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Hydrotropy: A Promising Solubilization Technique for Poorly Water-Soluble Drugs

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Abstract:

The low aqueous solubility has continued to be one of the greatest challenges in the current pharmaceutical sciences since a great percentage of the emerging therapeutic molecules are characterized by low water solubility and dissolution-limited absorption. Drugs that fall under Biopharmaceutics Classification System (BCS) Class II and IV are often characterized by poor dissolution properties, unpredictable oral bioavailability, slow absorption and unpredictable therapeutic effects. Traditional methods of solubility enhancement like micronization, salt formation, co-solvency, surfactant system, cyclodextrin complexation, solid dispersions and nanotechnology-based methods have demonstrated a lot of success but are also accompanied by some limitations like toxicity, solvent contamination, high cost of production, physical instability and complicated scale-up processes. Hydrotropy has become a cost-effective, environmentally friendly, and industrially viable alternative to enhance aqueous solubility of poorly water-soluble drugs. Hydrotropic agents, including sodium benzoate, sodium salicylate, sodium citrate, nicotinamide, and urea, enhance solubility and increase the wettability via self-aggregation, hydrogen bonding, π–π interactions, solvent structure alteration, and solubility enhancement. Recent developments in mixed hydrotropy also enhanced pharmaceutical applications by decreasing toxicity, and augmenting synergistic solubilization effects. Hydrotropic systems have proved to be widely applicable in oral, parenteral, topical, transdermal, ocular and analytical preparations. This review critically discusses the historical background, mechanisms, classifications, pharmaceutical applications, advantages, limitations, comparative evaluation, and future perspectives of hydrotropic solubilization. Mixed hydrotropy and green pharmaceutical manufacturing have been given a special focus.

Keywords: Hydrotropy, mixed hydrotropy, poorly water-soluble drugs, solubilization enhancement, bioavailability, hydrotropic agents, pharmaceutical formulation

Introduction

Poor aqueous solubility is widely recognized as one of the most critical formulation challenges in modern pharmaceutical research and development (Savjani et al., 2012; Bhalani et al., 2022). The shift toward drug discovery methods such as combinatorial chemistry and high-throughput screening has led to a significant increase in the identification of lipophilic drug molecules (Kumari et al., 2023; Nica et

al., 2024). Statistics indicate that approximately 40%–70% of new drug candidates exhibit low aqueous solubility, and nearly 90% of drugs currently in the development pipeline are classified as poorly soluble (Bhalani et al., 2022; Kumari et al., 2023). These compounds typically fall into Biopharmaceutics Classification System (BCS) Class II and IV, where dissolution remains the rate-limiting factor for absorption and bioavailability (Savjani et al., 2012; Beig et al., 2016). Water-insoluble drugs are often characterized by incomplete absorption, slow onset of action, and unpredictable pharmacokinetic and plasma concentration profiles, ultimately leading to decreased therapeutic efficacy (Savjani et al., 2012; Kumari et al., 2023). Consequently, higher doses are frequently required to achieve therapeutic levels, which increases the risk of toxicity and adverse side effects (Bhalani et al., 2022). Furthermore, poor solubility presents substantial manufacturing hurdles across various administration routes, including oral, parenteral, transdermal, and topical dosage forms (Dhapte & Mehta, 2015; Kumari et al., 2023).

Some conventional methods have been explored to enhance aqueous solubility and dissolution characteristics of low solubility drugs. These include:

- Sizing and micronization of particles.
- Salt formation
- pH adjustment
- Co-solvency
- Surfactant systems
- Cyclodextrin inclusion complexes
- Drug delivery systems based on lipids.
- Solid dispersions
- Nanotechnology-based formulations

Even though these techniques have proved effective, they are often limited by the following factors:

- Toxicity related to organic solvents.
- Residual solvent contamination
- Physical and chemical instability.
- Precipitation of drug when diluted.
- High manufacturing cost
- Multifaceted scale-up processes in industry.

