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Multicomponent Synthesis of N-Heterocycles in Natural Deep Eutectic Solvents (NADES): A Critical Review

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Abstract: Green solvents are intended to provide more sustainable alternatives in chemical synthesis, yet they often come with a trade-off in reaction efficiency. Natural Deep Eutectic Solvents (NADES) have recently attracted significant interest due to their intrinsic advantages-namely, biocompatibility, low toxicity, and readiness to biocompatibility, low toxicity, and readiness to biocompatibility, low toxicity, and readiness to biodegrade. Despite these benefits, several practical limitations remain, including their notably high viscosities (50-10,000 cP) , susceptibility to thermal degradation above 80°C , and compositional changes that occur during recycling, all of which restrict their broader applicability. This review critically examines the progress made from (2025 to 2025) in using NADES as a mediator for multicomponent reactions (MCRs) leading to nitrogen- based heterocyclic rings. Using rigorous inclusion criteria relevant to NADES- assisted MCRs within the specified timeframe, a total of 127 articles were found through systematic searches of Web of Science, Scopus, and PubMed. Many NADES- mediated transformations demonstrated remarkable efficiencies throughout these investigations; several reports indicated yields of 85 – 98 % and substantial increases in E- factor values of 40 – 70 % . The environmental benefits are somewhat offest by higher energy requirements, primarily because some protocols require higher temperatures and longer reaction times. NADES technology is still a feasible alternative to the conventional hazardous flow synthesis technique , and its promise is especially pertinent to sectors that largely depend on heterocyclic scaffolds, like fine chemicals, agrochemicals, and medicines. Moving forward, research should prioritize the development of task- specific NADES, optimization of reaction conditions for scale-up, and the establishment of standardized experimental procedures to enhance reproducibility across different laboratories. In addition to identifying important research gaps that need to be filled, this study advances the field by offering a fundamental framework for assessing (NADES) performance in industrial settings and setting reasonable standards for upcoming advancements in sustainable synthetic techniques.

Keywords: Natural Deep Eutectic Solvents (NADES), Deep Eutectic Solvents (DES), Multicomponent Reactions (MCRs), Nitrogen Heterocycles (N-heterocycles), Green Chemistry.

Introduction

The global trend towards more sustainable and environmentally friendly chemicals technologies has led to the emergence of natural deep biotechnological solvents (NADES) as reliable alternatives to traditional organic solvents (Ma et al, 2024) (Khalid et al, 2024). These biotechnological formulations, which are typically composed of natural materials such as sugars, amides, organic acids, and amino acids, are often praised for their renewable nature, low toxicity, and biodegradability (Ruan et al, 2023) (Bertrand et al, 2024). Despite these benefits, the growing interest in NADES in synthetic chemistry frequently masks the need for a fair evaluation of their operational limitations and actual industrial applicability (Wang et al, 2024) (Weerasinghe et al, 2024). The creation of nitrogen containing heterocycles continues to be key component of both pharmaceutical and agrochemical synthesis, and Multicomponent Reactions (MCRs) provide extremely atom-efficient pathways to structurally complex molecules (Kyriakoudi et al 2024) (Hu et al, 2023). Acritical analysis of the available data reveals significant discrepancies between laboratory reports and the requirements of large scale implementation, despite the fact that the integration of NADES with MCR methodologies has garnered significant scientific interest (Mohlala et al, 2024) (Graebin et al, 2019). 127 studies met the requirements of our systematic review of the literature (n = 127 studies published between 2020 and 2025; inclusion criteria: English-language, peer reviewed experimental studies; exclusion criteria: reviews theoretical work and non- NADES systems). Our analysis shows that fewer than 30% of these publications provide meaningful comparative assessments against traditional solvents, and less than 15% discuss scalability or process transferability (Dos santos et al, 2023) (Russo et al, 2022). Only 60– 70% of reproducibility assessments across several studies are successful, which reflects ongoing problems with methodological consistency and inadequately standardized protocols (Divyavani et al, 2024). In order to assess the real benefits and practical constraints of NADES- based MCR strategies for the synthesis of nitrogen heterocycles. This review takes a critical stance. We seek to close the gap between the conceptual promise and practical application of 127 peer-reviewed studies published between 2020 and 2025. Only NADES -mediated MCRs for nitrogen heterocycle synthesis are discussed: non-NADES deep eutectic systems, extraction-oriented applications, and MCR pathways aimed at other heterocyclic frameworks are not.. We specifically address four critical limitations that emerge repeatedly in the literature: (1) high viscosity and associated mass-transfer constraints (Section 2.2), (2) water sensitivity and its impact on solvation properties (Section 2.3), (3) thermal instability under reaction conditions (Section 2.4), and (4) practical challenges in solvent recyclability (Section 2.5). A detailed assessment of these factors across the principal classes of multicomponent reactions- Biginelli, Mannich, Hantzsch, and click – type transformations (Section 3) – allows this review to provide researchers and industry professionals with practical, evidence-based recommendations. The discussion further extends to industrial deployment, where we examine both scalability and economic considerations (Section 6, Table 3) outlining the technical challenges that must be resolved for NADES to progress from laboratory applications to viable industrial solvents. In addition, the review proposes realistic criteria that can guide future developments in this rapidly evolving domain (Garcia et al, 2015).

