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THE HYDROTROPIC EFFECT: A NOVEL STRATEGY FOR ENHANCED BIOAVAILABILITY

P. R. Gawandar * and K. R. Biyani

Department of Pharmaceutics, Anuradha College of Pharmacy, Buldana - 443201, Maharashtra, India.

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Correspondence to Author:
Ms. P. R. Gawandar

Assistant Professor,
Department of Pharmaceutics,
Anuradha College of Pharmacy,
Buldana - 443201, Maharashtra, India.

E-mail: poojagawandarsaj@gmail.com

ABSTRACT: Several techniques were applicable to increase the aqueous solubility's of poorly water-soluble drugs. Hydrotropy technique is one of them. In the present study, the hydrotropic agent has been used as a Solubilizing agent to solubilize BCS Class-II drugs that is poorly water-soluble drugs. Hydrotropy is an increase in the solubility of a solute in water by adding an agent termed hydrotrope. Increasing the solubility of various drugs in water is a very important aspect of hydrotropy. Various formulations need some substances or drugs to solubilize in water. Also, it is very important to analyze the drug formulations. Hydrotropy can be incorporated with spectrophotometric and chromatographic analysis for accurate, rapid, easy and precise analysis. The hydrotropic agent did not interfere with spectrophotometric determination. Most of the investigations concluded that hydrotropy was the most efficient tool for solubility enhancement. Solubility enhancement over 100-fold was observed in some investigations. Hydrotropic agents possess high industrial demand. This review article also highlights the applications and future prospects with the employment of hydrotropes and hydrotropic agents in modified drug delivery or parental delivery systems to enhance solubility profile the drugs are also discussed.

INTRODUCTION: Pharmaceutical Science and high throughput screening techniques have been employed by pharmaceutical industries to hasten their drug discovery and development processes. These techniques have enabled to synthesis and qualify of a very huge number of compounds per day. As a result, a huge number of new chemical entities or potential drug candidates are introduced or discovered for a particular therapeutic activity. However, that is not the end of the process, as further drug development process encounters several challenges. Among these are solubility, permeability, stability, safety, efficacy, *etc*. [5] The Indian Pharmacopoeia and US Pharmacopoeia consist of more than one-third of poorly water-soluble or water-insoluble drugs.

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The main reason behind the failure of new drug development is the poor physicochemical properties like water insolubility. One of the most important physicochemical properties of drug development is solubility [1]. Many of the newly developed drug molecules have a nature like lipophilicity and poor solubility. For the solubilization phenomenon of these poorly water-soluble drugs various organic solvents like methanol, chloroform, dimethyl formamide, and acetonitrile are used. But the use of these organic solvents Solubility is an intrinsic property of any formulation, i.e. properties of active compound can be improved by internal modification *i.e.* by complexation of poorly soluble drugs with the water-soluble carrier.

On the other hand, dissolution is an extrinsic property of drug product, wherein properties or nature of active compound can be enhanced by external modification i.e. by size reduction, due to which the effective surface area of the active component will be increased and enables more time

of contact with intestinal fluids for better absorption of the drug. The solubility of a drug product can be defined both quantitatively and qualitatively. Quantitative solubility is defined as the milligram of solute particles required to make a saturated solution. Qualitative solubility is defined as where two phases are mixed to form a homogenous solution [3].

The newly developed active compound shifted towards higher molecular weight and the lipophilicity of the compound increased, this resulted in a decrease in the aqueous solubility of the compound. There are some aspects where active compounds possess low solubility. These above-mentioned aspects are referred to as the Lipinski rule, which demonstrates active compounds as non-aqueous or poorly aqueous soluble. Solubility of the drug substance can be altered on two levels either through material engineering of the drug substance or through formulation approaches. Besides aqueous solubility, permeability is another critical aspect of oral bioavailability. The Biopharmaceutical Classification System (BCS) was introduced in the mid-1990s to classify drug substances concerning their aqueous solubility and membrane permeability. Biopharmaceutics Classification System (BCS) has provided a mechanistic framework for understanding the concept of drug absorption in terms of permeability and solubility [1].

