REVIEW ARTICLE

Advanced Solubility Science: Mixed Hydrotropy

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Abstract

Although the majority of the hypotheses proposed to comprehend the mechanism of hydrotropic agents have not supported the solubility enhancement mechanism, we have elaborated on a few of them in this review. In addition, the articles emphasize the factors that affect improving solubilizing capacity. Due to their special properties, hydrotropes are frequently utilized in the solubilization of drugs, as removal go-betweens for different phytoconstituents, as separation agents for pharmaceutical analysis, and for boosting the amount and harvest of biochemical reactions. Due to this, hydrotropic solutions are highly sought after in industry. Mixed hydrotropy, on the other hand, is mostly used to increase solubility, extract phytoconstituents, and discrete materials using more than one hydrotropic agent. This review paper emphasizes the applications as well. It is necessary to screen a large number of hydrotropic candidates to find the best hydrotropic agent for a poorly soluble medication. However, once the right hydrotropic agent for a medicine is found, it is simple to increase its solubility significantly. Meanwhile, the state fixes non-call for the chemical alteration of the medication, the usage of carbon-based thinners, or the creation of suspension schemes, the hydrotropic method is the prospective strategy with the most potential for poorly soluble pharmaceuticals. The main goal of this study was to increase the oral bioavailability of furosemide by improving its solubility utilizing hydrotropes and their combinations.

Key words: Application of hydrotropes, bioavailability enhancement, mechanisms of hydrotropes, mixed hydrotropy, solubility, solubilizing agent

INTRODUCTION

More than one-third of the medications in the Indian and US Pharmacopoeia are either water insoluble or poorly water soluble. Poor biopharmaceutical characteristics such as water insolubility are the primary cause of new drug development failure. The solubility of a medicine is one of its most crucial physicochemical characteristics. Many of the recently created pharmacological compounds exhibit properties including lipophilicity and low solubility.[1] Numerous scholars came to the conclusion that hydrotropic is amphiphilic in wildlife because they take binary pieces, 1glacial and one non-ionic, in a solitary particle. A relative investigation revealed that the non-polar region is smaller than the polar portion. Another investigation showed that the hydrotrope and surfactant properties were related to a small system difference in the molecular structure. In contrast to surfactants, which are made up of long hydrocarbon chains, hydrotropic agents are structurally defined as short, bulky, and compact moieties. In addition, researchers showed that hydrotropes can be classified as cationic, anionic, or neutral molecules.[2]

Several organic solvents, including acetonitrile, methanol, chloroform, and dimethyl formamide, are utilized to dissolve these insufficiently water-soluble medicines. However, using these organic solvents has certain disadvantages, such as high cost, volatility, pollution, and some toxicities. Hence, a solvent known as a hydrotropic agent, an eco-friendly, cost-effective option, can be utilized. The solubilization marvels recognized as hydrotropism happens once a substantial quantity of a additional solute is added and causes a rise in the water solubility of a third solute.[3] Sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and

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sodium acetate are a few examples of concentrated aqueous hydrotropic solutions. Hydrotropes or hydrotropic agents are substances used to improve the solubility of poorly soluble substances in solvents. It is impossible to explain solubilization as a simplex difficulty procedure or marvel that is significantly prejudiced through the effects of a average containing salting-in or co-solvency because it involves molecular interactions that are balanced by multiple factors at the molecular level. Salting-in and salting-out procedures are frequently used to promote solubility. Salts that exhibit the "salting popular" of non-electrolytes are known as "hydrotropic salts," and the phenomenon is referred to as "hydrotropism." Salting-in is the opposite of salting-out. By creating a weak interaction with them, hydrotropic salts increase the solubilizing ability of the solute; yet, this interaction has no effect on the solute's ability to form colloids. Hydrotropy has the potential to become a useful industrial method.[4]

The mainstream of research on the solubilization device of hydrotropes emphases on possible connections among the hydrotropes and the solute, leading to the conclusion that the solubilization is caused by complexation among the two. It is simple to tie hydrotropy to the solubilization process that increases a solute's water solubility when another solute (hydrotropic agents) is also present. Tetraalkylammonium halides, urea, nicotinamide, aromatic sulfonates, guanidinium chloride, sodium thiocyanate, etc., are among the commonly used hydrotropes. Due to its low cost, non-toxicity, and eco-friendliness, the concept of mixed hydrotropy was invented.[5] The hydrotropic agents' synergistic action led to a spectacular increase in solubility. This distinguishing attribute of varied hydrotropism gives it an advantage ended humble hydrotropism, subsequent in an enhanced percent yield of ingredients during the extraction process as well as in procedures for parting similar chromatography. This review will concentrate on hydrotropic and hydrotropic go-betweens, potential methods through which they improve the solubility of the medicine in solvent, and various hydrotrope properties. The significance of the approach in the pharmaceutical sector will also be highlighted, and its benefits and drawbacks will be covered.[6]

The hydrotropy, even if it is a precisely applied scientific method, aids in everyone's solubilization. From its inception in 1916 to its initial application in 1982 for the purpose of facilitating drug solubility in the direction of better pharmaceutical analysis, it took 66 years. Given the ongoing significance of pharmaceutical sciences and subsequently analysis, a thorough understanding of the history, development, cumulative trend, and precise applications of pharmaceutical analysis is essential.[7] This was done by looking back at and comparing experiments that were previously done on using hydrotropic agents alone as well as in combination to help with pharmaceutical analysis and making badly soluble drugs more soluble.[7] We were surprised to discover ibuprofen sodium, lignocaine, niacin amide, and metformin HCl as atypical hydrotropic drugs in this thorough review's careful evaluation of the body of research. In addition, we contrasted mono and mixed approaches, showing that mono hydrotropy predominates over mixed. For further understanding, the potential mechanisms of solubilization are discussed. To aid in future applications, arbitrary classification has been stated in a crucial endeavor.[8] This study's clear objective was to assess how important hydrotropic substances are to pharmaceutical analysis for improved medication delivery. This in-depth analysis covers every element from the beginning to the most recent updates, and it will serve as a suitable manual for pharmaceutical analysts who want hydrotropy to support their analysis of potential treatments for the present and the future.[9]

THE CATEGORIZATION OF HYDROTROPES

Sales *et al*. observed that the biochemical assemblies of the typical Neuberg hydrotrope particles consist of two key components: an anionic detergent, or water-soluble, group and a hydrophilic perfumed circle or circle scheme.

While the hydrophilic ionic component aids in increasing the hydrotrope's solubility in water, the planar repellent moiety is thought to be crucial for causing stack-type aggregation. If an ionic group's only function is to improve an aqueous hydrotrope's solubility, then the cationic or non-ionic polar groups should be adequate. The cationics procaine hydrochloride, dubacaine hydrochloride, and amino benzoic acid hydrochloride were researched by Sahel *et al*. to evaluate this. They discovered that these cationic were good hydrotropes and could very well solubilize the representative lipophile riboflavin. Using all of these, they put out a novel definition of hydrotropes: "The organic compounds that are freely soluble and can be either cationic, anionic, or neutral." Hydrotropic agents are chemicals that significantly increase the solubility of organic materials in water that are otherwise nearly insoluble. Only organic compounds with a planar hydrophobic ring structure and polar groups linked to it should be regarded as hydrotropes, according to the term used above. In that case, the inorganic molecules that McKee classified as hydrotropes – KI, KSCN, and NH_4CN – would not fall within that category. This may be relevant in that the solubilizing ability brought about by these inorganic compounds is due to the process of salting, which may or may not remain the actual device underlying hydrotropism.

The additional thing around the meaning is that it emphasizes the amphiliid countryside of the hydrotropism particles, in which the polar group contributes to the high solubility of the hydrophobic moiety and the hydrophobic moiety is the "functional" portion [Figure 1].

