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Review Article

## Review: Hydrotropy as Prominent Approach for Enhancement of Aqueous Solubility of Drugs

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### Abstract



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Solubility is crucial element to achieve the desired drug absorption in the total pharmacological response. Low water solubility can considerably limit the medication efficacy, and to improve aqueous solubility, a variety of approaches are employed. The capacity which increases water solubility for particular drug can thus be a useful tool for enhancing efficiency and/or decreasing negative effects. This is true for parental administered, topically applied and orally consumed solutions. It is a difficult work for researchers and pharmaceutical scientist to use solubility features in bioavailability, pharmacological effect and solubility enhancement of diverse weakly soluble substance. Hydrotropy is one of the strategies for increasing solubility. The purpose of this paper is to examine the hydrotropy Solubilization technique and to highlight the mechanism and different prospective of this method.

**Keywords:** Hydrotropy, mechanism, formation of hydrotropes, Solubility

### Introduction:

The present major issue in the pharmaceutical manufacturing is tactics for increasing medication solubility. This is because water solubility is an issue for roughly 40% of newly identified medication users. One of the most important variables in getting the intended effect of medical research is melting. A drug's therapeutic impact is determined by its bioavailability and, eventually, its commercialization. To increase the melting and dispersion of oral bioavailability profiles, a variety of design approaches are available<sup>1, 2</sup>.

### Solubility

A Solution may be a molecular dispersion of a substance during a solvent. There may be quite one substance, and therefore the solvent will carriers with it over one substance. The solution should be looked in a very a lot of quantitative manner so on perceive the idea and application of the phenomena of solubility. The solubility outlined because the spontaneous interaction of 2 or a lot of substances to create a undiversified molecular dispersion.<sup>3</sup> of the 9 potential style of mixture, supported the 3 states of matter, system of solids in liquid embody the foremost on times encountered and doubtless the foremost vital from of pharmaceutical solutions<sup>4</sup>. Solute square measure classified as nonelectrolytes and electrolytes. The solubility of nonelectrolytes and weak electrolytes largely belongs to the categories of weak electrolytes largely belongs to the categories of weak acids ad

weak bases, that is of substantial importance to the pill pusher<sup>5</sup>. The connected aspects of solubility square measure mentioned within the following sections.

### Applications:

In pharmacy, medication solubility in liquids has a wide range of applications<sup>6</sup>

- Drug solubility in water and hydro alcoholic solution is required for the production of liquid orals such syrups and elixirs.
- Drugs are dissolved in solvents, such as 5%w/v dextrose infusion fluids, to make intravenous, Intramuscular and subcutaneous injections.
- Drug solubility in GI Fluids (dissolution) is a crucial step in improving drug absorption.
- There will be no problems with absorption if the drugs water solubility is more than 1% in the pH range of 1-7 at 37°C.potential difficulties may rise if you go beyond this limit. A Soluble salt is required if the solubility is greater than 1mg/ml.especially if the medicine is to be packaged as a tablet or a capsule.

The degree of saturation of a drug in the solvent determines its release and absorption from an ointment or an intramuscular injection.<sup>7</sup>

- A drug's action can be substantially hampered by its inability to dissolve in water. Similarly, certain medications' adverse effects are caused by their low solubility.
- A substance's solubility is used as a standard test for purity.
- Information about the structure and intermolecular forces of interaction is provided by solubility. Predicting drug-receptor interactions can be done using this information.<sup>8</sup>
- For the crystallization of medicines from solvents, the saturated solution theory is critical.

#### Solubility Impacting Factors

- The physicochemical properties of a solute.
- The properties and nature of solvent.
- Temperature.

### Physical modification of drugs

As the particle size lowers, The water solubility of hydrophobic medication particles rises. Spray drying, emulsion, solvent extraction, micro-fluidization, high-pressure homogenization, ball milling, media milling, jet milling, and fast expansion from supercritical fluid are all typical methods for producing micro particulates preparations of poorly soluble medicines.<sup>9</sup>

#### Use of cosolvents

Cosolvent systems can significantly increase a drug's water solubility, however biocompatible solvents such as glycerine, propylene glycol, polyethylene glycols, dimethyl sulfoxide, N, N-dimethylformamide, cremophor, and ethanol are limited. Aqueous solutions are more biocompatible than cosolvent systems.<sup>10</sup>

