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Technical Applications of Hydrotropes: Sustainable and Green Carriers

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Abstract: Hydrotropes are amazingly water-solvent natural materials that focus on improving drugs' dissolvability with poor aqueous solvency at elevated concentrations, just as in a water medium. Advances in the disintegration of ineffectively dissolvable mixes in fluid media expect a significant function in detailing medications, cleaning specialists, and individual consideration items. Besides, they are likewise of urgent importance identified with mechanical cycles, for example, crystallization and refinement. The end of dangerous solvents in compound cycles and their substitution by eco-accommodating solvents, i.e., hydrotropes, is a significant objective of current engineered science. The fluid arrangement of hydrotropes can be viewed as an ecologically favorable response medium and is safe, nonflammable, less expensive, and is inexhaustible. Attempts have been made to explore different domains of the hydrotropes, their believable functions, and exciting constitutes in expanded innovations to fill in as a superior substitution for toxic organic solvents like methanol, $(CH_3)_2CO$, DCM, ethers, including many other processes utilized in cutting edge research applications. Hydrotropes are dynamically engaged with various areas to upgrade and improve the dissolvability of inadequately water-solvent medications, explicitly BCS class II medications. Advances in their utility lead to their participation in extracting bioactive materials substance union of natural compounds. Hydrotropic agents had a compelling function as transporters for dynamic drug fixings. It also helps handle different items from drug to curative, agrochemical, and medication modifiers.

Keywords: Hydrotropes; hydrotropic solubilization; solubility; green; sustainable carriers; pharmaceutical; applications.

Abbreviations: UV: Ultraviolet; AuNPs: Gold nanoparticles; $HAuCl_4$: Hydrogen tetrachloroaurate; Cu: Copper; Ag: Silver; Au: Gold; FMN-Na: Sodium salt of Flavin mononucleotide; NaPTS: Sodium p-toluene sulfonate; ATP: Adenosine triphosphate; MD: Molecular Dynamic; CTAB: Cetyl tri-methyl ammonium bromide; 1-H NMR: Proton nuclear magnetic resonance; PRISM: Polymer Reference Interaction Site Model; NIC: Nicotinamide; SXS: Sodium xylene sulfonate; NaCS: Sodium cumene sulfonate; Na-CIN: Sodium Cinnamate; DABCO-16:4-aza-1-hexadecyl-1-azoniabicyclo [2.2.2] octane bromide; DS: Diclofenac sodium; DESs: Deep eutectic solvents; DHPMs: Dihydropyrimidones; TMH_2O: Cyrene/water/ geminal diol mixture; FT-IR: Fourier transforms infrared; DFT: Density functional theory; EST-MS: Electrospray ionization mass spectrometry.

1. Foundation of Hydrotropes

Instability and low aqueous solubility are a few technical causes reported in the formulation development. Significant problems associated with newly developed drug molecules are lipophilicity and poor water solvency. Gaining knowledge about the limit of absorbability of drug candidates, i.e., the maximal or optimal rate and extent of absorption in their acceptable available form during the pre-formulation step, became open. To gain access to the dissolvability of limited soluble drugs for pharmaceutical analysis and formulation development became prime importance [1-3]. Similarly, pharmaceutical elegance like the taste, physical attributes, and viscosity of the concerned formulations and establishment of novel solubilization techniques are always in need and require great care. It is already researched that the affectivity of drug candidates is critically restricted by their poor aqueous solubility and manifesting the side effects and narrowing their future use. Thus developing and enhancing the water dissolvability of drug molecules has become one of the most critical discoveries towards improving the efficacy and defeating the side effects of a few drugs. It is demonstrated that desirable aqueous solubility is the prime feature to execute the pharmacological response of drug candidates [4]. Thus, the novel hydrotropic agents appear to be promising for resolving solubility issues. “Hydrotropy” is described as enhancement in solubility of an insoluble solute in water, attained by the hydrotropes. Therefore, hydrotropes are organic acids metallic salts, encouraging increment of the aqueous dissolvability of poorly water-soluble compounds when added at relatively high reasonably concentrations. Due to technology advancements and continuous research, many uses of hydrotropes have been discovered, viz. in the extraction of bioactive materials, in chemical processing of materials, in aqueous dye solution preparation, pharmaceutical formulations manufacturing, in the food industry, in making of detergent solutions, as the process of the solute separation process, as a coater in the paint industry, additives for plastic products, for selective separation in reaction kinetics [5-7]. Hydrotropic agents also have distinctive applicability as carriers for active pharmaceutical ingredients ranging from pharmaceuticals to cosmetics, agrochemicals, and alternative drug deliveries. Due to these facts, industrial demands and supplies of these agents have been spiked. Thus, the comprehensive physicochemical feature of hydrotropes is successfully employed as a green solvent for the organic reactions and in analytical drug estimation of pure form and formulations thriving their more future use [8-10].