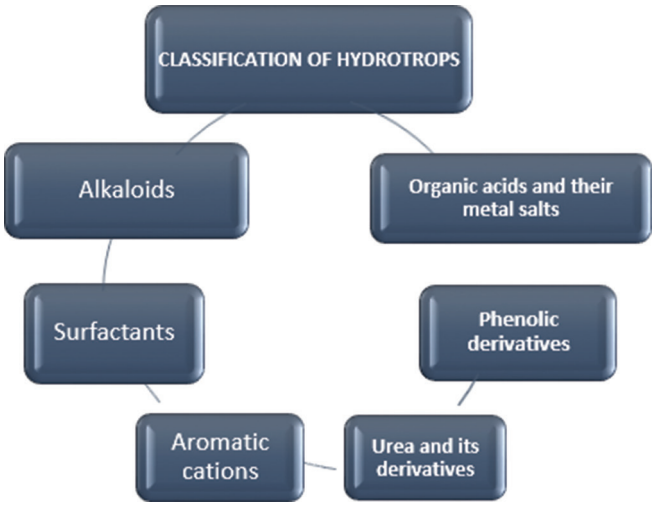

Figure 1: Classification of hydrotropes

STRUCTURE OF HYDROTROPIC AGENT

The foundation for hydrotropes

A few technical causes mentioned in the formulation development include instability and poor aqueous solubility. Lipophilicity and poor water solubility of recently created pharmacological compounds are significant issues. The possibility of learning about the maximum or ideal rate and extent of absorption in a drug candidate's acceptable available form during the pre-formulation process became available.[10] For pharmacological analysis and formulation creation, it became crucial to have access to the dissolvability of restricted soluble medicines. Similar to this, pharmaceutical elegance such as the flavor, physical characteristics, and viscosity of the relevant formulations, as well as the development of novel solubilization processes, are constantly needed and call for considerable care. Research has shown that certain factors severely inhibit the efficacy of medication candidates. As a result, one of the most important discoveries in the quest to boost medicine efficacy and reduce side effects is the development and improvement of drug molecules' water dissolvability. The pharmacological response of drug candidates is shown to be executed by suitable aqueous solubility as the key factor.[11,12] To address solubility problems, the novel hydrotropic agents seem promising. "Hydrotropy" is defined as the improvement of an mysterious solute's solubility in aquatic, accomplished by the hydrotropic. Since hydrotropism is carbon-based doses metal table salt, they promote an increase in the aqueous solubility of weakly water-soluble substances when applied at relatively high, reasonable quantities. Many uses of hydrotropes have been found thanks to technological developments and ongoing study, including the extraction of medicinal compounds. Additives for plastic products used in reaction kinetics to separate substances with preference.[13,14] The application of hydrotropic compounds as carriers for pharmaceutical active components, including those found in medicines, cosmetics, agrochemicals, and alternative drug delivery systems, is also noteworthy.[15]

These facts have led to an increase in the supply and demand for these agents in industry. The extensive physicochemical properties of hydrotropes are therefore successfully utilized as a lime flush for carbon-based processes and in logical medication assessment of pure form and preparations flourishing their additional upcoming application.[16]

- Hydrotropes that increase the solubility of pharmaceuticals in water.
- Concept of hydrotropy in hydrotropic solubilization of poorly water-soluble drugs.

Technical applications of hydrotropes

Novel catanionic hydrotropes help to make personal care products by improving the solubility of biomolecules that are not very soluble in water

According to research, the ionic fluids remained strong cationic hydrotropic that together increased the solubility of vanillin and gallic cutting in unadulterated aquatic. These biomolecules' poor dissolvability was caused by the chemical composition of the ionic liquid, temperature, and consequently concentration.[17,18] The unique applicability of these ionic liquid aqueous solutions, which were used as replacements to traditional removal methods to improve removal and address the solubility problems of vanillin and gallic cutting in pure aquatic, remained related to the device of high-performance biomolecule elimination from biomass.[19] As a result, the use of this ionic liquid increased the solubility of these two biomolecules by a factor of 40, demonstrating the extraordinary ability of ionic fluids to purpose as hydrotropism. Recently, the best recovery of these biomolecules' solutes in unadulterated aquatic has also been documented in aqueous media through the precipitation procedure.[20]

Classification of the lignin obtained from birch wood using a adapted hydrotropic procedure

The research using the term "hydrotrope" conservative and a adapted method finished the adding of formic cutting and atomic number 1 bleach used in the removal of lignin from manufacturing birch timber chips demonstrated the utility of the hydrotropic process.[21] Other chemicals used included extractives, sugars, and the analysis of the lignin's' elemental compositions. The acquired lignin's contained substantial amounts of non-lignin chemicals, which produced both lignin's up to 16.1%. Significant modifications to the lignin's structure result in a decrease in aliphatic hydroxyls and an increase in phenolic ones.[22]

Drugs with limited water solubility can be dissolved using a non-micellar hydrotrope

Nicotinamide's employment as a hydrotrope. Rigid statistical thermodynamic theory associated with Kirkwood-Buff theory of solutions was used to explain the chemical basis of nicotinamide's hydrotropic efficacy. The mechanism of

nicotinamide's solubility improvement was based on two opposing pressures.[23]

Preferential drug-nicotinamide contact is substantially greater than urea interaction and dramatically increases with concentration due to strong nicotinamide self-association, which reduces the effectiveness of per-hydrotrope solubilization. On solubility, amplified above minimum hydrotrope concentration (MHC), found consequently, provides a fresh perspective on hydrotropic, that is, nicotinamide's non-stoichiometric accumulation surrounding the medication.[24]

In a microwave-based hydrotropic solution extraction of ginger oil, the mass transfer coefficient is used as a substitute

With the help of a hydrotropic solvent and a microwave-assisted extraction method were able to extract ginger oil while shifting the phase equilibrium. This enhanced the ginger oil's content and allowed for the production of zingiberene. Apparently, the procedure was completed in two steps: Experimental work and perfect. It proves that the form abdication continuous (Kla) on zingiberene form transmission replicas red headed lubricant removal afterward surfaces of solid bodily interested in runny flush on the hard absorbent and the dispersal of zingiberene ginger oil into runny flush was attained at numerous hydrotropic keys, which shows more than 142 Kla worth than stated on the removal by electronic boiler.[25]

Aza-Micheal reaction is carried out in a sustainable hydrotropic aqueous medium containing glycerin

According to Kamble, hydrotropes can be employed as a valuable green solvent due to its useful qualities such as non-toxicity, colorless, odorless liquid, wide availability, and renewability.[26] The Aza-Michael reaction was carried out using glycerin in an aqueous medium. Different concentrations of glycerin were used in the water, and the response remained carried out aimed at apiece attentiveness to discover that the 50% attentiveness was appropriate aimed at the alteration and also yielded a tall amount of the result. As a result, hydrotropes were chosen to be a 50% aqueous glycerin solution in water.[27]

Similar to this, a series of investigations successfully documented the synthesis of amino nitriles through the Aza-Michael reaction in a solution of 50% glycerin.

By making flavin mononucleotide (FMN) more water soluble, sustainable energy storage systems can be designed

According to Orital FMNs, sodium salt functions as an aqueous electrolyte and is thus used as a flow battery to catalyze a variety of redox processes involving extremely adaptable electroactive chemicals in organic schemes. Nicotinamide (Vitamin B3) was utilized as a hydrotropic go-between to increase the aquatic solubility of FMN.[28] In a study, it was discovered that the solubility of FMN-Na was improved by the redox flow battery that FMN negative and ferrocyanide positive electrolytes form. This battery demonstrated over 99% capacity retention over the course of 100 cycles in a solid base and established steady cycling performance. FMN-Na was able to exist in its oxidized and reduced forms because the resonance structures preserved the stability.[29]

The prospective medication delivery method using cubosomes as hydrotropes

For the delivery of specialized drugs employed cubosomes. To create nanostructured liquid crystalline particles, their amphiphilic lipid characteristic was also used in certain quantities as a biocompatible carrier.[30] It has shown remarkable potential for encapsulating a variety of different actives, such as hydrophilic, hydrophobic, and amphiphilic compounds identified as promising drug delivery systems, because to its tiny scope amid 10–500 nm and hole scope of 5–10 nm.[31] The release of loaded actives (controlled or sustained) and the dissolution of lipophilic pharmaceuticals, as well as the enhanced diffusion rate brought on by the increased surface area of dispersed nanostructured particles, were two key characteristics that were taken into account for drug encapsulation. Cubosomes, on the other hand, were also used to regulate the drug loading by absorbing.[32]