Methodology

Objectives

The overall aim of this work is to provide an in – depth and critical evaluation of natural (NADES) solvents in deep multi – component reactions (MCRs) used in the synthesis of nitrogen- containing heterocyclic compounds between (2020- 2025).

The study aims to :

1. Evaluate the performance of (NADES) in these transformations by reviewing (127) poor- reviewed research articles from reputable scientific databases.
2. Highlight issues that are not adequately addressed in the current literature, such as inconsistencies, unresolved problems, and practical limitations.
3. Assess the effectiveness of (NADES) in terms of reaction productivity and environmental performance, considering the actual energy requirements associated with their use.
4. Describe a mythological framework for evaluating (NADES) in industrial settings and establish reasonable benchmarks for future studies and technology adoption.
5. Identify critical knowledge gaps that must be filled before (NADES) can become a viable alternative to conventional organic solvents in industrial chemistry.

Result and Discussion

Physical and Chemical Properties of NADES

1) Formation Principles and Thermodynamic Considerations

The formation of (NADES) depends on the interactions between hydrogen bond donors (HBD) and acceptors (NBA). Forming a network that keeps the liquid state stable below each component's melting point (Brahmachari et al, 2023) (Yu et al, 2024). Eutectic formation thermodynamics in natural systems are frequently oversimplified, with many studies ignored the impacts of temperature- despondent phase behavior and water content (da Silva et al, 2020) (Tahmassebi et al, 2022). According to density fundamental theory (DFT) simulations, NADES stability is extremely sensitive to water content , with optimal hydrogen-binding networks taking place at (5-15 %) water (Perna et al, 2020) (Hansen et al, 2021). In contrast, anhydrous (NADES) experimental claims raise the possibility of measurement errors or inadequate characterisation [23]. Concerns regarding long- term industrial stability are raised by the fact that many (NADES) occur as metastable phases rather than true thermodynamic eutectics, according to molecular dynamics simulations (Alonso et al, 2016). The enthalpy of mixing (ΔH_mix) , which typically ranges from (-5 to -25) kJ/mol, indicates weaker intermolecular interactions compared to ionic liquids (between-50 and -150) kJ/ mol), which can pose a challenge to stability processing conditions (Martins et al) (Francisco et al, 2013). Furthermore , many of the reactions occur at temperatures higher than the thermal stability of the (NADES) matrix, highlighting often overlooked thermodynamic constraints (Paiva et al, 2014) (Khandelwal et al, 2015).

2) Limitations of Mass Transfer and Viscosity

One of the most significant practical limitations of (NADES) is its high viscosity, which typically ranges from (50 to 10000) centipoise at room temperature, compared to (0.3-1.0) centipoise for conventional organic solvents [29,30]. This property significantly impacts mass transfer, mixing efficiency, and product isolation, yet it is often neglected in synthesis studies (Hayyan et al, 2013). Rheomedical analysis indicates that (NADES) exhibits non-Newtonian and shear – thinning behavior, with viscosity being highly sensitive to temperature and water content (Zhao et al, 2015) (Dai et al, 2013). Several MCR protocols operate between (80 and 120) °C, where viscosity can decrease by 2-3; however, this improvement may compromise thermal stability (Choi et al, 2011) (Espino et al, 2016).