1.1. Hydrotropes involved in improving water solubility of drugs.

Due to a substantial number of additives, the supersize in aqueous solubility, various lipophilic compounds were assigned. Henceforth, the employment of concentrated aqueous solutions of sodium citrate, sodium acetate, sodium benzoate, sodium salicylate, sodium ascorbate, urea, and Niacinamide was assigned for a vast number of poorly water-soluble drugs in order to accelerate their aqueous solubilities, and the reported data is well presented in Table 1. Figure 1 shows the mechanism of hydrotropes with important key factors for effective solubilization of drugs:

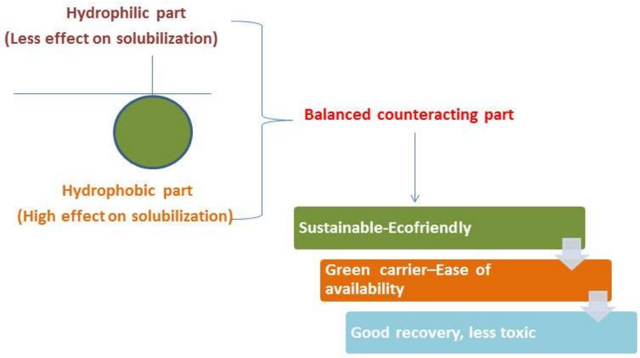

Figure 1. Important key factors for effective solubilization of drugs by Hydrotropes.

Table 1. Report on drugs with improved solubility by using different Hydrotropes.

Candidate drugs	Selected hydrotropes	References
Diazepam, Medazepam, Oxazepam, Nitrazepam, Clonazepam	*Sodium salicylate*	[11]
Monodione	*Sodium salicylate, Sodium benzoate*	[12]
Benzoic acid, Salicylic acid	*Urea, Methyl urea, 1,3-Dimethyl urea*	[13]
Nifedipine	*Urea, Methyl urea, Ethyl urea, Butyl urea, Nicotinamide, N-methyl nicotinamide, N, N-dimethyl nicotinamide Nipecotamide*	[14]
Ketoprofen	*Sodium benzoate Sodium o-hydroxybenzoate Nicotinamide Sodium m-hydroxybenzoate Sodium ascorbate Sodium 2,5-dihydroxybenzoate*	[15,16]
Piroxicam	*Nicotinamide Sodium ascorbate Sodium benzoate Sodium o-hydroxybenzoate Sodium m-hydroxybenzoate Sodium 2,5-dihydroxybenzoate*	[17,18]
Saquinavir	*Nicotinamide Ascorbic acid Dimethyl urea Resorcinol*	[19]
Temazepam	*Sodium salicylate Nicotinamide*	[20]
Progesterone, Testosterone, 17- β Estradiol, Diazepam, and Griseofulvin	*Nicotinamide, Isonicotinamide, Nipecotamide, N-methyl nicotinamide, N, N-dimethyl nicotinamide*	[21]
Salicylamide, Acetaminophen	*Pheniramine maleate, Chlorpheniramine maleate, Brompheniramine maleate*	[22]
Nimesulide	*Sodium ascorbate, Sodium salicylate, Sodium benzoate, Nicotinamide*	[23]
Albendazole	*Sodium salicylate, Sodium benzoate, Nicotinamide, Sodium ascorbate*	[24]
Rofecoxib, Celecoxib, Meloxicam	*Sodium salicylate, Sodium benzoate, Nicotinamide*	[25]

1.2. Concept of Hydrotropy in hydrotropic solubilization of poorly water-soluble drugs.

Hydrotropes aids in the solubilization of many compounds by hydrotropes like Urea, Nicotinamide, Sodium benzoate, Sodium citrate, Sodium salicylate. Numerous researchers summarized this unique applicability. Summarily elaborating Vinnakota *et al*., their research estimated and validated Atenolol in Tablets by hydrotropic solubilization phenomenon using 5M urea solution by spectrophotometry [26]. Whereas improved solubility was achieved for

Ibuprofen using hydrotropic solution reflected in a study done by Patel *et al.* [27]. Determination of Fenofibric acid in analytical estimation by hydrotrope through UV Spectrophotometrically was also succeeded [28]. The use of Niacinamide as hydrotropes was also reflected in the solubility enhancement of Escitalopramoxalate [29]. Mangal *et al.* applied the concept of hydrotropic solubilization in phytoconstituents extraction. Aceclofenac in bulk drugs and tablets extended through the utility of the hydrotropic technique involving Ibuprofen sodium as a hydrotropic solubilizing agent [30-33].

2. Report on Technical Applications of Hydrotropes

2.1. Novel catanionic hydrotropes enhance the solubility of poorly soluble bio-molecules in water and develop personal care products.