#### Emulsions, micelles, and liposomes

Emulsions are droplets of one liquid dispersed in another immiscible liquid. Emulsifiers, also known as surfactants, are used to keep the droplets from aggregating. Oil-in-water (o/w) emulsions are commonly employed to deliver poorly soluble medicines. Triolein, triglyceride, propylene glycol dicaprylate, and soybean oil are all common oil cores. Liposomes and micelles have also been widely researched for drug delivery of essential weakly soluble medicines. The main drawback of this method is that the liposomes and micelles prefer to stick together to have poor stability.<sup>11</sup>

### Complexation

The Complexation method has been widely utilised to improve the water solubility of medications that are poorly water soluble.<sup>12</sup>

#### Solid dispersion Technology<sup>13</sup>

Solid dispersion refers to the solid state dispersion of a poorly soluble medication in an inert polymeric carrier (such as PVP). These are made by melting or using a solvent. This procedure necessitates an understanding of drug melting or the use of organic solvents.

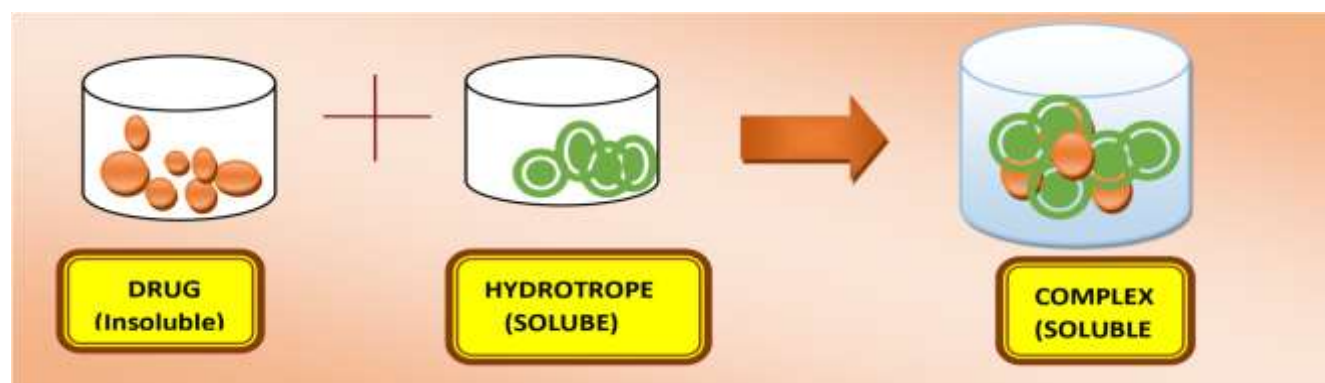
#### Hydrotropic agents (hydrotropes) are used<sup>14</sup>

To improve drug solubility, hydrotropic agents have also been applied. The hydrotropic effect is when a significant amount of a solute is used to increase the solubility of compounds that are poorly water soluble. Sodium benzoate, Sodium acetate, Sodium glycinate, nicotinamide, beta-cyclodextrin, lysine, gentisic acid urea and tryptophan are only a few examples of hydrotropes.

The hydrotropes strategy, among the several ways outlined above, is a very promising new method with a lot of promise for poorly soluble medicines in general. The current study looks on increasing the drugs solubility and thus its bioavailability. A range of modern technologies, such as hydrotropic solubilisation and solid dispersions, can boost the drugs solubility.

In addition to this technology, "Hydrotropy" is one of the well-known problem-solving techniques. Carl Neuberg coined the word hydrotropy in 1916<sup>15</sup> but it was Thomas and his 17 coworkers who published the first true results in 1976. During this procedure, The soluble substance's water solubility is increased in this method by adding a substantial amount of the second solute. When an amount of solvent is added to another solute, the aqueous solubility of the other solute increases. To increase the solubility of highly soluble pharmaceuticals in water, aqueous hydrotropic solutions liquid of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been discovered<sup>16</sup>.

In an aqueous solution, hydrotrope is a chemical that solubilizes hydrophobic substances. Hydrotropes usually combine with watery solutions. Hydrotropes typically combine a hydrophilic and a hydrophobic element (such as surfactants), but the hydrophobic component is usually insignificant enough to prevent compounding.



