Hydrotropy as an Emerging Solubilization Technique: Mechanisms, Applications, and Future Perspectives

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ABSTRACT

Poor water solubility continues to be a significant obstacle in the development of oral dosage forms, especially for drugs in Classes II and IV of the Biopharmaceutics Classification System (BCS), where absorption is primarily governed by dissolution. The usage of organic solvents, stability issues, and high cost are some of the drawbacks of traditional solubility augmentation methods like micronization, solid dispersions, and cyclodextrin complexation. Using tiny, amphiphilic organic compounds called hydrotropes to increase solubility through π–π interactions, hydrogen bonding, and water structure disruption, hydrotropy has become a viable substitute. Without changing pH or necessitating surfactants, these compounds can significantly increase solute solubility above a specified minimum hydrotrope concentration (critical hydrotropic concentration). Applications in food, cosmetics, agrochemicals, pharmaceuticals, and hydrotropes include scalability, safety, affordability, and environmental friendliness. However, there are still issues such as precipitation upon dilution, structural specificity, and a lack of established selection criteria. Further investigation combining hydrotropy with computational screening and nanotechnology may allow for wider acceptance as an effective, environmentally friendly solubilization technique.

Keywords: Hydrotropy, Solubility, Critical hydrotropic concentration, Green chemistry, Surfactant-free, Computational screening

INTRODUCTION

One of the most significant factors influencing the bioavailability of orally administered drugs is solubility.[1] It determines the rate and degree of drug absorption across biological membranes and is a necessary condition for drug dissolution in gastrointestinal fluids.[2] It is unlikely that a drug will achieve therapeutic concentrations in the systemic circulation, regardless of its pharmacodynamic potency, if it is unable to dissolve sufficiently under physiological conditions. This all significantly impacts clinical efficacy, formulation design, and drug development.[3] The pharmaceutical industry has seen a sharp increase in the discovery of new chemical entities (NCEs) with low water solubility during the past 20 years. Nearly 90% of molecules in development pipelines and more than 40% of drugs currently on the market are thought to have low aqueous solubility.[4] Oral drug delivery is severely hampered by this physicochemical limitation, which frequently leads to inconsistent absorption profiles, decreased bioavailability, inconsistent therapeutic results, and the requirement for higher dosages, all of which can exacerbate side effects.[5] Amidon and associates introduced the Biopharmaceutics Classification System (BCS) in 1995 as a methodical solution to the problems of permeability and solubility. The BCS divides drugs into four groups according to intestinal permeability and aqueous solubility:

Class I: High permeability and solubility

Class II: High permeability, low solubility

Class III: Low permeability, high solubility

Class IV: Poor permeability and solubility [6]

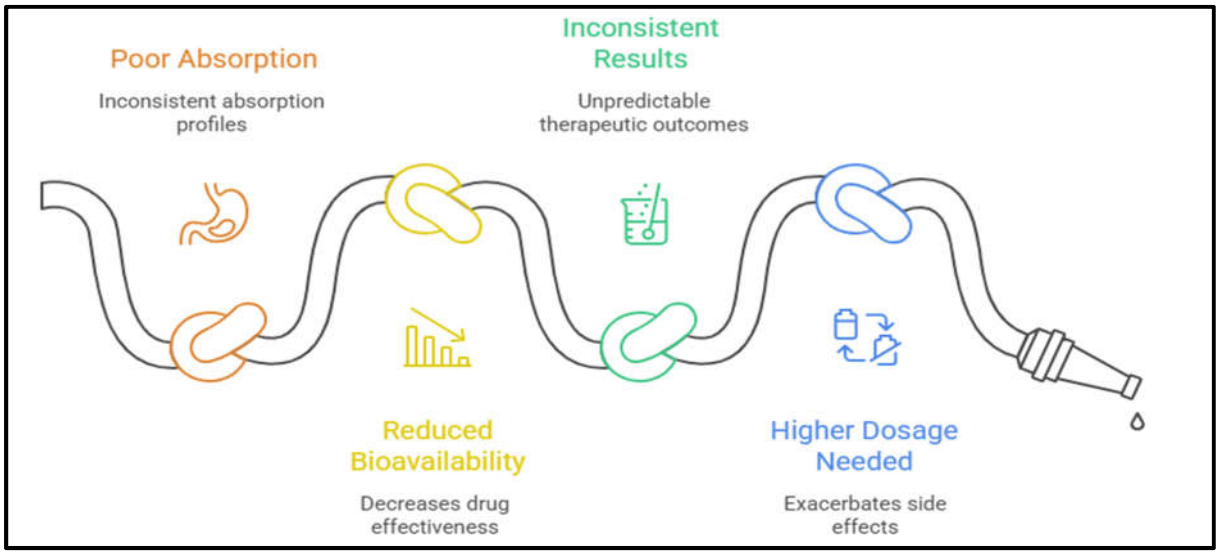

Fig. 1: Solubility challenges in oral drug delivery

From a formulation standpoint, BCS Class II and Class IV drugs are especially troublesome. Ibuprofen, ketoprofen, and carbamazepine are examples of class II drugs that have adequate membrane permeability; however, their slow and incomplete dissolution in gastrointestinal fluids limits their absorption. Without the use of permeability enhancers, bioavailability can be greatly increased by improving these drugs' solubility.[7] Class IV drugs, on the other hand, like furosemide and hydrochlorothiazide, are the most challenging to formulate due to their poor permeability and poor solubility. Improving solubility is a prerequisite for increasing the oral bioavailability of these compounds, but it is not always enough. However, for both classes, solubilization strategies are an essential first step in the logical creation of successful formulations. To get around solubility-related obstacles in drug formulation, a variety of strategies have been developed. Several strategies are employed to enhance the solubility of poorly water-soluble drugs.[8]

Cosolvents such as ethanol, propylene glycol, or polyethylene glycol are frequently used in this method because they promote drug solubility by decreasing the polarity of the solvent environment. Polysorbates and sodium lauryl sulphate are examples of surfactants that create micelles that encapsulate poorly soluble drugs and aid in their dispersion in aqueous media.[9] Another technique is cyclodextrin complexation, which increases the water solubility of hydrophobic drugs by enclosing them in the hydrophobic cavity of cyclodextrins.[10] Furthermore, the drug's surface area and rate of dissolution are increased when the particle size is decreased via micronization or nanonization.[11] By molecularly dispersing the drug in a hydrophilic carrier matrix, solid dispersions increase solubility.[12] In conclusion, salt production improves the drug's solubility in water by changing its ionisation properties.[13]

These solubility augmentation techniques are often associated with a number of challenges, despite their varying degrees of success. These include the use of potentially dangerous organic solvents, high production costs, and difficulties scaling up the manufacturing process. Additionally, formulations may have low patient acceptance due to discomfort or an unpleasant taste, and regulatory limits on the use of particular excipients or residual solvents are common. Furthermore, the shelf life and quality of the product may be compromised by the physical or chemical instability of the final formulations. [14,15] New and eco-friendly solubilisation techniques that are safe, economical, and ecologically beneficial are therefore becoming more and more popular. One such approach that shows promise is hydrotropic solubilisation. After seeing that certain organic salts, such as sodium benzoate, may significantly improve the solubility of substances that were not very soluble in water, Carl Neuberg first used the word "hydrotropy" in 1916.[16] Hydrotropes are a type of tiny, amphiphilic compounds that increase

the solubility of hydrophobic drugs in aqueous media by molecular aggregation and solvent structure alteration.[17] Instead of forming micelles, hydrotropes improve the solubility of poorly soluble drugs through a variety of mechanisms, including hydrogen bonding between the drug and the hydrotrope's hydrophilic regions, disrupting the structure of the water solvent, which lessens the tendency of water to exclude nonpolar solutes, step-wise self-association of hydrotrope molecules into loose aggregates or clusters that can entrap drug molecules, and, at concentrations above a critical hydrotropic concentration (often referred to as the minimum or critical hydrotropic concentration, MHC/CHC).[18]