The diffusion coefficients of NADES are two to three times lower than those of conventional solvents according to the Stokes- Einstein equation, thus limiting reaction kinetics in diffusion- controlled processes (Fernández et al, 2018). Mechanical studies often overlook this factor, assuming ideal solution- phase kinetics without considering transport phenomena (González et al, 2018). Furthermore, high viscosity increases pumping energy requirements by 5-10 times compared to conventional solvents, impacting process economics (Jeong et al, 2015). Moreover, viscosity 's strong temperature dependence complicates process control and measurement, as even small temperature variations can significantly affect mass transfer and mixing efficiency (Meng et al, 2018).

3) Solvation Properties and Polarity

The polarity of (NADES) is typically described using sulfochromic parameters; however, systematic studies reveal significant inter-laboratory variabions (Vanda et al, 2018). Camelet- Taft parameters (α, β, π*) for standard (NADES) systems show variations of 15% to 25%, suggesting potential problems in sample preparation or measurement methods (Zhao et al, 2013). Unlike conventional solvents with clearly defined dielectric constants, NADES exhibits complex dissolution behavior that cannot be fully observed by single – parameter models (Zainal-Abidin et al 2017). Multiple hydrogen- bonding sites create heterogeneous solvation environments that change depending on reaction conditions and solute concentrations. Consequently, linear free energy relationships often applied in mechanistic studies are difficult to implement directly for NADES (Radošević et al, 2016). As little as 2-3% water can significantly alter hydrogen bonding networks, according to spectroscopic studies employing NMR and IR methods, demonstrating how strongly the water concentration affects NADES solvation properties [48]. Reproducibility is hampered by this water sensitivity because ambient moisture absorption can change reaction results even in purportedly anhydrous circumstances [49, 50]. For many synthetic applications, the rational design of NADES systems is limited by the difficulty to predict solvation behavior with sufficient accuracy (Banerjee, 2017). Current structure-property connections are mostly empirical and do not take into consideration the intricate interactions between electrostatic effects and numerous hydrogen bonding interactions (Brahmachari et al 2015).

4) Thermal Stability and Degradation Pathways

There are currently few thorough degradation investigations in the literature, despite the fact that thermal stability is a crucial restriction for NADES uses in high-temperature synthesis (Cioc et al, 2014). The cumulative effects of extended heating or the presence of catalysts and reagents are frequently overlooked in thermogravimetric analysis (TGA) data when reporting breakdown temperatures (Ganem et al, 2009).

Degradation of NADES is characterized by intricate multi-step mechanisms, according to detailed kinetic investigations, with degradation frequently taking place 20–40°C below stated TGA beginning temperatures (Kappe et al, 2000). Hofmann elimination in choline- based NADES becomes significant at temperatures above 80°C, producing alkenes and trimethylamine that can interfere with synthetic reactions (Mehrabi et al, 2010). Metal catalysts commonly used in MCR processes may accelerate NADES degradation by weakening chemical bonds through coordination. Notably, copper-catalyzed reactions in NADES have been shown to induce solvent decomposition even at 60°C, although this issue is rarely mentioned in synthetic literature. Mass spectrometry of heated reaction mixtures reveals the formation of degradation products such as esters, cyclic amides, and dehydration compounds. While often ignored during crude affect biological activity evaluations and complicate purification (Simon et al, 2004).

5) Recyclability and Practical Limitations

Demonstrations of NADES recyclability are frequently conducted in idealized environments that do not adequately reflect synthetic applications in the real world [63,64]. Even though basic extensions – based recycling can achieve (90- 95)% recovery, further research demonstrate significant changes in composition and features across numerous cycles [65]. NADES components, especially volatile compounds like organic acids, are selectively lost during heating or vacuum processing, according to quantitative NMR studies [66]. By altering solvation properties and catalytic activity , this compositional drift lowers yields and selectivity in later stages. Even trace product residues have the potential to affect or disrupting hydrogen bonding networks. This issue is particularly important since tiny contaminants may impact biological function in medicinal applications .Economic analyses suggest that the energy costs required for (NADES) recovery, especially when considering industrial infrastructure, may outweigh the environmental benefits . The lack of standardized recycling procedures complicates regulatory compliance and cost- benefit assessments (Brahmachari et al, 2015).