Hydrotropy: Therefore, a safe eco-friendly, cost-effective solvent known as a hydrotropic agent can be used. Hydrotropy was first reported by Neuberg (1916). The solubilization phenomenon whereby the addition of a large amount of a second solute increases the aqueous solubility of another solute is called hydrotropy. Some of the examples include concentrated aqueous hydrotropic solution of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate [3].

Hydrotropy is a solubilization process, whereby increasing the concentration of the second solute, the hydrotropic operator brings about an expansion in the fluid solvency of the first solute. Hydrotropic agents are ionic natural salts and comprise antacid metal salts of different natural acids. Added substances or salts that expand dissolvability in a given dissolvable are said to "salt in" the solute and those salts that lessen solvency "salt out" the solute. A few salts with huge anions or cations that are themselves solvent in water bring about "salting in" of nonelectrolytes called "hydrotropic salts"; a wonder known as "hydrotropism." Hydrotropy assigns the increased dissolution in water because of the nearness of enormous measure of added substances.

The instrument by which it improves dissolvability is all the more firmly identified with complexation including a powerless connection between the hydrotropic agents such as sodium benzoate, sodium acetic acid derivation, sodium alginate, urea, and the ineffectively solvent medications. Hydrotropy is a developing ground-breaking drug solubilization procedure that has appeared to fundamentally improve the dissolvability of numerous medications. Hydrotropy alludes to the procedure by which a lot of solutes improve the dissolvability of another compound.

They are as often as possible anionic sweet smelling and non-sweet-smelling mixes and can be once in a while impartial. The hydrotropes are known to self-collect in the arrangement. The order of hydrotropes based on the atomic structure is troublesome since a wide assortment of mixes has been accounted for to show hydrotropic conduct. Some models may incorporate ethanol, sweet-smelling alcohols such as resorcinol, pyrogallol, catechol, α and β-naphthols and salicylates, and alkaloids such as caffeine and nicotine, and ionic surfactants such as diacids, sodium dodecyl sulfate, and dodecyl oxybenzone. The fragrant hydrotropes with anionic head gatherings are for the most part contemplated mixes. They are enormous in number because of isomerism, and their successful hydrotrope activity might be due to the accessibility of the intuitive pi (π) orbital.

Hydrotropic Agent: The hydrotropic agents are non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of insoluble solubilizing compounds. The chemical structure of the conventional Neuberg‟s hydrotropic salts (prototype sodium benzoate) usually consist of two essential parts, an anionic group, and a hydrophobic aromatic ring or ring system. The anionic organization is concerned in bringing approximately excessive aqueous solubility, that is

a prerequisite for a hydrotropic substance. The sort of anion or steel ion regarded to have a minor impact at the phenomenon. On the other side, the planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization. Additives or salts that growth the solubility in a given solvent are stated to "salt in" the solute and salts that lower the solubility "salt out" the solute. Several salts with big anions or cations which might be themselves very soluble in waterend result in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon acknowledged as "hydrotropism". Hydrotropic answers do not display colloidal houses and contain a vulnerable interplay among the hydrotropic agent and solute [6]. The **Fig. 1** indicate the structure of hydrotropic agent.

