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Review Article

SUSTAINABLE SOLUBILITY ENHANCEMENT USING BIODEGRADABLE HYDROTROPES: A GREEN CHEMISTRY PERSPECTIVE

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The growing demand for sustainable, environmentally friendly solutions in pharmaceutical formulations has led to the exploration of biodegradable hydrotropes as an alternative to traditional solubilizing agents. Hydrotropes are compounds that enhance the solubility of poorly soluble drugs in aqueous environments without forming micelles, making them ideal for replacing toxic organic solvents in pharmaceutical applications. This review focuses on the potential of biodegradable hydrotropes to address challenges related to the solubility and bioavailability of poorly water-soluble drugs, which are prevalent in the Biopharmaceutical Classification System (BCS) Class II and Class IV categories. These hydrotropes offer a green chemistry solution by providing an eco-friendly and sustainable means of enhancing solubility while maintaining biocompatibility and biodegradability. We highlight the applications of biodegradable hydrotropes in various drug delivery systems, including oral, topical, and injectable formulations, as well as their role in nanoparticle-based drug delivery**,** controlled release**,** and personalized medicine**.** The integration of biodegradable hydrotropes into greener pharmaceutical manufacturing processes also aligns with increasing regulatory demands for reduced environmental impact and toxicity. Future advancements in the design, production, and application of biodegradable hydrotropes are expected to enhance their effectiveness in improving solubility and bioavailability, facilitating more efficient, cost-effective, and sustainable drug development. This review emphasizes the promise of biodegradable hydrotropes as an essential tool for green pharmacy, offering both environmental and therapeutic benefits in pharmaceutical practice.

Keywords: Biodegradable hydrotropes, Solubility enhancement, Bioavailability, Green chemistry, Pharmaceutical formulations

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INTRODUCTION

Biodegradable hydrotropes are a class of eco-friendly compounds that enhance the solubility of hydrophobic substances in water. Unlike traditional solvents or surfactants, hydrotropes work by disrupting the water's hydrogen bonding network, allowing poorly soluble compounds to dissolve more easily without forming micelles. As the need for sustainable and non-toxic alternatives to conventional chemical processes grows, biodegradable hydrotropes have emerged as a key solution in green chemistry. These compounds are typically derived from renewable, naturally occurring materials such as plant-based fatty acids, sugars, or amino acids, and they degrade into non-toxic byproducts, making them environmentally benign.

The use of biodegradable hydrotropes offers a promising path for improving solubility in a variety of applications, from pharmaceuticals and biochemistry to green extraction processes and industrial cleaning. By replacing toxic solvents with biodegradable agents, these hydrotropes support the goals of reducing environmental pollution, minimizing resource depletion, and promoting the use of sustainable materials. As research continues to explore their potential, biodegradable hydrotropes are expected to play an increasingly important role in making chemical processes more environmentally friendly and efficient.

In the realm of green chemistry, the focus is shifting towards reducing the environmental impact of chemical processes by minimizing waste, toxicity, and resource consumption. One of the significant challenges in achieving this goal is enhancing the solubility of hydrophobic (water-insoluble) substances in water, which is often a necessary step in various chemical, pharmaceutical, and industrial applications. Traditional methods to improve solubility typically rely on toxic solvents or surfactants, which can lead to environmental pollution and health hazards. Biodegradable hydrotropes offer a promising alternative, combining the ability to improve solubility with environmental safety and sustainability.

What Are Hydrotropes?

Hydrotropes are small organic molecules that enhance the solubility of hydrophobic substances in water without forming aggregates like surfactants do. Unlike surfactants, which reduce surface tension and form micelles, hydrotropes function by disrupting the water's hydrogen bonding network, effectively increasing the solubility of nonpolar compounds. This phenomenon is known as hydrotropy. Hydrotropes generally interact with water molecules in a way that reduces the extent of the hydrogen bonding, allowing hydrophobic molecules to dissolve more readily in the aqueous phase.

While hydrotropes do not aggregate into micelles, they still manage to dissolve hydrophobic molecules more effectively than water alone. This makes them highly useful in various industrial processes, such as chemical synthesis, drug formulation, and extraction processes, where solubility is a critical factor.

The Importance of Biodegradable Hydrotropes

Traditional hydrotropes are often synthetic compounds derived from petrochemicals that may be toxic, persistent in the environment, and non-biodegradable. The accumulation of such substances can result in long-term ecological damage, which contradicts the principles of green chemistry. As a result, there is a growing need for biodegradable alternatives that not only perform effectively but also break down into harmless byproducts after use.

Biodegradable hydrotropes are designed to degrade naturally into non-toxic substances, minimizing environmental impact and reducing the potential for harmful accumulation in ecosystems. These hydrotropes are typically derived from renewable resources like plant oils, sugars, amino acids, or fatty acids, which are more sustainable and less harmful to the environment. Their biodegradability ensures that they do not persist in the environment, aligning with the core principles of green chemistry, which prioritize waste reduction and the use of non-toxic, sustainable materials.

Applications of Biodegradable Hydrotropes

Biodegradable hydrotropes offer a wide range of applications across industries, particularly where solubility enhancement is required without the use of toxic solvents. Key areas of application include:

1. **Pharmaceuticals**:

o Many pharmaceutical compounds, especially those that are poorly water-soluble, require solubilizing agents to improve their bioavailability and therapeutic efficacy. Traditional solubilizing agents often involve organic solvents, which can be toxic and harmful to both human health and the environment. Biodegradable hydrotropes can replace these toxic solvents, enhancing the solubility of hydrophobic drugs in water-based formulations while maintaining safety and sustainability. This is particularly important in the development of drug delivery systems, where achieving high solubility is crucial for ensuring the effectiveness of the drug.

2. **Green Extraction Processes**:

o In the food, fragrance, and natural product industries, extraction of bioactive compounds like essential oils, vitamins, and antioxidants is often carried out using organic solvents. These solvents can be harmful to both the environment and human health. Biodegradable hydrotropes offer a green alternative by enabling the extraction of these compounds in water-based systems, reducing the need for volatile organic compounds (VOCs) and other harmful chemicals. This approach also reduces the environmental footprint of extraction processes by using renewable, non-toxic agents.

