3,3-tetramethylguanidine chloride: thymol	Ultrasound assisted DLLME	200	HPLC/UV	5–2000	1.11% to 16.9%.	[91]
Parabens	Personal care products	5	Menthol: formic acid	Vortex assisted DLLME	80	UHPLC/UV	20–4000	≤3.33%	[93]
Mercury	Water samples	9	Decanoic acid: DL-menthol	Vortex assisted DLLME	50	LC/UV–Vis	10–200	≤19%	[92]
Alkylphenols, bisphenols and alkylphenol ethoxylates	Microbial-fermented functional beverages and bottled water	10	Methanol: octanoic acid	Vortex assisted DLLME	100	UHPLC-MS	0.4-50	≤19.5%	[95]
Sudan I	Food samples	0.2 g	ChCl: sesamol	Vortex assisted DLLME	800	HPLC/UV	0.2–100 mg /kg	<4.5%	[105]
Beta-blockers	Water samples	9.5	Azelaic acid: thymol	Vortex assisted DLLME	55	HPLC/DAD	0.5-100	<6%	[108]
Phthalate Esters	Soft drinks	10	Thymol: octanoic acid	Vortex assisted DLLME	125	UPLC-MS/MS	0.10−5.00	<11.5%	[94]
Phthalate esters	Grape-based beverages	7.5	ChCl: acetic acid	Vortex assisted DLLME	500	Nano-LC/UV	5-403	<17%	[109]
Benzoic acid and sorbic acid	Condiments	10	L-Menthol Acetic acid: decanoic acid	Vortex assisted DLLME-SFOD	800	HPLC/DAD	70-100000	≤5.66%	[96]
Phthalates and one adipate	Water samples	10	Thymol: menthol	Vortex assisted DLLME	100	UHPLC-QqQ-MS/MS	0.100–250	<14%	[97]
Chloramphenicol	Honey sample	5	Menthol: acetic acid	Vortex assisted DLLME	100	LC/UV	1–100 µg /kg	≤4.5%	[98]
Triarylmethane) dyes	Shrimp and water samples.	10	Thymol and camphor	Vortex assisted DLLME	200	HPLC/DAD	0.2 -200	≤2.3	[99]
Acaricides	Egg samples	5	Choline chloride-acetic acid-*n*-octanol	In-syringe DLLME	74	GC/FID	2.7‑4000	≤11%	[110]
Phthalic acid esters	Soft drinks and infusions	20	Menthol: acetic acid	Manual agitation assisted DLLME-SFO	100	HPLC/UV	6-1190	1-22 %	[100]
Phthalic acid esters	Water and beverage samples	20	Menthol: acetic acid	Manual agitation assisted DLLME	100	HPLC/UV	4-425	≤ 20%	[101]

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3.3. Applications of NADES in HLLME

HLLME is a method of sample preparation that involves the formation of a homogeneous phase between an aqueous sample and a small amount of a water-miscible extractant, such as acetonitrile, acetone or tetrahydrofuran. The separation of phases is achieved using a phase separating agent (PSA), which may be a salt, sugar, or hydrophobic substance. Depending on the type of PSA used, HLLME can be classified into three categories: salt-assisted LLME (SALLME) [111,112], sugar-assisted LLME (SULLME) [113,114], and hydrophobic substance-assisted or aprotic solvent assisted HLLME [115,116]. The manipulation of physical conditions such as temperature or pH, and the introduction of gas bubbles into the homogeneous system could achieve phase separation [117,118]. It is worth mentioning that HLLME is characterized by infinite contact surface area between the aqueous and organic phases, which permits highly quick and effective extraction [119]. Another advantage of this microextraction process is that there is no need for an evaporation/reconstitution step due to the hydrophilicity of the donor phase. In the standard HLLME approach, hydrophilic organic solvents such as acetonitrile, acetone, ethanol, and propanol are frequently used as extractants. NADESs have recently attracted a lot of attention as a more eco-friendly alternative to the poisonous and volatile organic solvents used in the HLLME process. The most common mode that was used in HLLME is the aprotic solvent-assisted HLLME, which depends on using a water miscible extractant and an aprotic solvent a PSA such as THF, ACN and acetone. Unlike other HLLME modes, this mode gives the ability to use a large sample volume, enhancing sensitivity of the proposed method. Khezeli et al. [120] were the pioneers of this mode. In this work, the NADESs used were prepared by combining choline chloride (ChCl) as an HBA with phenol as an HBD. The developed method was used to successfully extract several organic chemical components from water samples. This procedure produced a homogeneous solution by adding the extraction solvent (the hydrophilic NADES) to the aqueous sample solution (donor phase). Finally, an aprotic solvent (THF) was used to produce phase separation. It has been proposed that introducing an aprotic solvent into a homogeneous solution can greatly diminish the interactions between DES and water molecule because of the π- π and hydrogen bonding interactions between the DES ingredients. Therefore, the DES molecules can self-aggregate and migrate out of the water phase. Shishov et al. [121] proposed another theory in the mechanism of phase separation. They investigated the solvent-assisted HLLME process with hydrophilic DES based on choline and phenol utilizing gas chromatography-mass spectrometry analysis and coulometric Karl-Fischer titration. The results of this study supported the instability of a hydrophilic DES in aqueous conditions. Thus, they hypothesize

that hydrophilic DESs based on choline and phenol breaks down in the aqueous phase in the solvent-assisted HLLME process. The findings of this study revealed that the organic phase recovered comprised phenol, THF, and water. As indicated in Table 2 , this mode was successfully applied for extraction various compound from different matrices including water [122], food [123], biological samples [124] and beverages [125]. The most common water miscible NADES used in aprotic solvent-assisted HLLME was composed of phenol and ChCl [123,126–130]. In addition to that, THF was widely used in this mode as PSA [123,126,131,132]. It is worth mentioning that other aprotic solvent were used as PSA in aprotic solvent assisted HLLME such as ACN [133] and acetone [134]. The applications of NADES in HLLME have high potential because of being greener, simpler, cheaper, and more sensitive in comparison with other conventional extraction modes.

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Analyte	Sample	Sample volume (mL)	NADES component	HLLME	PSA	Extractant volume (µL)	PSA(vol /amount) µL	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Copper	olive oil and water samples	15	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	450	450	FAAS	NA	<5.0%	[126]
Arsenic and antimony	Water samples	125	ChCl: oxalic acid	Aprotic solvent assisted HLLME	THF	700	300	Hydride generation-atomic absorption spectrometry	15-570 ng/L	2.1% and 2.7%	[122]
Benzotriazole derivatives and benzothiazole derivatives	Surface water	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	1000	500	UHPLC-ESI(+)-QToF-MS	5 -200	1 -8%	[127]
Pesticides	Chinese medicine	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	650	550	HPLC/DAD	50-107000	4.7%	[128]
Methyl mercury and total mercury	Water and fish sample	2.5	betaine-sorbitol	Aprotic solvent assisted HLLME	ACN	600	375	Spectrophotometer	0.7–340	1.9–5.5%	[133]
Caffeine	Turkish coffee	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	800	HPLC/UV	500-100000	2.20%	[129]
Curcumin	Tea and honey samples	5	ChCl: Maltose	Aprotic solvent assisted HLLME	THF	762.5	107.5	Spectrophotometer	0.4–120	≤4.3%	[135]
Curcumin	Food and herbal tea	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	400	Spectrophotometer	NA	1.8 %.	[123]
Malachite green	Aquarium fish water	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	Spectrophotometer	45-900	2.7 %.	[130]
Sulfonamides	Water samples	1.5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	193	100	HPLC/UV	500–100000	≤2.10	[131]
Thiophenols	Water samples	1.5	ChCl:p-cresol	Aprotic solvent assisted HLLME	Acetone	50	50	GC/FID	2-100000	<4.1%	[134]

Polycyclic aromatic hydrocarbons	Water samples	1.5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	100	100	HPLC/UV	0.1-400	<4.5	[120]
Antidepressants	Pharmaceutical and water samples	6	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	200	430	HPLC/UV	10-8000	3.6-5.7%	[136]
Selenium species	Water and food samples	25	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.2-8	≤4.1	[137]
Phenoxy acid herbicides	Paddy field and water samples	1.5	ChCl:2-chlorophenol	Aprotic solvent assisted HLLME	THF	50	100	HPLC/UV	5–100	≤4.6	[138]
Phthalate	Beverages	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	440	440	HPLC/DAD	170-2700	<11%	[125]
Caffeine	Beverages	1	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	50	50	HPLC/UV	100-200000	≤6%	[139]
Mercury	Water and biological samples	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.3-10	≤–5.72%	[124]
Cadmium	Food and water samples	50	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	600	ETAAS	5–150 ng/ L	3.1%	[132]

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3.4. Applications of NADES in single drop microextraction