As a green solvent with nanostructures

By giving Cyrene more adjustable solubilization capabilities in water, described interesting studies. Cyrene is able to produce exceptional amounts of its internal olefin capability. It was essential that the ketone-geminal diol harmony be with the ketone with the majority of ketones in fluid arrangements in this regard. In addition, a lot of ketones, such cyclo-heptanone, are insoluble in water.[33]

In experiments using micropolarity

Using a diversity of logical approaches, counting fluorescence, conduction, superficial tautness, resonance bright handful, and lively light sprinkling dimension, the research work presented assessed the aggregation behavior of a form of cationic hydrotrope, BmimTOS.[34] The micropolarity and conductivity of the microstructure where the probe pyrene was placed were shown to be reduced as a result of the creation of tiny aggregates following C1. The subsequent surface tension drop was substantially slower.[35] The tiny aggregate underwent structural change and produced larger aggregates when the concentration of BmimTOS was higher than C2. As a result, a much slower increase in conductivity was noted although the micropolarity of the microstructure continued to diminish. Briefly, the development of tiny aggregate was caused by BmimTOS aqueous solution at low temperatures.[36]

ESSENCE OF SOLVABILITY

Numerous factors, including as the drug's poor water solubility and poor membrane permeability, have an impact on the gastrointestinal tracts (GIT's) ability to absorb drugs. When a medication is taken verbally, it necessity primary melt in stomach or colonic fluids beforehand it container pass through the GIT barrier.[37]

Therefore, low water-soluble medications' solubility and dissolution rate should be improved. As a result, the medicine must be accessible at the right site of action and in the recommended dosages. The therapeutic efficacy of a medicine may be affected by its bioavailability and solubility.[38]

Short amphiphiles having three characteristics in common are referred to as hydrotropes

(i) They do not form organized structures like spherical micelles when they aggregate; instead, they procedure dimers and trimers that connect to other assemblies in a pair-wise way through feeble communications like H-closeness. Hydrotropes exhibit weaker hydrophobic effects than surfactants in water due to their shorter and/or branched alkyl chains
(ii) Hydrotropes allow vast amounts of hydrophobic substances to dissolve in water over a specific concentration. Power laws are present in the solubilization versus hydrotrope concentration graphs
(iii) At large concentrations, hydrotropes disperse ordered lyotropic phases (mesophases)
(iv) The solubility of the drug is the most crucial factor in determining how to get the necessary concentration of the drug in the systemic circulation for pharmacological response.[39]

About 40% of the potential lipophilic drugs fail due to inadequate bioavailability. When the concentration of surfactant in water rises above the critical micellar concentration (CMC), the molecules of the surfactant self-assemble into micelles. Hydrotropes have a lower ability to self-aggregate in water compared to real surfactants due to their short hydrocarbon components, which results in a weaker hydrophobic effect. As a result, they fix non-procedure micelles. Some authors have also attempted to comprehend the transition from hydrotropy to micellar performance, but they have come to the conclusion that it may not be able to draw a distinct line or establish a precise preliminary opinion when hydrotropic gives way to micellar conduct.[40] In contrast to surfactants, which have extended hydrocarbon manacles, hydrotropes have a short, bulky, compact moiety (often, but not always, an aromatic ring) that is aquaphobic by wildlife. They serve to decrease foam, limit low-temperature phase separation, stabilize solutions, and alter viscosity and cloud points. It has been thought that the self-aggregation of the hydrotropes is a requirement for a number of applications in different domains, including drug solubilization, biochemical responses, departure of carbon-based mixes, and removal. Studies on individual hydrotropes or surfactant-hydrotrope mixtures provide evidence that hydrotropes can self-aggregate in aqueous solutions above a specific minimum concentration known as the MHC, which is similar (approximately intelligences even claim that they are not strictly analogous to the critical mass for surfactants [CMC]). Hydrotrope concentration and hydrotrope itself have a significant impact on how relative volatility is affected. According to the authors, relative volatility for some hydrotropes approaches a constant value at higher concentrations and increases rapidly with increasing hydrotrope concentration.[41,42] They also looked at the relationship between the hydrotropic effect and the octanol-water partition coefficients since these numbers are utilized to relate a variety of properties of biologically active chemicals to pharmacological activity. According to the authors, hydrotropes' solubility characteristic is the primary distinction between them and micellar surfactants. A hydrotrope differs from another in terms of how easily it is soluble and how selective it is. In contrast, micellar solubilization is more widespread and less constrained.[43]

MECHANISM OF HYDROTROPIC COMPOUNDS

Numerous studies have examined the unclear mechanism of action of hydrotropic chemicals; examples of these studies' analyses can be found. The following ideas merit the most consideration out of all those that explain how hydrotropes work: Water structure disruption, the development of substance-hydrotropic agent complexes, and the production of aggregates based on hydrotropic chemicals are all methods of solubilization. Small molecules called hydrotropes are amphiphilic that have significant industrial value as solubilizes of hydrophobic compounds in aqueous settings.[18] For many years, academic discussion and disagreement have centered on the physiochemical basis and mechanism of hydrotrope activity. How closely the physical chemistry of hydrotropes' solution mimics that of typical surfactants is an essential consideration. By contrasting thermodynamic, phase, spectroscopic, and scattering studies of hydrotrope aqueous solutions, this article aims to broaden readers' understanding of the subject. Alkyl-hydrotropes are also explored; they reflect a structural progression from traditional hydrotropes toward typical surfactants and have solution properties that are more comparable to those of surfactants.[44]

Self-aggregate generation of hydrotropes

According to this idea, the hydrotropes' molecules self-aggregate, which prepares the method aimed at the development of efficient bunches in the hydrophilic fluid. Furthermore, it was proposed that solute particles became stuck in these efficient bunches, increasing the hydrophilicity

of the solute. Although MHC is the crucial concentration, at which hydrotropes start to assemble. It has been assumed that the hydrotropes mounds' planar aromatic rings, which are found in their molecular structure, stack one on top of the other to form aggregates. Similar to the process of micellization, the phenomenon of aggregation occurs in the aqueous solvent concurrently with the beginning of the solubilization of hydrophobic compounds.[45]

The water's structure has changed

It was suggested that hydro tropes don't directly cause problems by not having enough or the right kind of solutes to dissolve them. Instead, they mess up the way the water is built to stop icebergs from forming.[46]

Compounds between solute and hydrotropic form

Higher water solubility is caused by weak complexation between the non-polar chemical and the hydrotrope, which causes solubilization to occur. These complexation theory attributes the origin of hydrotropy to low stoichiometry complexes (such as 1:1 or 1:2).[47]

Hydrotrope building up around the medication

A number of substances have been used in various experimental studies using additives to determine the mechanism of hydrotrope. These studies showed strong interactions between the solute and additive that result in micelles being formed, acting as a bridge and concentrating around the hydrophobic solute without interaction.[48] The following are some more mechanisms:

a. Compound formation between hydrotropes and dissolved solutes,
b. Molecular aggregation of hydrotrope,
c. Caused by donor-acceptor electrostatic forces between hydrotrope and solute molecules,
d. Stake-type aggregation,
e. Formation of molecule complex at low hydrotrope concentration.

HYDROTROPY PARAMETER

MHC

The concentration of hydrotropes considerably increases the solubility of the least water-soluble solutes. An real concentration of hydrotropism container works wonders by way of it multiplies the solubility of the solute.[49] It remained also discovered that hydrotropes overhead MHC had a tendency to collect, which is analogous to the occurrence of micelle formation outside of CMC as seen in the case of conventional surfactants.

Concentration maximum of hydrotropes (C_{max})

The maximum concentration of hydrotropes in the hydrous phase, or C_{max}, can be understood as the point beyond which the solubility of the solute does not significantly increase. The concentration of each hydrotrope affects how much it is soluble.

Setschenow constant

The Setschenow constant, or Ks Empirical formula, was created in 1889 and was used to figure out how well the hydrotrope worked at a certain concentration when added to the liquid. This thing is also known as the "Setschenow constant." It's not enough to just connect a solute's changing solubility to a certain hydrotrope to understand how different salt mixtures affect things. Setschenow later came up with a better model and planned an estimate.[50]

$$\text{LogS/Sm} = \text{Ks (Cs}-\text{Cm)}$$

Where,
S and Sm = Solubility of compound at any hydrotrope concentration
Cs = Concentration of salt.