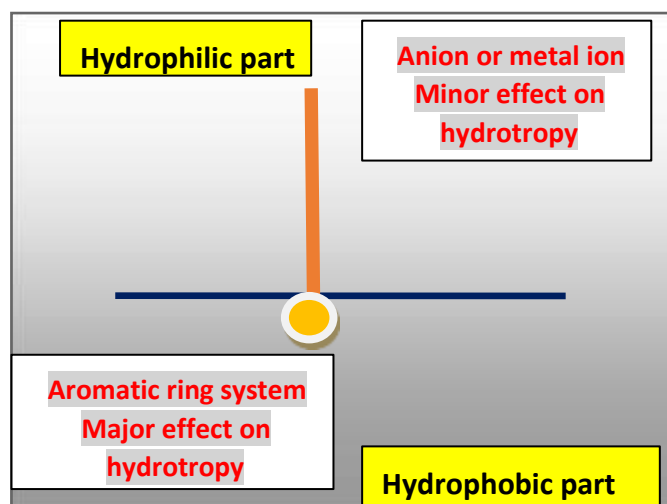
### Advantages of Hydrotropic Solubilization Technique:<sup>17</sup>

1. As the solvent Character is independent of pH and has a high selectivity which does not require emulsification.
2. API mix with the hydrotrope in water.
3. There is no chemical modification required of hydrophobic drugs (use of organic solvents, or preparation of emulsion system).

**Disadvantages:**

1. There might be shown weak interaction between Hydrotropes and drug.
2. To reach the MHC limit the relatively high concentration required.
3. Excess use of hydrotropic agent result in toxicity.

In solution, the hydrotropes are known to self-accumulate<sup>18</sup>. Because a broad variety of substances have been report to display hydrotropic performance, classifying hydrotropes on the basis of molecular arrangement is problematic. Ethanol<sup>19</sup>. The most researched compounds are aromatic hydrotropes with anionic head groups. Because of isomerism, they have a significant number of them, and their effective hydrotrope activity could be owing to the availability of interacting p-orbitals., are unusual hydrotropes having cationic hydrophilic groups. Aside from improving chemical solubilization in water, They are known to have effects on surfactant aggregation leading to micelle formation, phase manifestation of multi component systems with reference to nano-dispersions and conductance percolation, clouding of surfactants and polymers, and so on, in addition to improving compound solubilization in water.



**Figure 2: Structure of hydrotropic agent**<sup>[20]</sup>

Hydrotropes are amphiphilic in nature as it contains both hydrophobic and hydrophilic groups. However, the hydrophobic percentage is insignificant. The hydrotropic efficacy is generally better when the layer is the hydrophobic component. Non-micelle forming chemicals are commonly used as hydrotropic agents. They can be anionic, cationic, or neutral in nature, and they can be organic or inorganic, liquid or solid. We can improve the water solubility of organic substances by forming stack-type aggregation, so hydrotropic agents are readily soluble in organic solvents as illustrated in figure 2.

### Mechanism of Hydrotrope Action

The solubility of poorly soluble drugs can be improved by using the hydrotrope's molecular self-association and the association of hydrotrope molecules with the solution. Despite the wide usage of hydrotropic drugs, information on the mechanisms of hydrotropy is limited. Various hypotheses and research studies are being conducted in attempt to better understand the mechanism of hydrotropy.

As a result, the available mechanism can be divided into three types:

- a) Self-aggregation potential.
- b) The Structure breaker and Structure maker
- C) The formation of a micelle-like structure.

These hydrotropes can be recognised from other solubilizers because of their distinct geometrical features and association patterns.

#### (a) SELF AGGREGATION POTENTIAL<sup>18-19</sup>

Minimum Hydrotropic Concentration (MHC) is the critical concentration at which hydrotrope molecules begin to combine, i.e. self-aggregation potential. The solubilization power of hydrotropic agents is governed by the self-aggregation potential of these molecules. The amphiphilic properties of a solute molecule, as well as the type of the solute molecule, may influence its self-aggregation potential. This may primarily demonstrate the solubilization potential of volume fractions. Initially, the hydrotrope molecule's primary connection in a pairwise manner may occur. The formation of trimers, tetramers, and other polymers may be followed by a sequence of steps. Higher aqueous solubility may result from the generated complexes. Fluorescence emission, crystallographic analysis, molecular dynamics replication, and thermodynamic solubility studies are some of the approaches that can be employed for this. They may also help to improve the solubility of some substances. They may also increase the solubility of a solute by acting as bridging agents by reducing the Gibb's energy. A true key for understanding the origin of the self-aggregation potential is the structure of the hydrotrope-water mixture around the drug molecule.