Hydrotropy is recognized as a promising and greener method for enhancing the aqueous solubility of hydrophobic species (Dhapte & Mehta, 2015). This technique involves the incorporation of high concentrations of water-soluble compounds, known as hydrotropic agents, which facilitate the dissolution of poorly soluble substances (Lee et al., 2006). Common hydrotropic agents utilized in pharmaceutical formulations include sodium benzoate, sodium salicylate, sodium citrate, sodium acetate, nicotinamide, and urea (Abdullah Ali & Kamal Omer, 2022; Maheshwari, 2006).

Hydrotropic solubilization offers several advantages over traditional methods, primarily its environmental sustainability, as water serves as the major solvent, reducing the reliance on toxic organic solvents (Dhapte & Mehta, 2015). These agents are generally low-cost, biodegradable, pharmaceutically acceptable, and easily scalable for industrial manufacturing (Maheshwari & Jagwani, 2011). Furthermore, the process enhances solubility without requiring chemical modification of the drug, thereby preserving its original pharmacological activity (Maheshwari, 2006).

Recent studies have demonstrated significant improvements in the solubility and bioavailability of various drugs, including ibuprofen, ketoprofen, nifedipine, aceclofenac, hydrochlorothiazide, diclofenac, and curcumin, through the use of hydrotropic systems (Maheshwari & Indurkhya, 2010; Kumari et al., 2023).

Additionally, the development of mixed hydrotropy has expanded the scope of these applications by providing synergistic solubilization and reducing the potential for toxicity or irritation associated with high concentrations of a single agent (Jain & Patel, 2017; Maheshwari & Jagwani, 2011).

History and Idea of Hydrotropy

The phenomenon of an organic salt increasing the aqueous solubility of poorly soluble compounds was first described by Carl Neuberg in 1916 as hydrotropy (Neuberg, 1916; Dhapte & Mehta, 2015). Neuberg observed that certain organic salts significantly enhanced the dissolution of hydrophobic compounds in water without the formation of emulsions or alterations to the chemical structure, an observation that serves as the foundation for modern hydrotropic solubilization technology (Dhapte & Mehta, 2015; Hodgdon & Kaler, 2007).

Hydrotropes are amphiphilic molecules containing both hydrophilic and hydrophobic groups (Bauduin et al., 2005). However, in contrast to surfactants, hydrotropic agents typically lack long hydrocarbon chains and do not form classic micelles at low concentrations (Shimizu & Matubayasi, 2014). Instead, they exhibit self-aggregation behavior only after reaching a threshold known as the Minimum Hydrotropic Concentration (MHC) (Booth et al., 2015). Above the MHC, these molecules form dynamic microenvironments that facilitate the dissolution of hydrophobic compounds (Booth et al., 2015; Shimizu & Matubayasi, 2014).

Hydrotropic solubilization differs fundamentally from micellar solubilization (Bauduin et al., 2005). While surfactants entrap hydrophobic drugs within the stable cores of micelles, hydrotropic systems consist of weak and mobile molecular assemblies that enhance solubility through cooperative intermolecular forces rather than fixed micellar structures (Dhapte & Mehta, 2015; Hodgdon & Kaler, 2007).

A number of mechanisms have been put forward to describe hydrotropic behavior:

- Self-aggregation of hydrotropes
- Hydrogen bonding interactions
- π–π stacking interactions
- Water structure modification
- Decrease of interfacial tension.
- Weak complex formation

Booth and colleagues demonstrated that hydrotropic molecules concentrate around hydrophobic drug molecules, effectively decreasing the energy barrier to dissolution (Booth et al., 2015). Similarly, research by Shimizu and Matubayasi identified that hydrotropes exist in an equilibrium state between monomers and aggregates, which facilitates a significant increase in solubilization once the Minimum Hydrotropic Concentration (MHC) is exceeded (Shimizu & Matubayasi, 2014).

The pharmaceutical significance of hydrotropy has grown as modern drug discovery consistently produces lipophilic molecules with poor aqueous solubility (Bhalani et al., 2022; Kumari et al., 2023). Hydrotropy provides a cost-effective and environmentally friendly alternative for enhancing dissolution and bioavailability without the need for complex or resource-intensive processing methods (Dhapte & Mehta, 2015; Bandivadekar & Ved, 2025).