Filipa M *et al.* (2013) [34] investigated that the ionic liquids were potent cationic hydrotropes that synergistically extended the dissolvability of vanillin and gallic acid in pure water. The reasons for the poor dissolvability of these biomolecules were the ionic liquid chemical structures, temperature, and thus the concentration. The observed mechanism of high-performance extraction of biomolecules from biomass was related to the unique applicability of these ionic liquid aqueous solutions, which were used as alternative solutions for improving the extraction and combating the solubility issues of Vanillin and Gallic acid in pure water. Thus, the use of this ionic liquid has accelerated the solubility up to 40-fold of these two bio-molecules that confirmed the remarkable potential of ionic liquids to be acted as hydrotropes. Lately, the best recovery of solutes in the pure water of these biomolecules was also reported in aqueous media through the precipitation process.

2.2. Characterization of Lignin extracted from birch wood by a modified hydrotropic process.

The utility of the hydrotropic process was seen in the research demonstrated by Gabov *et al.* (2017) [35] based on the concept of “hydrotrope” conventional and a modified approach through the addition of formic acid and hydrogen peroxide used in the extraction of lignin from industrial birch wood chips. Other chemicals used were included carbohydrates, extractives, and the determination of elemental compositions of the lignins. The obtained lignins had high contents of non-lignin compounds that yield both lignins up to 16.1%. The significant changes in the structure of the lignins decrease in aliphatic hydroxyls and an increase in phenolic ones. Using hydrotropic lignin that assists the hydrotropic process as an expression in the pulp and bio-refinery industry involving 10 L rocking digester utilized 36% hydrotropic solution based on wood (2.5%) and the amount of formic acid [36].

2.3. Anon-micellar hydrotrope in the solubilization of drugs with low aqueous solubility.

The use of Nicotinamide as a hydrotrope wascited by *J. Booth et al.* (2015) [37]. The molecular basis of nicotinamide’s hydrotropic effectiveness was explained with rigrorous statistical thermodynamic theory related to Kirkwood–Buff theory of solutions. The mechanism of solubility enhancement by nicotinamide drew on two conflicting driving forces. Preferential drug–nicotinamide interaction is much stronger than urea drastically escalates with concentration through strong nicotinamide self-association, diminishing per-hydrotrope solubilization efficiency. Found on solubility amplify above MHC Thus, set up a new view of hydrotropic, i.e., Nicotinamide’s non-stoichiometric accumulation around the drug.

2.4. Mass transfer coefficient in ginger oil extraction by microwave hydrotropic solution as an alternative approach.

Handyani *et al*. (2015) [38] extracted the ginger oil by employing hydrotropic solvent, which shifted the phase equilibrium; from the microwave-assisted extraction process and improved the content of ginger oil, zingiberene was attained. Reportedly, the process was carried out in two stages, namely experimental and modeling work. It shows that the mass transfer coefficient (Kla) on zingiberene mass transfer models ginger oil extraction from surface of solid material into liquid solvent on the solid porous and the diffusion of zingiberene ginger oil into liquid solvent was attained at various hydrotropic solutions, which shows more than 14±2 Kla value than reported on the extraction with electric heating. The mass transfer on the extraction process rate on faster concerning the more considerable value of Kla. To obtain the same yields, heating the microwave-assisted extraction process would require less time when compared with the conventional extraction process.

2.5. Sustainable hydrotropic aqueous medium of glycerin utilized in Aza-Micheal reaction.

Demonstration of utility properties of hydrotropes as water like non-toxicity, colorless, odorless liquid, extensive availability, renewability were highlighted by Kamble *et al.*(2015) [39] to be used as a valuable green solvent. Attention was given to glycerin in an aqueous medium to carry out the Aza-Michael reaction. Different concentration of glycerin in water was utilized, and the reaction was performed for each concentration found that the 50% concentration was suitable for the transformation, and a high yield of the product was also obtained. Hence, a 50 % aqueous glycerin solution in water was selected as hydrotropes. Similarly, the synthesis of β-amino nitriles by Aza-Micheal reaction in 50% glycerin solution was successfully reported involving a series of experiments at room temperature conditions, and the remarkable increase in the percentage conversion rate of reaction in 50% glycerin solution was achieved.

2.6. Cucurbita pepo L. biomass used for the synthesis of gold nanoparticles (AuNPs) prepared from the green hydrotropic route.

Gonnellia *et al*. (2015) [40] productively utilized Cucurbita pepo extracts for the bio-catalyzed synthesis of AuNPs through the green hydrotropic route ultimately. The culture medium with excess metal ions treated from plants affects AuNPs' yield and structure; extracts. Shoot extracts yielded many spherical nanoparticles collated with the root extract (AuNPs) with smaller sizes. In the presence of Cu (II), Ag (I), or Au (III) grown interestingly from root extracts furnish nanoparticles with treatment-dependent shape; in contrast, shoot extracts were not observed in this phenomenon. Plants were known to produce metal-chelating compounds for their detoxification, and antioxidant compounds preserve the cell redox status, affected by the metals' presence.