The benefit of hydrotropy lies in its simplicity and environmental friendliness. Many hydrotropes are approved for pharmaceutical use and are safe, biodegradable, and cost-effective. These include piperazine, urea, sodium benzoate, sodium salicylate, and nicotinamide. The process is safer and more eco-friendly for both patients and the environment because they can be used in aqueous solutions instead of organic solvents. Hydrotropic solubilization is particularly important for BCS Class II and IV drugs, where enhancing water solubility is the main goal of formulation.[19] Numerous studies have demonstrated that hydrotropes can increase the solubility of poorly soluble drugs by several times, improving dissolution rates and, consequently, oral absorption.[20] For instance, hydrochlorothiazide, a BCS Class IV antihypertensive diuretic, has been successfully dissolved using combinations of sodium benzoate and piperazine, which resulted in significantly improved dissolution [21]; ibuprofen, a common Class II NSAID, has shown an increase in solubility when formulated with urea.[22] Moreover, hydrotropic agents can work in combination to increase their impact. This method, known as mixed hydrotropy, has been employed to enhance the solubility of drugs such as nifedipine and aceclofenac more effectively than individual hydrotropes.[23] Hydrotropy is believed to function through several non-covalent interactions from a physicochemical standpoint.[24] More recent research indicates that self-association, stacking interactions, and partial inclusion complexes may also play a role in the solubilization process, whereas previous models assumed a purely thermodynamic process.[25] According to this perspective, hydrotropic solubilization is a dynamic process in which the solubilizing molecules either form loose aggregates or associate with drug molecules to reduce the system's free energy.[26] The critical hydrotropic concentration (CHC), or the lowest concentration required for a hydrotrope to exert its solubilizing effect, is an important statistic. Following this, solubility usually increases linearly with the concentration of hydrotrope. This ability makes hydrotropic systems very tunable for formulation. Additionally, drugs may precipitate when the hydrotropic media are diluted or removed, suggesting that hydrotropic solubilization

is largely reversible. This capability could be helpful when developing controlled-release or in-situ precipitation systems for site-specific drug administration.[27] Hydrotropic agents are very appealing for pharmaceutical applications because they offer a number of formulation-related benefits. These substances can be used in human treatments without raising serious safety issues because they are non-toxic, biodegradable, and generally recognized as safe (GRAS). They are appropriate for large-scale industrial manufacturing because of their low cost and simple synthesis. From the standpoint of green chemistry, hydrotropes make it possible to do away with organic solvents, which lessens the impact on the environment and increases the sustainability of pharmaceutical processes. Additionally, hydrotropic systems are very adaptable and compatible with a wide variety of excipients and active pharmaceutical ingredients (APIs). Notably, they make it possible to create injectable and liquid dosage forms based on aqueous solutions for medications that were previously only available in solid oral formulations and are not very water-soluble. Additionally, when paired with other strategies like solid dispersion, pH manipulation, or co-solvency, hydrotropic solubilization can work in association to improve formulation design flexibility and efficiency. These benefits make hydrotropy an especially effective technique for poorly soluble drugs in environments of scarce resources where affordability and ease of formulation are essential. The current work aims to explore, assess, and synthesize the body of information regarding hydrotropes and hydrotropic solubilization, with a focus on their usage with BCS Class II and IV drugs. The review highlights the types and characteristics of hydrotropes (natural and synthetic), the fundamental processes of hydrotropic solubilization, and the latest experimental methods used in formulation science.[28] The classification and salient features of widely utilized hydrotropes, a thorough mechanistic analysis of hydrotropic solubilization, and real-world case studies derived from peer-reviewed literature are all covered in this article's thorough overview of hydrotropy. It provides a critical comparison with traditional solubilization methods and assesses the formulation, regulatory, and environmental implications of hydrotropic systems. Additionally, the assessment provides suggestions for future possibilities of inquiry in the field of green formulation science. This work attempts to assist pharmaceutical scientists in implementing sustainable, effective, and scalable solubilization strategies, specifically for addressing the solubility limitations inherent in BCS Class II and IV drugs, by synthesizing current knowledge and highlighting both the benefits and challenges of hydrotropy.[29]

HYDROTROPES

Hydrotropes are a class of amphiphilic, non-micelle-forming organic compounds that increase the solubility of solutes in aqueous media that are poorly soluble in water. Unlike surfactants,

hydrotropes do not self-assemble into micelles; instead, they enhance the solubility of solute molecules in water through specific chemical interactions. The concept was first put forth by Neuberg in 1916, when he described how sodium benzoate might increase the solubility of a range of organic molecules in water.[30] Generally speaking, compounds that have both hydrophilic (usually polar or anionic) and hydrophobic (commonly alkyl or aromatic) components are called hydrotropes. By enabling drug–hydrotrope interactions via a mix of hydrogen bonding, van der Waals forces, π–π stacking, and hydrophobic interactions, this dual nature facilitates the solubilization of hydrophobic drugs. Hydrotropic solubilization is fundamentally different from micellar solubilization since it depends on the restructuring of water networks and direct molecular interactions with solute species instead of the formation of colloidal aggregates (micelles).[31] Based on where they come from, hydrotropes can be broadly divided into two groups: natural and synthetic.

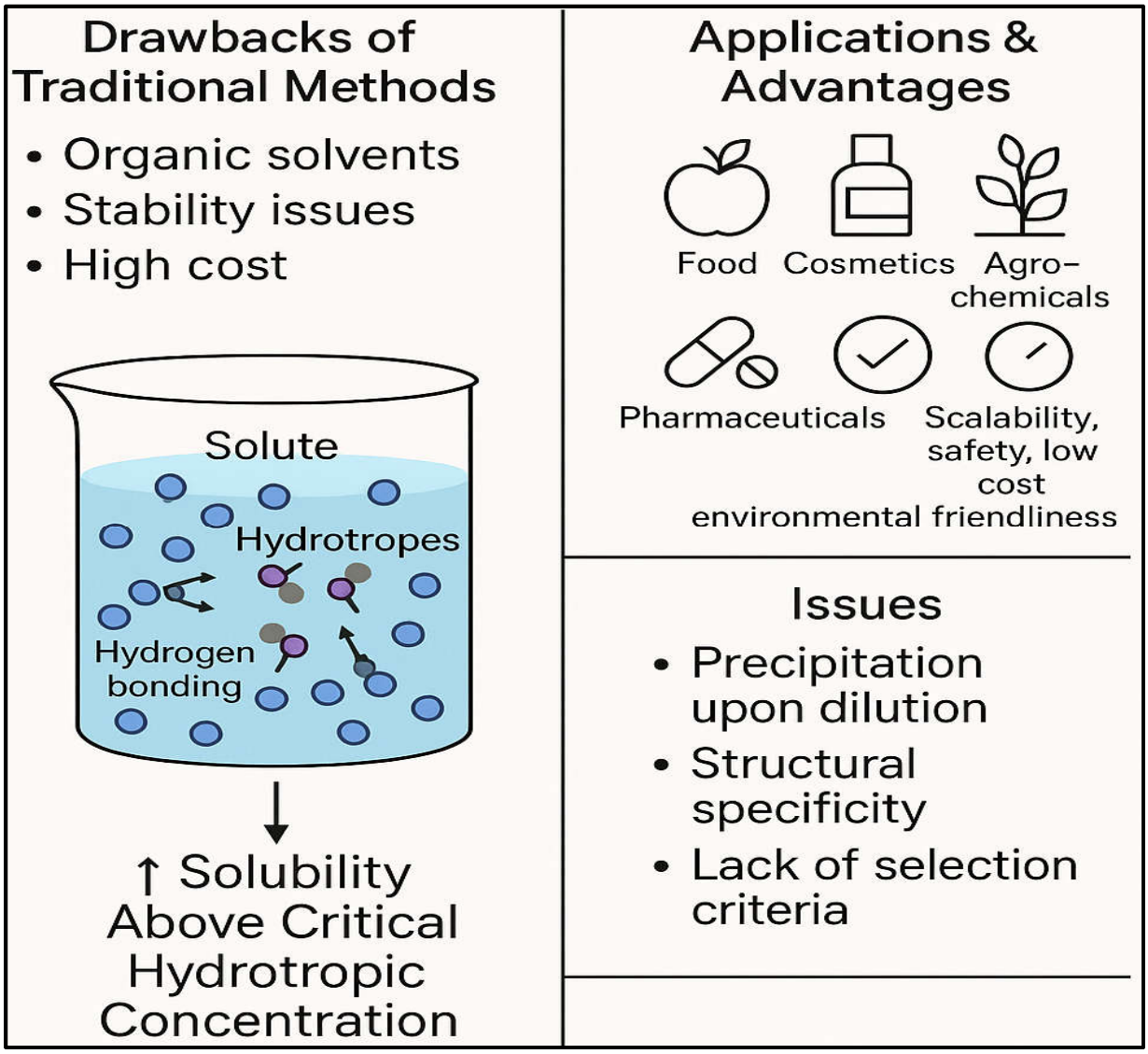

Fig. 2: Hydrotropy for Solubility enhancement

SYNTHETIC HYDROTROPES:

Synthetic hydrotropes are widely used in the detergent, cosmetic, and pharmaceutical industries. These molecules are often designed to be as soluble in water and as compatible as possible with a wide range of drug compounds. Common examples of synthetic hydrotropes include Sodium benzoate, which is a typical GRAS-listed preservative. It possesses remarkable solubilizing properties due to its carboxylate group and aromatic ring, which encourage hydrogen bonding and π–π stacking interactions with hydrophobic drugs.[32] Sodium salicylate has a structure similar to sodium benzoate, but it includes an additional hydroxyl group that enhances its hydrogen bonding capabilities. Numerous studies have investigated its ability to solubilize a range of drugs, including sulphonamides and antibiotics. [33] Despite having a simpler structure than other hydrotropes, urea promotes entropy-driven solubilization of hydrophobic substances and disrupts hydrogen-bonding networks in water. It is commonly coupled with other hydrotropes for synergistic effects.[34] Sodium citrate, sodium acetate, and sodium cumene sulfonate function through charge-based and hydrogen bonding methods and are widely used in the cleaning and formulation industries. Synthetic hydrotropes have the advantages of being inexpensive, scalable, and chemically stable. They are also easily modified by changing their functional groups to modify their hydrotropic efficiency.[35]

NATURAL HYDROTROPES

Natural hydrotropes are substances of biological origin that exhibit inherent hydrotropic activity. They are particularly desirable for application in green chemistry and ecologically friendly pharmaceutical formulations due to their natural origin, non-toxicity, and biocompatibility. Notable examples include: Piperine: Piperine is an alkaloid found in black pepper. Apart from its bio-enhancing properties, Piperine has been studied for its ability to produce hydrotropic effects, most likely through π–π interactions, which could boost the solubility of hydrophobic medicines. The methylxanthine alkaloid caffeine is widely recognized for its ability to form non-covalent complexes with a diverse range of aromatic and non-aromatic compounds. Its hydrotropic activity is driven by stacking interactions and hydrogen bonds.[36] Resveratrol is a polyphenolic compound found in grapes and red wine. Many weakly soluble chemicals become more soluble due to its many hydroxyl groups and aromatic rings.[37] Nicotinamide: This hydrotrope has been thoroughly studied because of its great solubility and low toxicity. Nicotinamide's planar aromatic structure facilitates the stacking of drug molecules. In the context of green pharmaceutical development, natural hydrotropes are gaining popularity due to their sustainability and suitability for regulatory trends that encourage the use of non-toxic excipients.[38]

PHYSICOCHEMICAL PROPERTIES RELEVANT TO HYDROTROPIC ACTION

Several significant physicochemical properties influence a compound's effectiveness as a hydrotrope: Aromaticity: Most potent hydrotropes have aromatic rings that facilitate their ability to stack with medication molecules. Water solubility: The hydrotrope needs to be easily soluble in water in order to function well in watery conditions.[39] Functional groups: Amine, hydroxyl, and carboxyl groups promote hydrogen bonding and water affinity. Molecular weight: Hydrotropes with smaller molecular weights tend to be more effective because of their superior ability to interface and diffuse with medication molecules. pKa and ionisation: The ionisation state of the hydrotropes affects their solubilising capacity and suitability for various pH conditions. These characteristics can be chemically altered to increase a molecule's hydrotropic efficiency or to customise it for a particular drug.[40]

THE IMPORTANCE OF CRITICAL HYDROTROPIC CONCENTRATION (CHC):

The Critical Hydrotropic Concentration (CHC) is the lowest concentration of a hydrotrope required to significantly improve a solute's solubility. Below this threshold, the hydrotropic effect is negligible, but above it, solubility usually increases linearly with concentration. CHC values are influenced by both the hydrotrope structure and the medication in issue.[41] What makes CHC important is its application in formulation optimization:

Over CHC: The maximum solubilization effect is seen above CHC, making it appropriate for creating liquid and semi-solid dosage forms.

Lower than CHC: inadequate to attain the required solubility; the formulation might continue to be ineffectual.

At or close to CHC: Optimal balance between solubility enhancement and excipient load. Badwan et al. (1982) noted that once CHC is exceeded, the solubility profiles of different drugs show sigmoidal or exponential increases, supporting the idea that self-aggregation or cooperative molecular interactions play a part at this concentration.[42] The CHC is a crucial parameter in hydrotropic solubilization research since it also establishes toxicity limits, formulation volume, and dosage form design.[43] Understanding hydrotrope classification and processes is essential for rational drug design, particularly for BCS Class II and IV drugs. By carefully selecting hydrotropes based on molecular structure, solubility profile, and CHC, formulators can dramatically increase the water solubility of poorly soluble medicines, leading to increased bioavailability and therapeutic efficacy. Hydrotropic solubilization is a promising alternative to traditional pharmaceutical development techniques that is scalable, patient-friendly, and environmentally benign.[44]

HYDROTROPIC SOLUBILIZATION MECHANISM:

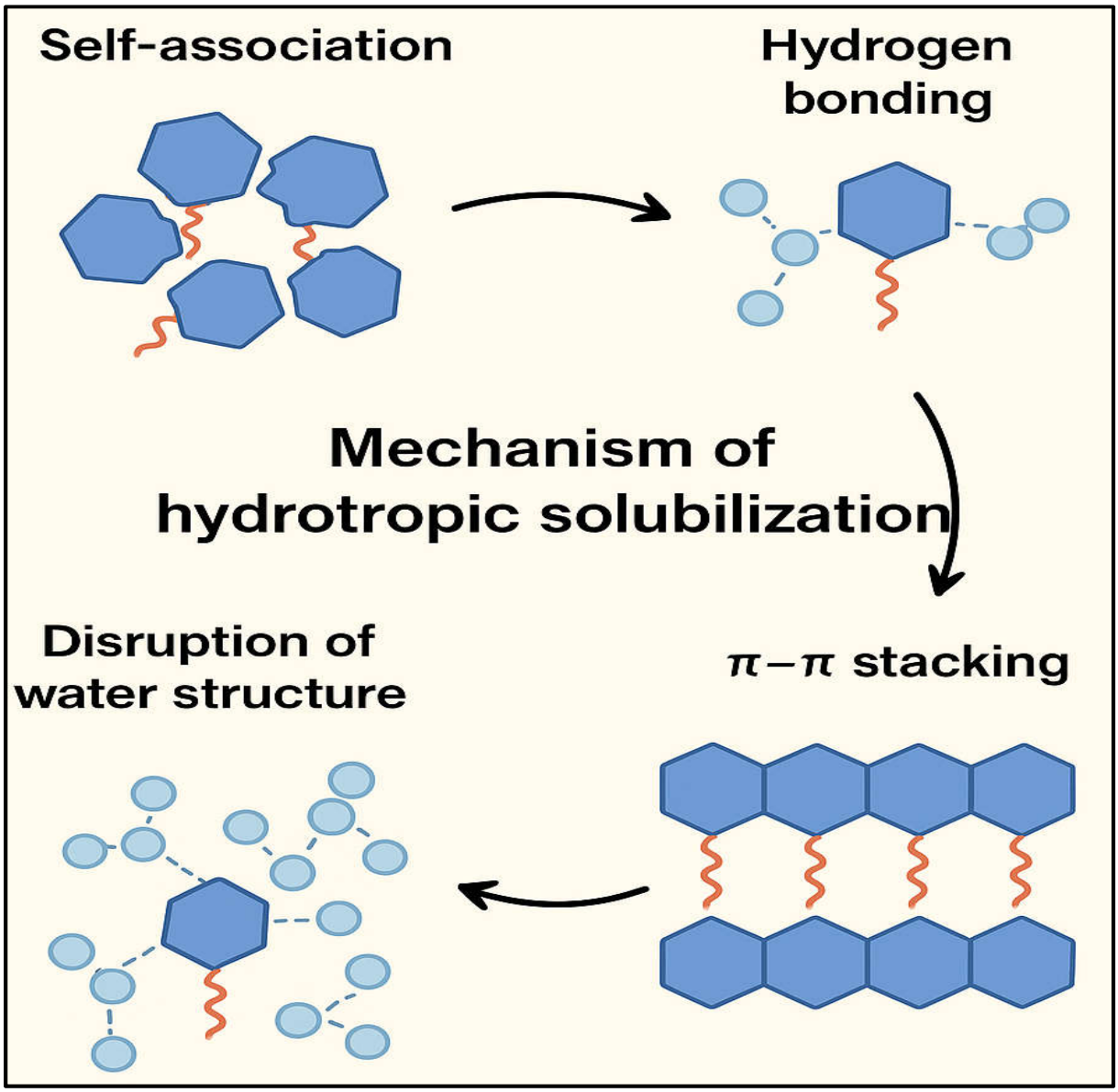

Fig. 3: Mechanism of hydrotropic solubilization

Hydrotropic solubilization, a unique, non-micellar phenomenon, increases the aqueous solubility of drugs that are poorly soluble in water through molecular-level interactions. Unlike surfactants, which produce ordered micelles beyond their critical micelle concentration (CMC), hydrotropes work by more subtle, cooperative self-association, hydrogen bonding, π–π stacking, and disruption of water structure. These processes work together to solubilize hydrophobic drug molecules in water conditions. The following paragraphs look at the thermodynamics, aggregation behaviour, molecular interactions, and temperature and concentration effects that characterize hydrotropic solubilization mechanisms.[45]

DRUG-HYDROTROPE MOLECULAR INTERACTIONS:

Non-covalent interactions between hydrotrope molecules and drug solutes are the main cause of hydrotropic solubilization. These consist of:

π–π STACKING INTERACTIONS: Delocalized π-electrons found in aromatic hydrotropes like caffeine, salicylate, and sodium benzoate can stack with the π-systems of aromatic or heterocyclic drug molecules. Breaking the crystal lattice and stabilizing the drug in the aqueous phase promotes solubilization.[46]

HYDROGEN BONDING: Hydrotropes with hydroxyl, carboxyl, amine, or amide groups (such as urea, salicylate, or nicotinamide) and drug molecules generate strong hydrogen bonds. The drug is more soluble in polar solvents like water and has a bigger hydration shell as a result of this interaction. [47]

VAN DER WAALS AND HYDROPHOBIC INTERACTIONS: The hydrophobic portions of hydrotropes can interact with non-polar drug areas, especially in Class II and IV drugs with large hydrophobic cores. These connections keep the medicine stable in solution by shielding it from water. Reversible complex formation is made possible by these dynamic and transient interactions, which are beneficial for regulated drug release and bioavailability.[48] Such weak, transient hydrotrope–drug complexes can serve as molecular vehicles to transport hydrophobic molecules in biological environments without the use of emulsifying agents or surfactants.

HYDROTROPES' AGGREGATION BEHAVIOUR (NON-MICELLAR)

Unlike surfactants, hydrotropes do not form discrete micelles. However, at a threshold known as the Critical Hydrotropic Concentration (CHC), some hydrotropes display self-association behaviour. The loose, dynamic aggregates or "pseudo-micellar" structures formed by this interaction may cause drug molecules to become soluble. According to Kunz et al. (2004), many hydrotropes exhibit "cluster-like aggregation" above their CHC, which is different from typical micelle formation. The se aggregates are sustained by π–π interactions and hydrogen bonding rather than a hydrophobic core. Since the aggregates are more labile, drug and hydrotrope molecules can exchange more quickly. Hydrotropes typically have a smaller aggregation number (number of molecules in a cluster) than surfactants. Important aspects of hydrotrope aggregation include: Unlike micelles, there is no distinct hydrophobic core. These are frequently reversible and sensitive to changes in the environment and are highly dependent on temperature, pH, and hydrotrope concentration. Because of this behavior, hydrotropes can be used in formulations that require reversible solubilization, such as injectable systems or drug delivery that responds to pH. [49,50]

SOLUBILIZATION THERMODYNAMICS:

Favourable variations in both enthalpy (ΔH^o) and entropy ($T\Delta S^o$) propel the hydrotropic solubilization of poorly soluble, crystalline drugs, successfully overcoming their high lattice energies. The Gibbs free energy equation governs it: $\Delta G^o = \Delta H^o - T\Delta S^o$. In this case, $T\Delta S^o$ records greater disorder upon solute dispersion and water restructuring, whereas ΔH^o indicates energy shifts from creating new drug–hydrotrope contacts and breaking drug–drug and drug–solvent connections. The breakdown of hydrophobic hydration shells usually results in a positive entropy change ($\Delta S^o > 0$), making the process primarily entropy-driven, particularly for aromatic compounds. The drug-hydrotrope pair can affect enthalpy changes (ΔH^o), which can range from modestly endothermic to exothermic. In order to further increase entropic gain and, thus, solubilization efficacy, some hydrotropes also function as structure breakers, or "chaotropes," upsetting the hydrogen-bond network in water. [51,52,53]

TEMPERATURE AND HYDROTROPE CONCENTRATIONS' IMPACT ON SOLUBILIZATION:

HYDROTROPE LEVEL: The concentration relationship for hydrotropic solubilization is non-linear; solubility enhancement is either linear or negligible below the Critical Hydrotropic Concentration (CHC). Because of cooperative self-association and improved drug–hydrotrope interactions, solubility frequently increases significantly exponentially or sigmoidally once the CHC is exceeded. This behaviour allows formulations to be precisely tuned: concentrations below CHC are ineffective; at CHC, the most economical and balanced delivery is achieved; and above CHC, even though maximum solubilization is reached, factors like osmolarity or possible toxicity come into play, particularly for systemic use. Formulation optimization for oral and parenteral dosage forms requires determining the lowest effective hydrotrope concentration that guarantees sufficient solubility while preserving safety.[54]

The Temperature: Temperature has a major effect on solubility because it influences the entropic contributions to solubilization, the dynamics of the water structure, and the strength of the hydrotrope–drug interaction. By increasing molecular mobility and decreasing drug-drug lattice interactions, increasing the temperature generally enhances solubilization. Additionally, by reducing viscosity, it accelerates the rate of dissolution. High temperatures, however, can degrade thermolabile drugs and alter the patterns of hydrotrope aggregation (aggregation is temperature-sensitive in some systems). Temperature-dependent solubility improvement reflects entropy-dominated solubilization mechanisms, consistent with the observation that hydrotropes function better at higher temperatures. Without changing the chemical composition of the drug, hydrotropes and even modest temperature changes can

greatly boost solubility in BCS Class II and IV drugs, which often have high melting points and poor water solubility.[55]

HYDROTROPIC SOLUBILIZATION APPLICATIONS

Hydrotropic solubilization has gained popularity in a number of scientific and industrial domains due to its non-toxic and eco-friendly nature. It can increase the aqueous solubility of poorly soluble compounds, particularly Biopharmaceutics Classification System (BCS) Class II and IV drugs, without the need for organic solvents or surfactants, making it a valuable tool in consumer product industries like food and cosmetics, pharmaceutical formulations, herbal drug delivery, nutraceuticals, and green chemistry. The practical applications of hydrotropes in industrial and medicinal contexts are reviewed and categorized in this article.[56]

FORMULATIONS FOR PHARMACEUTICALS

Many active pharmaceutical ingredients (APIs) oral bioavailability is severely limited by their poor aqueous solubility. A flexible substitute for traditional solubilization methods like pH adjustment, salt formation, co-solvency, and surfactant use is provided by hydrotropic agents.