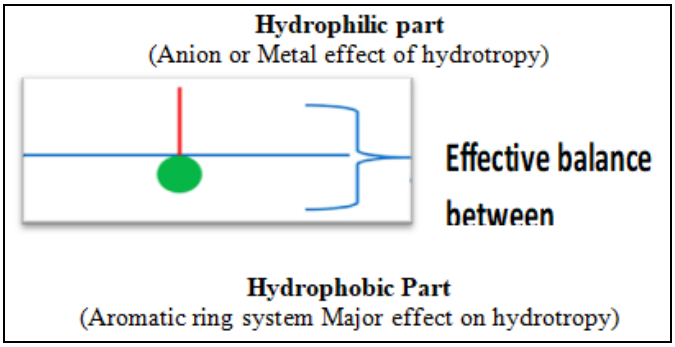

FIG. 1: THE STRUCTURE OF A HYDROTROPIC AGENT

Readiness of Hydrotropes: Hydrotropes are created by sulfonation of a fragrant hydrocarbon dissolvable (i.e., toluene, xylene, or cumene). The subsequent fragrant sulfonic corrosive is killed utilizing a fitting base (e.g., sodium hydroxide) to create the sulfonate or hydrotropic agent. The hydrotropes are "unadulterated" substances yet are delivered and moved in either fluid arrangements, normally at a 30–60 % degree of action, or in granular solids commonly at a 90–95% degree of action. Different segments of granular solids incorporate sodium sulfate and water. Fluid items are created in a shut framework. Granular hydrotropes item is created by shower drying that incorporates source control and residue accumulation. Hydrotropes are made for use and are not utilized as intermediates/subordinates for further compound assembling procedures or employments. A hydrotropic agent is an intensity that solubilizes hydrophobic mixes in watery arrangements. Ordinarily, hydrotropes comprise a hydrophilic part and a hydrophobic part (like surfactants), yet the hydrophobic part is commonly too little to even consider causing unconstrained self-conglomeration [2].

Different Perspectives of Hydrotropy [11]: The progress in hydrotropy has boosted their application in various operational fields. Specifically, the utilization of hydrotropic compounds has been increasingly recognized in formulation development. Various experimental studies have confirmed their solubility parameter is potential along with a non-toxic, non-flammable eco-friendly nature. However, many challenges remain with respect to their structure-based mechanism. When progress in hydrotropy as well as novel drug delivery approaches catch up with contest, hydrotropic mechanisms, stability in biological solutions, biocompatibility and enhanced efficacy along with delivery techniques will be one step closer to reality.

Mckee's View: Mckee makes use of hydrotropes for chemical engineering and commercial packages via way of means of the yr 1946.He confirmed that focused aqueous answers of soluble impartial salts of natural acids together with sodium benzoate (NaB), salicylate (NaS), benzenesulfonate (NaBS), p-toluene sulfonate (NaPTS), xylene sulfonate (NaXs) and cumene sulfonate (NaCS) increase the solubility of various organic and inorganic compounds in water. The in advance perspectives of Neuberg and others, who taken into consideration simplest natural compounds to characteristic as hydrotropes, in contrast to this Mckee shows that even a number of the inorganic materials can be introduced to the magnificence of hydrotropes. Some of these are alkali iodides, thiocyanates, oxalates, and bicarbonates. But the latest exercise is that inorganic salts aren't blanketed withinside the class of hydrotropes. In any event, Mckee introduced a few essential capabilities of hydrotropy. He referred to that maximum hydrotropic answers precipitate the solubilizers on dilution with water. This helps in recovering the hydrotrope for further use. NaXS may be very beneficial withinside the paper pulp production system as it seems to be much less pricey than the commonplace alkaline system.

Finally, Mckee arrived at two important conclusions about hydrotropy as follows:

- ✓ A instead huge attention of the hydrotrope in water is needed for it to show its motion and
- ✓ The phenomenon is similar to the "salting in" process. According to Mckee, the phenomenon of hydrotropy will be defined primarily based totally at the idea of combined solvents [11, 31-33].

Booth and Everson's View: They used 40% NaXS answer in water to solubilize a variety of substances such as aliphatic and aromatic hydrocarbons, alcohols, ethers, aldehydes, ketones, amines, oils, and so on. Also determined this solvent to be a splendid hydrotropic agent. They also compared the solubilizing ability of the ortho, para, and meta isomers of the xylene sulfonate towards a variety of hydrophobic substances and observed that all three isomers exhibit comparable hydrotropic efficiency. However, the meta isomer is preferable at a lower temperature due to its higher water solubility. Among them, xylene sulfonate appears to have the maximum solubilizing ability. With increasing hydrotrope concentration, the agent having increased solubility is neither linear nor monotonic but displays a sigmoidal behavior. Winsor's view: In 1948, Winsor attempted to relate hydrotropic action to solubilization and emulsification. He noted that a hydrotrope induces mutual solubilization of organic and aqueous liquids and regarded hydrotropy to be quite similar to solvency.