2.7. In designing sustainable energy storage systems by increasing the water solubility of Flavin mononucleotide.

Orital *et al*. (2016) [41] had manifested that the sodium salt of Flavin mononucleotide act as an aqueous electrolyte hence utilized as a flow battery that catalyzes a multitude of redox reactions undertaking highly versatile electroactive molecules in biological systems. For extending the water solubility of Flavin mononucleotide, Nicotinamide (vitamin B3) was used as a hydrotropic agent. In a study, the solubility of FMN-Na was enhanced as Flavin mononucleotide negative and Ferrocyanide positive electrolytes act as a redox flow battery which had exhibited over 99% capacity retention throughout 100 cycles in a solid base and established stable cycling performance. The resonance structures maintained the stability, which enabled oxidized and reduced forms of FMN-Na.

2.8. Cubosomes as hydrotropes in potential drug delivery.

Karami *et al*. (2016) [42] used Cubosomes for special drug delivery. Their amphiphilic lipids behavior was further utilized as a biocompatible carrier in definite proportions in the formulation of nanostructured liquid crystalline particles. Due to its small size between 10-500 nm and pore size of 5-10 nm, it has exhibited excellent prospects for encapsulating various other actives like hydrophilic, hydrophobic, and amphiphilic molecules reported as promising drug delivery systems. Two significant attributes were considered for drug encapsulation, the dissolution of lipophilic drugs and liberation of loaded actives (controlled or sustained), and increased diffusion rate due to enlarged surface area of dispersed nanostructured particles. On the contrary, Cubosomes were also employed to control the drug loading by assimilating the surfactants to escalate the release behavior of loaded drugs. Various drug administration routes were suggestively possible with Cubosomes like pre-oral, intravenous, intranasal, ophthalmic, and topical delivery reflected in the study. Cubosomes have executed specific parameters for delivery of different actives, i.e., bio-adhesive behavior effortlessly implemented through topical and mucosal depositions.

2.9. Bioactive compound Piperine isolated from black pepper via hydrotropic solubilization aiming at medicinal formulations.

Gorgani *et al.* (2016) [43] have isolated the Piperine from Black pepper, a major bioactive component of pepper. Although its biological applications were limited due to its poor solubility in aqueous environments, naturally occurring alkaloids have demonstrated numerous health effects and beneficial therapeutic properties. The addition of the extraction yield of Piperine from pepper was implemented by the advanced extraction approach and improved the *in-vivo* bioavailability; therefore, new formulations had been generated containing Piperine. The dissolvability of slightly soluble or water-insoluble organic materials had intensified by the hydrotrope in an aqueous solution via accumulated around hydrophobic molecules by amphiphilic hydrotrope molecules. Consequently, compared to surfactants' the accumulations were likely very minor and much less cooperative. A biotechnological advancement has also been researched for nanoparticle formulations of Piperine or its incorporation in lipid formulations, consequently upgrading its bioavailability.

2.10. Enzymatic hydrolysis of cellulosic raw materials through hydrotropy at different substrate loading.

Denisoval *et al*. (2016) [44] have executed modern biotechnology as a dominant field that produced nutrient broths for the microbiological synthesis of ethanol and other valuable products. Toward the enzymatic hydrolysis, the hydrotropic treatments intensify the

Miscanthus reactivity by 7.1 times and for oat hulls by 7.3 times. The pulping conditions were 35 % aqueous sodium benzoate, 180 °C, 3 h, and 10:1 liquid-to-solid ratio. The process was carried out under the following conditions as the temperature rises to 180 °C for 30min and the treatment at 180 °C for 3h for the best reproducibility of the result; hence it should repeat two to five times under the same conditions.

2.11. ATP as a biological hydrotrope in solubility enhancer of protein.

Patel *et al.* (2017) [45] utilized hydrotropes as a biological ATP. They are amphiphilic molecules, differ from classical surfactants, show low co-operatively aggregation, and are employed as molar concentrations. It prevents both the formation and dissolves formed protein aggregates. At physiological concentrations lie between 5 and 10 mill-molar manifests by chemical property for which micromolar concentrations were sufficient being an energy source for biological reactions. Thus, it kept protein dissolvable due to their millimolar concentrations of ATP.

2.12. Hydrotropes enhance the solubility of non-polar substances in water.

Novikov *et al.* (2017) [46] viewed as a cluster, i.e., "pre-micelles" or as "micellar-like" structural fluctuations proclaimed that Hydrotropes form dynamic clusters with water molecules. The mixtures of water and cyclohexane were performed by molecular dynamics (MD) simulations in two methods, i.e., interfacial phenomena and liquid−liquid equilibrium, in addition to a typical nonionic hydrotrope and tertiary butanol. By MD simulations of the interfacial tension and water−oil interfacial profiles also, a model representing the ternary system, predicting hydrotropes at higher concentrations, upon approach to the liquid−liquid critical point executed as a co-solvent with the interfacial tension throughout the per scaling power-law. On the other side, hydrotropes at low concentrations behave as a surfactant by adsorption of hydrotrope molecules by diminishing the interfacial tension on the interface.