Impact of infection

The Setschenow constant is also used to calculate the hydrotrope's efficiency in relation to various temperature ranges [Table 1].

MATERIAL AND METHODOLOGY

Modern Laboratories Pvt. Ltd., Indore, Indore kindly donated furosemide. From Signet Chemicals in Mumbai, India, sodium acetate, sodium benzoate, and sodium citrate were acquired. The supplier of urea was Loba Chemie in Mumbai, India. Analytical grade materials were utilized throughout. Initially, furosemide's solubility in answers of four hydrotropic go-betweens (Ha) – urea (U), atomic number 11 acetate rayon (A), atomic number 11 benzoate (B), and sodium citrate (C) – was assessed separately using pure water as the solvent at concentrations of 10%, 20%, 30%, and 40% solutions. A 10 mL volumetric flask was filled with precisely measured 3 mL of a specific hydrotropic agent blend, to which extra medication was added, and manually agitated until a saturated solution formed. The solution was allowed to equilibrate for 24 h after the volumetric flask was shaken on a mechanical shaker for 12 h to reach equilibrium solubility. Then, the solution was centrifuged at 2000 rpm for 5 min in an ultra-centrifuge before being filtered using a Whatman 41 filter.[50]

Using a ultraviolet (UV) spectrophotometer set to 333 nm, an aliquot was appropriately diluted with filtered water. Based on

Table 1: MHC C_{max} of individual hydrotropes.

Hydrotropes	Compounds	MHC	C_{max}
Diethyl nicotinamide	Aminonitrobenze	0.5	2.4
Sodium pseudocumene sulfonate	Aminonitrobenze	0.4	2.4
Sodium thiocyanate	Aminonitrobenze	0.3	2.2
Rea	Ethylbenzene	0.50	2.20
Nicotinamide	Ethylbenzene	0.40	2.20
Sodium salicylate	Ethylbenzene	0.30	2.40

MHC: Minimum hydrotropic concentration, C_{max}: Maximum hydrotropic concentration

the findings of the aforementioned research, it was determined that furosemide's solubility increased when hydrotropic agent concentrations grew. For instance, the solubility of furosemide in a 40% urea answer was shown to be significantly advanced than that in 10%, 20%, or 30% urea answers. The solution of 40% sodium benzoate, however, had the highest solubility. Then, various ratios of the aforementioned 4 hydrotropic agents were combined to see if they could improve solubility. The final concentration of hydrotropic go-betweens remained continuously 40% w/v. The mixture U + B + C in the ratio of 15:20:5 provided the best solubility improvement; hence, this enhanced hydrotrope grouping was chosen for the groundwork of rock-hard dispersion.[51]

In the present study, a mixed-hydrotropy approach has been used to improve the drug zaltoprofen's aqueous solubility by creating blends (while maintaining total concentrations of 40% w/v) of chosen water-soluble substances from among the hydrotropes (urea, sodium benzoate, sodium citrate, and nicotinamide); water-soluble solids (polyethylene glycol [PEG]-4000, PEG-6000); and cosolvents (propylene). The drug's aqueous solubility in 12 different blends ranged from 9.091 0.011 mg/mL to 43.055 0.14 mg/mL (as opposed to 0.072 0.012 mg/mL in pure water). The improvement in the drug's solubility in a mixture of solvents contain 10% Na citrate, 5% sodium benzoate, and 25% S cosolvent (25% S cosolvent covers PEG 200, PEG 400, PEG 600, glycerin, and propene glycol) >600 times. This demonstrated a mixed cosolvent effect, which synergistically increased the solubility of a poorly water-soluble medication. Using UV and infrared methods, each solubilized product was evaluated. Surface tension, specific gravity, viscosity, and other solution parameters were investigated. The stability of the developed formula, both chemically and physically, was investigated. For the pharmaceutical sectors, the development of dosage forms for medications that are not very water soluble will unquestionably benefit from this mixed solvency. Stock solution was made by dissolving 10 mg of Ebastine in 10 mL of ethanol, mixing at a vortex mixer for 30 min, and then diluting with ethanol to a final concentration of 100 g/mL in a volumetric flask. In addition, to get the final concentration of 10, 10 mL of the previously prepared solution was taken and diluted up to 100 mL.[52]

ADVANTAGES AND DISADVANTAGES OF MIXED HYDROTROPY

Advantages

- It is the best method since, in this case, pH has no bearing on the solvent character
- This could be really selective
- Emulsification is optional
- By avoiding the use of organic solvent, it avoids the issue of residual solvent toxicity
- This procedure is brand-new, easy, affordable, secure, and environmentally responsible
- Only requires the medication and hydrotropes to be combined in water
- Chemical alterations are not necessary
- Large concentration of hydrotropic agents can be reduced
- Comprehensive formulation, effectiveness and compatibility, low cost, and greener solvent
- Hydrotropy was argued to be superior as a safe, inexpensive, straightforward, accurate, and exact procedure due to their great selectivity over other solubilization techniques
- Mixed hydrotropy prevents the use of an organic solvent to fix the issue
- One of the finest methods for achieving the best criterion is mixed hydrotropy
- Hydrotropy is utilized in science for things such as extraction and separation, for instance
- Some characteristics of hydrotropes, such as strong selectivity, pH-independent solvent character, and absence of emulsification
- Easy recovery of the solute by straightforward dilution from hydrotropes solutions
- The primary advantages of varied hydrotropism comprise the mixture of tablets through letting down the discrete attention that would be real as fine as fewer harmful. Solutions to solubility issues in a wide range of industrial and pharmaceutical applications
- Widespread application in the ever-complex formulations of today
- The primary benefit of the hydrotropic approach is that it does not interfere with the chemical action of the medicinal compounds.

Disadvantages

- Hydrotropic agents may cause toxicity-related issues if they are used excessively
- Drugs and hydrotropic agents may no longer interact as well
- Because water is used as the solvent, it is impossible to completely remove water.

HYDROTROPE SELECTION FOR WATER-SOLUTION DRUGS

The literature review makes it clear that when hydrotrope concentration increases, so does the aqueous solubility

of medications that are not very water soluble. Thus, in the present study, hydrotropic agent solutions that were extremely concentrated were used. Using distilled water, hydrotropic solutions were created. Hydrotropic solutions were used, including 2 M sodium benzoate (2 M SB), 2 M niacinamide (2 M NM), 2 M sodium salicylate (2 M SS), 4 M sodium acetate (4 M SA), 10 M urea (10 M UR), and 1.25 M sodium citrate (1.25 M SC).

The method below (an approximate method for determining solubility) was used to choose appropriate hydrotropes (for a sufficient boost in solubility) for a variety of weakly water-soluble medicines. A 50 mL glass container containing 25 mL of hydrotropic solution and distilled water was filled, and the total weight – including the cap – was recorded. The drug's fine powder was then added to the bottle in a few milligrams (based on visual inspection). The bottle was forcefully shaken (by hand). After the medicine dissolved, more medication – a few milligrams, based on visual inspection – was added to the bottle, and it was shaken ferociously once more. After 10 min of continuous, violent shaking, the same procedure was repeated as long as some extra medicine was not dissolved.

Once more, the gross weight was recorded. Solubility improvement relations (solubility in hydrotropic solution/ solubility in purified aquatic) were computed for all chosen medications for all six variables based on the difference between the two weight measurements, which yielded an approximate solubility. A hydrotropic solution was chosen for a medication when the solubility enhancement ratio was found to be at least 5. 1.0 M calcium disodium edetate solution was used to solubilize benzoic acid, a topical antifungal medication that is somewhat water soluble, using a titrimetric measurement method. Compared to the solubility in distilled water, the aqueous solubility of benzoic acid in 1.0 M calcium disodium edentate solution was enhanced by more than 15 times. Theophylline, a sparingly water-soluble keratolytic medication, can be quantitatively determined in bulk through titrimetric estimates, which was established using 2 M sodium salicylate as a hydrotropic solubilizing agent. Theophylline's aqueous solubility increased by more than 18 times in 2 M sodium.