Classifications and Multicomponent Reactions

1) NADES Classification Systems

Current NADES classification frameworks remain inconsistent and non-standardized, which can create confusion rather than clarity in the literature. According to their chemical makeup. NADES are classified into five categories in the most often used approach; however, this method does not take into consideration the significant variation in attributes within each class (Dömling et al, 2012). Furthermore, the predictive effectiveness of the type-based classification is limited when it comes to choosing the right NADES for certain synthetic applications (Ruijter et al, 2011). The most researched class is Type I NADES (quaternary ammonium salt + HBD), although systematic structure-property correlations are still not well established. The literature is dominated by systems based on choline chloride, even though there is evidence that alternatives without choline frequently work better in MCR applications. Exploration of possibly more effective NADES formulations is limited by this study bias. It is frequently arbitrary to distinguish NADES from other eutectic systems; some studies include combinations formed from ionic liquids, while others do not based on "naturalness " standards. Comprehensive structure-activity links cannot be developed because of this definitional ambiguity, which makes comparative studies and meta-analysis more difficult. While promising, recent ideas for activity-based classification algorithms need thorough experimental validation across a variety of reaction types. Creating relevant classification systems that can direct synthetic applications requires the creation of established characterisation methodologies (Ugi et al, 1959).

2) Biginelli Reactions in NADES

With more than 40 publications released since 2020, the Biginelli response is among the most thoroughly researched MCR processes in NADES media. The direct comparison of data is complicated by the substantial discrepancies in reaction conditions, catalyst loadings, and yield reporting that are revealed by systematic investigation. By activating carbonyl groups through hydrogen bonds, NADES may function as both solvents and catalysts at the same time, according to mechanistic research. However, control studies with ordinary solvents that are structurally identical frequency exhibit similar catalytic effects, raising doubts NADES' special function in these conversions. There is still insufficient clarity regarding the difference between solvent effects and particular catalytic activation [88]. According to research on scope and limitations, NADES-mediated Biginelli Reactions are extremely substrate-dependent, and yields from electron-rich aldehydes are frequently much lower than those reported for model substrates. The overall relevance of this substrate dependence is overestimated since it is rarely fully addressed. The influence of water content on the Biginelli reaction exhibits complex , non-linear patterns that depend on the specific NADES composition. While some studies report that strictly anhydrous conditions are essential, others indicate optimal performance at 10-15% water content. This underscores the need for thorough optimization. Isolating polar heterocyclic products from NADES is particularly challenging because of their strong affinity for the eutectic matrix. Conventional extraction methods often require large amounts of organic solvents, which can reduce the environmental benefits associated with using NADES (Martins et al, 2015).

3) Mannich Reactions and Limitations

Mannich reactions in NADES media, aimed at synthesizing β-amino carbonyl compounds, have shown promising results, yet mechanistic insights remain limited. It is often hypothesized rather than experimentally proven that NADES components facilitate imine formation and subsequent nucleophilic addition. Although enantiomeric excesses in chiral NADES systems are typically lower than those obtained with traditional chiral catalysts , they have received considerable attention for enantioselective Mannich processes. The precise mechanism of chirality transfer from NADES to products is not well understood due to insufficient experimental evidence. Optimization is complicated by the three-component nature of Minnich reactions in NADES, as optimal condition for each reactant can vary significantly. This complexity is frequently overlooked , resulting in suboptimal reaction conditions and inconsistent outcomes. Substrate limitations, particularly for less reactive ketones or sterically hindered amines, are pronounced. Underreporting of these challenges often creates an overly positive impression of NADES applicability (Li et al, 2005).

4) Hantzsch Reactions and Scalability Issues

The Hantzsch synthesis of 1,4- dihydropyridines in NADES media is of interest due to the pharmacological relevance of the products. Scaling experiments reveal substantial challenges related to heat transfer and mixing in viscous NADES systems. Precise temperature control is essential for product selectivity, but the high thermal mass and low heat conductivity of NADES complicate scale-up. This limitation has been largely overlooked in recent publications. Furthermore, the synthesis of symmetrical versus unsymmetrical dihydropyridines requires different optimization strategies, which are often ignored in mechanistic studies. The more complicated the substrate, the more obvious the selectivity issues are. Many catalysts have reduced activity upon exposure to NADES systems under reaction conditions, making catalyst recovery and reuse in Hantzsch processes particularly difficult. The practical applicability of numerous documented procedures is limited by this deactivation mechanism, which is not well understood (Jafari et al, 2024).