3. **Industrial Cleaning and Degreasing**:

o In many industries, cleaning and degreasing are essential for maintaining machinery, equipment, and surfaces. Traditionally, these processes rely on harsh chemical solvents that can be toxic and damaging to the environment. Biodegradable hydrotropes can replace these solvents in cleaning formulations, improving their efficiency while also being safer for workers and less harmful to the environment. The use of biodegradable hydrotropes can also make the cleaning process more sustainable by reducing the generation of hazardous waste.

4. **Catalysis and Reaction Media**:

o In chemical synthesis, the solubility of reactants in the reaction medium can significantly influence reaction efficiency and selectivity. Biodegradable hydrotropes can be used as solvents or co-solvents in catalytic reactions to enhance the solubility of hydrophobic substrates in aqueous environments. This can lead to more efficient reactions with fewer byproducts, thereby supporting more sustainable industrial chemical processes.

5. **Pesticide and Agrochemical Formulation**:

- The formulation of pesticides, herbicides, and other agrochemicals often requires the use of solvents to dissolve active ingredients, which may be poorly soluble in water. Biodegradable hydrotropes can enhance the solubility of these active ingredients, improving their performance and reducing the environmental impact of pesticide application by eliminating the need for toxic or non-renewable solvents.

Examples of Biodegradable Hydrotropes

1. **Sugar-Based Hydrotropes**:

- Derivatives of sugars, such as alkyl glucosides and sucrose esters, have shown promise as biodegradable hydrotropes. These compounds are non-toxic, derived from renewable resources, and capable of improving the solubility of a variety of hydrophobic compounds.

2. **Amino Acid Derivatives**:

- Amino acids and their derivatives, such as glycine or glutamate-based compounds, are often biodegradable and have been explored as hydrotropic agents. They can solubilize a range of hydrophobic substances while being compatible with environmentally friendly processes.

3. **Fatty Acids and Fatty Alcohols**:

- Natural fatty acids, such as lauric acid or oleic acid, and their derivatives can also act as hydrotropes. These compounds are biodegradable, non-toxic, and derived from renewable sources like plant oils, making them suitable for green chemistry applications.

4. **Rhamnolipids**:

- These are biosurfactants produced by bacteria like *Pseudomonas aeruginosa*. Rhamnolipids are biodegradable, environmentally friendly, and have been investigated for their ability to enhance the solubility of hydrophobic compounds in water.

Biodegradable Hydrotropes: Why Green Chemistry Needs Them

The traditional hydrotropes used in chemical processes often contain synthetic, non-biodegradable components that persist in the environment and may cause long-term ecological damage. This raises concerns about their sustainability, particularly when used on a large scale in industrial applications. The transition to biodegradable hydrotropes is a key step in addressing these concerns.

Biodegradable hydrotropes are typically derived from renewable, naturally occurring resources, such as plant-based fatty acids, sugars, or amino acids. They are designed to break down into non-toxic byproducts after use, minimizing environmental impact. By focusing on natural and biodegradable materials, these hydrotropes support the following key principles of green chemistry:

- **Environmental Friendliness**: They degrade quickly and do not accumulate in the environment.
- **Non-toxicity**: Their degradation products are typically non-toxic to aquatic life and other organisms.
- **Sustainability**: Being derived from renewable resources, biodegradable hydrotropes contribute to a circular economy.

Applications in Green Chemistry

1. **Pharmaceuticals and Biochemical Processes**:
   - Hydrotropes can be used to enhance the solubility of poorly soluble pharmaceutical compounds, which is a common challenge in drug formulation. By improving solubility, these hydrotropes can facilitate more effective drug delivery systems, reduce the need for organic solvents, and increase bioavailability.
2. **Green Extraction Methods**:
   - The use of hydrotropes in aqueous extraction methods can enable more sustainable alternatives to solvent-based extractions. This is especially important in food and fragrance industries where non-toxic, biodegradable solvents are increasingly sought after for extracting essential oils, bioactive compounds, and other valuable natural products.
3. **Cleaning and Degreasing**:
   - In industries that require cleaning of oils and grease (e.g., in cleaning formulations for machinery or textiles), biodegradable hydrotropes could replace harsh synthetic solvents, reducing toxicity and environmental damage.
4. **Catalysis and Reaction Media**:
   - In catalysis, especially in aqueous-based reactions, hydrotropes can serve to improve the solubility of reactants, allowing for more efficient and selective reactions in green chemistry. This is particularly important in processes where high solubility is needed but without relying on toxic or volatile organic solvents.
5. **Pesticide Formulation**:
   - The formulation of environmentally friendly pesticides can benefit from the use of biodegradable hydrotropes, which help in dissolving active ingredients that would otherwise be poorly soluble in water, thereby improving the performance of the pesticide without increasing environmental toxicity.

In recent years, the demand for environmentally friendly and sustainable alternatives in chemical processes has grown. One of the challenges in green chemistry is enhancing the solubility of poorly soluble compounds in aqueous media without relying on toxic solvents or harmful chemicals. Hydrotropes—molecules that enhance the solubility of hydrophobic substances in water—have emerged as a potential solution. The use of biodegradable hydrotropes is an important development in this field, aligning with the principles of green chemistry by reducing the environmental impact of industrial and laboratory processes.

Hydrotropes are organic compounds that can increase the solubility of hydrophobic (water-insoluble) substances in water. Unlike surfactants, which form micelles, hydrotropes do not aggregate into large structures, making them particularly useful in systems where the goal is simply to enhance solubility rather than alter phase behavior.

Hydrotropy is a phenomenon where the addition of certain hydrotropic agents increases the solubility of nonpolar compounds in water, often without causing significant changes in the physical properties of the aqueous phase. Hydrotropes typically act by disrupting the structure of water, decreasing its hydrogen bonding network and allowing the hydrophobic molecules to dissolve more easily.

Challenges and Future Directions

Despite their promise, the development and application of biodegradable hydrotropes face several challenges:

- **Efficiency and Selectivity**: The efficiency of biodegradable hydrotropes in solubilizing a broad range of hydrophobic compounds can vary. New strategies are needed to design hydrotropes that can effectively solubilize diverse substances without sacrificing biodegradability or non-toxicity.
- **Cost and Availability**: While many biodegradable hydrotropes are derived from renewable resources, the cost and availability of such materials may be higher compared to synthetic alternatives. Ongoing research into scalable and cost-effective production methods is critical to making these materials viable for industrial applications.
- **Long-Term Environmental Impact**: Though biodegradable, the rate of degradation and potential for bioaccumulation of certain hydrotropes must be thoroughly studied to ensure their environmental safety over extended periods.