APPROACHES FOR ASSESSING SOLUBILITY

There are two steps involved in determining a solid's solubility in a liquid:

Soaked answer preparation

The all-out quantity of a chemical that may dissolve in a flush at a specific fever is known as its solubility. A saturated solution is one such as this. The number of moles in 1 L of the solution or grams per 100 g of solvent (g/100 g) is used to measure solubility.

Examining the saturated solution

Following preparation, the saturated solution is analyzed to determine its solubility. It is dependent on the type of solute and how precisely the technique is used. The analytical techniques employed are as follows.

- Evaporation method
- Volumetric approach
- The gravimetric technique
- Instrumental approach.

A NOVEL APPLICATION OF HYDRPTROPIC SOLUBILIZATION IN THE SPECTROPHOTOMETRIC ANALYSIS

Different methods have been used to improve the aqueous solubility of medicines with low water solubility. Such a technique is hydrotropic solubilization. Hydrotropes are a type of chemical substances that modify the aqueous solubility of some solutes that are very slightly soluble in water under normal circumstances. The ability of a medicine to acquire the target concentration in systemic circulation depends on both its bioavailability and, eventually, its solubility. The rate-limiting stage in their absorption and systemic bioavailability is their dissolution from delivery systems due to their low water solubility and high permeability. For the spectrum measurements, a UV/visible spectrophotometer (Model-UV-1700, Shimadzu, Japan) was used. A kind sample of lornoxicam was provided by Pondicherry's Life Care Formulations Pvt. Ltd. The neighborhood pharmacy sold commercial lornoxicam tablets. All other substances, including solvents, were of analytical grade.[52]

In comparison to pure water, the solubility studies' findings showed that lornoxicam's aqueous solubility was improved in a hydrotropic mixed solution of 2 M sodium benzoate. Pure lornoxicam was found to be 0.012 mg/mL soluble in distilled water, whereas it was shown to be roughly 5 mg/mL soluble in 2 M sodium benzoate. There was a >100-fold increase in solubility. To analyze the tablet composition, this method was improved and used. For 24 h, a portion of the solution was held at room temperature to test the drug's stability in the presence of sodium benzoate. As no precipitation was seen, the study found that lornoxicam estimations could be performed within 24 h without having an adverse impact on the drug's stability. According to the results of this study, 2 M sodium benzoate had no effect on the measurement of lornoxicam at 381 nm. Based on this, a wide number of medicines with a max of <250 nm that are weakly water-soluble may be tried for estimate using the suggested method, provided that early solubility investigations show an improvement in solubility

in 2 M sodium benzoate. Since sodium benzoate is more affordable than the majority of organic solvents, it might be a superior alternative to the pricey organic solvents typically employed in pharmaceutical analysis.[53]

A NOVEL APPROACH FOR SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS

The study and development of drugs has a significant impact on the globe and benefits people. The formulation of new chemical entities and the solubilization of poorly soluble medicines present significant challenges in screening tests. Several approaches can be modified to increase the solubility of medications that are not very water soluble. A certain type of molecular event called a hydrotrope container brand medicines that remain just slightly and feebly answerable in aquatic additional answerable. It is possible to define it as incorporating a second solute with the original. High selectivity, non-inflammability, environmental friendliness, accessibility, and cost effectiveness are a few benefits that make the solubilization approach outstanding. Cost, toxicity, and environmental risks are a few drawbacks that this method might have.

Hydrotropic agents that are less expensive can be used to overwhelm this. These existences, hydrotropic substances are utilized to generate amount procedures in a diversity of formats, counting solid dispersion, mouth-dispersing tablets, and injections. These are for enhancing the therapeutic efficiency and bioavailability of medications that are not very water soluble.[54]

HYDROTROPIC SOLUBILIZATION TECHNIQUE NEW PHARMACEUTICAL APPLICATIONS

Quantitative assessments of poorly water-soluble medications using UV visible

Avoiding the use of organic solvents in spectrophotometric analysis. Several organic solvents, including ethanol, methanol, chloroform, acetone, and dimethyl formamide, have been employed to conduct the titrimetric tests for the solubilization of medicines that are poorly water soluble. Utilized organic solvents could have various drawbacks such as greater costs, toxicity, and pollution. For the spectrophotometric assessment of pharmaceuticals that are poorly water soluble, a wide range of organic solvents, including methanol, chloroform, ethanol, dimethyl formamide, benzene, hexane, acetone, and toluene, are frequently utilized. Most organic solvents may have certain negatives, such as toxicity, pricier price tags, and sources of pollution. In addition, because organic solvents are volatile, spectrophotometric estimates may not be accurate. Selected poorly water-soluble medications have their aqueous solubility significantly improved in the presence of high concentrations of hydrotropic agents. We must, therefore, apply hydrotropic solubilization techniques to build novel titrimetric and spectrophotometric approaches for the examination of medicines that are poorly water soluble.

Determining the hydrotropic agent's interaction with drug estimation using spectrophotometry

Spectrophotometric measurements are made using a UV-Visible recording spectrophotometer with 1 cm matched silica cells. Both with distilled water alone and in the presence of the highest concentration of the hydrotropic agent, the absorbance of the standard drug solution is measured for spectrophotometric analysis or for formulation purposes. By doing this, it is possible to determine whether hydrotropic substances interfere with the spectrophotometric estimation of medications.

A regression formula for medications

For this, a medication stock solution is originally made. The prescribed amount of medicine is then dissolved in the proper volume of a concentrated aqueous solution of hydrotropic agents, and the volume is then made up with more water. To create the standard solution, the generated stock solution is further diluted with distilled water to bring the drug concentration within the bounds of Beer's law. These solutions' absorbance values are recorded at maximum against distilled water, which is treated as a blank. To create the regression equation, these standard solution absorbance values are employed.

Applied to the spectrophotometric analysis of medications that are sold as tablets

The weighed 20 commercial tablets into a fine powder. Transfer a precisely weighed amount of tablet powder (equal to the amount of medication required to obtain the regression equation) to a 25 mL volumetric flask. The volume of a concentrated hydrotropic agent's aqueous solution was then added to this to solubilize the medication present. After roughly 10 min of shaking, the flask is filled to the appropriate level with distilled water. Filtration is carried out using Whatman filter paper number 41 after the mixture of the components.

Apply in titrimetric analysis for the quantitative evaluation of medications that are weakly water soluble

Costlier organic solvents are more frequently used to solubilize the weakly water-soluble medicines in titrimetric

examination. Such solvents have problems such as volatility and contamination. There are several methods to improve the aqueous solubility of weakly prescription medications that dissolve in water. The hydrotropic solubilization phenomenon has been extensively employed to increase the aqueous solubility of pharmaceuticals with poor water solubility.

Drugs that are weakly water soluble are prepared as hydrotropic solid dispersions

Solid dispersion made by solvent evaporation, solvent fusion, or solvent melting of one or more active medicinal components in an inert and non-toxic carrier matrix. Most medications with low water solubility will have lower dissolving rates, and those with low membrane permeability will have incomplete absorption and penetration rate-limited absorption. Prescription drugs are soluble in water. Pharmaceuticals with poor water solubility have been made more aqueous soluble through the broad use of the hydrotropic solubilization phenomena.

Employed as solubilizing agents in pharmaceutical formulations

Hydrotropes have been utilized to prepare ternezapam formulations and stable the formulation through lyophilization. The formulations of the cardiac vasodilator medication nifedipine more recently included hydrotropes. Instead of acting as an emulsion or multiphase solution in these situations, the hydrotropes is to operate as a non-toxic carrier that solubilizes and maintains the medication in a stable homogenous phase. It has been demonstrated that administering hydrotropes with the medication theophylline and the hormone insulin improves their absorption in laboratory animals. Drugs delivered by transdermal distribution have also been discovered to work well in hydrotropes as a vehicle.[55]

Applications relating to biology

Both the increased antibacterial activity of cresols in hydrophobic solutions and the impact of hydrotropes on the activity of the enzymes dehydrogenases have been documented. Some hydrotropes have the ability to hemolysis human erythrocytes. Sahel *et al*. discovered that the hydrotrope Na benzoate has an impact on the structure of hemoglobin. This was a result of the hydrotropic salts' impact on the Fehistidine bond's water structure. The hydrotrope aspirin's anti-inflammatory properties have been related to its suppression of prostaglandin production.