Tablets: Hydrotropic solubilization is increasingly being employed in the pre-formulation and granulation stages of tablet manufacturing, especially for BCS Class II drugs that are poorly soluble in water, such as nifedipine, aceclofenac, and ibuprofen. Hydrotropes, including sodium benzoate, urea, and nicotinamide, are added to direct compression mixes or wet granulation processes to improve solubility, reduce particle size, and accelerate drug dissolution. This facilitates the production of immediate-release tablets without the need for surfactants or solubilizing excipients, which may raise safety or legal concerns.[57]

Suspensions: Hydrotropes are also used in oral and topical solutions to improve the drug's aqueous solubility and decrease sedimentation. By changing the solubility equilibrium, hydrotropes help to maintain a homogenous dispersion, which is necessary for stability and accurate dosage. For example, in paediatric formulations of paracetamol, caffeine, or chlorpheniramine, hydrotropic compounds have been employed to stabilize suspensions and reduce the required concentration of viscosity enhancers or preservatives.[58]

Injections and Parenteral: Injectable formulations have some of the highest requirements for tolerability, sterility, and solubility. Hydrotropes enable the production of hydrophobic pharmaceuticals in clear aqueous injectables, reduce systemic toxicity, improve bioavailability, and reduce dependence on co-solvents, surfactants, or emulsifiers. Hydrotropic injectable solutions have proven especially useful for the intramuscular and intravenous delivery of non-polar medications in circumstances where conventional solubilizers are either ineffective or poorly tolerated.[59]

SOLUBILIZATION OF HERBS AND NUTRACEUTICALS

Making herbal drugs and nutraceuticals, which frequently contain plant-derived active ingredients like alkaloids, polyphenols, flavonoids, terpenoids, and essential oils, many of which are hydrophobic, is one of the most promising applications for hydrotropic solubilisation.

ENHANCEMENT IN THE EXTRACTION OF PHYTOCONSTITUENTS:

Traditional methods of extracting phytoconstituents include the use of organic solvents (methanol, ethanol, and chloroform), which are expensive, potentially hazardous, and bad for the environment. The efficient extraction of active phytoconstituents in an aqueous medium utilizing hydrotropes such as sodium salicylate, urea, and nicotinamide has led to higher yields, cleaner extracts, and better safety. Mishra et al. (2006) used hydrotropic solubilization to extract andrographolide from Andrographis paniculata, showing a notably greater recovery rate without the use of organic solvents.[60]

HERBAL DOSAGE FORMS

Hydrotropic solubilization has also been used to create stable oral liquids, gels, and capsules that include herbal active ingredients that are poorly soluble, such as berberine, gingerol, resveratrol, and curcumin. These hydrotrope-based herbal formulations follow the principles of green chemistry and show greater dissolving, enhanced absorption, and better clinical performance.[61]

Application of Green Chemistry

The green chemistry tenets of reduced use of hazardous solvents, enhanced atom economy, waste minimisation, and safer reaction conditions are all in line with hydrotropic solubilisation.

Replacement of Solvents:

Since hydrotropes are a non-volatile, non-flammable, and water-compatible medium, they present a strong green chemistry substitute for volatile organic compounds (VOCs). They are therefore useful for purification processes in the production of chemicals or pharmaceuticals, crystallization or recrystallization of APIs, and aqueous-phase synthesis of fine compounds and intermediates. The ability of hydrotropes to facilitate size control and crystallization without volatile organic compounds (VOCs) is demonstrated by the notable application of hydrotropic antisolvent crystallization to decrease the particle size of methyl cobalamin.[62]

Environmentally Friendly Procedures

The use of hydrotropes in industrial activities creates a safer, more economical, and environmentally friendly image since they lower carbon emissions, lessen the burden of solvent waste, and enhance worker safety. For example, when hydrophobic APIs crystallize in a

hydrotropic medium, acetone or chloroform is not needed, making the process safer and more eco-friendly.[63]

Industrial Significance of Food and Cosmetic Products

In the food and cosmetics industries, where improving the solubility of active or flavouring agents is crucial but the use of organic solvents is strictly regulated, hydrotropic solubilization has been investigated outside of the pharmaceutical sector.

Cosmetics

In the constantly evolving field of cosmetics, hydrotropes are molecular maestros that readily solubilize a wide range of challenging compounds. Think of them as small molecular matchmakers that combine otherwise incompatible substances, such as potent essential oils, pleasing fragrances, necessary UV filters (such as benzophenones), and vibrant colorants, to form a single, harmonious solution. The items we use daily, from nutritious sunscreens and luxurious lotions to stimulating shampoos and seductive aromas, often contain hydrotropes like sodium toluene sulfonate and sodium cumene sulfonate. Their inclusion goes beyond merely mixing ingredients; these clever agents are essential to enhancing a product's overall attractiveness. They significantly improve a product's stability, ensuring that it looks perfect and prolonging its shelf life and clarity. [64]

The Food Sector

In the intricate compositions of food products, particularly beverages, hydrotropes are hidden heroes who meticulously ensure both nutritional integrity and sensory enjoyment. These incredible molecules are utilized to skillfully dissolve flavouring oils and blend them into aqueous systems to provide consistent taste experiences. Hydrotropes significantly enhance the dispersion of vital fat-soluble vitamins A, D, E, and K, boosting their bioavailability and consistent distribution throughout the product in addition to imparting flavour. They also act as molecular guardians, carefully making sure that delicate colorants and sensitive preservatives stay stable, preserving the product's aesthetic appeal and extending its shelf life. Crucially, because they come into direct contact with customers, hydrotropes in food applications are subject to stringent regulations. Their food-grade purity, non-toxicity, and distinguished GRAS (Generally Recognized as Safe) accreditation need cautious selection. This stringent condition makes natural hydrotropes—like the well-known caffeine or the vitamin-derived nicotinamide—especially appealing possibilities. As the food industry continues its dynamic change to clean-label, organic, and green products, the use of hydrotrope-based solubilization systems is not just a trend; rather, it is a scientifically validated

and increasingly popular path to safer, more stable, and more aesthetically pleasing food and beverage innovations.[65]

BENEFITS AND DRAWBACKS OF HYDROTROPIC SOLUBILISATION

Hydrotropic solubilization has emerged as a practical and eco-friendly alternative to traditional solubilization techniques in pharmaceutical sciences. Enhancing the aqueous solubility and bioavailability of weakly water-soluble drugs, particularly those classified under BCS Classes II (low solubility, high permeability) and IV (low solubility, low permeability), is especially relevant. Despite all of its advantages, the approach has limitations and disadvantages that should be carefully considered while developing the formulation.[66]

HYDROTROPIC SOLUBILIZATION'S BENEFITS

1. Safe and non-toxic

Two of hydrotropes' greatest benefits are their low toxicity and biocompatibility. Caffeine, urea, sodium benzoate, and nicotinamide are only a few of the hydrotropic compounds that are already approved as food additives or pharmaceutical excipients. Because of this, it can be safely added to topical, parenteral, and even oral formulations. For example, sodium benzoate is FDA-approved as GRAS (Generally Recognized as Safe) and is commonly utilized in injectable formulations and paediatric oral suspensions. Hydrotropes' safety profile makes them suitable for usage in chronic drugs, herbal formulations, and nutraceuticals where patient safety and adherence are crucial.[67]

2. Reasonably priced and easily accessible

Hydrotropes are usually affordable, chemically stable, and easily obtainable in large quantities; they are economical excipients. Hydrotropic systems do not require expensive polymers or surfactants or complex manufacturing processes, in contrast to advanced solubilization techniques like nanoemulsions or cyclodextrin inclusion complexes. This is especially beneficial for drug development, resource-constrained contexts, and over-the-counter (OTC) pharmaceutical items.[68]