Challenges

While biodegradable hydrotropes show great potential, several challenges remain in their development and application:

- **Efficiency and Selectivity**: Not all biodegradable hydrotropes are equally effective for all hydrophobic compounds. Ongoing research is focused on improving the selectivity and efficiency of these agents to broaden their applicability across different industries.

- **Cost-Effectiveness**: Many biodegradable hydrotropes derived from natural sources may be more expensive than synthetic alternatives. Research into cost-effective production methods and scalable processes is essential for making these materials commercially viable.
- **Environmental Safety**: While biodegradable, the degradation products of hydrotropes must be thoroughly studied to ensure they do not pose long-term risks to ecosystems. Additionally, the rate of biodegradation and potential for bioaccumulation must be considered.

Aim:

The primary aim of exploring and utilizing biodegradable hydrotropes in green chemistry is to develop environmentally sustainable and non-toxic alternatives to traditional solubilizing agents. These hydrotropes can enhance the solubility of hydrophobic substances in water-based systems, offering a safer, more efficient, and eco-friendly solution for various industrial and scientific applications, while minimizing the environmental footprint and reliance on toxic, non-biodegradable solvents.

Objectives:

1. **Enhance Solubility of Hydrophobic Compounds:**
   - To improve the solubility of poorly water-soluble compounds, such as pharmaceuticals, bioactive molecules, and industrial chemicals, by using biodegradable hydrotropes in place of conventional toxic solvents.
2. **Promote Sustainability and Environmental Safety:**
   - To reduce environmental pollution by developing hydrotropes derived from renewable, biodegradable resources that break down into non-toxic byproducts, minimizing the ecological impact compared to traditional chemical solvents.
3. **Minimize Toxicity and Harmful Waste Generation:**
   - To decrease the need for toxic solvents in various applications (e.g., drug formulation, extraction, cleaning), thereby reducing the potential for hazardous waste and the toxicity of chemical processes.
4. **Improve Efficiency in Industrial Processes:**
   - To investigate and optimize the use of biodegradable hydrotropes in improving the efficiency of chemical reactions, extractions, and formulations, while reducing reliance on harmful and non-renewable resources.
5. **Develop Cost-Effective and Scalable Solutions:**
   - To explore cost-effective methods for producing biodegradable hydrotropes on an industrial scale, ensuring their practicality and wide adoption in real-world applications.
6. **Broaden Application Areas in Green Chemistry:**

- To explore the potential applications of biodegradable hydrotropes in diverse fields, including pharmaceuticals, food processing, agrochemicals, and green extraction technologies, contributing to a more sustainable future across various industries.

7. **Ensure Biodegradability and Ecological Compatibility:**

- To ensure that the hydrotropes not only perform effectively in solubilizing hydrophobic substances but also degrade rapidly and safely in the environment, without leading to harmful accumulation or bioaccumulation in ecosystems.

8. **Investigate New Materials and Innovations:**

- To investigate new materials, including naturally derived hydrotropes such as sugar derivatives, amino acid-based compounds, and biosurfactants, that could offer superior performance and further enhance the sustainability of chemical processes.

Key Concepts in Hydrotropy and Green Chemistry

1. **Hydrotropes**:

- Hydrotropes are substances that, when added to water in small amounts, can increase the solubility of poorly soluble compounds without forming micelles, unlike traditional surfactants.
- They work by modifying the structure of water, lowering its interfacial tension and facilitating the solubilization of organic and inorganic compounds.

2. **Green Chemistry**:

- Green chemistry is a discipline focused on designing chemical processes and products that minimize waste, reduce toxicity, and use renewable resources.
- In this context, biodegradable hydrotropes are key because they support sustainable formulations that degrade after use, minimizing long-term environmental impact.

3. **Biodegradable Hydrotropes**:

- These are hydrotropes that can be broken down into non-toxic products by biological processes, typically through microbial or enzymatic activity.
- They are a critical alternative to synthetic hydrotropes and traditional solvents, which may persist in the environment and contribute to pollution.

Advantages

1. **Improved Solubility of Pharmaceuticals and Agrochemicals**:

- Many pharmaceutical and agrochemical compounds are poorly soluble in water, which limits their bioavailability and efficacy. Biodegradable hydrotropes can be used to improve the solubility of these compounds, allowing for more efficient formulations and better performance.
- For instance, hydrotropes can be used in

drug formulations to enhance the solubility of active pharmaceutical ingredients (APIs), leading to more effective drug delivery systems.

2. **Reduced Toxicity**:

○ Many organic solvents used in industrial applications are toxic and persistent in the environment. By replacing these with biodegradable hydrotropes, manufacturers can reduce their reliance on hazardous solvents.

○ This is especially important in applications such as cleaning agents, paints, coatings, and detergents, where volatile organic compounds (VOCs) are often used.

3. **Water-based Formulations**:

○ Hydrotropes can facilitate the creation of water-based formulations, eliminating the need for organic solvents in many chemical processes. This is crucial in industries such as cosmetics, food processing, and pharmaceuticals, where sustainability and safety are paramount.

○ Water-based systems tend to have lower environmental impact, as water is a renewable resource, and the formulations are often easier to dispose of safely after use.

4. **Facilitating Green Synthesis**:

○ In green chemistry, it's crucial to minimize energy consumption and waste production. Biodegradable hydrotropes can help in achieving greener syntheses of chemicals by enhancing the solubility of reactants, reducing the need for harsh conditions or toxic solvents in chemical reactions.

5. **Reduction of Environmental Persistence**:

○ Since biodegradable hydrotropes break down into harmless byproducts, their use eliminates the long-term environmental issues associated with traditional hydrotropes or other solubilizing agents, which might remain in ecosystems for extended periods.

Challenges in Developing Biodegradable Hydrotropes

1. **Efficacy**:

○ One of the main challenges is ensuring that biodegradable hydrotropes exhibit a high enough efficacy in enhancing solubility for industrial and pharmaceutical applications. They need to perform as well as traditional, non-biodegradable hydrotropes, which often have high solubilizing capacities.

2. **Stability**:

○ Biodegradable hydrotropes must be stable enough to perform effectively during the required application processes, whether in a chemical reaction, a pharmaceutical formulation, or an industrial cleaning process. Instability can hinder their practical use.

3. **Cost**:

○ Biodegradable alternatives can sometimes be more expensive to produce than conventional chemical agents, especially if they require more complex synthesis methods or less abundant raw materials. Balancing cost with sustainability remains a key challenge.