Classification of Hydrotropic Agents

The hydrotropic agents are usually categorized according to the ionicity nature and chemical structure since those properties greatly determine the solubilization ability, the interaction between molecules and pharmaceutical use. The classification assists formulation scientists to determine suitable hydrotropic systems to increase

aqueous solubility of drugs that are insoluble in water.

The classification on the basis of the ionic character

Hydrotropic agents are generally classified into ionic and nonionic categories based on their ionization behavior in aqueous media (Dhapte & Mehta, 2015). Ionic hydrotropes dissociate in water to release ions, enhancing drug solubility through electrostatic interactions, modification of the water structure, and molecular aggregation (Bauduin et al., 2005; Hodgdon & Kaler, 2007). Widely used examples include sodium benzoate, sodium salicylate, sodium citrate, sodium acetate, and sodium toluene sulfonate (Abdullah Ali & Kamal Omer, 2022). Aromatic ionic hydrotropes, such as sodium benzoate and sodium salicylate, are particularly effective as they overcome $\pi–\pi$ interactions between aromatic drug molecules, thereby reducing drug aggregation and improving dispersion (Booth et al., 2015; Maheshwari, 2006). These agents have been studied extensively for boosting the solubility of nonsteroidal anti-inflammatory drugs (NSAIDs) and other hydrophobic compounds (Maheshwari & Indurkhya, 2010).

In contrast, nonionic hydrotropes do not ionize in aqueous solutions; instead, they promote solubilization primarily through hydrogen bonding, dipole interactions, and alterations to the solvent structure (Shimizu & Matubayasi, 2014; Dhapte & Mehta, 2015). Significant examples include urea, nicotinamide, sorbitol, glucose, and polyethylene glycols (Nasrallah & Minceva, 2025). Urea, the oldest and most broadly used agent, interferes with intermolecular hydrogen bonding in drug crystals to increase dissolution (Booth et al., 2015). Nicotinamide is considered one of the most effective nonionic hydrotropes due to its dual hydrophilic and hydrophobic properties, showing an excellent ability to enhance the solubility of drugs such as carbamazepine, progesterone, and riboflavin (Beig et al., 2016; Rasool et al., 1991). In pharmaceutical formulations, nonionic hydrotropes are often favored due to their lower toxicity and reduced risk of ionic incompatibility (Dhapte & Mehta, 2015; Maheshwari & Jagwani, 2011).

Classification, according to Chemical Structure

Hydrotropic agents are frequently categorized based on their chemical structure into aromatic, aliphatic, and heterocyclic groups, each interacting with drug molecules through distinct molecular mechanisms (Dhapte & Mehta, 2015; Hodgdon & Kaler, 2007).

Aromatic hydrotropes consist of benzene rings or other aromatic moieties that facilitate $\pi–\pi$ stacking interactions with aromatic drug molecules (Maheshwari, 2006). Common examples include sodium salicylate and sodium benzoate (Abdullah Ali & Kamal Omer, 2022). These compounds are highly effective at solubilization because their aromatic interactions minimize the cohesive intermolecular forces between hydrophobic drug molecules, thereby enhancing aqueous solubility (Booth et al., 2015; Maheshwari, 2006).

Aliphatic hydrotropes possess straight or branched carbon chains and lack aromatic rings (Dhapte & Mehta, 2015). Examples include sodium acetate and certain alcohol derivatives (Nasrallah & Minceva, 2025). While their solubilization capacity is typically lower than that of aromatic hydrotropes, they remain applicable in specific pharmaceutical systems where moderate solvent effects are sufficient to improve dissolution characteristics (Dhapte & Mehta, 2015).

Heterocyclic hydrotropes feature ring structures containing heteroatoms such as nitrogen, oxygen, or sulfur (Dhapte & Mehta, 2015). Nicotinamide is the most vital heterocyclic hydrotrope in pharmaceutical preparations (Beig et al., 2016; Rasool et al., 1991). These agents are highly effective solubilizers because they contain both polar and nonpolar structural regions, allowing for multiple types of intermolecular interactions, including hydrogen bonding and dipole-dipole interactions (Shimizu & Matubayasi, 2014). Heterocyclic hydrotropes are particularly successful at improving the solubility of lipophilic drugs with complex chemical skeletons (Beig et al., 2016; Rasool et al., 1991).