Licht and Weiner's View: The equilibrium solubility information for the water-hydrotrope benzoic acid gadget at 30, 40, and 60 diploma Celsius became received for those authors. To study the impact of similarity in shape among the solute and the hydrotrope, solubility facts became received with the six one of a kind hydrotropes. They, in the order of decreasing effectiveness are P-cymenesulfonate >o-xylenesulfonate >m-xylenesulfonate > p-bromobenzenesulfonate >p-toluenesulfonate >benzenesulfonate. Their interpretation of these results was that the increased solubility is due to the "salting in" effect rather than due to similarity in their view of hydrotropy therefore is of the same opinion with that of Mckee [11, 34-38].

Determination of Interference of Hydrotropic Agents in the Spectrophotometric Estimation of Drugs [7,14]: A UV-Visible recording spectro-photometer with 1 cm matched silica cells was employed for spectrophotometric determinations. For determination of interference of hydrotropic agents in the spectrophotometric estimation of the standard solutions of drugs were determined in distilled water alone and in the presence of the maximum concentration of the hydrotropic agent employed for spectrophotometric analysis. The absorbances were recorded against respective reagent blanks at appropriate wavelengths. Titrimetric analysis method employed for determining equilibrium solubility at room temperature. Enhancement ratios in solubilities were determined by following formula - Enhancement ratio = Solubility in hydrotropic solution÷ Solubility in distilled water Smita Sharma, Mukesh C. Sharma [25] were investigating that hydrotropic solution of 8M urea has been employed as solubilizing agent to solubilization poorly water-soluble drug Pseudoephedrine Sulphate, Desloratidine, from fine powder of its tablet dosage form for spectrophotometric determination in ultraviolet region. Pseudoephedrine Sulphate, Desloratidine shows maximum absorbance at resulting solutions were measured at 274.4 nm and 289.1nm. R. K. Maheshwari, s. R. Bishnoi, d. Kumar, murali Krishna [26], in the present investigation, hydrotropic solution of ibuprofen sodium (0.5M) was employed as solubilizing agent to solubilize the poorly water-soluble drug, ornidazole from fine powder of its tablets for spectrophotometric determination. Ornidazole shows its maximum absorbance at 320 nm and Beer's law was obeyed in concentration range of 5-25 mcg/ml.

Importance of Hydrotropy: Hydrotrope solutions can be regarded as a green solvent as they are cheap, easy to handle, non-toxic, and environmentally friendly. Averting the use of organic solvents is one step closer to increasing the solubility in hydrotrope *i.e.*, avoiding the use of organic solvents; aqueous solutions of hydrotropes demonstrated the unique features of an alternative reaction media for organic synthesis, as organic solvents were frequently employed which may be sources of pollution while some of them may be

toxic, costlier also. While volatility may also lead to inaccuracy [4].

Approach: Use of different solubilization methods such as hydrotropes being employed as a solvent for the extraction of the drug, while in the analytical field, mixed hydrotropes helped in the identification, novel separation technique, spectrometric analysis, HPLC, and many other instrumental approaches and the field of pharmaceutical science, hydrotropes are used in formulation and method development processes. Mainly hydrotropes and mixed hydrotropy are effectively used in pharmaceutical chemistry for various purposes that are linked to thermodynamics, mass coefficient, temperature studies, concentration phenomenon, green solvent, pH-dependent study, micelle formation, etc.

On the other side industrial scenario of the hydrotrope is entirely different as it was used in cleaning and personal care product formulation but in the pharmaceutical industry hydrotropes are used for "green synthesis" for the formulation of dosage form and various approaches in the formulations of the dosage form (examples, parenteral, oral, transdermal, nasal, *etc*) [4].