4. **Regulatory Approval**:

○ The approval of new biodegradable hydrotropes for use in pharmaceuticals, food, or industrial applications often involves extensive testing to ensure safety and efficacy. Meeting regulatory requirements can be time-consuming and expensive.

Examples of Biodegradable Hydrotropes

- **Alcohols and Polyols**: Simple alcohols, such as ethanol and propylene glycol, have hydrotropic properties and are biodegradable. They are commonly used in formulations where moderate solubilizing power is required.
- **Amino Acid Derivatives**: Amino acid-based hydrotropes, such as derivatives of glycine or alanine, offer biodegradable alternatives with good solubilizing capacity and are often used in personal care or pharmaceutical products.
- **Carboxylic Acids and Their Salts**: Some carboxylic acids and their salts can act as biodegradable hydrotropes. For example, citric acid, lactic acid, and succinic acid can increase the solubility of a variety of substances.
- **Biopolymer-based Hydrotropes**: Natural polymers like cellulose and chitosan, when modified, can exhibit hydrotropic behavior. These biopolymers are naturally biodegradable and could offer a green alternative for solubilizing organic compounds.

Applications of Biodegradable Hydrotropes in Industry

1. **Pharmaceutical Industry**:

○ For drug formulations, particularly those involving poorly soluble compounds. Hydrotropes can enhance solubility, leading to improved bioavailability and therapeutic efficacy.

2. **Agricultural Industry**:

○ In agrochemical formulations, where hydrotropes can help in the formulation of pesticides, herbicides, and fungicides with improved solubility and efficacy in aqueous systems.

3. **Cosmetic and Personal Care Products**:

○ Used in formulations for shampoos, body washes, and moisturizers to improve the solubility of active ingredients while remaining eco-friendly.

4. **Cleaning and Detergents**:

○ Biodegradable hydrotropes are useful in the production of green cleaning products, offering enhanced performance without relying on toxic solvents or surfactants.

5. **Food Industry**:

○ In food processing, hydrotropes can be used to improve the solubility of food additives, flavors, and preservatives in aqueous systems, while maintaining food safety standards.

Materials:

1. **Chemicals and Reagents:**

○ **Starting materials for hydrotrope synthesis**:

▪ **Amino acids** (e.g., glycine, alanine, serine) (Sigma-Aldrich)

▪ **Polyols** (e.g., glycerol, ethylene glycol, propylene glycol) (Sigma-Aldrich)

▪ **Fatty acids** (e.g., oleic acid, lauric acid) (Acros Organics)

▪ **Citric acid** (Sigma-Aldrich)

▪ **Lactic acid** (Sigma-Aldrich)

▪ **Acids** (e.g., hydrochloric acid, sulfuric acid) for pH adjustments (Sigma-Aldrich)

▪ **Solvents** (e.g., methanol, ethanol, acetone) (Sigma-Aldrich)

▪ **Distilled water** (for aqueous formulations)

2. **Biodegradable Hydrotropes:**

○ **Amino acid-based hydrotropes** (e.g., glycine derivatives)

○ **Polyol-based hydrotropes** (e.g., glycerol derivatives)

○ **Carboxylic acid derivatives** (e.g., citric acid esters)

3. **Test Compounds:**

○ Poorly soluble organic compounds (e.g., phenanthrene, napthalene, anthracene) for solubility studies

○ Model pharmaceuticals or agrochemicals with low solubility in water (e.g., ibuprofen, curcumin, chlorpyrifos)

4. **Instruments:**

○ **Nuclear Magnetic Resonance (NMR)** (Bruker 400 MHz) for structural characterization

○ **Fourier Transform Infrared Spectroscopy (FTIR)** (PerkinElmer Spectrum 100)

○ **High Performance Liquid Chromatography (HPLC)** (Agilent Technologies) for quantifying solubility and purity

○ **UV-Vis Spectrophotometer** (Shimadzu UV-1800) for solubility analysis of hydrophobic compounds

○ **Dynamic Light Scattering (DLS)** (Malvern Zetasizer) for particle size distribution of micelles or aggregates

○ **Thermogravimetric Analysis (TGA)** for thermal stability studies

1. Synthesis of Biodegradable Hydrotropes:

Step 1: Synthesis of Amino Acid-Based Hydrotropes:

1. **Amino Acid Derivatization**:

○ To synthesize hydrotropes from amino acids, react an amino acid (e.g., glycine or alanine) with a fatty acid (e.g., oleic acid or lauric acid) in the presence of a mild base (e.g., NaOH) to form an amide bond. The reaction is carried out in an appropriate solvent such as ethanol.

○ The reaction mixture is heated at 60–80°C for 2–4 hours under reflux conditions, followed by cooling to room temperature.

○ The product is purified by precipitating out unreacted fatty acid using cold methanol, followed by vacuum filtration.

Step 2: Synthesis of Polyol-Based Hydrotropes:

1. **Polyol Modification**:

○ To prepare polyol-based hydrotropes, modify glycerol or other polyols with long-chain fatty acids (e.g., oleic acid) through esterification.

This can be achieved by heating the polyol and fatty acid in the presence of an acid catalyst (e.g., sulfuric acid).

○ The reaction is conducted under reflux conditions for 3–5 hours, followed by neutralization and purification using methanol washing to remove excess fatty acid.

Step 3: Synthesis of Carboxylic Acid Derivatives:

1. **Carboxylation**:

○ Modify citric acid or lactic acid with aliphatic or aromatic hydrocarbons to form ester derivatives, improving their solubilizing properties. The esterification reaction is performed using an alcohol (e.g., ethanol) and a catalyst (e.g., sulfuric acid).

○ The esterification process is conducted under reflux for 3 hours, followed by the removal of the solvent under reduced pressure.

Step 4: Purification:

- After the reaction, products are typically purified by solvent extraction, recrystallization, and vacuum drying.
- The purity of the final product is confirmed using NMR (proton and carbon) and FTIR spectroscopy to ensure the formation of the desired hydrotrope structure.

2. Characterization of Biodegradable Hydrotropes:

1. **Fourier Transform Infrared Spectroscopy (FTIR)**:

○ Analyze the synthesized hydrotropes using FTIR to identify key functional groups such as amides, esters, hydroxyl groups, and carbonyl groups, confirming successful derivatization.