Mechanisms of Hydrotropic Solubilization

Hydrotropic solubilization is a complicated physicochemical process that includes multiple collaborative intermolecular interactions, which enhance the aqueous solubility of poorly aqueous-soluble substances together. Hydrotropes, in contrast to traditional surfactants, do not usually form classical micelles at low concentrations since they have no long hydrophobic hydrocarbon chains. Rather, their solubilization characteristics rely on the dynamic interactions of the molecules and aggregation and alteration of the solvent properties.

The mechanisms of hydrotropic solubilization are multifaceted, involving a combination of molecular aggregation, chemical bonding, and thermodynamic changes that collectively enhance the solubility of poorly water-soluble drugs.

Self-aggregation

Self-aggregation of hydrotropic molecules above the "Minimum Hydrotropic Concentration (MHC)" is one of the most well-known mechanisms of hydrotropic solubilization (Booth et al., 2015; Shimizu & Matubayasi, 2014). Below the MHC, hydrotropic molecules are mostly dispersed as monomers; however, beyond this threshold, they spontaneously assemble into small, disorganized molecular assemblies that can incorporate hydrophobic drug molecules (Booth et al., 2015; Dhapte & Mehta, 2015). This process lowers the free energy barrier to dissolution and stabilizes dissolved drugs, leading to the characteristic sigmoid-like increase in solubility observed only beyond the MHC (Shimizu & Matubayasi, 2014; Balasubramanian et al., 1989).

Hydrogen Bonding

Hydrogen bonding contributes significantly to solubilization, particularly for nonionic hydrotropes like urea and nicotinamide (Rasool et al., 1991). These agents possess functional groups that form hydrogen bonds with both drug and water molecules, reducing the crystal lattice energy of the drug and inhibiting recrystallization (Beig et al., 2016; Booth et al., 2012). This stabilization of supersaturated systems is crucial for BCS Class II drugs, where the dissolution rate limits bioavailability (Savjani et al., 2012).

π- π Stacking Interactions

Aromatic hydrotropes, such as sodium benzoate and sodium salicylate, interact with aromatic drug moieties through π- π stacking (Maheshwari, 2006). This overlap of aromatic electron clouds decreases drug aggregation and increases molecular stability in solution (Kim et al., 2010). Drugs like ibuprofen, diclofenac, ketoprofen, and curcumin are particularly responsive to these interactions, often resulting in higher solubilization efficiency compared to aliphatic agents (Dhapte & Mehta, 2015; Maheshwari & Indurkhya, 2010).

Water Structure Modification

Hydrotropic agents alter the hydrogen-bonding network of water around hydrophobic solutes (Bauduin et al., 2005). By disrupting the highly ordered water structure that typically surrounds hydrophobic molecules, hydrotropes minimize the entropic consequence associated with dissolution (Shimizu & Matubayasi, 2014). This modification increases the entropy of the system, facilitating the spontaneous solubilization of otherwise insoluble drugs (Bauduin et al., 2005; Hodgdon & Kaler, 2007).

Improved Wettability

Enhanced wettability is a critical mechanical factor in hydrotropy. Hydrotropic agents reduce the interfacial tension between drug particles and the aqueous medium, allowing water to penetrate the crystal lattice more effectively (Dhapte & Mehta, 2015; Maheshwari & Jagwani, 2011). This increase in effective surface area and rapid dispersion is especially vital for oral solid dosage forms like tablets and capsules (Kumari et al., 2023; Savjani et al., 2012).

Mixed Hydrotropy

Mixed hydrotropy has emerged as a novel and highly promising pharmaceutical solubilization methodology, utilizing the concomitant action of two or more hydrotropic agents to achieve synergistic solubility enhancement (Maheshwari, 2006; Jain & Patel, 2017). While traditional systems often require excessively high concentrations of a single agent (up to 30–50% w/v), which can lead to toxicity, gastrointestinal irritation, osmotic imbalance, and poor palatability, mixed hydrotropy overcomes these constraints by using lower concentrations of each individual agent (Maheshwari & Jagwani, 2011; Dhapte & Mehta, 2015).