2.13. Designing nanostructures causes structural alterations in templates, modulating the architecture of nano-metric structures.

Sethi *et al.* (2017) [47] investigated hydrotrope-triggered growth in CTAB/ butanol / water / isooctane reverse micellar system at different water loadings in the micellar pool under ambient conditions. It can be controlled by tuning the water-to-surfactant molar ratio from the one-dimensional cylinder to a prolate ellipsoid while the hydrotrope modulates the growth of the micellar droplets. Inside the micellar assembly, the location of the hydrotrope and its interaction with different components of the reverse micellar system with the help of 1H NMR studies was probed. The key finding of this work was the revelation of structural parameters of hydrotrope–based cationic reverse micellar systems, which was specific to each surfactant/solvent/hydrotrope system.

2.14. Riboflavin drug molecule, sparingly soluble dissolved in hydrotropic aqueous solution, i.e., nicotinamide solution.

Das *et al.* (2017) [48] investigated Riboflavin drug molecules as a sparingly soluble compound by utilizing hydrotrope nicotinamide (NIC) established complexes through self-associate with Riboflavin molecules. With the increasing concentration of the hydrotropes solution, water molecules have tended to stay at the periphery of the Riboflavin molecules. In the ratio of 1:1 or 1:2 complex formations between drug and hydrotrope molecules, van der Waals interaction played a vital role between Riboflavin and Nicotinamide, contributing to the solubilization process electrostatic energy component. Similarly, the negative Flory−Huggins interaction parameter value had also recommended the favorable interactions between the hydrotrope and drug molecules.

2.15. Valorization of sugarcane bagasse by fractionation using a water-based hydrotropic process.

Gabova *et al.* (2017) [49] demonstrated the fractionation of sugarcane bagasse using a green hydrotropic process. Sodium xylene sulfonate (SXS) with a purity of >90% was used as a hydrotropic agent potentially utilized as a source of valuable compounds and biopolymers as much agro-industrial waste. With a 44–67% yield, the cellulose pulp was a significantly produced fraction and 60–92% cellulose content. Lignins dissolved during the treatments were isolated by dilution with water and filtration. The composition of the solutions also varied with the treatment conditions, and, besides the lignins, they contained different amounts of dissolved hemicelluloses, sugar monomers, furfural, acetic acid, and formic acids. Consequently, by its fractionation into lignin, cellulose, and other products, it successfully applied for the valorization of sugarcane bagasse through the hydrotropic process.

2.16. Deployment of the watery blend of hydrotropes to crystallize curcumin and cinnamic acid.

Rathi *et al*. (2018) [50] was performed alternate heating and cooling cycles for the crystallization process to occupy crystals of curcumin and cinnamic acid in an agitated reactor through a hydrotropic agent sodium cinnamate (Na-CIN) as a photosensitive agent. In studies, curcumin formed spheroidal crystals while subjected to thermal cycles, whereas porous aggregates form has presented by cinnamic acid. Meanwhile, the micelle formation of surfactants, its amphiphilic nature, and the aggregation formation of hydrotropes in watery solutions cause in dissolvability of an organic molecule. Wherefore, the hydrotrope molecules aggregated by their hydrophobic structure and opposed the electrostatic repulsion accommodated between similarly charged head groups had provided an optimum aggregation number (m) of these self-assemblies accordingly.

2.17. Influence of hydrotropic compounds on the solubilization properties and self-organization of cationic surfactants.

Gaynanovaa *et al.*(2018) [51] described the effect of hydrotropic additives (salts of aromatic acids and choline chloride) on the micelle forming properties of cationic surfactants and the solubilization capability of mono- and di-cationic surfactants examined as a Sudan I spectral probe and curcumin natural dye acted upon hydrophobic compounds. The structure of the head group of surfactants, the nature of the solubilizates, hydrotropic additives, and the medium's pH have played a significant role in controlling the solubilization capacity. Whereas the phenolic hydroxyl groups in a curcumin molecule thus offered additional control over its solubility by varying the pH of the medium. Cationic surfactants have exhibited high solubilization activity toward hydrophobic dyes, depending on the structure of the head group of surfactants and the nature of the solubilizates. Additions of hydrotropic compounds and variations in the pH of the solution were additional factors that improved the solubilizing abilities of surfactants.

2.18. Cationic aggregation as templates for organized nano-assemblies of liposome and noisome.

Rajput *et al.* (2018) [52] utilized different concentrations of Diclofenac sodium (DS) drug to study the micellar transition of tetra alkyl ammonium as a cationic surfactant in the aqueous solution [The use of hydrotropic drug DS showed the mechanistic insights into transforming the spherically shaped micellar aggregates of the traditional surfactants to the vesicles and demonstrated by using these low-cost surfactants as drug delivery vehicles for enhanced bioavailability.