- By forbidding topical solution formulation using organic solvents
- Injecting a medication formulation with low water solubility
- Employed as permeation boosters
- Poorly water-soluble medications can be quickly released from suppositories through hydrotropy
- Injectable dose forms of medications with low water solubility can be created using mixed hydrotropy.
- They have uses in nanotechnology,
- Use in the process of separating crude medicines' active ingredients
- Attempts were made to create fluids for dissolving tests of dose forms of medicines with low water solubility.

Artificial neuronal applications

The determination and prediction of the quantitative assessment of various hydrotrope physicochemical parameters in the pharmaceutical sciences rely on artificial neuronal networks (ANN), computer models created by the application of machine learning. To apply the hydrotrope-enhanced property, utilize a computer model, and anticipate using ANNs to ascertain how hydrotropes contribute to the improvement of drug solubility in water.[56]

DIFFERENT PERSPECTIVES OF HYDROTROPY

Mckee's point of view

By 1946, Mckee was by means of hydrotropism in biochemical manufacturing and other manufacturing settings. He established that unbiased carbon-based acid soluble neutral salts such as atomic number 11 benzoate (NaB), salicylate (NaS), benzene sulfonate (NaBS), toluene sulfonate (NaPTS), xylene sulfonate (NaXs), and cumene sulfonate (NaCS) upsurge the solubility of numerous carbon-based and mineral mixes in aquatic. In contrast to the previous theories put forth by Neuberg and others, who believed that only organic chemicals could act as hydrotropes, Mckee proposes that some inorganic compounds might also be added to the hydrotropes class. These include alkali iodides, thiocyanates, oxalates, and bicarbonates, to name a few. However, as of late, inorganic salts are no longer considered to be hydrotropes. McKee, however, highlighted a few crucial aspects of hydrotropy. He mentioned how most hydrotropic solutions precipitate the solubilizate on water dilution. The hydrotrope can then be recovered and used in other ways. NaXS is particularly helpful in the production of paper pulp since it seems to be fewer luxurious than the standard basic procedure.[57] Mckee lastly reached two crucial deductions on hydrotropy, which are as shadows:

- It takes a rather high concentration of hydrotrope in water for it to work, and the effect resembles "salting in" in two ways
- According to Mckee, the idea of mixed solvents can be used to explain the occurrence of hydrotropy.

Booth and Everson's perspective

They solubilized a range of compounds, including aliphatic and aromatic hydrocarbons, alcohols, ethers, and phenols, using a 40% NaXS solution in water. Oils, aldehydes, ketones, amines, and so forth also discovered that this solvent was a great hydrotrope. They also contrasted the abilities of the ortho, para, and meta isomers of xylene sulfonate toward many different hydrophobic substances and it was noticed that all three isomers exhibit similar hydrotropic efficacy. Nevertheless, the meta isomer is preferred at reduced temperature as a result of its higher water solubility. The xylene is one of them. Sulfonate appears to have the most solubilizing power. As they grow, the agent is having a high hydrotrope concentration. Both linear and non-linear increases in solubility monotone which yet exhibits a sigmoidal behavior.[27]

View from Winsor

In 1948, Winsor attempted to connect solubilization and emulsification to hydrotropic activity. He experimental that a hydrotropic reasons the mutual solubilization of organic and aqueous liquids and thought hydrotropism were very close to solvency.

Licht and Weiner's view

The symmetry solubility information for the water-hydrotrope benzoic cutting scheme at 30, 40, and 60° Celsius was got for these writers. In instruction to appearance at the inspiration of resemblance in construction amid the solute and the hydrotropism, solubility data were got with the six dissimilar hydrotropes. They, the instruction of lessening efficiency is as follows:

Na p-cymenesulfonate > o-xylenesulfonate > m-xylenesulfonate > pbromobenzenesulfonate > ptoluenesulfonate > benzenesulfonate.

Their clarification of these consequences was that the augmented solubility is due to "salting in" result somewhat than due to resemblance in construction. Their opinion of hydrotropic therefore decides by that of Mckee.[58]

LIPOPHILIC DRUG SOLUBILIZATION

When two or more hydrotropic agents are used, the toxicity and concentration of the single hydrotropic agent are decreased. This is known as mixed hydrotropy. The notion of mixed solvency postulated that all substances, whether they be solid, liquid, or gas, had the ability to dissolve. For some substances, they can be solvents while they are not. Liquid carbon dioxide gas is liquefied in supercritical fluid technology to create nanoparticles by acting as a solvent. The solubilizing ability of solids is demonstrated by numerous examples. Using the right solubilizes can turn any weak solvent into a powerful solvent.[59,60] By adding the right additive to increase solubility, it might significantly reduce the amount of solubilizing agents needed, which may help prevent solubilizer-related safety concerns. This method can be used to manufacture the poorly soluble medication in various dose forms. In addition to being useful for developing novel drug delivery systems employing safer solvents instead of hazardous, polluting organic solvents, the mixed solvency technique can be used to undertake titrimetric and spectrophotometric studies. Numerous analytical techniques, including titrimetric, spectrophotometric, thin-layer chromatography, and high-performance liquid chromatography analysis, have effectively used the aforementioned concepts.

A formulation that enables solubility based on hydrotropes has the potential to significantly boost water solubility while also decreasing intestinal permeability. Therefore, it is advisable to consider permeability in addition to solubility when employing hydrotropic drug solubilization. Reaching the ideal balance between permeability and solubility could advance the formulation's overarching objective of maximizing drug exposure after oral delivery.[60]

In today's biopharmaceutics, low water mobility is a big concern. Although hydrotropy may help make a lipophilic medicine appear more soluble, its impact on the drug's permeability has not yet been studied throughout the solubilization process.[21] The evaluation of the interaction between solubility and permeability in lipophilic drug formulations that use hydrotropy to enhance solubility was the main goal of this investigation. It turned out that hydrotropy is linked to a solubility – penetrability compromise phenomena, which implies that the solubility increase provided by the formulation carries the "price" of concurrent permeability loss, just like cyclodextrins, surfactants, the and cosolvents, but not Amorphous solid dispersions (ASD) preparations. This discovery has a substantial impact on the application of hydrotropic drug solubilization since it makes evident that the solubility-permeability interaction must be taken into consideration when developing formulations; maximum solubility alone is insufficient; instead, the ideal solubility-permeability balance must be achieved to optimize oral drug absorption in its entirety.[61,62]

In earlier research, we identified a basic mechanistic cause for the solubility – permeability interplay; super saturation, which is attained by ASD formulation, is a non-equilibrium/kinetic rise in the drug's apparent solubility, whereas the drug's equilibrium aqueous solubility is altered by cyclodextrins, surfactants, and cosolvents-based solubilization. The solubility–permeability tradeoff achieved with cyclodextrins, surfactants, and cosolvents is due to the fact that increased equilibrium solubility naturally reduces the drug's partitioning and overall permeability since the drug's equilibrium aqueous solubility panels the state membrane/aqueous divide coefficients, which, in turn, controls the drug's (passive) intestinal permeability.[63] The solubility–permeability tradeoff

is avoided, however, by ASD formulations that enable the achievement and maintenance of super saturation, a non-equilibrium rise in the drug's apparent solubility, which does not impact the drug's partitioning or permeability. This analysis draws attention to the fact that the results given in this article unmistakably show that the process responsible for hydrotropic solubilization of drugs includes altering the drug's equilibrium water solubility. This discovery might advance our knowledge of hydrotropic solubility of medicines in general since the precise mechanism underlying hydrotropy is still under investigation.[64,65] Hydrocarbon fragments and an ionic moiety make up the primary structural features of hydrotropes. Hydrotropic drug solubilization is thought to be aided by its amphiphilic molecular structure. It is believed that a stacking mechanism causes the hydrotrope molecules to self-aggregate in a way that is similar to surfactants. Hydrotrope self-aggregation may not be as important as micellar solubilization, though, as the influence of hydrotropy on surface tension and other parameters was found to differ significantly from surfactants. Hydrotropy has also been proposed to be caused by altering the solvent's capacity to join structure formation by intermolecular hydrogen bonding; however, the significance of this process has also been questioned by current enthalpy calculations.[66] Hydrotrope molecules are thought to fit around the solute and increase its susceptibility to solvation. This mechanism may not involve a direct mutual attraction between the drug and the hydrotrope, but rather an interaction to reduce the solute's contact with water. In summary, the potent hydrotropic drug solubilization is probably the result of several mechanisms working together rather than a single central process. The improvement in biphasic solubility with urea was observed. Despite using a relatively simple prediction method, there was a good agreement amid the new permeability data and the anticipated values for composed *in vitro* and *in vivo* scenarios.[67] We have previously demonstrated that this simplified approach might not be enough to allow for this level of prediction in situations where the unstirred marine coating (UWL) next to the duodenal divider theatres a noteworthy part as an preoccupation fence for lipotropic medications. Instead, a more complex quasi-equilibrium transport analysis might be required. Since the UWL for carbamazepine does not function as a major penetration barrier.[68]