Mechanism and Synergy

The principle of mixed hydrotropy relies on cooperative intermolecular interactions, including hydrogen bonding, electrostatic attraction, and solvent structure modification (Maheshwari, 2006; Booth et al., 2015). Because different hydrotropes possess unique physicochemical properties, their combined use often results in a "greater than additive" solubilization effect (Maheshwari & Jagwani, 2011). Commonly explored combinations include sodium benzoate and urea, sodium citrate and nicotinamide, and sodium acetate with sodium salicylate (Abdullah Ali & Kamal Omer, 2022; Maheshwari & Indurkhya, 2010).

Pharmaceutical Applications of Mixed Hydrotropy

Enhanced Bioavailability: Significant solubility rises have been documented for drugs such as ibuprofen (several hundred-fold increase), ketoprofen, aceclofenac, and curcumin (Maheshwari & Indurkhya, 2010; Kumari et al., 2023).

Curcumin Delivery: Mixed systems using sodium benzoate and nicotinamide have profoundly improved the dissolution rate and oral absorption of curcumin, expanding its potential in anticancer and anti-inflammatory therapies (Kumari et al., 2023; Dhapte & Mehta, 2015).

Pediatric and Parenteral Safety: Lower individual concentrations minimize bitterness and irritation, enhancing patient compliance in pediatrics and reducing the need for toxic organic co-solvents like DMSO or ethanol in injectables (Maheshwari & Jagwani, 2011; Beig et al., 2016).

Green Analytical Chemistry: Mixed hydrotropic solutions serve as eco-friendly alternatives to methanol and chloroform in UV spectrophotometry and HPLC sample preparation, promoting sustainable

pharmaceutical analysis (Dhapte & Mehta, 2015; Maheshwari, 2006).

Current research is integrating mixed hydrotropy with nanotechnology and computational formulation design to optimize drug loading and stability in carriers like solid dispersions and nanoparticles (Kumari et al., 2023; Jain & Patel, 2017). Despite challenges regarding solution viscosity and osmotic pressure, mixed hydrotropy remains one of the most industrially viable strategies for addressing the solubility crisis in modern drug development (Dhapte & Mehta, 2015).

Hydrotropy in Pharmaceuticals.

Hydrotropy has become one of the most useful and industrially convenient methods of solubilization in the sciences of pharmaceuticals. This method is widely applicable in oral, parenteral, topical, transdermal, ocular, and analytical systems since it greatly enhances aqueous solubility without involving the use of damaging organic solvents or the complex production processes. Hydrotropic systems are coming into the limelight of modern pharmaceutical research due to their high percentage of novel therapeutic molecules that have poor aqueous solubility and bioavailability that is limited by dissolution.

Oral Delivery Systems

Oral delivery remains the most desirable administration method due to convenience, patient compliance, and cost-effectiveness (Savjani et al., 2012). However, low aqueous solubility often hinders oral bioavailability. Hydrotropic agents are utilized in tablets, capsules, and suspensions to enhance drug particle wettability and dissolution rates (Dhapte & Mehta, 2015; Kumari et al., 2023). Notably, mixed hydrotropic systems (e.g., sodium benzoate and urea) have demonstrated over a 250-fold improvement in the solubility of drugs like ibuprofen, as well as significant enhancements for aceclofenac, ketoprofen, and curcumin (Maheshwari & Indurkhya, 2010; Kumari et al., 2023). This is particularly beneficial in pediatric formulations where aqueous preparations improve palatability and ease of administration (Maheshwari & Jagwani, 2011).

Parenteral Formulations

Parenteral delivery requires sterile, stable, and isotonic solutions. Traditionally, hydrophobic drugs in injectables relied on toxic co-solvents like ethanol, propylene glycol, or DMSO, which are often linked to tissue irritation and hemolysis (Dhapte & Mehta, 2015; Beig et al., 2016). Hydrotropy provides a safer alternative, allowing for clear aqueous solutions of drugs such as diazepam, paclitaxel, and diclofenac sodium (Maheshwari & Indurkhya, 2010). A major advantage in injectables is the reduced risk of drug precipitation upon dilution in blood plasma compared to traditional co-solvent systems (Dhapte & Mehta, 2015).