3. Organic Solvent Removal

Traditional solubilization methods frequently employ a range of organic solvents, such as ethanol, methanol, chloroform, and dimethyl sulfoxide (DMSO). Despite their efficacy, these conventional solvents have a number of drawbacks, such as the possibility of toxicity, the requirement for strict regulatory oversight due to their hazardous nature, and the possibility of undesirable solvent residue in the final product. In contrast, hydrotropic solubilization offers a revolutionary, completely aqueous, solvent-free alternative. This innovative technique naturally eliminates the need for resource-intensive additional purification procedures, greatly

reduces the residual solvent concentration, and enhances patient safety. This distinction is particularly crucial in specialized applications such as herbal extracts and parenteral dosage forms (injections), where even trace levels of residual solvents can be highly troublesome and directly affect patient health and regulatory compliance. Thus, hydrotropic solubilization represents a significant breakthrough in the creation of formulations that are safer, cleaner, and more efficient.[69]

4. Eco-Friendly and Complementary to Green Chemistry

Hydrotropes are among the best examples of sustainable industrial methods. One major advantage is that they are often biodegradable and have minimal environmental persistence, meaning they break down rapidly and do not persist in ecosystems. This immediately complies with the fundamental principles of green chemistry by reducing the need for dangerous solvents. By facilitating effective procedures that produce fewer hazardous byproducts, their use exemplifies concepts like waste minimization. Hydrotropes also make it easier to utilize safer chemicals by substituting less harmful ones for poisonous ones. Most importantly, their use contributes to a considerable reduction in the carbon footprint of various production processes. As a result, industries including food, cosmetics, and pharmaceuticals that are facing mounting pressure to enhance their environmental performance are finding hydrotropic solubilization to be a more desirable and responsible choice.[70]

HYDROTROPIC SOLUBILIZATION'S DRAWBACKS

Notwithstanding its many advantages, hydrotropic solubilization has some formulation, compatibility, and regulatory issues that need to be resolved in order to allow for wider industrial use.

1. Limited Adherence to Specific Substances

The molecular makeup and functional groups of the target substance are essential to this ingenious technique's efficacy, particularly in drug administration. Drugs that lack crucial structural components, such as aromatic rings, hydrogen bond donors/acceptors, or unique hydrophobic cores, may interact with hydrotropes minimally or not at all, leading to disappointingly low solubilization efficiency. For instance, strongly polar or completely ionized medicines often do not respond well to the characteristic stacking interactions or hydrotropic aggregation that drive the solubilization mechanism. However, BCS Class II drugs often possess the ideal chemical structure for hydrotropic interaction. These drugs are characterized by low water solubility and high permeability. Examples of compounds with a lot of aromatic and lipophilic moieties that have a large affinity for hydrotropes and greatly boost their solubility include ketoprofen and naproxen. In order to ensure that this powerful

solubilization method is applied where it will have the biggest impact, drug-hydrotrope compatibility screening is essential in the early stages of pharmaceutical formulation development.[71]

2. The Impact of Ionic Strength and pH

Although hydrotropic solubilization is a useful method, it has limitations. One important factor affecting its efficacy is pH dependence. Even slight changes in the medium's pH can significantly affect hydrotropes' ability to solubilize active ingredients because they may be weak bases or acids themselves. This suggests that a carefully calibrated environment is often necessary for the best performance. Similarly, the ionic strength of the system introduces an additional layer of complexity, particularly in the presence of several salts. Ionic strength variations can drastically alter the way hydrotropes aggregate by disrupting the precise structures that lead to solubilization. Predictions become challenging since it can also directly alter solubility profiles and interfere with crucial hydrogen bonding interactions. This sensitivity to pH and ionic strength significantly hinders formulation development, especially in complicated multicomponent systems like buffered solutions or fixed-dose combinations. Maintaining pH stability across a product's shelf life is a persistent challenge that formulators must solve, highlighting the precise control required for successful hydrotropic applications. [72,73]

3. The possibility of precipitation after dilution

One of the main issues with using hydrotropic solubilization is the inherent risk of drug precipitation when the hydrotrope concentration drops below the critical hydrotropic concentration (CHC). Numerous physiological contexts might cause this effect, such as the transit of the gastrointestinal tract, the dilution that occurs after oral or parenteral administration, or even the diffusion into tissues after injection. The potential for reduced drug bioavailability, increased patient dosage variability, and a higher risk of tissue irritation at the administration or absorption site are only a few of the serious consequences of such precipitation. Consequently, it is essential to thoroughly evaluate the behaviour of hydrotropic formulations upon dilution. Other stabilizing agents or carefully selected cosolvents are often needed to lower this risk and successfully prevent recrystallization. This ensures reliable drug delivery and the best possible therapeutic results.[74]

4. Selection of Hydrotropes is not standardized

Despite its promising properties, the widespread implementation of hydrotropic solubilization is now hampered by the absence of uniform rules or standardized frameworks. This critical gap is evident in several significant domains. To begin with, there are no predetermined methods

for choosing the optimal hydrotropes for certain drugs, which often causes selection to depend more on empirical trial-and-error than on rational design. Second, the inability to forecast a hydrotrope's efficacy just from its molecular structure or that of the target solute hinders effective development. Finally, the toxicological thresholds for various hydrotropes are not well-defined and standardized, which is crucial for ensuring patient safety and regulatory compliance, especially in pharmaceutical applications. This current status demonstrates the urgent need for a more systematic and predictive scientific approach to fully fulfill the potential of hydrotropic solubilization. Trial-and-error screening or solubility enhancement investigations are still the main empirical methods used to choose hydrotropes. This uncertainty complicates scale-up and regulatory approval, especially for combination drugs or novel compounds. Additionally, several hydrotropes, especially synthetic ones, lack safety evidence for long-term or high-dose use, which may exclude their use in therapeutic formulations.[75]

Techniques for Getting Past Limitations

Several tactics can be used to overcome these restrictions:

- Hydrotrope-drug compatibility can be predicted with the use of computational modelling and QSAR (Quantitative Structure–Activity Relationship) techniques.[76]
- Hydrotrope-cosolvent or hydrotrope-polymer mixtures are examples of hybrid solubilization systems that can increase efficacy while lowering the necessary hydrotrope concentrations.[77]
- Encapsulation methods, such as inclusion complexes or hydrotropic solid dispersions, may reduce precipitation and improve physical stability.[78]
- More investigation into new, natural hydrotropes (like flavonoids and polyphenols) could provide safer, more biocompatible substitutes for their synthetic counterparts. [79,80]

CONCLUSION

Hydrotropy has emerged as a versatile and eco-friendly strategy for enhancing the aqueous solubility of poorly water-soluble drugs, offering advantages such as high selectivity, safety, and compatibility with a wide range of formulations. This method can greatly accelerate dissolution rates without the use of hazardous chemical solvents by employing hydrotropes, which are tiny, amphiphilic molecules that can alter the structure of water and create non-covalent bonds with hydrophobic solutes. Improvements in molecular modelling, combination methods, and the incorporation of hydrotropy with nanotechnology show promise for overcoming obstacles such as structural selectivity, precipitation upon dilution, and the absence of defined selection criteria. Hydrotropic solubilization has the potential to become a common,

sustainable method in pharmaceutical development with further research and regulatory backing, especially for BCS Class II and IV drugs, where solubility is still a major obstacle to therapeutic effectiveness.

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Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Siepmann J, Siepmann F, Florence AT. Factors influencing oral drug absorption and drug availability. In Modern Pharmaceutics Volume 1 2009 May 28 (pp. 135-172). CRC Press.
2. Schanker LS. Mechanisms of drug absorption and distribution. Annual review of pharmacology. 1961 Apr;1(1):29-45.
3. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. International Scholarly Research Notices. 2012;2012(1):195727.
4. Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, Porter CJ. Strategies to address low drug solubility in discovery and development. Pharmacological reviews. 2013 Jan 1;65(1):315-499.
5. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. Journal of pharmacological and toxicological methods. 2000 Jul 1;44(1):235-49.
6. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research. 1995 Mar;12(3):413-20.
7. Wu CY, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharmaceutical research. 2005 Jan;22(1):11-23.
8. Benet LZ. The role of BCS (biopharmaceutics classification system) and BDDCS (biopharmaceutics drug disposition classification system) in drug development. Journal of Pharmaceutical Sciences. 2013 Jan 1;102(1):34-42.
9. Strickley RG. Solubilizing excipients in oral and injectable formulations. Pharmaceutical research. 2004 Feb;21(2):201-30.
10. Loftsson T, Duchene D. Cyclodextrins and their pharmaceutical applications. International journal of pharmaceutics. 2007 Feb 1;329(1-2):1-1.
11. Patravale VB, Date AA, Kulkarni RM. Nanosuspensions: a promising drug delivery strategy. Journal of pharmacy and pharmacology. 2004 Jul;56(7):827-40.
12. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. European journal of Pharmaceutics and Biopharmaceutics. 2000 Jul 3;50(1):47-60.
13. Serajuddin AT. Salt formation to improve drug solubility. Advanced drug delivery reviews. 2007 Jul 30;59(7):603-16.

14. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug discovery today. 2007 Dec 1;12(23-24):1068-75.
15. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. International Scholarly Research Notices. 2012;2012(1):195727.
16. Neuberug C. Hydrotropy. Biochem z. 1916;76:107.
17. Maheshwari RK, Dewangan A, Soni PK, Kansagra PK, Jain SK. Novel application of hydrotropic solubilization in the spectrophotometric analysis of paracetamol tablet. Asian Journal of Chemistry. 2006 Jul 1;18(4):2879.
18. Fusina A, Kerkel F, Touraud D, Kunz W, Nardello-Rataj V. Hydrotropic and solvent strategies to enhance the solubilization of polyphenols in relation to their chemical structure. Journal of Molecular Liquids. 2024 Aug 15;408:125321.
19. Kalyani G, Bhuvaneswari P, Hemalatha B, Padmalatha K. Hydrotropy: a promising tool for solubility enhancement. Asian Journal of Pharmacy and Technology. 2022;12(2):146-50.
20. Beig A, Lindley D, Miller JM, Agbaria R, Dahan A. Hydrotropic solubilization of lipophilic drugs for oral delivery: the effects of urea and nicotinamide on carbamazepine solubility–permeability interplay. Frontiers in Pharmacology. 2016 Oct 25;7:379.
21. Saharawat A, Deepali, Nainwal N. Natural plus synthetic hydrotropic solubilization using response surface methodology to optimize the solid dispersion of hydrochlorothiazide. Combinatorial Chemistry & High Throughput Screening. 2022 Feb 1;25(2):307-23.
22. Singh S, Dash UN, Talukdar M. Solubility enhancement and study of molecular interactions of poorly soluble ibuprofen in presence of urea, a hydrotropic agent. Materials Today: Proceedings. 2020 Jan 1;30:246-53.
23. Maheshwari RK, Indurkhya A. Formulation and evaluation of aceclofenac injection made by mixed hydrotropic solubilization technique. Iranian Journal of Pharmaceutical Research: IJPR. 2010;9(3):233.
24. Jeong S, Ryu J, Yang Q, Zhu JY, Yoo CG. Recent advances in hydrotropic solvent systems for lignocellulosic biomass utilization. Green Chemistry. 2024;26(4):1806-30.
25. Evstigneev MP, Lantushenko AO, Golovchenko IV. Hidden entropic contribution in the thermodynamics of molecular complexation. Physical Chemistry Chemical Physics. 2016;18(11):7617-25.

26. Cea-Klapp E, Abranches DO, Marin-Rimoldi E, Gajardo-Parra NF, Canales RI, Garrido JM, Maginn EJ. Understanding Solute-Hydrotrope Aggregation in Aqueous Solutions: A Molecular Dynamics Approach. The Journal of Physical Chemistry B. 2025 May 9;129(20):5016-25.
27. Jeong S, Ryu J, Yang Q, Zhu JY, Yoo CG. Recent advances in hydrotropic solvent systems for lignocellulosic biomass utilization. Green Chemistry. 2024;26(4):1806-30.
28. Senthilkumar R, Sridhar R, Surendran G, Jayakumar C. Hydrotropic Solubilization: A Promising Approach for Enhancing the Solubility of Poorly Water-Soluble Drugs. Pharmaceutical Research: Recent Advances and Trends Vol. 5. 2024 Aug 13:127-44.
29. Jain S, Farooqui N, Manocha N, Bhawsar D. A Review on "Advance Solubility Enhancement Techniques": Significant Strategy in Development of Formulation.
30. Mehringer J, Kunz W. Carl Neuberg's hydrotropic appearances (1916). Advances in Colloid and Interface Science. 2021 Aug 1;294:102476.
31. Patel AD, Desai MA. Progress in the field of hydrotropy: mechanism, applications and green concepts. Reviews in Chemical Engineering. 2023 May 1;39(4):601-30.
32. Sharma U, Saroha K. A review of hydrotropic solubilization techniques for enhancing the bioavailability of poorly soluble drugs. International Journal of Toxicology. 2024 Feb;43(1):63-71.
33. Joshi S, Dubey I, Bilaiya A, Yadav K, PARASHAR DD. A Practical Approach for Solubility Enhancement of Albendazole. Oriental Journal of Chemistry. 2022 Feb 1;38(1).
34. Cui Y. Hydrotropic solubilization by urea derivatives: a molecular dynamics simulation study. Journal of Pharmaceutics. 2013;2013(1):791370.
35. Jeong S, Ryu J, Yang Q, Zhu JY, Yoo CG. Recent advances in hydrotropic solvent systems for lignocellulosic biomass utilization. Green Chemistry. 2024;26(4):1806-30.
36. Shen Y, Xiao Y, Edkins RM, Youngs TG, Hughes TL, Tellam J, Edkins K. Elucidating the hydrotropism behaviour of aqueous caffeine and sodium benzoate solution through NMR and neutron total scattering analysis. International Journal of Pharmaceutics. 2023 Nov 25;647:123520.
37. Elakiyaasokan VK, Kalyanaraman G, Nagarajan NG. Aqueous Solubility Enhancement and Thermodynamic Aggregation Behavior of Resveratrol Using an Eco-Friendly Hydrotropic Phenomenon. Russian Journal of Physical Chemistry A. 2019 Dec;93(13):2681-6.

38. Booth JJ, Omar M, Abbott S, Shimizu S. Hydrotrope accumulation around the drug: the driving force for solubilization and minimum hydrotrope concentration for nicotinamide and urea. Physical Chemistry Chemical Physics. 2015;17(12):8028-37.
39. Kim JY, Kim S, Papp M, Park K, Pinal R. Hydrotropic solubilization of poorly water-soluble drugs. Journal of pharmaceutical sciences. 2010 Sep 1;99(9):3953-65.
40. Nasrallah S, Minceva M. Solubility Enhancement of Active Pharmaceutical Ingredients through Liquid Hydrotrope Addition: A Thermodynamic Analysis. Molecular Pharmaceutics. 2025 Feb 13;22(3):1408-18.
41. Namdev B, Venkatachalam S, Jawahar N, Chorsiya A. A brief review on solubility enhancement technique: hydrotropy. Indian J Pharm Educ Res. 2022 Apr 1;56(2):347-55.
42. Badwan AA, El-Khordagui LK, Saleh AM, Khalil SA. The solubility of benzodiazepines in sodium salicylate solution and a proposed mechanism for hydrotropic solubilization. International journal of Pharmaceutics. 1982 Dec 1;13(1):67-74.
43. Thenesh-Kumar S, Gnana-Prakash D, Nagendra-Gandhi N. The effect of hydrotropes on the solubility and mass transfer coefficient of 2-nitrobenzoic acid. Polish Journal of Chemical Technology. 2009;11(2):55-9.
44. Xie B, Liu Y, Li X, Yang P, He W. Solubilization techniques used for poorly water-soluble drugs. Acta Pharmaceutica Sinica B. 2024 Nov 1;14(11):4683-716.
45. Yang B, Ren P, Xing L, Wang S, Sun C. Roles of hydrogen bonding interactions and hydrophobic effects on enhanced water structure in aqueous solutions of amphiphilic organic molecules. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2023 Aug 5;296:122605.
46. Lessa MD, Stoyanov SR, de Carneiro JW, da Costa LM. Density functional theory investigation of the contributions of π-π stacking and hydrogen bonding with water to the supramolecular aggregation interactions of model asphaltene heterocyclic compounds. Journal of Molecular Modeling. 2024 May;30(5):145.
47. Kim JY, Kim S, Papp M, Park K, Pinal R. Hydrotropic solubilization of poorly water-soluble drugs. Journal of pharmaceutical sciences. 2010 Sep 1;99(9):3953-65.
48. Suzuki H, Sunada H. Mechanistic studies on hydrotropic solubilization of nifedipine in nicotinamide solution. Chemical and pharmaceutical bulletin. 1998 Jan 15;46(1):125-30.
49. Kunz W, Holmberg K, Zemb T. Hydrotropes. Current Opinion in Colloid & Interface Science. 2016 Apr 1;22:99-107.