2.19. A redox flow battery enabled by hydrotropic solubilization.

Ding *et al.* (2018) [53] had employed a hydrotrope-enhanced H2BQ solution invented a novel hybrid redox ion flow battery that acts as a catholyte and as an analyte deed by the Al-based DES. To improve the aqueous dissolvability of hydroquinone (benzene-1, 4-diol: H2BQ) thus, a hydrotropic agent, i.e., urea, was executed in water. A combined experimental and computational study was conducted to elucidate the nature and mechanisms of the hydrotropic process. Using urea as a hydrotropic agent, the elevation of solubility in hydroquinone (H2BQ)-based catholyte was achieved up to three-fold and displays the universal effect of urea on a variety of organic redox species as well. The flow battery's working potential was developed by deep eutectic solvents (DESs) as analytes.

2.20. Hydrotropes emerging as organic transformations of Ni-ZnO and ZnO nano-flasks.

Shinde *et al*. (2018) [54] synthesized the biologically active dihydropyridines (DHPMs) for dissolvability enhancement using hydrotropic agent sodium p-toluene sulfonate (NaPTS) in the water and also catalyzed with Ni-ZnO nanoparticles in addition with ZnO nanoflakes at room temperature. It demonstrated the catalytic application of nanomaterials in the water at room temperature for organic transformation. At room temperature, the synthesis of 3, 4-dihydro pyrimidine-2(1H)-ones and their catalytic application were ameliorated in an aqueous hydrotropic solution. For ZnO nanoflakes, the crystallite size was 24.28, while Ni-ZnO nanoparticles show their crystallite size of 12.15 nm. Compared with the ZnO nanoflakes, the small particle size of Ni-ZnOs deliberate better yields of DHPMs with a larger surface area for the proposed reaction has been formed. For the biologically active synthesis of DHPMs, the Ni-ZnO nano-catalyst at room temperature shows up fold in aqueous hydrotropic nano-catalyst in contrast to the ZnO nanoflakes.

2.21. As a nanostructured green solvent.

De Bruyn *et al*. (2019) [55] described noteworthy experiments by enhancing the dissolution properties of Cyrene with controllable solubilization properties in water. Cyrene to create extraordinary measures of Cyrene's geminal diol capacity. In this regard, it was imperative that with most ketones in fluid arrangements, the ketone geminal diol harmony was with the ketone. Moreover, numerous ketones are likewise insoluble in water, for instance, cyclo-heptanone. As a switchable and reversible hydrotrope, an amphiphilic atom, Cyrene's geminal diol, has been used. Dissolvability increments of up to 100-crease (over water solvency) can be accomplished. Assessment by a straight relapse of the solvency profiles of the scope of mixes shows that the watched dissolvability profiles can be clarified distinctly about the presence of microenvironments in the TMH_2O framework. The Cyrene−water dissolvable blend is critically not mutagenic; it shows hydrophilic/hydrophobic properties and is eco-toxic and bio-derived.

2.22. In Micro polarity experiments.

Research work forwarded by Yina *et al.* (2019) [56] evaluated the aggregation behavior of a type of cationic hydrotrope, BmimTOS, by numerous analytical techniques such as fluorescence, conductivity, surface tension, resonance light scattering, and dynamic light scattering measurement. It was observed that the formation of small aggregate after C1 resulting out in decreased conductivity and the micro polarity of the microstructure where probe pyrene was located. After that, the surface tension decreased much slower. When the concentration of BmimTOS was above C2, the small aggregate experienced structure change and formed larger aggregates. Hence, the micro polarity of the microstructure declined further much slower increase in conductivity was reported. Summarily, the formation of small aggregate was of BmimTOS aqueous solution at low concentration, and more significant aggregates formation at high concentration was based on the structure change of these aggregates. Suggestive that the micro-polarity measurements of these aggregates were not typical micelle-like ones are, explaining the unique mechanism of an involved hydrotrope.

2.23. As in enhancing the dilution effect of hydrophobic solutes.

Shimizu *et al*. (2019) [57] evaluated two solubilizers, hydrotropes and salts, that behaved as strongly as pure water. A defined mechanism for their behavior was solute-solute self-association. During experiments, the hydrophobic drug under study had been adopted infinite dilution approximation with hydrotrope, which contributed to enhanced solubility of the drug, whereas; solubilization between drug and hydrotrope was due to hydrophobic solute self-association. Thus, the balance between solute-hydrotrope affinity and the hydrotrope self-association as the source of per-hydrotrope inefficiency was advocated by a unified picture of a hydrotrope.