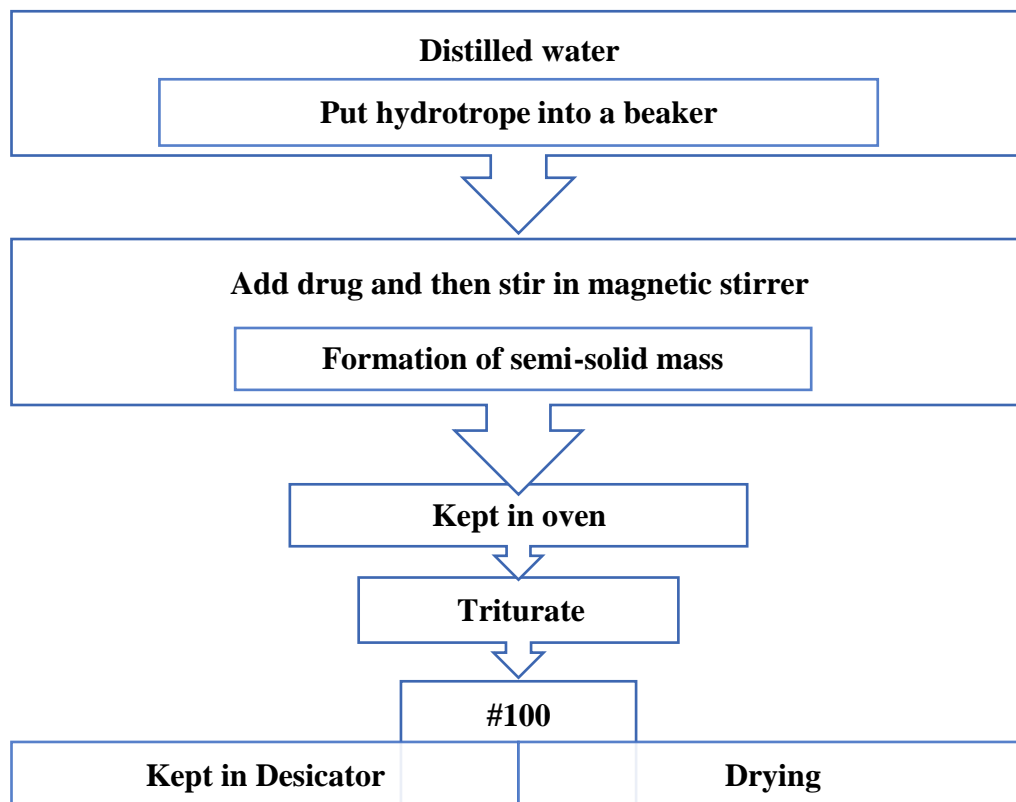
#### (b) STRUCTURE BREAKER AND STRUCTURE MAKER<sup>20-22</sup>

In a hydrotropic solubilization technique, the electrostatic force of the donor acceptor molecule played a critical role. So they are also termed as a structure breaker and a structure maker. When solutes capable of the both hydrogen donation and acceptance are present, solubility increase may occur. Some solubilize by modifying the character of the solvents, such as urea, which is a hydrotropic agent. This is accomplished by adjusting its ability to participate in structure formation via intermolecular hydrogen bonding or by altering the solvent's ability to do so. Kosmotropes and chaotropes are the names given to structure-maker and structure-breaker hydrotropes, respectively. Both of these have an impact on the cloud point. By increasing hydrophobic interactions, kosmotropes can lower the Critical Micelle Concentration (CMC), lowering the cloud point. Kosmotropes can influence the cloud point in two ways. For example, it aids in the formation of larger micelles and the reduction of hydration.

#### (c) The formation of a micelle-like structure.<sup>15-19]</sup>

This stage is based on hydrotropes self-associating with solutes to form a micellar configuration. With the addition of a solute molecule, they form stable mixed micelles, reducing electrostatic repulsion between the head groups. Some hydrotropic agents, such as alkyl benzenesulfonates, lower alkanolates, and alkyl sulphates, self-associate with solutes and form micelles. Some aromatic anionic hydrotropic agents, such as nicotinamide, increase riboflavin solubility by a self-association process. Sodium salicylate, like anionic hydrotropic agents, forms stable mixed micelles by reducing electrostatic repulsion between the head groups.