50. Klossek ML, Touraud D, Kunz W. Eco-solvents–cluster-formation, surfactantless microemulsions and facilitated hydrotropy. Physical Chemistry Chemical Physics. 2013;15(26):10971-7.
51. Shimizu S, Matubayasi N. Temperature Dependence of Hydrotropy. The Journal of Physical Chemistry B. 2024 Oct 28;128(44):10915-24.
52. Elakiyaasokan VK, Kalyanaraman G, Nagarajan NG. Aqueous Solubility Enhancement and Thermodynamic Aggregation Behavior of Resveratrol Using an Eco-Friendly Hydrotropic Phenomenon. Russian Journal of Physical Chemistry A. 2019 Dec;93(13):2681-6.
53. Desai M, Parikh J. Thermodynamic study for aggregation behavior of hydrotropic solution. World Academy of Science, Engineering and Technology. 2009;57:227-9.
54. Subbarao CV, Chakravarthy IK, Sai Bharadwaj AV, Prasad KM. Functions of hydrotropes in solutions. Chemical engineering & technology. 2012 Feb;35(2):225-37.
55. Senthil Nathan M, Jayakumar C, Nagendra Gandhi N. Effect of hydrotropes on solubility and mass transfer coefficient of methyl benzoate. Modern Applied Science. 2009 Mar;3:101-11.
56. Paul R, Chattaraj KG, Paul S. Role of hydrotropes in sparingly soluble drug solubilization: insight from a molecular dynamics simulation and experimental perspectives. Langmuir. 2021 Apr 14;37(16):4745-62.
57. Chen L, Dang Q, Liu C, Chen J, Song L, Chen X. Improved dissolution and anti-inflammatory effect of ibuprofen by solid dispersion. Frontiers of Medicine. 2012 Jun;6(2):195-203.
58. Shete AS, Yadav AV, Dabke AP, Sakhare SS. Formulation and evaluation of hydrotropic solubilization based suspensions of Griseofulvin. International Journal of Pharma Sciences and Research. 2010;1(1):51-7.
59. Jain AK. Solubilization of indomethacin using hydrotropes for aqueous injection. European Journal of Pharmaceutics and Biopharmaceutics. 2008 Mar 1;68(3):701-14.
60. Mishra SP, Gaikar VG. Aqueous hydrotropic solution as an efficient solubilizing agent for andrographolide from andrographis paniculata leaves. Separation science and technology. 2006 May 1;41(06):1115-34.
61. Tripathi D, Mishra S, Rai AK, Sahoo J, Sharma DK, Singh Y. Curcumin-loaded hydrotropic solid dispersion topical gel development and evaluation: A greener approach towards Transdermal delivery of drugs. Current Green Chemistry. 2022 Apr 1;9(1):26-39.

62. Patel AD, Desai MA. Hydrotropic Antisolvent Crystallization for the Reduction in the Particle Size of Methylcobalamin. ACS Sustainable Chemistry & Engineering. 2023 Mar 20;11(16):6250-60.
63. Patel AD, Desai MA. Life Cycle Assessment of Hydrotropic Antisolvent Crystallization and Antisolvent Crystallization: A Comparative Study. ACS Sustainable Resource Management. 2024 Mar 7;1(4):644-51.
64. Hodgdon TK, Kaler EW. Hydrotropic solutions. Current opinion in colloid & interface science. 2007 Jun 1;12(3):121-8.
65. Evstigneev MP, Evstigneev VP, Santiago AH, Davies DB. Effect of a mixture of caffeine and nicotinamide on the solubility of vitamin (B2) in aqueous solution. european journal of pharmaceutical sciences. 2006 May 1;28(1-2):59-66.
66. Zakharova LY, Vasilieva EA, Mirgorodskaya AB, Zakharov SV, Pavlov RV, Kashapova NE, Gaynanova GA. Hydrotropes: Solubilization of nonpolar compounds and modification of surfactant solutions. Journal of Molecular Liquids. 2023 Jan 15;370:120923.
67. Maines E, Urru SA, Burri E, Piccoli G, Pedrolli A, Pasqualini A, Burlina AL, Temporin G. Formulation and clinical evaluation of sodium benzoate oral solution for the treatment of urea cycle disorders in pediatric patients. AAPS PharmSciTech. 2020 Mar 9;21(3):100.
68. Kumar VS, Raja C, Jayakumar C. A review on solubility enhancement using hydrotropic phenomena. Int. J. Pharm. Pharm. Sci. 2014;6(6):1-7.
69. Jassim ZE. Investigating the Effect of Mixed Hydrotropy Approach on Solubility Enhancement of Felodipine.
70. El Hamd MA, Obaydo RH, Nashed D, El-Maghrabey M, Lotfy HM. Hydrotropy and co-solvency: sustainable strategies for enhancing solubility of poorly soluble pharmaceutical active ingredients. Talanta Open. 2025 Aug 1;11:100391.
71. Lee J, Lee SC, Acharya G, Chang CJ, Park K. Hydrotropic solubilization of paclitaxel: analysis of chemical structures for hydrotropic property. Pharmaceutical research. 2003 Jul;20(7):1022-30.
72. Benfica J, Martins AC, Peréz-Sanchéz G, Schaeffer N, Coutinho JA. Exploring the impact of sodium salts on hydrotropic solubilization. Physical Chemistry Chemical Physics. 2023;25(38):26327-40.
73. Martins AC, Benfica J, Peréz-Sanchéz G, Shimizu S, Sintra TE, Schaeffer N, Coutinho JA. Assessing the hydrotropic effect in the presence of electrolytes: competition between

solute salting-out and salt-induced hydrotrope aggregation. Physical Chemistry Chemical Physics. 2022;24(36):21645-54.

74. Pawar BM, Goswami A, Rahman SN, Sree A, Shunmugaperumal T. On the use of linear model-based optimization to obtain optimum solubility permeability balance (OSPB) in cinnarizine-hydrotropic blends. Journal of Molecular Liquids. 2023 Jul 1;381:121817.
75. Sales I, Abranches DO, Sintra TE, Mattedi S, Freire MG, Coutinho JA, Pinho SP. Selection of hydrotropes for enhancing the solubility of artemisinin in aqueous solutions. Fluid Phase Equilibria. 2022 Nov 1;562:113556.
76. Das S, Paul S. Exploring the binding sites and binding mechanism for hydrotrope encapsulated griseofulvin drug on γ-tubulin protein. Plos one. 2018 Jan 11;13(1):e0190209.
77. Tripathi D, Mishra S, Rai AK, Sahoo J, Sharma DK, Singh Y. Curcumin-loaded hydrotropic solid dispersion topical gel development and evaluation: A greener approach towards Transdermal delivery of drugs. Current Green Chemistry. 2022 Apr 1;9(1):26-39.
78. Tripathi D, Mishra S, Rai AK, Sahoo J, Sharma DK, Singh Y. Curcumin-loaded hydrotropic solid dispersion topical gel development and evaluation: A greener approach towards Transdermal delivery of drugs. Current Green Chemistry. 2022 Apr 1;9(1):26-39.
79. Arora B, Lather V, Pathalingappa MB, Walia R. Enhancement of aqueous solubility of hesperidin and naringenin utilizing hydrotropic solubilization technique: characterization and in vitro evaluation. Journal of Asian Natural Products Research. 2024 Oct 2;26(10):1207-18.
80. Jackson JK, Letchford K. The effective solubilization of hydrophobic drugs using epigallocatechin gallate or tannic acid-based formulations. Journal of pharmaceutical sciences. 2016 Oct 1;105(10):3143-52.