2. **Nuclear Magnetic Resonance (NMR)**:

○ **^1H-NMR and ^13C-NMR** are used to confirm the structure of the hydrotrope by analyzing the chemical shifts of the protons and carbons in the molecular structure.

○ Comparison of the NMR spectra with the starting materials confirms the extent of modification and the presence of the hydrotropic functional group.

3. **Thermogravimetric Analysis (TGA)**:

○ TGA is used to determine the thermal stability and degradation temperature of the hydrotropes, ensuring that the biodegradable agents are stable under typical conditions.

4. **Dynamic Light Scattering (DLS)**:

○ To analyze the size distribution of micelles or aggregates formed by hydrotropes, DLS is used to measure the hydrodynamic diameter in solution. This helps assess whether the hydrotropes form stable colloidal structures in aqueous environments.

5. **Surface Tension Measurements**:

○ Surface tension measurements (using a **drop shape tensiometer**) are performed to determine the hydrotropic behavior of synthesized compounds in water. Hydrotropes generally lower the surface tension of water, a key characteristic that allows them to enhance solubility.

3. Solubility Enhancement Studies:

Step 1: Solubility Determination:

- The solubility of poorly soluble compounds (e.g., phenanthrene, ibuprofen, or curcumin) is tested in the presence of synthesized hydrotropes.
- A known concentration of hydrotrope is added to an aqueous solution of the poorly soluble compound. The mixture is shaken for a set period (e.g., 24 hours) at room temperature to ensure thorough solubilization.
- The solubility of the compound is then determined by **UV-Vis Spectrophotometry** at a specific wavelength, comparing the absorbance in the presence and absence of the hydrotrope.

Step 2: Analysis of Solubilization Efficiency:

- The enhancement factor is calculated by comparing the solubility of the compound in pure water and in the presence of various concentrations of hydrotropes.
- For example, a solubility enhancement factor can be calculated as:

Enhancement Factor=Solubility in hydrotrope solution Solubility in pure water \ text {Enhancement Factor} = \ frac {\text {Solubility in hydrotrope solution}}{\text{Solubility in pure water}}Enhancement Factor=Solubility in pure waterSolubility in hydrotrope solution

Step 3: Comparison with Commercial Hydrotropes:

- The synthesized biodegradable hydrotropes are compared to traditional, non-biodegradable hydrotropes (e.g., sodium xylene sulfonate, urea derivatives) in terms of solubility enhancement, cost, and biodegradability.

4. Biodegradability Studies:

1. **Biodegradation Testing**:
   - To assess the biodegradability of the synthesized hydrotropes, a standard OECD 301 test is conducted, where the hydrotropes are exposed to a mixed bacterial culture (e.g., *Pseudomonas putida*).
   - The biodegradation process is monitored by measuring the carbon dioxide (CO_2) production, which is a byproduct of microbial metabolism, using a respirometer or chemical titration.
2. **Time Course Analysis**:
   - The degradation rate is determined by measuring the change in the concentration of the hydrotrope over time using HPLC or UV-Vis Spectrophotometry.

Statistical Analysis:

- All solubility experiments are performed in triplicates. Data are expressed as mean ± standard deviation (SD).
- Statistical significance is determined using one-way analysis of variance (ANOVA), followed by Tukey's post-hoc test for multiple comparisons.

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Rationale for the Study of Biodegradable Hydrotropes for Enhanced Solubility in Green Chemistry Applications

The rationale for exploring biodegradable hydrotropes in green chemistry applications stems from several key motivations, driven by both environmental concerns and the practical need for enhanced solubility in various industrial, pharmaceutical, and environmental contexts. The study is situated within the broader framework of **green chemistry**, which aims to reduce harmful environmental impacts while improving the performance of chemical processes.

1. Addressing the Challenge of Poorly Soluble Compounds

Many valuable chemical substances, particularly pharmaceuticals, agrochemicals, and industrial chemicals, suffer from poor water solubility. This limitation often leads to:

- **Reduced bioavailability** in pharmaceutical formulations (e.g., drug delivery systems),
- **Decreased efficacy** of agrochemicals (e.g., pesticides, herbicides),
- **Inefficient industrial processes** (e.g., in cleaning, extraction, and synthesis).

Traditional methods to overcome solubility issues often involve the use of organic solvents or co-solvents, which come with their own set of environmental and health concerns. These include:

- **Toxicity**: Organic solvents, especially volatile organic compounds (VOCs), can be harmful to human health and the environment.
- **Environmental Persistence**: Many synthetic solubilizing agents do not degrade readily and accumulate in ecosystems, contributing to long-term pollution.
- **High Cost and Safety Concerns**: The use of hazardous solvents increases the need for specialized handling, disposal, and regulatory oversight, which can add cost and complexity to chemical processes.

Thus, there is a strong need for **eco-friendly, biodegradable alternatives** that can enhance solubility without these associated risks.

2. The Role of Hydrotropes in Solubility Enhancement

Hydrotropes are a class of substances that can significantly enhance the solubility of poorly soluble compounds in water. Unlike traditional surfactants, hydrotropes do not form micelles but instead work by modifying the structure and properties of water itself. These molecules typically act by:

- **Disrupting the hydrogen bonding network** in water, which increases the solubility of hydrophobic compounds.
- **Reducing interfacial tension**, thus making it easier for poorly soluble substances to dissolve in water.

Hydrotropes have the potential to enhance solubility without the need for organic solvents, making them ideal candidates for greener formulations in pharmaceutical, agricultural, and industrial applications. However, the widespread use of hydrotropes has been limited by several factors, primarily related to their environmental impact.

3. Need for Biodegradability

One of the key challenges of using conventional hydrotropes, and indeed most solubilizing agents, is that many of them are **non-biodegradable** or degrade very slowly in natural environments. Non-biodegradable hydrotropes contribute to:

- **Environmental Pollution**: They can persist in water and soil, causing long-term pollution.
- **Toxicity**: Some hydrotropes, such as aromatic sulfonates, can be toxic to aquatic life.

The biodegradability of hydrotropes is therefore a critical feature for their sustainable use. Biodegradable hydrotropes, which break down into non-toxic components, provide a significant advantage over their traditional counterparts, as they:

- **Reduce long-term environmental impact** by breaking down into natural, non-toxic byproducts.
- **Support a circular economy** by promoting the use of renewable resources and reducing waste.

Incorporating biodegradable hydrotropes into green chemistry applications aligns with global efforts to create more sustainable, environmentally friendly processes.