2.24. Hydrotropic ATP functions in maintaining protein solubility in a fluid.

Grenier *et al.* (2019) [58] proposed the hydrotropic agent, i.e., ATP, as a fundamental mechanism that exhibited two significant functions, i.e., preventing protein aggregation and delaying the onset of age-related cataract genesis. As a function in the crystalline lens shows a high concentration of ATP supports its hydrotropic and maintains the homeostatic level at 3m MATP in millimolar concentrations usually presented as a hydrotrope in various cells/tissue helped in preventing protein aggregation, provided that ATP functions as a hydrotrope, the crystalline lens. ATP concentration was hypothesized to maintain protein solubility and prevent protein aggregation [59]. Maintaining intracellular proteins in a fluid, i.e., ATP, as an intracellular molecule, helped in the requisite hydrotropic properties non-aggregated state. The shielding of the hydrophobic regions on intra-lenticular fiber cell protein molecules was successfully achieved by amphiphilic. The exposed side chain was responsible for organizing intracellular, interstitial water with deuterium oxide on ATP, resulting in the interfacial rheological dynamic water layer and the side chain phosphates. Interestingly, with the decrement of the age-related cataract genesis process, ATP hydrotropic prevented the protein aggregation in regular intact lenses. [60].

3. Recent Updates in Applications of Hydrotropes

Table 2. Showing the details of recent applications of Hydrotopes.

Hydrotropes	Applications	Concluding Remarks	References
Glycerol Ethers	Enhanced the solubility of Gallic acid and syringic acids in water	Solubility enhancement was promoted by hydrotropy due to solute and hydrotrope hydrophobicities resulted in the estimation of solute recovery from hydrotropic solution using water as the antisolvent..	[61]
Recyclable acid hydrotropes (*p*-TsOH)	Enhanced the delignification capacities of lignin	High lignin removal was achieved by *P-TsOH* hydrotrope (86%, 1.5 h) due to C–H⋯π and strong H-bonding interactions, both contributed to the highest interaction energy (ΔE = 15.11 kcal mol−1).	[62]
Maleic Acid	Accelerated the Wood fractionation at atmospheric pressure and ≤100 °C	By enhancing the lubrication effect of lignin in mechanical nanofibrillation for producing cellulose nanofibril.	[63]
Tetraethylammonium chloride (TEAC)	Increased the interfacial adsorption of graphene oxide (GO) by emulsification and enhancing the froth flotation	Spontaneous and synergistic adsorption of hydrotropes to GO sheets was possible by their decreased negative charge, more amphiphilic nature, increased surface pressure and emulsion, and froth stability in a given system.	[64]
ATP as Biological hydrotrope	Acted as a solubilizing enhancer in Alzheimer's disease	By obstructing the thermal aggregation of proteins, by preventing the fibrillation of intrinsically disordered proteins, their accumulation due to the specific ion effect of a strongly hydrated and highly charged anion in the Hofmeister series.	[65]
Cholinium vanillate and Cholinium gallate	Enhanced the solubility of Naproxen up to 500-fold	The improved solubility of Naproxen, a hydrophobic drug, was obtained by cholinium-based ionic liquids at diluted concentrations (below 1 mol·kg−1).	[66]
Cholinium salicylate	Solubility of Ibuprofen up to 6000-fold was increased	Because of the bio-based nature of ionic liquids and low toxicity profiles of amphiphilic ions.	[66]
Choline salicylate	Improved the micellization of hexadecyltrimethylammonium	Increased the micelle elongation between hydrotrope and hydrated deep eutectic solvents resulted in worm-like micelles with tumble morphology and flexibility.	[67]
Amyl Xyloside short-chain alkyl polyglycosides (heptyl glucoside (C7Glu)	Increased the Carnosic acid solubilization	Heptyl glucoside (C7Glu) short-chain alkyl polyglycosides (APG) with alkyl chain lengths ranging from 4 to 10 carbon atoms with polar heads of pentoses and glucose enhanced the passive extractions of Carnosic acid due to high selectivity.	[68]
1-butyl-3-methylimidazolium-based ILs	Enhanced the aqueous solubility of Artemisinin	Ionic liquids (thiocyanate or dicyanamide anions) enhanced the solubility of Artemisinin in aqueous media due to the apolar medium and hydrotropes lower hydrogen-bond acceptor character.	[69]
***Ortho*-toluidine hydrochloride (*o*-TDH) and *para*-toluidine hydrochloride (*p*-TDH)**	Enhanced the Promethazine hydrochloride (PMH) solubility	Hydrotropes' greater contribution in mixed micelles and their values were increased by an exponential increase in mole fraction ($\alpha 1$) of hydrotropes o-TDH/p-TDH.	[70]
Meglumine (Meg) and arginine (Arg)	Enhanced the solubility and bioavailability of curcumin	Due to ionic bonds between Cur-Meg/Arg had reported the faster rate of drug release and area under curve 6.3-fold larger than that of the Cur suspensions.	[71]
1,3-Benzenedisulfonic acid disodium salt (BDS)	Enhanced the Mixed micellization process	Spontaneous mixed micellization was due to higher CMC values with increased hydrotrope concentration and temperature.	[72]