Single-drop microextraction (SDME) is a highly effective and environmentally sustainable sample pretreatment technique that involves the immersion of an organic solvent microdroplet into the sample with the aid of a microsyringe needle. SDME has gained widespread use in fields such as environmental monitoring, food quality control, and biological analysis, owing to its minimal solvent consumption and high sample-to-extractant phase ratio [140,141]. This technique has streamlined the analytical workflow by integrating extraction and enrichment processes. Furthermore, SDME is particularly well-suited for fluorescence spectroscopy, as the solvent used is transparent in the visible region and does not interfere with direct visual readout or spectral analysis [142,143]. The realm of green analytical chemistry is presently witnessing a huge interest in the creation and utilization of sustainable and eco-friendly solvents. This trend is particularly visible in the SDME field, in which a growing number of innovative solvents has been reported, for instance, ionic liquids, superheated water, deep eutectic solvents, surfactants, and supercritical fluids [144]. An important aspect that could significantly influence the efficacy of the extraction process is the choice of solvent. In particular, the utilization of a solvent with high viscosity can facilitate the suspension of larger and more stable droplets at the needle tip. This property makes NADESs a suitable option for the task, given their favorable attributes such as elevated viscosity at ambient temperature, considerable thermal stability, and low vaporization tendencies [145]. Yousefi et al. have introduced a novel technique for headspace single drop microextraction (HS-SDME) that employs a magnetic bucky gel derived from deep eutectic solvents (DES-MBG) as the extraction medium. This method offers several advantages, including high viscosity, magnetic susceptibility, and adjustable extractability. Additionally, it ensures droplet stability, allowing extraction at high temperatures and rapid agitation rates. This suggests the potential of DES-MBGs to exhibit superior resilience, facilitating the utilization of larger droplet volumes and consequently enhancing extraction efficiency, sensitivity, and detection limits [146]. Yıldırım et al. [147] proposed a novel approach for fluoroquinolone analysis in environmental waters via an automated Lab-In-Syringe direct immersion single drop microextraction method coupled online to HPLC with fluorescence detection (**Fig. 4)**. The method employed NADES as an extractant within an automatic syringe pump, thus eliminating the utilization of toxic solvents and augmenting the method's sustainability from an environmental perspective. The method's linearity range for fluoroquinolones lied between 0.1 and 5.0 μg/L, with quantification limits in the 20-30 ng/L and enrichment factors of 35-45. The trueness of spiked samples ranged from 84.6% to 119.7%, and the method exhibited low RSD values. The

method's advantages include its parallel operation with HPLC, low sample consumption, and environmentally friendly characteristics, aligning it with the principles of green analytical chemistry [147].

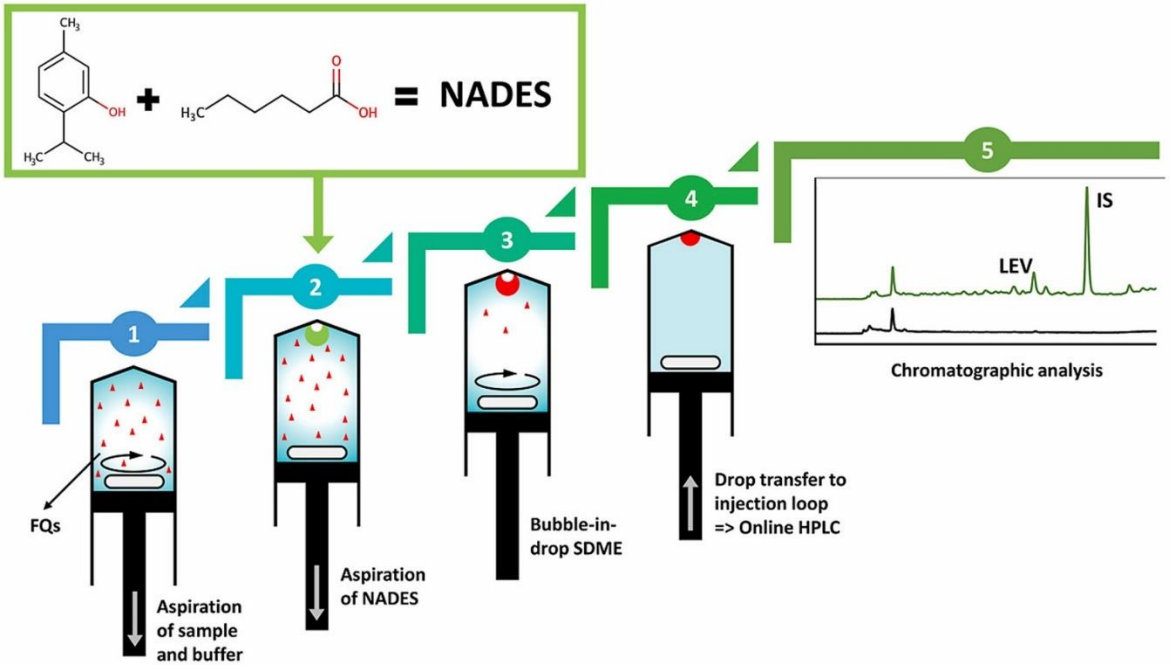

Fig. 4. A schematic representation for the automation of a lab-in-syringe technique using NADES-based direct immersion single drop microextraction, which is linked online to HPLC-FL to determine fluoroquinolones (With permission from [147])

3.5 Applications of NADES in DLLME-SFOD

The DLLME-SFOD approach is a microextraction method that employs a ternary solvent system (extractant, disperser and sample), in which the extractant is an organic solvent that solidifies in ice bathes at relatively low temperatures [148]. The injection of a suitable mixture into an aqueous sample results in the formation of a cloudy solution, which facilitates phase interaction [149]. Following phase separation and centrifugation, the sample is immersed in an ice bath and the solidified organic phase is gathered for analysis [150]. This method boasts high efficiency, enrichment factors, and rapid equilibrium, while necessitating minimal solvent volume and equipment. Nonetheless, its solvent options are restricted in a narrow range of long chain alcohols with high melting points in the range 10-25°C. However, deep eutectic solvents (DESs) are being investigated as a favorable, eco-friendly replacement for this technique [151,152]. NADES have been utilized in DLLME-SFOD, serving as both disperser and extracting solvents. An effective example is a NADES consisting of lactic acid, glucose, and water at a 5:1:3 molar ratio, which has demonstrated efficient dispersion of pesticides from

water and white wine through vigorous shaking. The addition of water has resulted in lower viscosity, which has facilitated the dispersion process. The dispersive NADES has achieved recoveries exceeding 90% for analytes tested due to its reduced viscosity and increased polarity, which have improved interactions among the aqueous sample, NADES, and extracting solvent [153]. The developed method offered a strong, efficient, and environmentally friendly alternative for determining pesticides, providing a novel application for NADES in sample preparation, as indicated in **Table 1**. Another study has incorporated menthol and decanoic acid in the preparation of NADES with a molar ratio of 1:2 for the extraction of antidepressants from urine samples prior to GC/MS analysis resulting in recoveries ranging from 74 to 147% [154]. In their research, Taşpınar et al. applied an environmentally friendly approach known as air-assisted DLLME-SFOD, which was designed to extract patulin from both fruit juice and dried fruit. This process involved the injection of NADES as extraction solvents at a volume of 410 µL into a sample solution that has been adjusted to a pH of 5.6. The solution was then drawn into a syringe and immediately reinjected six times to allow for the even dispersal of NADES droplets throughout the aqueous bulk, resulting in a cloudy solution. Afterwards, the tubes were submerged in an ice bath for roughly seven minutes, which enabled the NADES phase to solidify and become easily separable before undergoing UV/Vis spectrophotometric analysis. This method had an LOD of 3.5 µg/L and an EF of 150 [155].

4. Limitations of NADES

The interest and the applications of NADES in various fields, particularly in chemical analysis and LPME are increasing. However, NADES are not perfect solvents and have some challenges and limitations that need to be addressed, such as stability, viscosity, water content, and extraction efficiency. NADES are prone to decomposition or degradation over time. The hydrogen-bonding network that exists between the constituents significantly influences the stability of NADES. Hydrogen bonds are responsible for lowering the melting point of NADES [20]. Betaine-urea-water is a NADES that has been used for extracting bioactive compounds from plants. However, this NADES is not stable at room temperature and tends to crystallize after a few days. A recent study by Nava-Ocampo et al. investigated the structural properties and stability of betaine-urea-water using spectroscopic and computational methods. The researchers discovered that the formation of a metastable transparent liquid requires a minimum of two moles of water, whereas a stable NADES necessitates a minimum of three moles of water. They also showed that water plays a crucial role in forming stronger hydrogen bonds between urea and the carbonyl groups of betaine, and in deprotecting the methyl group

of betaine from forming intermolecular interactions [156]. NADES tend to have high viscosity compared to conventional solvents, which can limit their mass transfer and diffusion rates. This can reduce their extraction efficiency and increase the energy consumption and processing time. To address this, it is necessary to optimize the composition and ratio of the components of NADES to achieve the desired viscosity. Moreover, some methods can be used to reduce the viscosity of NADES, such as heating, dilution, ultrasonication, or adding co-solvents [13]. NADES usually contain a certain amount of water due to their hygroscopic nature or the presence of water in the natural components. Water can affect the polarity and solvation ability of NADES, as well as their interaction with the target compounds. So, it is important to control the water content of NADES according to the specific application and the solubility of the target compounds. Additionally, some techniques can be used to remove or reduce the water content of NADES, such as freeze-drying [157]. NADES may be less environmentally friendly than initially thought, urging a reevaluation of their large-scale applications [158]. According to Popović et al, The cytotoxic effect is primarily influenced by the structure of the HBD, with acidic systems showing the highest cytotoxic effects. Cytotoxicity depends on both the concentration of the NADES system in the cell medium and the chemical composition of the investigated systems [159].