Topical and Transdermal Systems

In creams, gels, and ointments, hydrotropy improves drug dispersion and release characteristics (Dhapte & Mehta, 2015). By enhancing aqueous solubility and reducing particle aggregation, hydrotropic systems maximize the amount of dissolved drug available to permeate the skin (Kumari et al., 2023). Certain agents even act as permeation enhancers by subtly modifying the lipid structure of the stratum corneum (Dhapte & Mehta, 2015).

Ocular Formulations

Ophthalmic tissues are highly sensitive, requiring formulations with superior transparency and minimal irritation. Hydrotropy enhances the clarity and stability of eye drops and ocular gels while causing less foaming and irritation than surfactant-

based systems (Dhapte & Mehta, 2015). This ensures better patient comfort and therapeutic efficacy for poorly soluble ophthalmic drugs.

Pharmaceutical Analysis

One of the most significant recent applications of hydrotropy is in Green Analytical Chemistry (Maheshwari, 2006). Hydrotropic solutions serve as eco-friendly substitutes for toxic organic solvents (like methanol or chloroform) in UV spectrophotometry, HPLC sample preparation, and titrimetric analysis (Dhapte & Mehta, 2015; Maheshwari & Jagwani, 2011). This transition minimizes environmental hazards and disposal difficulties associated with traditional analytical procedures.

Application of hydrotropy in the analysis of pharmaceuticals helps in the application of green chemistry concepts, such as lowering solvent toxicity, environmental pollution, and exposure of the operator to the toxic chemicals. Moreover, hydrotropic analytical techniques are cost-effective, non-toxic, and can be applied to quality control procedures conducted on a regular basis in pharmaceutical firms.

Table 1. Common Hydrotropic Agents and Their Pharmaceutical Applications (Bauduinet al2005, Booth et al.,2015, Dhapte et al., 2015)

Hydrotropic Agent	Type	Mechanism	Pharmaceutical Application
Sodium benzoate	Ionic aromatic	π–π interactions	NSAIDs, oral systems
Sodium salicylate	Aromatic ionic	Molecular aggregation	Anti-inflammatory drugs
Urea	Nonionic	Hydrogen bonding	Parenteral formulations
Nicotinamide	Heterocyclic	H-bonding and aggregation	Antifungal formulations
Sodium citrate	Ionic aliphatic	Water structure modification	Mixed hydrotropy
Sodium acetate	Aliphatic	Solvent interactions	Injectable systems

Table 2. Solubility Enhancement of Selected Drugs by Hydrotropy (Maheshwari et al., 2022, Abdullah et al.,2011)

Drug	Hydrotropic System	Solubility Enhancement
Ibuprofen	Urea + sodium benzoate	30–60 fold
Curcumin	Mixed hydrotropy	30–70 fold
Ketoprofen	Sodium citrate + urea	20–50 fold
Diclofenac	Sodium salicylate	40–80 fold
Hydrochlorothiazide	Mixed hydrotropy	Significant enhancement
Nifedipine	Sodium salicylate	Improved dissolution

Table 3. Comparison of Hydrotropy with Other Solubilization Techniques (Kim et al.,2011, Savjani,2012),

Technique	Advantages	Limitations	Industrial Feasibility
Hydrotropy	Eco-friendly, economical	High concentration requirement	High
Co-solvency	Simple processing	Organic solvent toxicity	Moderate

Surfactant systems	Effective micellar solubilization	Foaming and irritation	Moderate
Cyclodextrins	Strong complexation	High cost	Moderate
Nanotechnology	Excellent bioavailability	Complex manufacturing	Variable

Benefits and shortcomings of Hydrotropy

Hydrotropy is widely regarded as one of the most promising and industrially viable methods for improving the aqueous solubility of poorly water-soluble drugs (Dhapte & Mehta, 2015). This method offers significant pharmaceutical, economic, and environmental benefits compared to traditional techniques such as co-solvency and nanotechnology-based preparations (Maheshwari, 2006; Kumari et al., 2023). However, successful formulation development requires a careful balance of its advantages against inherent limitations.