CONCLUSION

In-depth descriptions of the many methods by which hydrotropes function to improve the solubility of a chemical with low aqueous solubility as well as their benefits and drawbacks are provided in this review. This method not only made it possible to develop dosages for medications that were not very water-soluble, but it also improved the extraction of potentially useful phytoconstituents. Due to their role as green solvents that are less polluting, economical, and environmentally friendly than organic solvents, hydrotrope method has the potential to replace important conventional techniques used in the pharmaceutical industry.[69] During the isolation, separation, and characterization of compounds, this technique can be utilized to substitute organic solvents and increase the percent yield of the constituents, as discussed in the field of pharmacognosy. Similar to how it improved water solubility in pharmaceutics, this approach improved the bioavailability of poorly soluble synthesized and isolated molecules. This review outlines the use of hydrotropes in numerous scientific fields and in-depth explores the suggested processes of hydrotropic agents. The studies mentioned above highlight the importance of using hydrotropes in the field of pharmaceutics for advancements in hydrotropy, particularly in drug formulation by utilizing a hydrotropic agent toward the development of solubility of poorly water-soluble pharmaceuticals to enhanced therapeutic delivery.

However, there are still many issues with mechanisms of hydrotropes, and they are still up for debate. The fundamental strategy involves a hydrotropic agent's interaction with a medication that is poorly water soluble, increasing both solubility and bioavailability. Hydrotropic method can replace the usage of organic solvents, according to numerous experimental studies. This technology is both secure and environmentally beneficial.

REFERENCES

1. Maheshwari RK. A novel application of hydrotropic solubilization in the analysis of bulk samples of ketoprofen and salicylic acid. Asian J Chem 2006;18:393-6.
2. Maheshwari RK. New application of hydrotropic solubilization in the spectrophotometric estimation of ketoprofen in tablet dosage form. Pharma Rev 2005;18:123-5.
3. Maheshwari RK. Application of hydrotropic solubilization in the analysis of aceclofenac. Asian J Chem 2006;18:1572-4.
4. Maheshwari RK. Analysis of frusemide by application of hydrotropic solubilization phenomenon. Indian Pharm 2005;34:55-8.
5. Maheshwari RK. Spectrophotometric determination of cefixime in tablets by hydrotropic solubilization phenomenon. Indian Pharm 2005;36:63-8.
6. Maheshwari RK. Novel application of hydrotropic solubilization in the spectrophotometric analysis of tinidazole in dosage form. Asian J Chem 2006;18:640-4.
7. Maheshwari RK. Spectrophotometric analysis of amoxycillin in tablets using hydrotropic solubilization technique. Asian J Chem 2006;18:3194-6.
8. Tarongoy FM Jr., Haddad PR, Boysen RI, Hearn MT, Quirino JP. Open tubular-capillary electrochromatography: Developments and applications from 2013 to 2015. Electrophoresis 2016;37:66-85.
9. Cheong WJ, Ali, F, Kim YS, Lee JW. Comprehensive overview of recent preparation and application trends

of various open tubular capillary columns in separation science. J Chromatogr A 2013;1308:1-24.
10. Tarongoy FM Jr., Haddad PR, Quirino JP. Recent developments in open tubular capillary electrochromatography from 2016 to 2017. Electrophoresis 2018;39:34-52.
11. Zhong H, Rassi ZE. Neutral polar methacrylate-based monoliths for normal phase nano-LC and CEC of polar species including N-glycans. J Sep Sci 2009;32:10-20.
12. Xu Y, Cao Q, Svec F, Fréchet JM. Porous polymer monolithic column with surface-bound gold nanoparticles for the capture and separation of cysteine-containing peptides. Anal Chem 2010; 82:3352-8.
13. Puangpila C, Nhujak T, Rassi ZE. Investigation of neutral monolithic capillary columns with varying n-Alkyl chain lengths in capillary electrochromatography. Electrophoresis 2012;33:1431-42.
14. Bilia AR, Bergonzi MC, Guccione C, Manconi M, Fadda AM, Sinico C. Vesicles and micelles: Two versatile vectors for the delivery of natural products. J Drug Deliv Sci Technol 2016;32:241-55.
15. Sharma R, Kamal A, Abdinejad M, Mahajan RK, Kraatz HB. Advances in the synthesis, molecular architectures and potential applications of Gemini surfactants. Adv Colloid Interface Sci 2017;248:35-68.
16. Parshad B, Kumari M, Khatri V, Rajeshwari R, Pan Y, Sharma AK, *et al*. Enzymatic synthesis of glycerol, azido-glycerol and azido-triglycerol based amphiphilic copolymers and their relevance as nanocarriers: A review. Eur Polym J 2021;158:110690.
17. McKee RH. Use of hydrotropic solutions in industry. Ind Eng Chem 1946;38:382-4.
18. Dhapte V, Mehta P. Advances in hydrotropic solutions: An updated review. St Petersburg Polytech Univ J Phys Math 2015;1:424-35.
19. Pandit A, Sharma MM. Intensification of heterogeneous reactions through hydrotropy: Alkaline hydrolysis of esters and oximation of cyclododecanone. Chem Eng Sci 1987;42:2517-23.
20. Kumar CJ, Gandhi NN. Hydrotropic study on furfural - Comprehensive design expert plot. Mod Appl Sci 2009;3:117-29.
21. Da Silva RC, Spitzer M, Da Silva LH, Loh W. Investigations on the mechanism of aqueous solubility increase caused by some hydrotropes. Thermochima Acta 1999;328:161-7.
22. Kate BA, Phulzalke SB, Deshmukh MT. Solubility enhancement of poorly water soluble drug zaltoprofen by mixed hydrotropy approach. Asian J Biomed Pharm Sci 2016;6:32-9.
23. Khan ZA. Effect of various cationic hydrotropes on association behaviour of imipramine hydrochloride at different temperatures. J Mol Liq 2019;281:333-43.
24. Yan C, Sagisaka M, James C, Rogers SE, Peach J, Eastoe J. Action of hydrotropes in water-in-CO_2 microemulsions. Colloids Surf A Physicochem Eng Asp 2015;476:76-82.
25. Madan JR, Pawar KT, Dua K. Solubility enhancement studies on lurasidone hydrochloride using mixed hydrotropy. Int J Pharm Investig 2015;5:114-20.
26. Ujwala K, Babu PR. Solubility enhancement of paroxetine hydrochloride by hydrotropy. Indian J Pharm Sci 2017;79:591-8.
27. Ghogare D, Patil S. Hydrotropic solubilization: Tool for eco-friendly analysis. Int J Pharm Pharm Res 2018;11:300-22.
28. Das S, Paul S. Computer simulation studies of the mechanism of hydrotrope-assisted solubilization of a sparingly soluble drug molecule. J Phys Chem B 2016;120:3540-50.
29. Booth JJ, Abbott S, Shimizu S. Mechanism of hydrophobic drug solubilization by small molecule hydrotropes. J Phys Chem B 2012;116:14915-21.
30. Das S, Paul S. Mechanism of hydrotropic action of hydrotrope sodium cumene sulfonate on the solubility of Di-t-Butyl-methane: A molecular dynamics simulation study. J Phys Chem B 2016;120:173-83.
31. Morais AB, Jayakumar C, Gandhi NN. Hydrotropic effect and thermodynamic analysis on the solubility and mass transfer coefficient enhancement of ethylbenzene. Korean J Chem Eng 2013;30:925-30.
32. Bauduin P, Renoncourt A, Kopf A, Touraud D, Kunz W. Unified concept of solubilization in water by hydrotropes and cosolvents. Langmuir 2005;21:6769-75.
33. Chikhle H, Pandey V, Ganeshpurkar A, Dubey N, Bansal D. Solubility enhancement of carvedilol using mixed hydrotropy. Asian J Biomater Res 2016;2:62-5.
34. Damiati SA, Martini LG, Smith NW, Lawrence JM, Barlow DJ. Application of machine learning in prediction of hydrotrope-enhanced solubilisation of indomethacin. Int J Pharm 2017;530:99-106.
35. Maheshwari RK, Deswal S, Tiwari D, Ali N, Pothen B, Jain S. Novel spectrophotometric estimation of frusemide using hydrotropic solubilization phenomenon. Indian J Pharm Sci 2007;69:822-4.
36. Maheshwari RK, Deswal S, Aher R, Wanare G, Jawade S, Indurkhya A, Jagwani Y. Ibuprofen sodium: A novel hydrotropic agent for estimation of poorly water soluble drugs. J Appl Chem Res 2009;10:56-60.
37. Maheshwari RK, Sharma S, Rai N, Rajput M. Simple titrimetric method to estimate ketoprofen in bulk using mixed hydrotropy. J Pharm Res 2010;3:442-3.
38. Shukla RS, Patel A, Soni ML, Modi V, Jaliwala YA. Quantitative spectrophotometric estimation of cefadroxil using hydrotropic solubilization technique. Asian J Pharm 2008;2:146-7.
39. Revathi R, Ethiraj T, Saravanan VS, Ganeshan V, Saranya V, Sengottuvel T. New spectroscopic determination of nifedipine using hydrotropic Solubilization. Int J Pharm Sci 2010;2:74-6.
40. Poochikian GK, Cradock JC. Enhanced chartreusin solubility by hydroxybenzoate hydrotropy. J Pharm Sci 1979;68:728-9.
41. Friberg E, Brancewicz C. O/W Microemulsions and