5. Perspectives

One of the major limitations in any LPME is phase separation. To overcome this problem, magnetic solvents have been introduced in recent years to shorten the time necessary for phase separation. These magnetic solvents can be quickly separated and collected without the need for time-consuming centrifugation processes, allowing for quick sample preparation. Magnetic solvents are easier to prepare and have higher reproducibility than magnetic materials. Magnetic ionic liquids have a low vapor pressure and good thermal stability, as well as the capacity to respond significantly to external magnetic fields [160,161]. However, they are costly and need drying or a rotary evaporation process [162]. Magnetic deep eutectic solvents (MDESs) not only exhibit paramagnetic characteristics similar to magnetic ionic liquids, but they also offer substantial cost and availability benefits. Most MDESs are currently hydrophilic, which limits their applicability to extracting polar analytes (such as thiophene and aldehydes) in non-polar solvents (such as n-heptane and oil samples) [163,164]. Therefore, the development of hydrophobic MDESs is necessary to extract non-polar analytes from different matrices. For these reasons, MDESs is a new growing area of research for the development green solvents in LPME. Duque et al [165] applied ferrofluid-based NADES in stir bar

dispersive liquid microextraction for the determination of UV filters in water samples. This ferrofluid was composed of a hydrophobic NADES (1:5 molar ratio of menthol and thymol as carrier solvent) and oleic acid-coated cobalt ferrite ($CoFe_2O_4$@oleic acid) magnetic nanoparticles. $CoFe_2O_4$ MNPs were first synthesized through wet chemical coprecipitation using an adapted procedure [166], and then coated with oleic acid. In this case, 100 mL of 0.4 M $FeCl_3$ aqueous solution was combined with 100 mL of 0.2 M $CoCl_2$ aqueous solution. Then, 100 mL of a 3 M sodium hydroxide aqueous solution was added dropwise at 80°C, under continuous stirring. The reaction mixture was then agitated at the same temperature for 1 hour after 2 mL of oleic acid was added. After carefully cooling the black precipitate result to ambient temperature, the MNPs were cleaned twice with ultrapure water and once with ethanol. Finally, the precipitate was dried overnight at 100°C and ground into a fine powder. A stable ferrofluid was prepared by weighing 25 mg of $CoFe_2O_4$@OA MNPs in a microcentrifuge tube and 1 mL of NADES was added. The resulting mixture was sonicated for 40 min. The results indicated that the developed analytical method produced comparable findings, demonstrating the promise of this ferrofluid as a less expensive and more environmentally friendly alternative to MILs in future analytical procedures [166].

6. Conclusion

NADESs have emerged as promising alternatives for liquid phase microextraction applications. NADES offer unique advantages such as high polarity, hydrophilicity, and environmentally friendly nature, making them suitable for liquid phase microextraction in diverse fields, including pharmaceutical, environmental, and food analysis. NADES have been successfully employed in different modes, including HF-LPME, DLLME, and SDME. These techniques aim to minimize the use of organic solvents, reduce extraction time, and enhance the preconcentration factor. NADES have shown promise in improving the efficiency and environmental friendliness of LPME processes. By replacing traditional solvents with NADES, researchers have achieved successful extraction of analytes from aqueous samples. Rising interest in NADES for analysis and LPME faces challenges in stability, viscosity, water content, and extraction efficiency. Further research and development in the synthesis methods, characterization techniques, and application of NADES are warranted to fully explore their potential in liquid phase microextraction and contribute to sustainable analytical practices. The automation of liquid-liquid microextraction processes using NADES has proven to be a valuable approach in minimizing reagent and sample usage while reducing human and environmental hazards.

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Author contributions

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Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review

Fotouh R. Mansour[1*], Alaa Bedair[2], Mahmoud Hamed[3], Galal Magdy[4], Imran Ali[5], Marcello Locatelli* [6]

[1] *Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Tanta University, Tanta 31111, Egypt*
[2] *Department of Analytical Chemistry, Faculty of Pharmacy, University of Sadat City, Sadat City 32958, Egypt*
[3] *Pharmaceutical Chemistry Department, Faculty of Pharmacy, Misr International University, Km 28 Ismailia Road, Cairo 44971, Egypt*
[4] *Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh 33511, Egypt*
[5] *Department of Chemistry, Jamia Millia Islamia (Central University), Jamia Nagar, New Delhi 110025, India*
[6] *Department of Pharmacy, University "G. d'Annunzio" of Chieti-Pescara, Chieti, 66100, Italy*

*** Corresponding authors**

Prof. **Marcello Locatelli**; Department of Pharmacy, University "G. d'Annunzio" of Chieti-Pescara, Via dei Vestini 31, 66100 Chieti, Italy E-mail: marcello.locatelli@unich.it

Prof. **Fotouh R. Mansour**; Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Elgeish Street, the medical campus of Tanta University, Tanta, Egypt 31111. E-mail: fotouhrashed@pharm.tanta.edu.eg

List of abbreviation:

NADES: Natural deep eutectic solvents,
LPME: liquid phase microextraction,
GAC: Green Analytical Chemistry,
GSP: Green Sample Preparation,
BIONPs: bismuth oxide nanoparticles,
HBD: hydrogen bond donner,
HBA: hydrogen bond acceptor,
DSC: Differential scanning calorimetry,
TGA: thermogravimetric analysis,
LPME: liquid-phase microextraction,
DLLME: dispersive liquid-liquid microextraction,
HF–LPME: hollow fiber–LPME,
EF: enrichment factor,
HF-MMLLE: hollow fiber-microporous membrane liquid-liquid microextraction,
SALLME: salt-assisted LLME,
SULLME: sugar-assisted LLME,
SDME: Single-drop microextraction,
HS-SDME: headspace SDME,
DLLME-SFOD: dispersive liquid-liquid microextraction based on solidification of floating organic droplet,

Abstract

Natural deep eutectic solvents (NADES) have gained significant attention as green solvents due to their unique properties, such as high solubility, low volatility, low toxicity, and tunability. ~~LPME~~Liquid phase microextraction (LPME) is a sample preparation technique that plays a crucial role in analytical chemistry, and the use of NADES as extraction solvents in LPME offers numerous benefits compared to traditional solvents. NADES can effectively extract bioactive compounds from natural sources without damaging their structure and activity. They can also serve as solvents and catalysts in organic reactions, enhancing the bioavailability of natural compounds. In addition, NADES can be utilized as mobile or stationary phases in chromatographic techniques for separating and analyzing natural compounds. The review highlights the efficiency of NADES in terms of extraction ability, analyte stabilization capacity, and detection compatibility. Moreover, the availability of their components, ease of preparation, low toxicity, cost-effectiveness, and biodegradability make NADES attractive for researchers in the field of analytical chemistry. The applications of NADES in LPME contribute to the principles of green analytical chemistry and green sample preparation by providing a sustainable and environmentally friendly approach to sample preparation. A comprehensive overview of the applications of NADES in liquid phase microextraction is provided, emphasizing their potential for advancing green practices in analytical chemistry.

Keywords

Natural deep eutectic solvents; Microextraction; Sample preparation; Analytical chemistry; NADES; Green analytical chemistry

1. Introduction

There is a growing interest in the development of new solvents and procedures that are safer for both analysts and the environment [1,2]. This is related to the fact that current organic solvents are highly hazardous, easily vaporized, and combustible. This shift aligns with the principles of green analytical chemistry (GAC) and green sample preparation (GSP) [3–5], which aim to create sustainable solvents, particularly for sample preparation [6,7], a process that can generate significant amounts of waste [8–10]. Natural deep eutectic solvents (NADES) are a novel class of green solvents that captured significant interest in recent years for their potential applications in the domain of research related to natural products. (**Fig. S1)** illustrates the upward trend of NADES publications recently [11].

The term "NADES" was coined by Choi et al [12] in 2011. NADES are formed by mixing a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) of natural origin (**Fig. 1)** [13] to form a liquid mixture at room temperature or below [14]. The robust hydrogen bonding interactions between the components lower the melting point of the mixture and drive the formation of NADES. For this reasons, NADES have several unique properties that make them attractive as green solvents. Some of these properties are high solubility, low volatility, low toxicity and tunability. Also, they can dissolve a wide range of compounds, such as proteins, lipids, nucleic acids, metal ions and organic pollutants and bismuth oxide nanoparticles (BIONPs) that are not soluble in water [15–18]. NADES have very low vapor pressure, which reduces the risk of evaporation [19–21]. These solvents are derived from biodegradable compounds, which minimize the environmental and health impacts of solvent use and disposal [22]. Additionally, they can be tailored to suit different applications by changing the type and ratio of the components, which affects the viscosity, polarity, acidity and conductivity of the solvent [23].

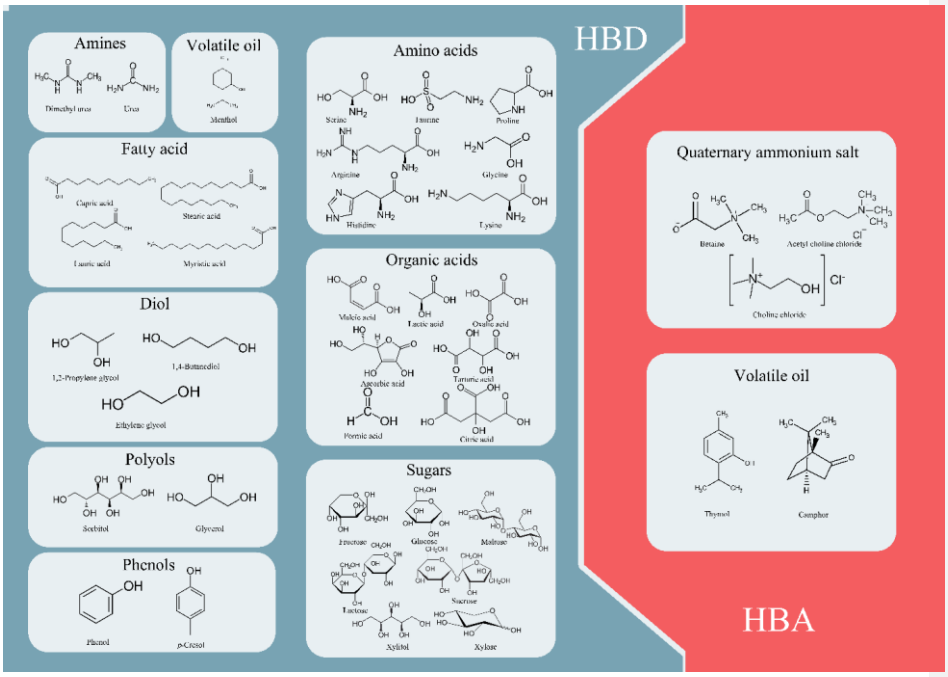

Fig. 1. Names and structures of the most common hydrogen bond donners and acceptors involved in NADES preparation.