TABLE 1: CLASSIFICATION OF HYDROTROPIC AGENTS [6]

Sr. no.	Class	Example
1	Organic acids and their metal salts	Citric acid, benzoic acid, sodium salicylate, sodium benzoate, sodium citrate, sodium acetate, sodium ascorbate, potassium citrate
2	Urea and its derivatives	Urea, N, N-dimethyl urea
3	Alkaloids	Caffeine, nicotinamide, N,Ndiethylnicotinamide, N,Ndimethylbenzamide
4	Phenolic derivatives	Resorcinol, pyrogallol, catechol, a,b-napthols
5	Surfactants	Sodium dodecyl sulphate
6	Aromatic cations	Procaine hydrochloride, para-amino benzoic acid

Hydrotrope Selection: From the literature review, it is evident that the aqueous solubility of poorly water-soluble drugs increases with an increase in the concentration of hydrotrope. So, the hydrotropic agent should be used in high-concentration forms. The hydrotropic solution was prepared using distilled water. Some examples of hydrotropic solutions are 2M sodium benzoate, 2M niacinamide solution, 2M sodium salicylate, 4M sodium acetate, 10 M urea, and 1.25M sodium citrate. For sufficient enhancement in solubilization as in Figure 2, the hydrotropes should be suitably selected, using the appropriate solubility determination method. To a 50ml glass bottle 25ml of distilled water or hydrotropic solution was taken and the gross weight was taken including the cap. Then it added a few milligrams of fine dry powder. The bottle was shaken by hand vigorously. When the drug was dissolved completely. Repeat the same procedure till some excess drug remained undissolved [3].

Mechanism of Hydrotrope Action: Based on the molecular self-association of the hydrotrope and the association of hydrotrope molecules with the solute, the solubility of poorly soluble drugs can be increased. Even though hydrotropic agents are widely used, their information on the mechanism of hydrotropy is less available. To clarify the mechanism of hydrotropy, various hypotheses, and research works are being made. Accordingly, the available mechanism can be abridged into 3 designs:

A. Potential of self-aggregation.

B. Structure maker and structure breaker.

C. Micelle-like structure formation.

These hydrotropes can be distinguished from other solubilizers based on these unique geometrical features and different association patterns of the hydrotropes.

Hydrotropes do not have a basic focus above which self-accumulation "all of a sudden" begin to happen. Rather, some hydrotropes total in a stage shrewd self-conglomeration process, bit by bit expanding accumulation size. To improve the dissolution of medication, an inadequately water-solvent medication by utilization of concentrated arrangement of urea (a hydrotropic operator). Hydrotropy is suggested to be superior to the other solubilization methods, such as miscibility,

micelles solubilization, Solid dispersion, solvency, and salting because the independent character of pH has been highly selected. It only requires the mixing of the drug with the hydrotropes in water. The hydrotropic agents are present in synthetic and natural forms which are defined as non-micelle-forming substances either liquids or solids, organic and inorganic, which are capable of solubilizing insoluble compounds. Various study of literature shows that a large number of poorly water-soluble drugs have been analyzed, namely, furosemide, cefixime, salicylic acid, piroxicam, ketoprofen, aceclofenac, aspirin, hydrochlorothiazide, naproxen, and paracetamol using a hydrotropic solubilizing agent.

There is various large number of hydrotropic agents have been employed to enhance the aqueous solubility of various poorly water-soluble drugs. While mixed solvency concept was used in various formulation development of syrups such as in liquid oral solution development of syrup of poorly water-soluble. This approach shall prove a wild scope in the pharmaceutical field to develop various formulations of poorly water-soluble drugs combining various water-soluble compounds in safe concentration to produce a desirable aqueous solubility of the poorly water-soluble drug. While using a synthetic hydrotropic agent such as sodium benzoate, urea, nicotinamide, citric acid, and salicylic acid, while using them in high concentration may cause toxicity, which is harmful to human beings.

Demonstration of natural hydrotropes while enhancing the solubility of poorly soluble drugs which are naturally occurring as caffeine, piperazine, tannic acid, and epigallocatechin gallate so that it involves the use of low concentration of them. Moreover, it supports overcoming environmental and energy issues along with the mentioned conventional method. Natural hydrotropes processing can be considered a green extraction since they are artificially dormant, effectively distinguishable, promptly reusable, and particularly focused mixes. Be that as it may, this technique experiences the constraint of expanded extraction time and a higher grouping of hydrotropes. Dissolvability investigations of a drug in various solvents: Solubility study was performed by the shake flask method [2].