4. Sustainability and Green Chemistry Principles

The development of biodegradable hydrotropes is rooted in the 12 Principles of Green Chemistry, particularly:

- **Prevention of Waste**: By eliminating the need for toxic organic solvents, hydrotropes can minimize the generation of chemical waste.
- **Atom Economy**: The use of naturally occurring or renewable raw materials (such as amino acids or polyols) in the synthesis of hydrotropes contributes to a more efficient use of resources.
- **Design for Degradation**: Biodegradable hydrotropes are designed to degrade into environmentally benign products, minimizing their persistence in the ecosystem.

Furthermore, green chemistry emphasizes the importance of using non-toxic, renewable resources to design safer chemicals and processes. Developing biodegradable hydrotropes aligns with these principles by offering a way to enhance solubility in aqueous environments while adhering to sustainability goals.

5. Economic Considerations and Market Demand

- **Cost-effective Alternatives**: Biodegradable hydrotropes offer an opportunity to replace toxic and expensive solvents with cheaper, safer, and environmentally friendly alternatives. This can lead to cost savings, particularly in industries such as pharmaceuticals and agrochemicals, where the need for safer, cost-efficient formulations is growing.

- **Regulatory Drivers**: Increasing regulatory pressure around environmental sustainability (e.g., REACH in Europe, TSCA in the U.S.) encourages industries to find safer alternatives to hazardous chemicals. Biodegradable hydrotropes could meet the growing regulatory demands for safer and more sustainable chemicals.

6. Biodegradability and Green Chemistry Innovation

The development of biodegradable hydrotropes also provides a pathway for **innovative green chemistry solutions**:

- **Synthetic Innovation**: Research into new hydrotropic molecules based on renewable resources (e.g., plant-derived fatty acids, biopolymers) offers potential for developing high-performance, eco-friendly solubilizing agents.
- **Multi-functional Applications**: Biodegradable hydrotropes could be designed to perform multiple roles, such as acting as solubilizers and stabilizers, which could be particularly valuable in complex formulations such as emulsions or suspensions.
- **Integration with Other Green Technologies**: The combination of biodegradable hydrotropes with other green solvents, such as ionic liquids or supercritical CO_2, could create highly efficient, low-impact systems for a range of industrial processes.

7. Health and Safety Benefits

- **Reduced Toxicity**: Biodegradable hydrotropes are likely to be less toxic than their synthetic counterparts, ensuring safer handling and minimizing risks to human health and the environment.
- **Non-accumulating in Ecosystems**: By breaking down into harmless byproducts, biodegradable hydrotropes will not accumulate in water bodies, reducing the risk of contamination in aquatic ecosystems and food chains.

Application of Biodegradable Hydrotropes in Pharmacy

Biodegradable hydrotropes have significant potential in **pharmaceutical applications**, primarily due to their ability to enhance the solubility of poorly soluble drugs. Poor solubility is a common issue for many drugs, particularly those in the Biopharmaceutical Classification System (BCS) Class II (low solubility, high permeability) and BCS Class IV (low solubility, low permeability). These drugs often face challenges related to **bioavailability**, which can impact their therapeutic effectiveness.

By using biodegradable hydrotropes in pharmaceutical formulations, it is possible to improve the solubility of hydrophobic drugs in water-based systems without resorting to toxic or harmful solvents. This has important implications for drug design, formulation, and delivery systems, while also contributing to **greener pharmaceutical practices**.

1. Enhancing Drug Solubility and Bioavailability

One of the most significant challenges in pharmaceutical development is enhancing the solubility of poorly water-soluble drugs. Hydrotropes act by:

- **Disrupting the hydrogen-bonding network in water**, thereby increasing the solubility of hydrophobic compounds.
- **Reducing interfacial tension** between water and poorly soluble drugs, making it easier for these drugs to dissolve.

Biodegradable hydrotropes, being water-soluble themselves, can solvate poorly soluble drug molecules without the need for toxic organic solvents or surfactants. The key benefits in pharmacy include:

- **Increased solubility**: The use of hydrotropes can significantly improve the solubility of lipophilic drugs, enhancing their bioavailability.
- **Faster dissolution rates**: By improving solubility, hydrotropes can also accelerate the dissolution rate of the drug, which is critical for effective absorption in the gastrointestinal tract.
- **Overcoming limitations of micelle-based formulations**: Unlike surfactants, which form micelles that may have limited solubilizing capacity, hydrotropes typically enhance solubility without forming these structures, allowing for more efficient drug delivery.

2. Drug Formulation Types

- **Oral Dosage Forms**: Biodegradable hydrotropes can be used in the formulation of oral dosage forms, including tablets, capsules, and liquid formulations. In these systems, hydrotropes can improve the solubility and, consequently, the bioavailability of drugs like:
  - **Nonsteroidal anti-inflammatory drugs (NSAIDs)** (e.g., ibuprofen, naproxen),
  - **Anticancer agents** (e.g., curcumin, paclitaxel),
  - **Antifungal drugs** (e.g., itraconazole),
  - **Antidiabetic drugs** (e.g., glibenclamide).
- **Topical Formulations**: For creams, lotions, gels, and ointments, hydrotropes can help dissolve lipophilic active ingredients and improve their penetration into the skin. This is especially useful in dermatology for drugs that need to be delivered through the skin (e.g., corticosteroids, antifungal agents).
- **Injectable Formulations**: Biodegradable hydrotropes can improve the solubility of poorly soluble drugs in parenteral (injectable) formulations, enabling effective drug delivery with water-based solutions. This can be useful for biologics, peptides, or small molecules that are difficult to inject without solubilizing agents.

3. Biodegradable Hydrotropes in Nanoparticle Drug Delivery Systems

Biodegradable hydrotropes can also be incorporated into **nanocarriers**, such as nanoparticles, liposomes, or micelles, for **controlled drug delivery**:

- **Enhancing drug loading**: By improving the solubility of poorly soluble drugs, hydrotropes can help to increase the **loading capacity** of nanoparticles and other drug delivery systems.
- **Reducing toxicity**: Traditional solubilizing agents (e.g., surfactants or organic solvents) used in nanoparticle formulations may be toxic or irritative. The use of biodegradable hydrotropes can eliminate this concern, making the delivery system safer for patients.
- **Controlled release**: When incorporated into controlled-release formulations (e.g., sustained-release tablets, injectable depot systems), biodegradable hydrotropes can help maintain therapeutic drug concentrations over time, reducing the need for frequent dosing.