NADES have been used for various applications in different fields, such as extraction, synthesis, separation, electrochemistry and bioavailability enhancement [24]. They are also able to extract bioactive compounds from natural sources [25], such as plants, algae and fungi, without damaging their structure and activity [26]. NADES can also act as both solvents and catalysts for organic reactions, such as esterification, transesterification and aldol condensation [27–30]. They can improve the bioavailability of natural compounds by increasing their solubility, stability, permeability, and absorption in biological systems [31]. By creating complexes or micelles [32–34] with poorly water-soluble drugs, NADES can increase their solubility and bioavailability [35]. They can also serve as carriers or adjuvants for various drug delivery systems like nanoparticles, liposomes, or hydrogels. Additionally, NADES can regulate the absorption and release of drugs by modifying their phase behavior or viscosity [36]. These solvents could also be used as antibacterial and antifungal agents [37].

~~In the field of analytical chemistry, NADES can separate mixtures of compounds based on their solubility and affinity to the solvent as mobile phases or stationary phases in~~

~~chromatographic techniques for separating natural compounds [37–40]. They are also presented as a green alternative in analytical chemistry, showing high extraction ability [41], analyte stabilization capacity~~ In the field of analytical chemistry, NADES can separate mixtures of compounds based on their solubility and affinity to the solvent as mobile phases or stationary phases in chromatographic techniques for separating natural compounds [38–41]. They are also presented as a green alternative in analytical chemistry, showing high extraction ability [42], analyte stabilization capacity [31]~~, and detection compatibility [42] [43]. These advantages make NADES suitable solvent for LPME, which is principally considered green due to the huge reduction in solvent and sample consumption. So, finding the most suitable solvent took massive effort along the years [44]. One major advantage, besides the previously mentioned benefits, is their high polarity, which allows them to dissolve a wide range of substances that are typically insoluble in conventional solvents such as cellulose [45].~~

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Several review articles on the microextraction techniques utilizing deep eutectic solvents can be found. Makoś et al. provided an article concentrating in hydrophobic deep eutectic solvents in different microextraction techniques ~~[46].~~[47]. Nakhle et al. focused on microextraction methods employing deep eutectic solvents as extraction solvents, and exploring the impact of these solvents' properties on extraction efficiency ~~[47].~~[48]. Andrade et al. presented an overview on the utilization of deep eutectic solvents for the analysis of biological matrices, with a particular emphasis on urine, blood, plasma, and oral fluid. The focus was placed on microextraction techniques, highlighting the various analytical features ~~[48].~~[49]. Santos et al. explored the application of deep eutectic solvents in LPME and their significant contributions to the field of green chemistry ~~[49].~~[50]. To the best of our knowledge, this is the first review article to highlight the applications of NADESs in liquid phase microextraction.

2. Preparation and characterization of NADES

NADES are prepared by blending specific natural metabolites at specific molar ratios to create a clear liquid at room temperature. Common components of NADES include amino acids, sugars, organic acids, choline salts, essential oil ingredients, and inorganic salts ~~[50–52].~~

~~The preparation techniques include thermal mixing, vacuum evaporation, ultrasound-based methods, and microwave-based methods. In the thermal mixing method, two components are heated and stirred with or without a predetermined amount of water to obtain a clear liquid [43,53–59]. Vacuum evaporation involves heating the NADES components under reduced pressure to remove excess water [43,53]. Ultrasound-based methods utilize ultrasonic waves to create cavitation and facilitate the formation of NADES [60]. Microwave-based methods use microwave energy to induce molecular agitation and collisions between the components [61,62]~~[51–53]. The preparation techniques include thermal mixing, vacuum evaporation, ultrasound-based methods, and microwave-based methods. In the thermal mixing method, two components are heated and stirred with or without a predetermined amount of water to obtain a clear liquid [44,54–60]. Vacuum evaporation involves heating the NADES components under reduced pressure to remove excess water [44,54]. Ultrasound-based methods utilize ultrasonic waves to create cavitation and facilitate the formation of NADES [61]. Microwave-based methods use microwave energy to induce molecular agitation and collisions between the components [62,63].

~~The characterization of NADES involves several analytical techniques. Nuclear magnetic resonance (NMR) [23,63], Fourier transform infrared spectroscopy (FTIR)~~The characterization of NADES involves several analytical techniques. Nuclear magnetic resonance (NMR) [23,64], Fourier transform infrared spectroscopy (FTIR)[23]~~, Raman spectroscopy [64,65], and mass spectrometry (MS) [66] are also used to determine the chemical composition of NADES. NMR, in combination with FTIR, helps identify the constituents and purity of components [67,68]. FTIR can also be employed to determine NADES' structures [69,70] while thermogravimetric analysis and differential scanning calorimetry are used to assess density, thermal features, and stability [43,71]. Density and viscosity measurements provide important physical property information for designing processes and evaluating solvent suitability and to determine the best ratio between HBD and HBA [72–74].~~

~~3. Application of NADESs in liquid phase microextraction~~

~~Despite obvious developments in analytical science and technology, sample preparation remains the bottleneck of all analytical procedures. Miniaturizing the analytical scale and/or using safer alternatives instead of hazardous solvents can be used to mitigate the negative environmental effect of analytical procedures [75,76].~~, Raman spectroscopy [65,66], and mass spectrometry (MS) [67] are also used to determine the chemical composition of NADES. NMR, in combination with FTIR, helps identify the constituents and purity of components [68,69].

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Despite obvious developments in analytical science and technology, sample preparation remains the bottleneck of all analytical procedures. Miniaturizing the analytical scale and/or using safer alternatives instead of hazardous solvents can be used to mitigate the negative environmental effect of analytical procedures [76,77]. Both hydrophilic and hydrophobic NADES have been employed in different modes of LPME, as shown in (**Fig. 2)**. In this section, the role of NADES in liquid phase microextraction approaches are discussed in details.

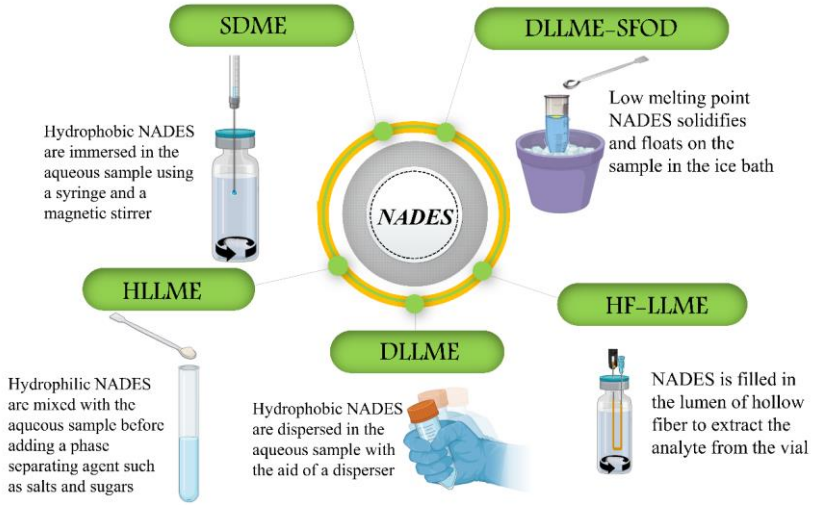

Fig. 2: Modes on LPME in which NADESs were employed

3.1. Applications of NADES in HF–LPME

Sample preparation trends tend to minimize the amount of organic solvent and extraction time. The liquid-phase microextraction (LPME) approach offers an alternative to typical preparation procedures ~~[77]. There are different modes of LPME including dispersive liquid-liquid microextraction (DLLME) [78], single-drop microextraction (SDME) [79], and hollow fiber-LPME (HF-LPME) [80]. Among these techniques, the HF-LPME has distinct benefits such as~~