Formation of solute-hydrotrope complexes Solubilization takes place due to weak complexation between the non-polar compound and the hydrotrope, which results in higher aqueous solubility [20]. These complexation hypothesis claims low stoichiometry complexes (such as 1:1 or 1:2) as the origin of hydrotropy [4, 16, 17].

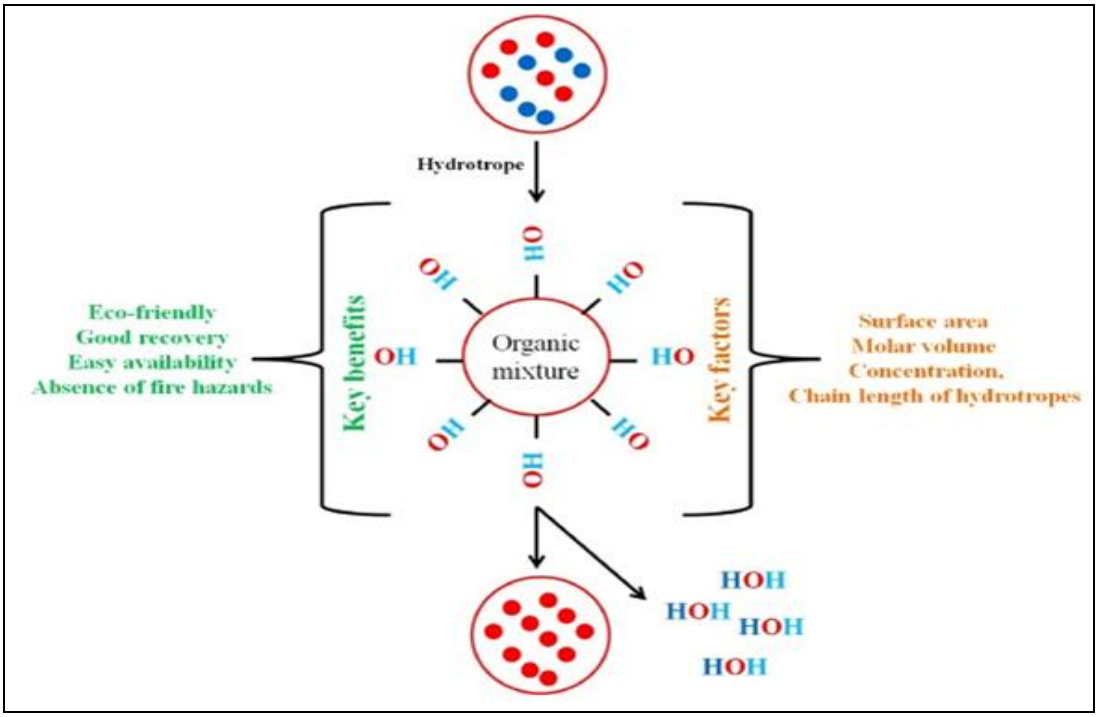

FIG. 2: MECHANISM OF HYDROTROPY

Mixed Hydrotropy: The mixed hydrotropic solubilization technique is the phenomenon to increase the solubility of poorly water-soluble drugs in the blends of hydrotropic agents, which may give miraculous synergistic enhancement effect on the solubility of poorly water-soluble drugs, utilization of it in the formulation of dosage forms of water-insoluble drugs and to reduce the concentration of individual hydrotropic agent to minimize the side effects were developed a novel, safe and sensitive method of spectrophotometric estimation in the ultraviolet region using a mixed hydrotropic solution, containing a blend of urea, sodium acetate, and sodium citrate for the quantitative determination of poorly water-soluble drugs.