4. Greener Pharmaceutical Manufacturing

Biodegradable hydrotropes align with the principles of **green chemistry**, which aims to reduce the environmental impact of pharmaceutical manufacturing. They offer several advantages over traditional solubilizing agents:

- **Reduction of solvent use**: Hydrotropes can replace toxic organic solvents (e.g., dimethyl sulfoxide, ethanol) that are commonly used to dissolve drugs. This results in greener manufacturing processes with reduced environmental impact.
- **Non-toxic and environmentally friendly**: The biodegradable nature of these hydrotropes ensures that they break down into non-toxic products after use, minimizing the environmental footprint of pharmaceutical production and reducing concerns about accumulation in ecosystems.
- **Cost-effective manufacturing**: Since biodegradable hydrotropes can often be derived from renewable sources (such as amino acids, sugars, or fatty acids), they can be produced in a sustainable and cost-effective manner. This makes them attractive for large-scale pharmaceutical manufacturing.

5. Regulatory and Safety Benefits

- **Reduced regulatory hurdles**: Many existing solubilizing agents and excipients may pose regulatory challenges due to their toxicity or environmental persistence. By using biodegradable hydrotropes, pharmaceutical manufacturers can mitigate these concerns and adhere to increasingly stringent regulations regarding excipient safety and environmental impact.
- **Biocompatibility**: Biodegradable hydrotropes derived from natural sources (e.g., amino acids, fatty acids) tend to have higher biocompatibility and lower toxicity, which is particularly important in drug formulations that

are injected, ingested, or applied to sensitive skin.

6. Examples of Biodegradable Hydrotropes in Pharmaceutical Applications

- **Amino acid derivatives**: Amino acids such as glycine or alanine, when modified with fatty acids, can act as biodegradable hydrotropes to improve the solubility of poorly soluble drugs. These derivatives are biodegradable, non-toxic, and compatible with many pharmaceutical excipients.
- **Polyol-based hydrotropes**: Polyols like glycerol or sorbitol, which are commonly used in pharmaceutical formulations, can also be modified to enhance their hydrotropic properties. These modified polyols can solubilize hydrophobic drugs, especially in oral liquid formulations, without the need for harmful solvents.
- **Citric acid esters**: Citric acid, a naturally occurring, biodegradable compound, is often used in pharmaceutical formulations to enhance the solubility of poorly soluble drugs. Citric acid derivatives or esters can improve the dissolution rate of drugs like ibuprofen, chlorpromazine, and other BCS Class II drugs.

7. Future Directions and Challenges in Pharmaceutical Applications

- **Optimization of Hydrotrope Performance**: While biodegradable hydrotropes hold great potential, optimizing their efficiency, stability, and compatibility with active pharmaceutical ingredients (APIs) remains a key challenge. The balance between solubilizing power and biocompatibility must be carefully considered.
- **Scale-up for Commercial Use**: Transitioning from laboratory-scale formulations to industrial-scale production of biodegradable hydrotropes and their incorporation into pharmaceutical formulations presents technical and economic challenges. Continued research and development into cost-effective production methods will be critical to realizing their full potential.
- **Personalized Medicine**: Biodegradable hydrotropes may also play a role in the formulation of personalized medicines. By enhancing the solubility of specific drugs tailored to an individual's therapeutic needs, these hydrotropes could help in developing customized treatment regimens for patients, particularly in the treatment of complex diseases like cancer or genetic disorders.

Future Aspects of Biodegradable Hydrotropes in Pharmacy

The use of **biodegradable hydrotropes** in pharmaceutical applications is an emerging field, and while there has been significant progress, there are still several exciting opportunities and challenges ahead. As the need for greener, more sustainable drug formulation and delivery systems grows, biodegradable hydrotropes are poised to play a crucial role. Below are several key areas where future advancements can be expected:

1. Advanced Drug Delivery Systems

Biodegradable hydrotropes have the potential to revolutionize advanced drug delivery technologies, including:

- **Nanoparticle-based drug delivery**: As research continues, the incorporation of biodegradable hydrotropes into **nanocarriers** (e.g., liposomes, polymeric micelles, or solid lipid nanoparticles) will become more refined. This could lead to the development of highly efficient, safe, and controlled drug release systems that are more targeted and have enhanced therapeutic effects, especially for poorly soluble anticancer agents, antifungals, or antiviral drugs.
- **Sustained and Controlled Release Formulations**: Hydrotropes can improve the **loading capacity** of poorly soluble drugs in controlled release formulations. The ability to tailor these systems for **site-specific drug release** (e.g., in the gastrointestinal tract or at tumor sites) opens up possibilities for personalized medicine. For instance, hydrotropes could help deliver drugs with a high degree of specificity and minimal side effects.
- **Biodegradable Hydrotropes in Combination Therapy**: As combination therapies (e.g., cancer treatment using multiple drugs) become more prevalent, biodegradable hydrotropes could be used to solubilize multiple active pharmaceutical ingredients (APIs) that are poorly soluble, improving the stability, delivery, and pharmacokinetics of the combination.

2. Integration with Other Green Chemistry Innovations

Biodegradable hydrotropes can be integrated with other green technologies to create even more sustainable drug formulation processes. Some areas for integration include:

- **Green Solvents and Ionic Liquids**: The combination of biodegradable hydrotropes with other **green solvents**, such as **ionic liquids** or **supercritical fluids**, could lead to synergistic systems that improve solubility, stability, and bioavailability, while also being less harmful to the environment.
- **Biopolymer-based Formulations**: The integration of biodegradable hydrotropes with **biopolymers** (e.g., chitosan, alginate, or starch-based polymers) could enhance the design of eco-friendly drug delivery systems. These formulations could offer more natural, safer alternatives to synthetic excipients, and could also reduce the environmental footprint of pharmaceutical production.
- **Hydrotropes in "Green Synthesis"**: Biodegradable hydrotropes could be employed in greener synthesis routes for pharmaceuticals, such as in solvent-free reactions, biocatalysis, or enzyme-assisted synthesis**.** By substituting toxic organic solvents

with biodegradable hydrotropes, drug synthesis could be made more sustainable.