~~low cost, high preconcentration factor, low solvent consumption, and environmental friendliness. The HF-LPME technique is based on the use of different materials such as porous polypropylene hollow fiber, polyvinylidene difluoride, or PTFE, which first extract analytes from an aqueous sample as the donor phase and then back-extract them into the acceptor phase situated in the HF lumen [81]. Organic solvents are often used in the HF-LPME technique, but they have various drawbacks, including volatility, toxicity, instability, and deleterious effects on laboratory workers. Nia et al [82] prepared amino acids hydrophobic NADES in two phase HF-LPME. In this application, NADES was prepared by mixing amino acids (as an HBA) with lactic acid (as an HBD) using a hollow fiber's supported liquid membrane. The lumens were impregnated with extremely stable NADESs (serine: lactic acid). The developed method was successfully applied to extract caffeic acid from green tea, tomato samples and coffee. The enrichment factor was in the range of 418–438. Morelli et al. [83] investigated both hydrophilic and hydrophobic NADESs hollow fiber-microporous membrane liquid-liquid microextraction (HF-MMLLE).~~[78]. There are different modes of LPME including dispersive liquid-liquid microextraction (DLLME) [79], single drop microextraction (SDME) [80], and hollow fiber–LPME (HF–LPME) [81]. Among these techniques, the HF-LPME has distinct benefits such as low cost, high preconcentration factor, low solvent consumption, and environmental friendliness. The HF-LPME technique is based on the use of different materials such as porous polypropylene hollow fiber, polyvinylidene difluoride, or PTFE, which first extract analytes from an aqueous sample as the donor phase and then back-extract them into the acceptor phase situated in the HF lumen [82]. Organic solvents are often used in the HF-LPME technique, but they have various drawbacks, including volatility, toxicity, instability, and deleterious effects on laboratory workers. Nia et al [83] prepared amino acids hydrophobic NADES in two phase HF-LPME. In this application, NADES was prepared by mixing amino acids (as an HBA) with lactic acid (as an HBD) using a hollow fiber's supported liquid membrane. The lumens were impregnated with extremely stable NADESs (serine: lactic acid). The developed method was successfully applied to extract caffeic acid from green tea, tomato samples and coffee. The enrichment factor was in the range of 418–438. Morelli et al. [84] investigated both hydrophilic and hydrophobic NADESs hollow fiber-microporous membrane liquid-liquid microextraction (HF-MMLLE). The best NADES was composed from thymol and camphor. Selected NADESs were introduced into the porous polypropylene membrane for 10 minutes, substituting widely used solvents (for example, hexane and octanol). The developed method was successfully applied and verified for 11 emergent contaminants from various classes, demonstrating the method's adaptability.

~~Analytical method automation, commonly employed to minimize reagent and sample usage, is a highly effective tool for integrating all stages of necessary analytical procedures onto a single manifold while minimizing human and environmental hazards. Shakirova et al. [84]~~Analytical method automation, commonly employed to minimize reagent and sample usage, is a highly effective tool for integrating all stages of necessary analytical procedures onto a single manifold while minimizing human and environmental hazards. Shakirova et al. [85] developed an automated liquid-liquid microextraction process for determining sulfonamides (sulfamethoxazole, sulfamethazine, and sulfapyridine) in urine samples utilizing NADES. The extraction of sulfonamides was based on the synthesis of colored Schiff bases in the presence of vanillin, which served as a derivatization reagent as well as a precursor of NADES (an extractant). Thymol was utilized in this process as both a medium for Schiff base synthesis and a second precursor of the NADES. Mass spectrometry verified the production of the Schiff bases. The microextraction method was automated using the Lab-In-Syringe approach as indicated in (**Fig. 3)**.

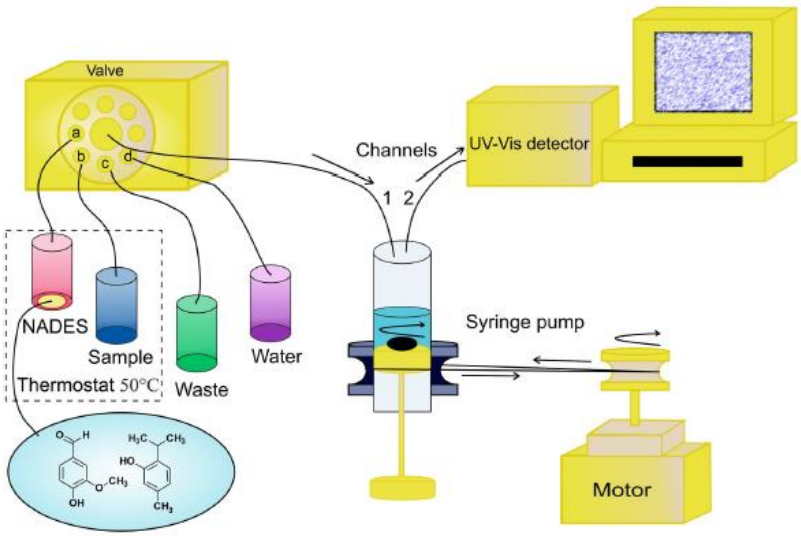

Fig. 3: manifold for the determination of sulfonamides in urine samples with permission from [~~84~~85].

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The developed approach had enough sensitivity to determine the concentration of sulfonamides at therapeutic levels. In addition to that, this method was ecologically benign, providing full automation with a sample throughput of six samples/h.

3.2. Applications of NADES in DLLME

DLLME is a miniaturized sample preparation process used in many analytical chemistry applications ~~[85,86]. In this mode, an immiscible organic solvent is used with an organic disperser, the two solvents are combined. The organic extractant is dispersed as tiny droplets by manual shaking resulting in a homogeneous hazy solution. DLMME has several benefits over other sample preparation approaches in terms of simplicity, affordability, convenience of use, and speed. However, the right selection of dispersing and extracting solvents (µL scale) is quite difficult [87]. The pioneers of DLLME mode (Rezaee et al. [88]) developed this mode as a modification of LLME in an attempt to boost the recovery rate in LLME. DLLME results in extending the contact surface between the extractant and the sample, and this dispersion procedure greatly increases extraction kinetics. The sample is then centrifuged to separate the extractant and break up the emulsion. It worth mentioning that dispersion could be achieved by using a disperser solvent or by using external mechanical force such as manual shaking, vortex agitation, magnetic stirrer power, ultrasonic power, and microwave irradiation. Traditional DLLME procedures use hazardous halogenated organic solvents such as chloroform, carbon tetrachloride, and chlorobenzene, which can be harmful to human health and the environment. In addition to using long chain alcohols as extractant and hazardous dispersers such as acetonitrile (ACN), methanol, acetone, tetrahydrofuran (THF), ethanol. Therefore, one of the GAC principles that should be adopted in method development is the replacement of harmful solvents with more benign ones. As a result, more environmentally friendly NADESs have recently been offered as a sustainable alternative in DLLME. In general, NADES is made up of two or more natural components (HBD and HBA) blended in a certain ratio to generate a homogeneous mixture with a eutectic point at a lower temperature than the separate substances. The most common components used in synthesis of NADESs are monoterpenes (menthol, thymol, and camphor) [89–100]. These solvents are biodegradable, less hazardous, widely accessible, and simple to make. Monoterpenes such as are considered an ideal choice of extractant because of their poor water solubility [101]. In general, hydrophobic NADESs were used as extractants in DLLME mode however, hydrophilic NADESs could be used as a disperser in the same mode. As reported in Table 1, the use of NADESs in DLLME was successfully applied for the extraction of different analytes from different matrices including water [100], biological samples [102], foods [103], beverages [92] and personal care products [91]~~[86,87]. In this mode, an immiscible organic solvent is used with an organic disperser, the two solvents are combined. The organic extractant is dispersed

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Table 1: Application of NADES in DLLME

Analyte	Sample	Sample volume (mL)	NADES component	Dispersion mode	Extractant volume (µL)	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Tetracyclines	Water	5	[ChCl]: [thymol]: [nonanoic acid]	Air assisted DLLME	400	HPLC/UV	18.2-500	≤11.2	~~[100]~~ [102]
Warfarin	Biological samples	10	Borneol: decanoic acid	Air assisted DLLME	60	HPLC/UV	5–500	<5.87	~~[102]~~ [104]
Vanadium	Food stuff	2	ChCl: phenol	Ultrasound assisted DLLME	1000	Electrothermal atomic absorption spectrometry (ETAAS)	N/A	3.4%	~~[104]~~ [106]
Tert-Butylhydroquinone	Soybean Oils	0.2 g	ChCl: sesamol	Ultrasound assisted DLLME	400	HPLC/UV	5-500 mg/kg	<2.3%	~~[105]~~ [107]
NSAIDs	Water and milk samples	10	1,1,3,3-tetramethylguanidine chloride: thymol	Ultrasound assisted DLLME	200	HPLC/UV	5–2000	1.11% to 16.9%.	~~[89]~~[91]
Parabens	Personal care products	5	Menthol: formic acid	Vortex assisted DLLME	80	UHPLC/UV	20–4000	≤3.33%	~~[91]~~[93]
Mercury	Water samples	9	Decanoic acid: DL-menthol	Vortex assisted DLLME	50	LC/UV–Vis	10–200	≤19%	~~[90]~~[92]
Alkylphenols, bisphenols and alkylphenol ethoxylates	Microbial-fermented functional beverages and bottled water	10	Methanol: octanoic acid	Vortex assisted DLLME	100	UHPLC-MS	0.4-50	≤19.5%	~~[93]~~[95]
Sudan I	Food samples	0.2 g	ChCl: sesamol	Vortex assisted DLLME	800	HPLC/UV	0.2–100 mg /kg	<4.5%	~~[103]~~ [105]
Beta-blockers	Water samples	9.5	Azelaic acid: thymol	Vortex assisted DLLME	55	HPLC/DAD	0.5-100	<6%	~~[106]~~ [108]
Phthalate Esters	Soft drinks	10	Thymol: octanoic acid	Vortex assisted DLLME	125	UPLC-MS/MS	0.10−5.00	<11.5%	~~[92]~~[94]
Phthalate esters	Grape-based beverages	7.5	ChCl: acetic acid	Vortex assisted DLLME	500	Nano-LC/UV	5-403	<17%	~~[107]~~ [109]
Benzoic acid and sorbic acid	Condiments	10	L-Menthol Acetic acid: decanoic acid	Vortex assisted DLLME-SFOD	800	HPLC/DAD	70-100000	≤5.66%	~~[94]~~[96]
Phthalates and one adipate	Water samples	10	Thymol: menthol	Vortex assisted DLLME	100	UHPLC-QqQ-MS/MS	0.100–250	<14%	~~[95]~~[97]
Chloramphenicol	Honey sample	5	Menthol: acetic acid	Vortex assisted DLLME	100	LC/UV	1–100 µg /kg	≤4.5%	~~[96]~~[98]
Triarylmethane) dyes	Shrimp and water samples.	10	Thymol and camphor	Vortex assisted DLLME	200	HPLC/DAD	0.2 -200	≤2.3	~~[97]~~[99]
Acaricides	Egg samples	5	Choline chloride-acetic acid-*n*-octanol	In-syringe DLLME	74	GC/FID	2.7‑4000	≤11%	~~[108]~~ [110]
Phthalic acid esters	Soft drinks and infusions	20	Menthol: acetic acid	Manual agitation assisted DLLME-SFO	100	HPLC/UV	6-1190	1-22 %	~~[98]~~[100]
Phthalic acid esters	Water and beverage samples	20	Menthol: acetic acid	Manual agitation assisted DLLME	100	HPLC/UV	4-425	≤ 20%	~~[99]~~[101]