It also obeyed Beer's law there was many folds enhancement in the aqueous solubility of poorly water-soluble drugs in mixed hydrotropic solution as compared with the solubility in distilled water precluding the use of organic solvents. 07 In review observed that the Spectrophotometric method using 2 M sodium acetate and 8 M Urea solution as a hydrotropic solubilizing agent for the quantitative determination of poorly water-soluble hydrochlorothiazide in a tablet dosage form. There were more than 55 and 70-fold enhancements in the solubility of hydrochlorothiazide increases in 2 M sodium acetate and 8 M Urea solution as compared to solubilities in distilled water. Hydrochloro-thiazide suggests most absorbance at 272 nm. Sodium acetate and urea did not show any absorbance above 240 nm, and thus no interference in the estimation was seen. Hydrochlorothiazide obeyed Beer's law in the concentration range of 10 t0 50µg/ml (r2= 0.999) in sodium acetate and 5 to 25 µg/ml (r2= 0.999) in urea with mean recovery 98.74 and 99.99% in sodium acetate and urea respectively [7].

Advantages of Hydrotropic Solubilization [6, 7]:

1. It precludes the use of organic solvents and thus avoids the issues of residual toxicity, error due to volatility, pollution, cost, *etc*.
2. It only requires mixing the drug with the hydrotrope in water.
3. Hydrotropy is suggested to be superior to other solubilization methods, such as miscibility, micellar solubilization, co-solvency, and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
4. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of various formulation systems.
5. It perhaps reduces the total concentration of hydrotropic agents necessary to produce a modest increase in solubility by employing a combination of agents in a lower concentration.
6. It is a modern, simple, cost-effective, safe, accurate, precise, and environmentally friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble tablets titrimetric and spectrophotometric precluding using natural solvents.
7. It precludes the usage of natural solvents and hence avoids the trouble of residual toxicity, blunders because of volatility, pollution, cost, etc. [7]

Disadvantages of Hydrotropic Solubilization Technique:

1. There is some problem related to toxicity associated with the excessive use of hydrotropic agents.
2. The relatively high concentrations required to reach the MHC limits the commercial application of hydrotropes.
3. There are chances of a weak interaction between the hydrotropic agent and drugs.
4. As there may be the usage of water as a solvent, whole elimination of water cannot be achieved.

Novel Applications of Hydrotropic Solubilization in Various Fields of Pharmacy: Hydrotropes are an advanced tool in both academic and pharmaceutical industries. They vary many realistic applications in both biomedical sciences and engineering fields also. Their uses play important parameters in the pharmaceutical formulation solute separations process, selective separation, and alternation in reaction kinetics.

The applications discussed below which related to the development of pharmaceuticals.

- Quantitative determination of poorly water-soluble drugs by titrimetric analysis such as naproxen, aspirin, furosemide, ibuprofen, salicylic acid, and aceclofenac using different hydrotropic agents such as sodium benzoate, and nicotinamide.
- Preparation of solid dispersions of poorly soluble drugs pre including the use of organic solvents.
- Application of hydro solubilization in the extraction of pure constituents from crude drugs which avoids toxicity.
- Applications of mixed solvency to broadly develop parentals dosage forms of poorly water-soluble drugs.
- The use of hydrotropy gives an instant release of poorly soluble drugs from the suppositories.
- The use of hydrotropic solubilizers as permeation enhancers. Used in manufacturing of syrups (for reconstitution) of poorly water-soluble drugs.
- Quantitative analysis and titrimetric analysis pre including the use of organic solvents [2, 7].
- Artificial neuronal application - The pharmaceutical sciences, Artificial Neuronal Network (ANN) which are computational model by the application of machine learning is of relative important for the determination and prediction the quantitative assessment of various hydrotrope physicochemical properties. For the application of hydrotrope-enhanced property, use of computational model, predict by utilization of ANN to determine the role of hydrotropes in enhancing the solubility of poorly water-soluble drug [4, 13].

Hydrotropic Solid Dispersion: Hydrotropic solid dispersion preparation of poorly water-soluble drugs. Solid dispersion of one or more active pharmaceutical ingredients in an inert and nontoxic carrier matrix into a solid state by using the solvent evaporation method, fusion method, and melting solvent method. Low aqueous solubility drugs will mostly show less dissolution rate and incomplete absorption and penetration rate-limited absorption is exhibited by drugs with poor membrane permeability. Biological applications of the effect of hydrotropes on the activity of the enzyme dehydrogenases have been reported, as also the increased antibacterial action of cresols in hydrophobic solutions. Some hydrotropes can cause hemolysis of human erythrocytes.