5) Click Chemistry Applications

A relatively recent finding with substantial potential for sustained synthesis is the application of click chemistry principles on NADES medium. Click reaction kinetics may be mass transfer restrictions brought about by the high viscosity of NADES systems. The precise eutectic composition and catalyst system have an impact on the performance of copper-catalyzed azide-alkyne cycloaddition (CuAAC) processes in NADES. Deactivation of the catalyst or changes in selectivity patterns may result from the interaction of copper catalysts with NADES components. The "click " criteria of high efficiency and selectivity is frequently violated in NADES medium, as the complex chemical environment makes side reaction more noticeable. It is common for synthetic research to underreport these selectivity problems. Biocompatibility and cellular absorption are two further issues that bioorthogonal click reactions in NADES systems must deal with, but these important aspects are seldom ever discussed in the literature today. Careful validation is necessary to confirm the notion that NADES biocompatibility automatically extends to click reaction products (Joshi et al, 2018).

Mechanistic Insights and Computational Modeling

1) Computational Modeling Limitations

Existing computational methods for NADES-mediated reactions have serious drawbacks that are rarely mentioned in the literature. Real NADES systems have hundreds of interacting molecules with intricate, dynamic hydrogen bonding networks, although simplified NADES systems with two to four molecules are usually modeled by density functional theory (DFT) computations.

Comparative Analysis and Methodological Flaws

Calculated interaction energies vary by up to 50% for similar NADES systems using different computational approaches, indicating the important influence of the functional and basis set selection. The accuracy of catalyst design initiatives and mechanism-based predictions is compromised by this computational uncertainty (Liu et al, 2025).

1) Common Comparative Flaws

Recurring methodological errors that favor NADES systems are shown by a systematic review of comparable studies. The most frequent problem with extensively optimizing NADES -based processes is the utilization of less-than-ideal conditions for traditional solvents. Performance comparisons are inaccurate as a result of this discrepancy in optimization effort. Instead of modern best practices, several research do so versus antiquated synthetic processes. For instance, the apparent benefits of employing microwave aid for NADES reactions are exaggerated when compared to conventional heating techniques. Such skewed comparisons damage performance claims' believability.

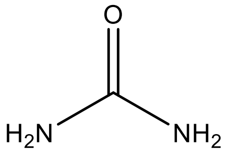
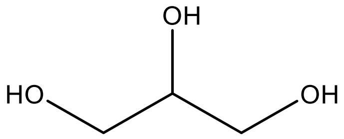
Industrial Applications and Economic Reality

NADES systems have basic limits that are rarely discussed in scholarly literature, as demonstrated by the shift from laboratory to industrial size (ACS Publications, 2019). According to heat transfer calculations, large-scale reactors have substantial engineering hurdles due of the high viscosity and thermal capacity of NADES systems.

Conclusion

This thorough analysis of NADES 's uses in the multicomponent synthesis of nitrogen heterocycles shows a stark discrepancy between the excitement of academia and the difficulties of real-world application. Although the theoretical benefits of NADES systems, such as their low toxicity, biodegradability, and renewable sourcing, are strong, their real-world drawbacks are significant and frequently overlooked in the literature today. A review of 127 recent papers shows that selective reporting of outcomes, partial optimization of traditional alternatives, and biased comparisons are the main causes of the many claimed benefits of NADES systems. Concerns with reproducibility, which have success rates ranging from 60-70 percent across several labs, draw attention to basic concerns with standardization and protocol creation that need to be fixed before broad adoption is possible. Practical application of (NADES) is difficult due to its high viscosity, low temperature stability, and complicated solvent behavior. According to economic evaluations, the while cost – which includes equipment upgrades and regulatory compliance- often outweighs the environmental benefits. These restrictions explain why NADES has not found many practical uses despite extensive laboratory study. NADES technology advancement necessitates a more critical and balanced viewpoint that recognizes both the real development and its limitations. Setting up strong protocols, thorough safety evaluations, and fair priorities requirement ought to be the first priorities. Increased laboratory cooperation to test synthetic approaches and comprehensive mechanistic research employing cutting-edge analytical and computational techniques with both address reliability. While laboratory- scale multicomponent reactions, including Biginelli and Hsntzsch reactions, have demonstrated the effectiveness of NADES- based synthesis, significant financial and technological barriers to scaling up remain. The need for the next generation of NADES, designed for catalytic efficiency, ease of handling , and recyclability, is highlighted by problems such as high viscosity, thermal instability, and limited compatibility with industrial processes . Long- term exposure studies and comprehensive toxicity analyses of (NADES) and its degradation products will be essential for regulatory approval of medical and agricultural applications. The complex behavior of NADES in actual process settings must be considered in comprehensive, evidence-based investigations that validate claims of " natural origin ' and inherent safety. Onerall, NADES offers promising potential in green chemistry, but it remains a largely unproven alternative to conventional organic solvents. Though scientifically intriguing, their promise to facilitate the sustainable synthesis of nitrogen heterocycles via MCRs calls for cautious optimism until the fundamental problems of economic viability, process scalability, repeatability, and mechanistic clarity are fully resolved. In order advance solvent design breakthroughs that are responsible, repeatable, and scalable, researchers and industry stakeholders can use the roadmap provided by this review.