3.3. Applications of NADES in HLLME

HLLME is a method of sample preparation that involves the formation of a homogeneous phase between an aqueous sample and a small amount of a water-miscible extractant, such as acetonitrile, acetone or tetrahydrofuran. The separation of phases is achieved using a phase separating agent (PSA), which may be a salt, sugar, or hydrophobic substance. Depending on the type of PSA used, HLLME can be classified into three categories: salt-assisted LLME (SALLME) [109,110], sugar-assisted LLME (SULLME) [111,112], and hydrophobic substance-assisted or aprotic solvent assisted HLLME [113,114]. Besides, the manipulation of physical conditions such as temperature, pH of the system, and, introducing gas bubbles to the homogeneous system could achieve phase separation [115]. It is worth mentioning that HLLME is characterized by infinite contact surface area between the aqueous and organic phases, which permits highly quick and effective extraction [116]. Another advantage of this microextraction process is that there is no need for an evaporation/reconstitution step due to the hydrophilicity of the donor phase. In the standard HLLME approach, hydrophilic organic solvents such as acetonitrile, acetone, ethanol, and propanol are frequently used as extractants. NADESs have recently attracted a lot of attention as a more eco-friendly alternative to the poisonous and volatile organic solvents used in the HLLME process. The most common mode that was used in HLLME is the aprotic solvent-assisted HLLME, which depends on using a water miscible extractant and an aprotic solvent a PSA such as THF, ACN and acetone. Unlike other HLLME modes, this mode gives the ability to use a large sample volume, enhancing sensitivity of the proposed method. Khezeli et al. [117] were the pioneers of this mode. In this work, the NADESs used were prepared by combining choline chloride (ChCl) as an HBA with phenol as an HBD. The developed method was used to successfully extract several organic chemical components from water samples. This procedure produced a homogeneous solution by adding the extraction solvent (the hydrophilic NADES) to the aqueous sample solution (donor phase). Finally, an aprotic solvent (THF) was used to produce phase separation. It has been proposed that introducing an aprotic solvent into a homogeneous solution can greatly diminish the interactions between DES and water molecule because of the π- π and hydrogen bonding interactions between the DES ingredients. Therefore, the DES molecules can self-aggregate and migrate out of the water phase. Shishov et al. [118] proposed another theory in the mechanism of phase separation. They investigated the solvent-assisted HLLME process with hydrophilic DES based on choline and phenol utilizing gas chromatography-mass spectrometry analysis and coulometric Karl Fischer titration. The results of this study supported the instability of a hydrophilic DES in aqueous conditions. Thus, they hypothesize

that hydrophilic DESs based on choline and phenol breaks down in the aqueous phase in the solvent-assisted HLLME process. The findings of this study revealed that the organic phase recovered comprised phenol, THF, and water. As indicated in Table 2 , this mode was successfully applied for extraction various compound from different matrices including water [119], food [120], biological samples [121] and beverages [122]. The most common water miscible NADES used in aprotic solvent-assisted HLLME was composed of phenol and ChCl [120,123–127]. In addition to that, THF was widely used in this mode as PSA [120,123,128,129]. It is worth mentioning that other aprotic solvent were used as PSA in aprotic solvent assisted HLLME such as ACN [130] and acetone [131]. The applications of NADES in HLLME have high potential because of being greener, simpler, cheaper, and more sensitive in comparison with other conventional extraction modes.

348 **Table 2:** Applications of NADES in HLLME

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394 **Table 2:** Applications of NADES in HLLME

Analyte	Sample	Sample volume (mL)	NADES component	HLLME	PSA	Extractant volume (µL)	PSA(vol /amount) µL	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Copper	olive oil and water samples	15	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	450	450	FAAS	NA	<5.0%	~~[123]~~[126]
Arsenic and antimony	Water samples	125	ChCl: oxalic acid	Aprotic solvent assisted HLLME	THF	700	300	Hydride generation-atomic absorption spectrometry	15-570 ng/L	2.1% and 2.7%	~~[119]~~[122]
Benzotriazole derivatives and benzothiazole derivatives	Surface water	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	1000	500	UHPLC-ESI(+)-QToF-MS	5 -200	1 -8%	~~[124]~~[127]
Pesticides	Chinese medicine	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	650	550	HPLC/DAD	50-107000	4.7%	~~[125]~~[128]
Methyl mercury and total mercury	Water and fish sample	2.5	betaine-sorbitol	Aprotic solvent assisted HLLME	ACN	600	375	Spectrophotometer	0.7–340	1.9–5.5%	~~[130]~~[133]
Caffeine	Turkish coffee	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	800	HPLC/UV	500-100000	2.20%	~~[126]~~[129]
Curcumin	Tea and honey samples	5	ChCl: Maltose	Aprotic solvent assisted HLLME	THF	762.5	107.5	Spectrophotometer	0.4–120	≤4.3%	~~[132]~~[135]
Curcumin	Food and herbal tea	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	400	Spectrophotometer	NA	1.8 %.	~~[120]~~[123]
Malachite green	Aquarium fish water	10	ChCl: Phenol	Aprotic solvent	THF	500	500	Spectrophotometer	45-900	2.7 %.	~~[127]~~[130]

Sulfonamides	Water samples	1.5	ChCl: Phenol	assisted HLLME	THF	193	100	HPLC/UV	500–100000	≤2.10	~~[128]~~[131]
Thiophenols	Water samples	1.5	ChCl:p-cresol	Aprotic solvent assisted HLLME	Acetone	50	50	GC/FID	2-100000	<4.1%	~~[131]~~[134]
Polycyclic aromatic hydrocarbons	Water samples	1.5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	100	100	HPLC/UV	0.1-400	<4.5	~~[117]~~[120]
Antidepressants	Pharmaceutical and water samples	6	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	200	430	HPLC/UV	10-8000	3.6-5.7%	~~[133]~~[136]
Selenium species	Water and food samples	25	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.2-8	≤4.1	~~[134]~~[137]
Phenoxy acid herbicides	Paddy field and water samples	1.5	ChCl:2-chlorophenol	Aprotic solvent assisted HLLME	THF	50	100	HPLC/UV	5–100	≤4.6	~~[135]~~[138]
Phthalate	Beverages	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	440	440	HPLC/DAD	170-2700	<11%	~~[122]~~[125]
Caffeine	Beverages	1	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	50	50	HPLC/UV	100-200000	≤6%	~~[136]~~[139]
Mercury	Water and biological samples	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.3-10	≤–5.72%	~~[121]~~[124]

	Cadmium	Food and water samples	50	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	600	ETAAS	5–150 ng/ L	3.1%	~~[129]~~[132]

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3.4. Applications of NADES in single drop microextraction

Single-drop microextraction (SDME) is a highly effective and environmentally sustainable sample pretreatment technique that involves the immersion of an organic solvent microdroplet into the sample with the aid of a microsyringe needle. SDME has gained widespread use in fields such as environmental monitoring, food quality control, and biological analysis, owing to its minimal solvent consumption and high sample-to-extractant phase ratio ~~[137,138].~~[140,141]. This technique has streamlined the analytical workflow by integrating extraction and enrichment processes. Furthermore, SDME is particularly well-suited for fluorescence spectroscopy, as the solvent used is transparent in the visible region and does not interfere with direct visual readout or spectral analysis ~~[139,140].~~[142,143]. The realm of green analytical chemistry is presently witnessing a huge interest in the creation and utilization of sustainable and eco-friendly solvents. This trend is particularly visible in the SDME field, in which a growing number of innovative solvents has been reported, for instance, ionic liquids, superheated water, deep eutectic solvents, surfactants, and supercritical fluids ~~[141].~~[144]. An important aspect that could significantly influence the efficacy of the extraction process is the choice of solvent. In particular, the utilization of a solvent with high viscosity can facilitate the suspension of larger and more stable droplets at the needle tip. This property makes NADESs a suitable option for the task, given their favorable attributes such as elevated viscosity at ambient temperature, considerable thermal stability, and low vaporization tendencies ~~[142].~~[145]. Yousefi et al. have introduced a novel technique for headspace single drop microextraction (HS-SDME) that employs a magnetic bucky gel derived from deep eutectic solvents (DES-MBG) as the extraction medium. This method offers several advantages, including high viscosity, magnetic susceptibility, and adjustable extractability. Additionally, it ensures droplet stability, allowing extraction at high temperatures and rapid agitation rates. This suggests the potential of DES-MBGs to exhibit superior resilience, facilitating the utilization of larger droplet volumes and consequently enhancing extraction efficiency, sensitivity, and detection limits ~~[143].~~ [146]. Yıldırım et al. ~~[144]~~[147] proposed a novel approach for fluoroquinolone analysis in environmental waters via an automated Lab-In-Syringe direct immersion single drop microextraction method coupled online to HPLC with fluorescence detection (**Fig. 4)**. The method employed NADES as an extractant within an automatic syringe pump, thus eliminating the utilization of toxic solvents and augmenting the method's sustainability from an environmental perspective. The method's linearity range for fluoroquinolones lied between 0.1 and 5.0 µg/L, with quantification limits in the 20-30 ng/L and enrichment factors of 35-45. The trueness of spiked samples ranged from 84.6% to 119.7%,

and the method exhibited low RSD values. The method's advantages include its parallel operation with HPLC, low sample consumption, and environmentally friendly characteristics, aligning it with the principles of green analytical chemistry [~~144~~147].