Sahel and coworkers also found that the hydrotropes Na benzoate affect the structure of hemoglobin and this was attributed to the effect of hydrotropic salts on the water structure of the Fe-histidine bond. The anti-inflammatory effect of hydrotrope aspirin has been attributed to the inhibition of prostaglandin synthesis. They can be applied in nanotechnology. Used to try to develop the dissolution fluids to carry out the dissolution studies of dosage forms of poorly water-soluble drugs [3].

Formulations Aspects: The widely used method for increasing the dissolution rate is the solid dispersion technology. By this, the rate of absorption and/or total bioavailability of the BCS Class-II drugs can also be increased. The methods widely used are solvent evaporation, fusion, and fusion solvent methods for the preparation of solid dispersions. A volatile organic solvent is used to dissolve the drug as well as a carrier in the case of the solvent evaporation method.

Then the solvent dispersion is obtained by removing the solvent with a suitable evaporation technique. But the major drawbacks of this method include toxicity of residual solvent, cost of solvent, and pollution. In the newly developed hydrotropic solid dispersion technology, the use of organic solvent was avoided. The characteristics of this new method are that the hydrotropic agent (carrier) is water soluble whereas the drug is insoluble in water. The drug gets solubilized in the presence of a large amount of hydrotropic agent in water. By using a suitable evaporation technique, the water is removed to get a solid mass i.e.; a solid dispersion. This method is different from the common solvent method, since that in the absence of a hydrotropic agent, water is not a solvent for a poorly water-soluble drug.

This method is a novel application of the hydrotropic solubilization phenomenon. These formed solid dispersion are known as hydrotropic solid dispersions [30].

Environmental Considerations: Normally, the hydrotropes have a low bioaccumulation potential. They are found to be very slightly volatile under specific vapor pressure. They are aerobically biodegradable. Removal of the activated sludge via the secondary wastewater treatment process is >94%. The hydrotropes can also be used in hydrotropes in household laundry and cleaning products and have been determined to not be an environmental concern. Hydrotropes may cause aggregate exposures to consumers in many ways including direct and indirect dermal contact, ingestion, and inhalation. This may be estimated to be about 1.42 kg/day. Some are shown to cause temporary slight eye irritation in animals like calcium xylene sulfonate and sodium cumene sulfonate. Many studies have not found hydrotropes to be mutagenic, carcinogenic, or have reproductive toxicity [3].

CONCLUSION: Various Approach to mechanisms of hydrotropes shows that the study of enhancement solubility of a compound that has poor aqueous solubility, as well as their advantages and disadvantages have been described thoroughly in this review. This technique not only paved a way for the dosage development of poorly water-soluble drugs but also helped in the enhancement of the various poorly water-soluble drugs. Hydrotrope techniques can replace major conventional techniques employed in the field of pharmaceuticals because they act as green solvents that cause less pollution, are environmentally friendly and economically, as well as they are cheaper than organic solvents as they utilized the minimum concentration of the compound. Similarly, in the field of pharmaceutics as a part of the pharmaceutical industry, this technique enhanced the aqueous solubility and increased the bioavailability of poorly solubilizing synthetic as well as isolated compounds. This review defines the application of hydrotropes in various fields of science and thoroughly explains the proposed mechanisms of the hydrotropic agent. The above studies raise the use of hydrotropes in the field of pharmaceutics for further progress in hydrotropy, especially in the formulation of drugs by utilization of hydrotropic agents towards the enhancement of solubility of a poorly water-soluble drug to enhance therapeutic delivery. However, many challenges remain with the mechanisms of hydrotropes, and these are still in debate. The basic approach involves the interaction of the hydrotropic agent with a poorly water-soluble drug, which boosted solubility as well as bioavailability.

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