hydrotropes: The coupling action of a hydrotrope. Langmuir 1994;10:2945-9.
42. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. Int J Pharm Sci Rev Res 2010;5:41-51.
43. Majeed A, Raza SN, Ahmad Khan N. Hydrotropy: Novel solubility enhancement technique: A review. Int J Sci Prog Res 2019;10:1025-36.
44. Maheshwari RK, Lakkadwala S, Vyas R, Ghode, P. Spectrophotometric determination of naproxen tablets using niacinamide as hydrotropic solubilizing additive. J Curr Pharm Res 2010;4:11-4.
45. Sable PN, Chaulang GM, Bhosale AV, Chaudhari PD. Novel spectrophotometric estimation of olanzepine using hydrotropic solubilizing agent. Res J Pharm Technol 2009;2:297-300.
46. Banerjee T, Banerjee B, Jain P, Shukla G, Banerjee A. Spectrophotometric estimation of lornoxicam and paracetamol tablet dosage form using hydrotropic solubilizing agent. Int J ChemTech Res 2012;4:232-9.
47. Mamata NG, Smita SA, Ravindra BS. Mixed hydrotropy technique for solubility enhancement- A review. Int J Inst Pharm Life Sci 2015:442-452.
48. Neha S, Sania ZS. Hydrotropy. Int J Pharm Pharm Res 2011;2:471-81.
49. Ashwini EP, Shila VD, Manoj MB, Shashikant DB. A review on novel solubility enhancement technique. Indo Am J Pharm Res 2013;3:4670-9.
50. Jain P, Goel A, Sharma S, Parmar M. Solubility enhancement techniques with special emphasis on hydrotropy. Int J Pharma Prof Res 2010;1:34-45.
51. Pareek V, Tambe S, Bhalerao S, Shinde R, Gupta L. Spectrophotometric estimation of cefprozil by using different hydrotropic agents. Int J Pharm Pharm Sci 2010;2:82-7.
52. Maheshwari RK. Analytical Techniques Using Hydrotropic Solubilization [Thesis]. Indore: Department of Pharmacy, Shri G.S., Institute of Technology and Science; 2008. p. 61-2.
53. Jain N, Jain R, Thakur N, Gupta B, Banweer J, Jain S. Novel spectrophotometric quantitative estimation of hydrochlorothiazide in bulk drug and their dosage forms by using hydrotropic agent. Int J Appl Pharm 2010;2:1114.
54. Sharma R, Pathodiya G, Mishra PG. A novel application of hydrotropic solubilization in development and validation of spectrophotometric method for simultaneous estimation of paracetamol and diclofenac sodium in solid dosage form. Int J Pharma Bio Sci 2010;1:1-9.
55. Jayakumar C, Deepak Kumar K, Nesakumar D, Gandhi NN. Quantitative analysis of theophylline bulk sample using sodium salicylate hydrotrope. Int J Pharm Pharm Sci 2010;2:80-1.
56. Choudhary G, Horvath C. Dynamics of capillary electrochromatography experimental study on the electrosmotic flow and conductance in open and packed capillaries. J Chromatogr A 1997;781:161-83.
57. Masthannamma SK, Naik BS, Kumar TA, Sridhar A. UV- Spectrophotometric determination of ofloxacin in bulk and pharmaceutical dosage form using hydrotropic solubilization technique (1 M Piperazine). Int J Pharm Technol 2015;6:7658-68.
58. Coffman RE, Kildsig DO. Effect of nicotinamide and urea on the solubility of riboflavin in various solvents. J Pharm Sci 1996a;85:951-4.
59. Coffman RE, Kildsig DO. Hydrotropic solubilization--mechanistic studies. Pharm Res 1996b;13:1460-3.
60. Cui Y, Xing C, Ran Y. Molecular dynamics simulations of hydrotropic solubilization and self-aggregation of nicotinamide. J Pharm Sci 2010;99:3048-59.
61. Dahan A, Beig A, Ioffe-Dahan V, Agbaria R, Miller J. The twofold advantage of the amorphous form as an oral drug delivery practice for lipophilic compounds: Increased apparent solubility and drug flux through the intestinal membrane. AAPS J 2013a;15:347-53.
62. Shimizu S, Booth JJ, Abbott S. Hydrotropy: Binding models vs. Statistical thermodynamics. Phys Chem Chem Phys 2013;15:20625-32.
63. Sun J, Dahan A, Amidon GL. Enhancing the intestinal absorption of molecules containing the polar guanidino functionality: A double-targeted prodrug approach. J Med Chem 2009;53:624-32.
64. Varghese Gupta S, Gupta D, Sun J, Dahan A, Tsume Y, Hilfinger J, *et al*. Enhancing the intestinal membrane permeability of zanamivir: A carrier mediated prodrug approach. Mol Pharm 2011;8:2358-67.
65. Wolk O, Agbaria R, Dahan A. Provisional *in-silico* biopharmaceutics classification (BCS) to guide oral drug product development. Drug Des Dev Ther 2014;8:1563-75.
66. Zur M, Cohen N, Agbaria R, Dahan A. The biopharmaceutics of successful controlled release drug product: Segmental-dependent permeability of glipizide vs. Metoprolol throughout the intestinal tract. Int J Pharm 2015;489:304-10.
67. Zur M, Gasparini M, Wolk O, Amidon GL, Dahan A. The low/high BCS permeability class boundary: Physicochemical comparison of metoprolol and labetalol. Mol Pharm 2014a;11:1707-14.
68. Zur M, Hanson AS, Dahan A. The complexity of intestinal permeability: Assigning the correct BCS classification through careful data interpretation. Eur J Pharm Sci 2014b;61:11-7.
69. Telange, D. R., Bhaktani, N. M., Hemke, A. T., Pethe, A. M., Agrawal, S. S., Rarokar, N. R., & Jain, S. P. Development and characterization of pentaerythritol-EudragitRS100 co-processed excipients as solid dispersion carriers for enhanced aqueous solubility, in vitro dissolution, and ex vivo permeation of atorvastatin. ACS omega 2023; 8(28):25195-25208.

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