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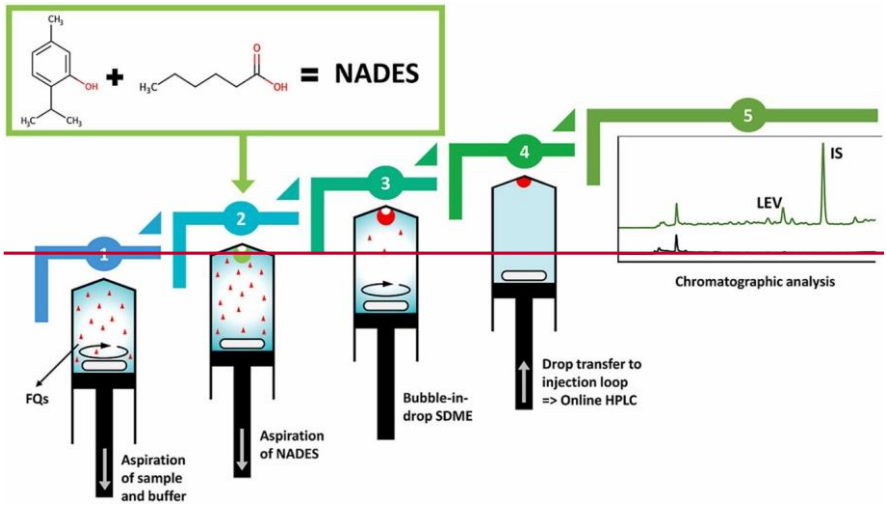

~~**Fig. 4.** A schematic representation for the automation of a lab-in-syringe technique using NADES-based direct immersion single drop microextraction, which is linked online to HPLC-FL to determine fluoroquinolones (With permission from [144])~~

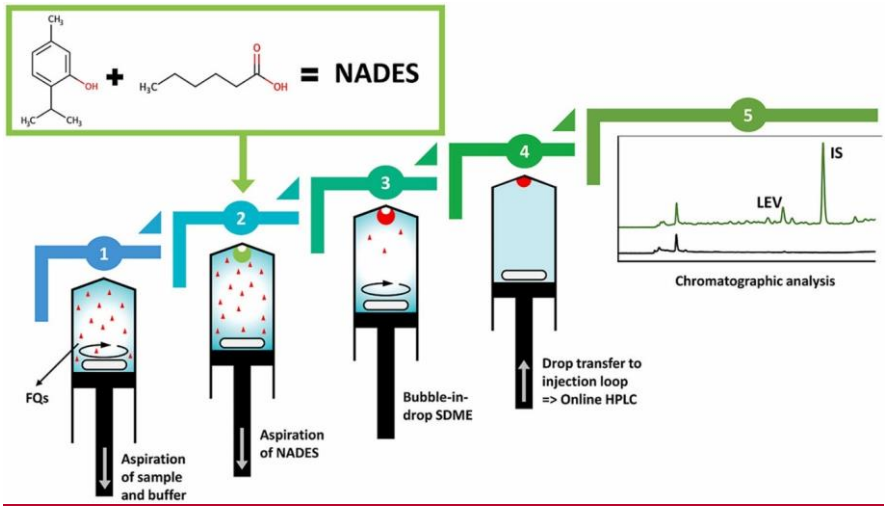

Fig. 4. A schematic representation for the automation of a lab-in-syringe technique using NADES-based direct immersion single drop microextraction, which is linked online to HPLC-FL to determine fluoroquinolones (With permission from [147])

3.5 Applications of NADES in DLLME-SFOD

The DLLME-SFOD approach is a microextraction method that employs a ternary solvent system (extractant, disperser and sample), in which the extractant is an organic solvent that solidifies in ice bathes at relatively low temperatures ~~[145].~~[148]. The injection of a suitable mixture into an aqueous sample results in the formation of a cloudy solution, which facilitates phase interaction ~~[146].~~[149]. Following phase separation and centrifugation, the sample is immersed in an ice bath and the solidified organic phase is gathered for analysis ~~[147].~~[150]. This method boasts high efficiency, enrichment factors, and rapid equilibrium, while necessitating minimal solvent volume and equipment. Nonetheless, its solvent options are restricted in a narrow range of long chain alcohols with high melting points in the range 10-25°C. However, deep eutectic solvents (DESs) are being investigated as a favorable, eco-friendly replacement for this technique ~~[148,149].~~[151,152]. NADES have been utilized in DLLME-SFOD, serving as both disperser and extracting solvents. An effective example is a NADES consisting of lactic acid, glucose, and water at a 5:1:3 molar ratio, which has demonstrated efficient dispersion of pesticides from water and white wine through vigorous shaking. The addition of water has resulted in lower viscosity, which has facilitated the dispersion process. The dispersive NADES has achieved recoveries exceeding 90% for analytes tested due to its reduced viscosity and increased polarity, which have improved interactions among the aqueous sample, NADES, and extracting solvent ~~[150].~~[153]. The developed method offered a strong, efficient, and environmentally friendly alternative for determining pesticides, providing a novel application for NADES in sample preparation, as indicated in **Table 1**. Another study has incorporated menthol and decanoic acid in the preparation of NADES with a molar ratio of 1:2 for the extraction of antidepressants from urine samples prior to GC/MS analysis resulting in recoveries ranging from 74 to 147% ~~[151].~~[154]. In their research, Taşpınar et al. applied an environmentally friendly approach known as air-assisted DLLME-SFOD, which was designed to extract patulin from both fruit juice and dried fruit. This process involved the injection of NADES as extraction solvents at a volume of 410 µL into a sample solution that has been adjusted to a pH of 5.6. The solution was then drawn into a syringe and immediately reinjected six times to allow for the even dispersal of NADES droplets throughout the aqueous bulk, resulting in a cloudy solution. Afterwards, the tubes were submerged in an ice bath for roughly seven minutes, which enabled the NADES phase to solidify and become easily separable before undergoing UV/Vis spectrophotometric analysis. This method had an LOD of 3.5 µg/L and an EF of 150 [~~152~~155].

Field Code Changed

4. Limitations of NADES

The interest and the applications of NADES in various fields, particularly in chemical analysis and LPME are increasing. However, NADES are not perfect solvents and have some challenges and limitations that need to be addressed, such as stability, viscosity, water content, and extraction efficiency. NADES are prone to decomposition or degradation over time. The hydrogen-bonding network that exists between the constituents significantly influences the stability of NADES. Hydrogen bonds are responsible for lowering the melting point of NADES [20]. Betaine-urea-water is a NADES that has been used for extracting bioactive compounds from plants. However, this NADES is not stable at room temperature and tends to crystallize after a few days. A recent study by Nava-Ocampo et al. investigated the structural properties and stability of betaine-urea-water using spectroscopic and computational methods. The researchers discovered that the formation of a metastable transparent liquid requires a minimum of two moles of water, whereas a stable NADES necessitates a minimum of three moles of water. They also showed that water plays a crucial role in forming stronger hydrogen bonds between urea and the carbonyl groups of betaine, and in deprotecting the methyl group of betaine from forming intermolecular interactions ~~[153].~~[156]. NADES tend to have high viscosity compared to conventional solvents, which can limit their mass transfer and diffusion rates. This can reduce their extraction efficiency and increase the energy consumption and processing time. To address this, it is necessary to optimize the composition and ratio of the components of NADES to achieve the desired viscosity. Moreover, some methods can be used to reduce the viscosity of NADES, such as heating, dilution, ultrasonication, or adding co-solvents [13]. NADES usually contain a certain amount of water due to their hygroscopic nature or the presence of water in the natural components. Water can affect the polarity and solvation ability of NADES, as well as their interaction with the target compounds. So, it is important to control the water content of NADES according to the specific application and the solubility of the target compounds. Additionally, some techniques can be used to remove or reduce the water content of NADES, such as freeze-drying ~~[154].~~[157]. NADES may be less environmentally friendly than initially thought, urging a reevaluation of their large-scale applications ~~[155].~~[158]. According to Popović et al, The cytotoxic effect is primarily influenced by the structure of the HBD, with acidic systems showing the highest cytotoxic effects. Cytotoxicity depends on both the concentration of the NADES system in the cell medium and the chemical composition of the investigated systems [~~156~~159].