3. Personalized and Precision Medicine

As the field of personalized medicine continues to expand, biodegradable hydrotropes could play a pivotal role in optimizing drug delivery for individual patients based on their specific pharmacogenetic profiles. Some areas of future application include:

- **Tailored drug formulations**: Biodegradable hydrotropes could be used to enhance the solubility of drugs in formulations tailored to the specific needs of a patient's genetic makeup, ensuring higher bioavailability and reducing the risk of side effects.
- **Dose optimization**: For drugs with narrow therapeutic windows or those that are poorly soluble, biodegradable hydrotropes can enable more precise dosing and a more consistent release profile, improving efficacy and safety in personalized therapies.
- **Gene therapies**: In gene therapy, where delivery of nucleic acids (e.g., DNA, RNA) to specific cells or tissues is critical, hydrotropes could be used to improve the solubility and stability of gene delivery vectors, such as viral or non-viral carriers.

4. **Environmentally Sustainable and Economically Feasible Drug Development**

As global pressure to reduce pharmaceutical pollution and improve sustainability increases, biodegradable hydrotropes represent an opportunity to align drug formulation with the principles of **green chemistry**:

- **Zero-waste pharmaceutical production**: Biodegradable hydrotropes can contribute to zero-waste manufacturing processes by replacing toxic solvents and excipients. The reduction of solvent waste and byproducts in pharmaceutical production will help lower manufacturing costs and environmental impact.
- **Cost-effectiveness**: With increasing pressure on pharmaceutical companies to reduce the environmental impact of their operations, hydrotropes derived from renewable resources (e.g., plant-based fatty acids, amino acids, and polyols) can lower the cost of drug formulation and provide a more sustainable alternative to synthetic chemicals. The mass production of biodegradable hydrotropes could drive down costs and make greener formulations more economically feasible for both generic and branded drugs.
- **Improved regulatory compliance**: Increasingly stringent environmental regulations around excipient use and pharmaceutical waste management are driving the demand for greener alternatives. Biodegradable hydrotropes could become more popular as regulatory frameworks around environmental safety and sustainability continue to evolve.

5. **Broadening the Range of Drugs That Can Benefit from Hydrotropes**

While biodegradable hydrotropes have already been demonstrated to improve the solubility of many hydrophobic drugs, future research could expand their application to a broader range of pharmaceutical compounds:

- **Macromolecules**: Beyond small molecules, hydrotropes could be used to enhance the solubility and stability of **biologics** (e.g., proteins, monoclonal antibodies, and peptides), which often suffer from low solubility or stability in aqueous formulations.
- **Natural Products and Herbal Medicines**: Biodegradable hydrotropes could also be explored in the solubilization of natural products (e.g., alkaloids, flavonoids, terpenes) used in herbal medicines. These compounds often have poor bioavailability due to low solubility, and hydrotropes could enhance their incorporation into effective drug formulations.
- **Vaccines**: The stability and solubility of **vaccine components** (e.g., antigens, adjuvants) can be problematic in aqueous formulations. Biodegradable hydrotropes could be used to improve the solubility and stability of these critical components, enhancing vaccine efficacy.

6. **Improved Biodegradability and Safety Profile**

While biodegradability is already a key advantage of hydrotropes, there is room for improvement in terms of the rate of biodegradation and the non-toxicity of degradation products. Future developments could focus on:

- **Optimizing degradation pathways**: Biodegradable hydrotropes should degrade into harmless byproducts, but further studies are needed to ensure that their degradation products are **non-toxic**, even in the long term. Developing hydrotropes that degrade rapidly without releasing harmful intermediates will be critical for their widespread adoption.
- **Biocompatibility studies**: More in-depth **in vivo studies** will be necessary to fully understand the biocompatibility of biodegradable hydrotropes, especially for long-term use in drug formulations. They should be safe for all routes of administration (oral, intravenous, topical), and not cause irritation or adverse reactions.

7. Regulatory and Market Acceptance

As the demand for greener pharmaceutical formulations rises, it is essential for regulatory agencies to establish clear guidelines for the use of biodegradable hydrotropes in pharmaceutical products. The future of hydrotropes in pharmacy will depend on:

- **Standardized testing protocols**: Regulatory agencies (e.g., FDA, EMA) will need to develop clear protocols for testing the safety, efficacy, and environmental impact of biodegradable hydrotropes.
- **Industry adoption**: Pharmaceutical companies will need to commit to adopting

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biodegradable hydrotropes, not just from a sustainability standpoint but also due to their potential to improve drug performance and reduce costs. This adoption may be driven by both regulatory requirements and increasing consumer demand for eco-friendly products.

Future Directions

- **Synthetic Pathways**: Ongoing research is focusing on developing new, cost-effective synthetic pathways for the large-scale production of biodegradable hydrotropes. The development of biotechnological methods, such as enzyme-catalyzed processes, could lead to greener, more efficient production.
- **Functionalization**: Further functionalization of hydrotropes could expand their application range. For example, introducing additional functionalities could enable them to act as dual-purpose agents, such as solubility enhancers and stabilizers for complex formulations.
- **Multi-component Systems**: Research is also exploring the combination of biodegradable hydrotropes with other green chemicals, such as ionic liquids or green solvents, to create advanced, multi-component formulations that offer superior performance while remaining environmentally friendly.

Conclusion:

Hydrotropes are compounds that enhance the solubility of poorly soluble drugs in aqueous environments without forming micelles, making them ideal for replacing toxic organic solvents in pharmaceutical applications. This review focuses on the potential of biodegradable hydrotropes to address challenges related to the solubility and bioavailability of poorly water-soluble drugs, which are prevalent in the Biopharmaceutical Classification System (BCS) Class II and Class IV categories. These hydrotropes offer a green chemistry solution by providing an eco-friendly and sustainable means of enhancing solubility while maintaining biocompatibility and biodegradability. We highlight the applications of biodegradable hydrotropes in various drug delivery systems, including oral, topical, and injectable formulations, as well as their role in nanoparticle-based drug delivery, controlled release, and personalized medicine. The integration of biodegradable hydrotropes into greener pharmaceutical manufacturing processes also aligns with increasing regulatory demands for reduced environmental impact and toxicity. Future advancements in the design, production, and application of biodegradable hydrotropes are expected to enhance their effectiveness in improving solubility and bioavailability, facilitating more efficient, cost-effective, and sustainable drug development. This review emphasizes the promise of biodegradable hydrotropes as an essential tool for green pharmacy, offering both environmental and therapeutic benefits in pharmaceutical practice.

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Conflict of Interest

The authors declare that they have no conflict of interest