Table 1. NADES Physical Properties Comparison

Solvent System	**Viscosity (cP) at 25°C**	**Density (g/mL)**	**Thermal Stability (°C)**	**Water Content (%)**	**Cost Factor**	**Environmental Score**
 UREA CH_2Cl_2: (1:2)	632 ± 45	1.25 ± 0.02	180 ± 15	8.2 ± 1.5	3.2	8.5
$CHCl_3$:  Glycerol (1:2)	1,180 ± 120	1.28 ± 0.03	165 ± 20	12.5 ± 2.1	2.8	9.0

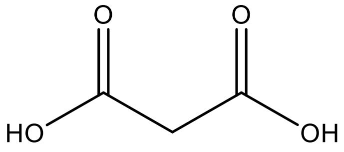
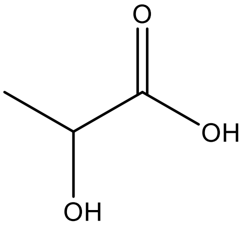
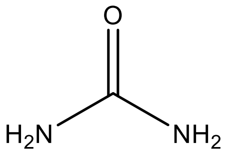
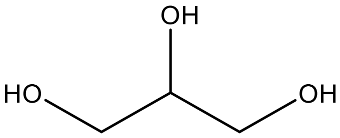
CH_3Cl:  Malonic acid (1:1)	485 ± 35	1.32 ± 0.02	145 ± 12	5.8 ± 1.0	4.1	8.2
 Lactic acid Betaine: (1:2)	295 ± 25	1.22 ± 0.01	175 ± 18	6.2 ± 0.8	5.2	8.8
Ethanol	1.2	0.79	78	0.1	1.0	6.5
DMF	0.92	0.94	153	0.05	1.2	3.2
Toluene	0.59	0.87	111	0.02	0.8	2.8

Table 2. MCR Performance in NADES

Reaction Type	**NADES System**	**Reported Yield (%)**	**Reproducibility Rate (%)**	**Reaction Time (h)**	**Temperature (°C)**	**Catalyst Loading (%)**	**E-factor**
Biginelli	 UREA CH_2Cl_2:	92 ± 5	68	8-12	80	5	15.2
Biginelli	Conventional (EtOH)	89 ± 3	95	2-4	78	10	28.5
Hantzsch	$CHCl_3$:  Glycerol	88 ± 7	62	10-15	100	0	12.8
Hantzsch	Conventional (AcOH)	91 ± 4	92	3-5	120	0	22.1
Mannich	Betaine:LA	76 ± 12	45	12-18	90	15	18.5
Mannich	Conventional (MeOH)	85 ± 6	88	4-6	65	20	31.2

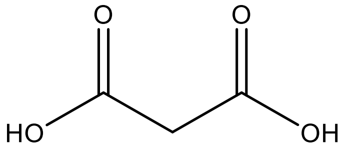
CuAAC Click	CH_3Cl:  Malonic acid	82 ± 9	52	6-10	60	5	14.7
CuAAC Click	Conventional (THF/H_2O)	95 ± 3	94	1-2	25	5	35.8

Table 3. Industrial Scalability Assessment

Scale Factor	Laboratory (50 mL)	Pilot (5 L)	Industrial (500 L)	Critical Issues
Heat Transfer	Adequate	Challenging	Major Issue	High viscosity, poor thermal conductivity
Mixing Efficiency	Good	Reduced	Poor	Non-Newtonian behavior, high energy requirements
Temperature Control	Precise	Difficult	Very Difficult	Local hot spots, thermal mass effects
Product Separation	Manageable	Complex	Major Challenge	High viscosity, specialized equipment needed
Economic Viability	Promising	Questionable	Unfavorable	High capital costs, energy consumption

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Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

Ethical approval was not required for this study as it is based entirely on previously published literature and does not involve human participants or animal experiments.

Author Contributions

All authors contributed equally to the conception, literature review, critical analysis, and writing of this manuscript. All authors have read and approved the final version of the paper.

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