Field Code Changed

~~**5. Perspectives**~~

~~One of the major limitations in any LPME is phase separation. To overcome this problem, magnetic solvents have been introduced in recent years to shorten the time necessary for phase separation. These magnetic solvents can be quickly separated and collected without the need for time-consuming centrifugation processes, allowing for quick sample preparation. Magnetic solvents are easier to prepare and have higher reproducibility than magnetic materials. Magnetic ionic liquids have a low vapor pressure and good thermal stability, as well as the capacity to respond significantly to external magnetic fields [157,158]. However, they are costly and need drying or a rotary evaporation process [159]. Magnetic deep eutectic solvents (MDESs) not only exhibit paramagnetic characteristics similar to magnetic ionic liquids, but they also offer substantial cost and availability benefits. Most MDESs are currently hydrophilic, which limits their applicability to extracting polar analytes (such as thiophene and aldehydes) in non-polar solvents (such as n-heptane and oil samples) [160,161]. Therefore, the development of hydrophobic MDESs is necessary to extract non-polar analytes from different matrices. For these reasons, MDESs is a new growing area of research for the development green solvents in LPME. Duque et al [162] applied ferrofluid-based NADES in stir bar dispersive liquid microextraction for the determination of UV filters in water samples. This ferrofluid was composed of a hydrophobic NADES (1:5 molar ratio of menthol and thymol as carrier solvent) and oleic acid-coated cobalt ferrite ($CoFe_2O_4$@oleic acid) magnetic nanoparticles. $CoFe_2O_4$ MNPs were first synthesized through wet chemical coprecipitation using an adapted procedure [163], and then coated with oleic acid. In this case, 100 mL of 0.4 M $FeCl_3$ aqueous solution was combined with 100 mL of 0.2 M $CoCl_2$ aqueous solution. Then, 100 mL of a 3 M sodium hydroxide aqueous solution was added dropwise at 80°C, under continuous stirring. The reaction mixture was then agitated at the same temperature for 1 hour after 2 mL of oleic acid was added. After carefully cooling the black precipitate result to ambient temperature, the MNPs were cleaned twice with ultrapure water and once with ethanol. Finally, the precipitate was dried overnight at 100°C and ground into a fine powder. A stable ferrofluid was prepared by weighing 25 mg of $CoFe_2O_4$@OA MNPs in a microcentrifuge tube and 1 mL of NADES was added. The resulting mixture was sonicated for 40 min. The results indicated that the developed analytical method produced comparable findings, demonstrating the promise of this ferrofluid as a less expensive and more environmentally friendly alternative to MILs in future analytical procedures [163].~~

5. Perspectives

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6. Conclusion

NADESs have emerged as promising alternatives for liquid phase microextraction applications. NADES offer unique advantages such as high polarity, hydrophilicity, and environmentally friendly nature, making them suitable for liquid phase microextraction in diverse fields, including pharmaceutical, environmental, and food analysis. NADES have been successfully employed in different modes, including HF-LPME, DLLME, and SDME. These techniques aim to minimize the use of organic solvents, reduce extraction time, and enhance the preconcentration factor. NADES have shown promise in improving the efficiency and environmental friendliness of LPME processes. By replacing traditional solvents with NADES, researchers have achieved successful extraction of analytes from aqueous samples. Rising interest in NADES for analysis and LPME faces challenges in stability, viscosity, water content, and extraction efficiency. Further research and development in the synthesis methods, characterization techniques, and application of NADES are warranted to fully explore their potential in liquid phase microextraction and contribute to sustainable analytical practices. The automation of liquid-liquid microextraction processes using NADES has proven to be a valuable approach in minimizing reagent and sample usage while reducing human and environmental hazards.

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Declaration of interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

All Authors contributed equally to Conceptualization; Investigation; Project administration; Resources; Supervision; Roles/Writing - original draft; and Writing - review & editing.

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Supplementary Material (Text with Changes marked)

Table 1: Application of NADES in DLLME

Analyte	Sample	Sample volume (mL)	NADES component	Dispersion mode	Extractant volume (µL)	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Tetracyclines	Water	5	[ChCl]: [thymol]: [nonanoic acid]	Air assisted DLLME	400	HPLC/UV	18.2-500	≤11.2	[100]
Warfarin	Biological samples	10	Borneol: decanoic acid	Air assisted DLLME	60	HPLC/UV	5–500	<5.87	[102]
Vanadium	Food stuff	2	ChCl: phenol	Ultrasound assisted DLLME	1000	Electrothermal atomic absorption spectrometry (ETAAS)	N/A	3.4%	[104]
Tert-Butylhydroquinone	Soybean Oils	0.2 g	ChCl: sesamol	Ultrasound assisted DLLME	400	HPLC/UV	5-500 mg/kg	<2.3%	[105]
NSAIDs	Water and milk samples	10	1,1,3,3-tetramethylguanidine chloride: thymol	Ultrasound assisted DLLME	200	HPLC/UV	5–2000	1.11% to 16.9%.	[89]
Parabens	Personal care products	5	Menthol: formic acid	Vortex assisted DLLME	80	UHPLC/UV	20–4000	≤3.33%	[91]
Mercury	Water samples	9	Decanoic acid: DL-menthol	Vortex assisted DLLME	50	LC/UV–Vis	10–200	≤19%	[90]
Alkylphenols, bisphenols and alkylphenol ethoxylates	Microbial-fermented functional beverages and bottled water	10	Methanol: octanoic acid	Vortex assisted DLLME	100	UHPLC-MS	0.4-50	≤19.5%	[93]
Sudan I	Food samples	0.2 g	ChCl: sesamol	Vortex assisted DLLME	800	HPLC/UV	0.2–100 mg /kg	<4.5%	[103]
Beta-blockers	Water samples	9.5	Azelaic acid: thymol	Vortex assisted DLLME	55	HPLC/DAD	0.5-100	<6%	[106]
Phthalate Esters	Soft drinks	10	Thymol: octanoic acid	Vortex assisted DLLME	125	UPLC-MS/MS	0.10−5.00	<11.5%	[92]
Phthalate esters	Grape-based beverages	7.5	ChCl: acetic acid	Vortex assisted DLLME	500	Nano-LC/UV	5-403	<17%	[107]
Benzoic acid and sorbic acid	Condiments	10	L-Menthol Acetic acid: decanoic acid	Vortex assisted DLLME-SFOD	800	HPLC/DAD	70-100000	≤5.66%	[94]
Phthalates and one adipate	Water samples	10	Thymol: menthol	Vortex assisted DLLME	100	UHPLC-QqQ-MS/MS	0.100–250	<14%	[95]
Chloramphenicol	Honey sample	5	Menthol: acetic acid	Vortex assisted DLLME	100	LC/UV	1–100 µg /kg	≤4.5%	[96]

Triarylmethane) dyes	Shrimp and water samples.	10	Thymol and camphor	Vortex assisted DLLME	200	HPLC/DAD	0.2 -200	≤2.3	[97]
Acaricides	Egg samples	5	Choline chloride-acetic acid-*n*-octanol	In-syringe DLLME	74	GC/FID	2.7‑4000	≤11%	[108]
Phthalic acid esters	Soft drinks and infusions	20	Menthol: acetic acid	Manual agitation assisted DLLME-SFO	100	HPLC/UV	6-1190	1-22 %	[98]
Phthalic acid esters	Water and beverage samples	20	Menthol: acetic acid	Manual agitation assisted DLLME	100	HPLC/UV	4-425	≤ 20%	[99]

Table 2: Applications of NADES in HLLME

Analyte	Sample	Sample volume (mL)	NADES component	HLLME	PSA	Extractant volume (µL)	PSA(vol /amount) µL	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Copper	olive oil and water samples	15	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	450	450	FAAS	NA	<5.0%	[123]
Arsenic and antimony	Water samples	125	ChCl: oxalic acid	Aprotic solvent assisted HLLME	THF	700	300	Hydride generation-atomic absorption spectrometry	15-570 ng/L	2.1% and 2.7%	[119]
Benzotriazole derivatives and benzothiazole derivatives	Surface water	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	1000	500	UHPLC-ESI(+)-QToF-MS	5 -200	1 -8%	[124]
Pesticides	Chinese medicine	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	650	550	HPLC/DAD	50-107000	4.7%	[125]
Methyl mercury and total mercury	Water and fish sample	2.5	betaine-sorbitol	Aprotic solvent assisted HLLME	ACN	600	375	Spectrophotometer	0.7–340	1.9–5.5%	[130]
Caffeine	Turkish coffee	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	800	HPLC/UV	500-100000	2.20%	[126]
Curcumin	Tea and honey samples	5	ChCl: Maltose	Aprotic solvent assisted HLLME	THF	762.5	107.5	Spectrophotometer	0.4–120	≤4.3%	[132]
Curcumin	Food and herbal tea	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	400	Spectrophotometer	NA	1.8 %.	[120]
Malachite green	Aquarium fish water	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	Spectrophotometer	45-900	2.7 %.	[127]
Sulfonamides	Water samples	1.5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	193	100	HPLC/UV	500–100000	≤2.10	[128]
Thiophenols	Water samples	1.5	ChCl:p-cresol	Aprotic solvent assisted HLLME	Acetone	50	50	GC/FID	2-100000	<4.1%	[131]

Polycyclic aromatic hydrocarbons	Water samples	1.5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	100	100	HPLC/UV	0.1-400	<4.5	[117]
Antidepressants	Pharmaceutical and water samples	6	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	200	430	HPLC/UV	10-8000	3.6-5.7%	[133]
Selenium species	Water and food samples	25	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.2-8	≤4.1	[134]
Phenoxy acid herbicides	Paddy field and water samples	1.5	ChCl:2-chlorophenol	Aprotic solvent assisted HLLME	THF	50	100	HPLC/UV	5–100	≤4.6	[135]
Phthalate	Beverages	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	440	440	HPLC/DAD	170-2700	<11%	[122]
Caffeine	Beverages	1	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	50	50	HPLC/UV	100-200000	≤6%	[136]
Mercury	Water and biological samples	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.3-10	≤–5.72%	[121]
Cadmium	Food and water samples	50	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	600	ETAAS	5–150 ng/ L	3.1%	[129]

Declaration of interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.