Bronsted acid hydrotrope combined	Used in the synthesis of indoloquinoxalines and bis-tetronic acids in water	An 83–90% yield was reported in 40% aqueous hydrotropic solutions utilized in the synthesis of Indoloquinoxaline derivatives from isatins and o-phenylene.	[73]
Promethazine hydrochloride	Enhanced Aniline hydrochloride (AnHCl) micellization	Showed the more vital interaction between PMH and AnHCl by obtaining the lower CMC values than ideal CMC values with increased micellar mole fraction values of AnHCl.	[74]
Aniline hydrochloride (AHC) and sodium salicylate (NaSal)	Micellization of Zwitterionic dimeric surfactant at different temperatures in aqueous medium	Promoted the micellar transition by altering the micellar surface curvature due to more hydrophobic interaction with hydrotropes, resulting in decreased cmc values.	[75]
Meglumine and Pyroglutamic acid	Soliubilization of Curcumin	Increasing the miscibility gap to the water phase (Megulmine) and oil-rich region (Pyroglutamic acid).	[76]
Adenosine triphosphate	Inhibited the formation of protein condensates	By unfolding the single chain and disrupting the aggregation of hydrophobic molecular assembly, proven the self-aggregation ability.	[77]
Sodium salicylate	Recovery of limonin from lemon (Citrus limon L.) seeds	Optimizing the process parameter of Box–Behnken experimental design enhanced the yield of limonin.	[78]
Butyl ethylene glycol, Butyl or pentyl diethylene glycol, and Hexyl triethylene glycol	Extraction of lipids from Dunaliella salina microalgae	Cloud point properties supported the lipids' transesterification and easy recovery of fatty esters used as biofuels.	[79]
Ethanol	Spontaneous emulsions formed by dilution with water	Due to morphological transitions (below MHC) in monophasic and biphasic regions of water/n-octanol/ethanol system resulted in the spontaneous formation of an emulsion.	[80]
Sodium benzote, sodium salicylate and Resorcinol	Theophylline solubility prediction by ANN Model	Physicochemical effects (Theophylline affinity of the hydrophobic cavity) had been used for in-silico in an ANN system for Theophylline tranquilize solubilization.	[81]
Niacinamide and Vanillin	Solubilization of Caffeine	By lowering the hydrotrope concentration in the combined hydrotrope, caffeine was dissolved in water at 25°C.	[82]

4. Discussions

Overall, this review attaches the technical applications of Hydrotropes as carriers, which is recognized as a phenomenal carrier for resolving solubility problems with poorly water dissolvable dugs. It is recognized to improve the insoluble solute's insolubility in water. Initially, hydrotropes' applicability was limited to the solubilization of poorly water-soluble drugs. Owing to technological advancements and continuous research, various facts of this carrier have been researched, viz. for extraction of bioactive materials, utilization in chemical industries for preparing aqueous dye solution, as carriers in cosmetic manufacturing, as agrochemical entities, and in various drug delivery systems as drug modifiers and many more relevant applications. More exceptional applications of hydrotropes implied in the use of ionic liquids that act as a robust cationic hydrotrope synergistically contributed to enhancing the solubility of biomolecules, i.e., vanillin and acid within the water. Furthermore, Nicotinamide as hydrotrope acts as a non-micellar agent within drugs with low aqueous solubility causing its solubilization. Meanwhile, hydrotropes were also acknowledged for the chemical synthesis of compounds like sodium xylene sulphonate, sodium cumene sulphonate, and sodium p-toluene sulphonate (NaPTS) were proven to be a better alternative for the chemical synthesis of compounds in terms of obtained product yield. Also, dynamic applicability was seen as plant-based ATP, which was miraculously investigated as a biological hydrotrope in managing the solubility of plant protein and maintaining cell stability and various functions of multi-molecular protein machines. The hydrotrope-assisted route has also appeared to be a promising and future-based technology for isolating and extracting bioactive compounds, extending the obtained yield. However, the scope of utility of hydrotropes is not limited here. There are so many other applications that need to be explored.

5. Conclusions

With the succession of different systems for dissolvability improvement, the Hydrotrope-based strategy is a right and acceptable means for solvency upgrade of ineffectively water-solvent medications. The benefits of hydrotropes have demonstrated countless usage in differentiated disciplines due to their outstanding properties like water solubilization, which makes it an alternative solvent, their inflammability to avoid any risk, and high electrical conductivity, which increases its acceptability. However, there are a lot more things that need to be addressed. Most of the studies have elucidated only the usefulness of hydrotropes, but none have discussed hydrotropes' relevancy and mechanism. The explanation about hydrotropes' working mechanism is still unexplained and has needed more future exploration. For instance, only a few lipophilic drugs developed the aqueous injection formulations using the hydrotropic solubilization technique, but many drugs still demand study. Therefore, it is suggestive that the utility of hydrotropes is to be researched to anticipate improved drug delivery of poor water dissolvable drugs and drug moieties with narrow therapeutic with the explanation of their effective structure-based mechanism.

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Conflicts of Interest

The authors declare no conflict of interest.

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