Advantages of Hydrotropy

Eco-Friendly and Sustainable: Hydrotropy aligns with the principles of Green Chemistry by utilizing water as the primary solvent, thereby reducing reliance on toxic organic solvents like methanol, chloroform, and DMSO (Dhapte & Mehta, 2015; Maheshwari, 2006).

Economical and Scalable: Agents such as sodium benzoate, urea, and nicotinamide are inexpensive and readily available. Unlike complex nanotechnology, hydrotropic formulations often require simple mixing, making them highly appealing for mass production in developing countries (Maheshwari & Jagwani, 2011; Maheshwari & Indurkhya, 2010).

Safety (GRAS): Most hydrotropic compounds are "Generally Recognized as Safe" (GRAS), offering lower toxicity compared to conventional co-solvents (Dhapte & Mehta, 2015). Mixed hydrotropy further enhances safety by lowering the required concentration of individual agents (Maheshwari, 2006).

Versatility: The technique is successfully applied across oral, parenteral, topical, and analytical preparations (Kumari et al., 2023; Maheshwari & Indurkhya, 2010).

Limitations of Hydrotropy

High Concentration Requirements: Effective solubilization often requires hydrotrope concentrations between 20% and 50%, which can affect the formulation's viscosity, osmolarity, and patient palatability (Dhapte & Mehta, 2015; Maheshwari & Jagwani, 2011).

Precipitation Upon Dilution: Because solubilization is highly concentration-dependent, diluting the formulation in biological fluids below the Minimum Hydrotropic Concentration (MHC) can lead to drug precipitation and reduced bioavailability (Shimizu & Matubayasi, 2014; Booth et al., 2015).

Stability and Taste: High concentrations of sodium salts or urea can cause gastrointestinal irritation or a bitter taste, affecting patient compliance. Additionally, long-term physical stability—such as crystallization during storage—remains a challenge (Dhapte & Mehta, 2015).

Future Perspectives

The future of hydrotropic technology lies in its transformation from a simple solubilization principle into a sophisticated drug delivery platform (Kumari et al., 2023; Bandivadekar & Ved, 2025).

AI-Assisted Design: Artificial intelligence and machine learning are being integrated to predict optimal hydrotrope combinations and concentrations based on molecular properties, significantly accelerating

formulation development (Bandivadekar & Ved, 2025).

Computational Chemistry: Advanced simulations (molecular docking and molecular dynamics) provide deeper insights into π- π stacking and hydrogen-bonding interactions, allowing for more rational and predictable formulation designs (Shimizu & Matubayasi, 2014; Kim et al., 2010).

Hybrid Systems: Combining hydrotropy with nanotechnology such as hydrotropic nanoparticles or solid dispersions is expected to create highly efficient delivery systems with enhanced drug loading and controlled-release profiles (Kumari et al., 2023; Jain & Patel, 2017).

New Hydrotropic Agents: Research is shifting toward discovering natural, amino acid-based, and biodegradable hydrotropes that offer superior safety and solubilization efficiency (Nasrallah & Minceva, 2025; Bandivadekar & Ved, 2025).

Conclusion

Hydrotropy is a very promising, cost-effective and environmentally friendly approach to improving aqueous solubility of poorly water-soluble drugs. The method enhances dissolution rate, bioavailability, therapeutic effect, and formulation stability and reduces use of toxic organic solvents. This technology has also been enhanced by mixed hydrotropy which has minimized toxicity and enhanced the effectiveness of synergistic solubilization.

The hydrotropic systems have proven to have extensive use in oral, parenteral, topical, ocular, transdermal, and analytical formulations. Despite some of its limitations like precipitation caused by dilution and lack of full mechanistic insights, sustained development of pharmaceutical sciences, computational chemistry and green manufacturing technologies will enable these challenges to be overcome.Hydrotropy will probably be part of future formulation and drug delivery approaches as pharmaceutical industries continue to deal with poorly soluble drug candidates.

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