## Formulation of hydrotropes



## Different Hydrotropy perspectives

### • McKee's point of perspectives:

By 1946, McKee is using hydrotropes in chemical engineering and industrial applications. He demonstrated that soluble neutral salts of organic acids increase the solubility of various organic and inorganic compounds in water when mixed with concentrated. To the earlier perspectives of Neuberg and others, who believed that only organic chemicals could serve as hydrotropes, McKee believes that some inorganic substances may be added to the class of hydrotropes. Alkali iodides, thiocyanates, oxalates, and bicarbonates are some of these. Inorganic salts, on the other hand, are no longer added in the group of hydrotropes.

In any case, McKee highlighted some key aspects of hydrotropy. He observed that when most hydrotropic solutions are diluted with water, the solubilized precipitates. This aids in the recovery of hydrotrope for future usage. Because it looks to be less expensive than conventional alkaline procedure, xylene sulfonate. Finally, McKee came to the significant conclusions about hydrotropy: A high concentration of the hydrotrope in water is required for it to work, and the phenomenon is comparable to that of "salting in." The phenomenon of hydrotropy, according to McKee, can be described using the mixed solvents theory.<sup>32-34</sup>

### • Everson's and Booth

40% xylene sulfonate solution in water to solubilize a variety of substances such as aliphatic and Alcohols, ethers, aldehydes, ketones, amines, oils, and other aromatic hydrocarbons are examples. This solvent was also proven to be an effective solvent. hydrotrope. They have also analysed and contrasted the Theortho, para, and post-operative ortho, para, and post-operative ortho, para, and post-operative ortho, para, Towrds of meta isomers of xylene sulfonate wide range of hydrophobic substances All three isomers have been found to have hydrotropic efficiency is equivalent. The meta isomer, on the other hand, is preferable at Due to its larger water

content, it has a lower temperature and solubility. Xylene is one of them. sulfonate seemed to be the most effective capacity to emulsify as the population grows, The agent has a high concentration of hydrotrope. Increased solubility isn't a straight line. monotonous, yet with a sigmoidal pattern behaviour.

### • Winsor's perspective

Winsor attempted to link hydrotropic activity to emulsification and solubilisation in 1948. it observed that a hydrotrope causes mutual solubilization of organic and aqueous liquids, and compared hydrotropy to cosolvency.

### • Weiner's and Licht view

The equilibrium solubility data for the water-hydrotrope benzoic acid system at 30, 40, and 60 degrees Celsius was acquired for these authors, according to Licht and Weiner. Solubility data was acquired with the six distinct hydrotropes in order to examine the influence of structural similarity between the solute and the hydrotrope. They are: [Na p-cymene sulfonate> oxylene sulfonate> m-xylene sulfonate> P-bromo benzenesulfonate p-toluenesulfonate> benzenesulfonate > benzenesulfonate > benzenesulfonate > benzenesulfonate > benzenes] their interpretation of these findings was that the enhanced solubility was due to a "salting in" effect rather than structural similarity. As a result, their understanding of hydrotropy is similar to Mcke<sup>35-39</sup>

## Mixed Hydrotropic

Mixed hydrotropic solubilization technique is the phenomenon of improving the solubility of low water-soluble drugs by means mixtures of hydrotropic agents, This may have a synergistic effect on the solubility of poorly water-soluble drugs, utilization of it within the formulation of dosage forms of water-insoluble drugs and to reduce concentration of individual hydrotropic agent to minimize the facet effects (in place of employing a giant concentration of one hydrotrope a

mix of, say, five hydrotropes are often utilized in 1/5th concentrations reducing their individual toxicities.

As mixed hydrotropy can reduced the total large concentration of hydrotropic agent necessary to produce moderate increase in solubility through a combination of agent with a low concentration.

## Conclusion

Infer from this article that solubility is one of the most significant elements of a drug and may be enhanced using several solubilization techniques, including The utilization of the hydrotropy approach has increased in a variety of fields by adding a second solute to the operational fields, which results in another solute's aqueous solubility.

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