

## Review Article

## Effect of Hydrotropes on Solubility of Drugs

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### ABSTRACT

Oral solid dosage forms (OSDF) are one of the most common & convenient way to deliver a drug substance to a patient hence it covers highest pharmaceutical market. About 40% of new chemical entities (NCE) faces problem of poor water solubility and solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for desired pharmacological response (bioavailability). Hence water solubility is the major obstruction for the development of potent pharmaceuticals. Thus enhancement of solubility of various poorly soluble compounds is a challenging task for researchers in screening studies of NCE as well as formulation research. From various employed techniques Hydrotropy is one of the best solubility enhancement techniques as a hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solution without chemical modification.

**Keywords:** Hydrotropy, Hydrotropes, solubility enhancement, Hydrophobic drug and bioavailability.

### INTRODUCTION

Solubility enhancement of various poorly soluble compounds is a challenging task for researchers. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. The study on solubility yields information about the structure and intermolecular forces of drugs. Drug efficacy can be severely limited by poor aqueous solubility and some drug also shows side effects due to their poor solubility. There are many techniques which are used to enhance the aqueous solubility. Thus increased aqueous solubility reduces side effects for certain drugs.

Neuberg in 1916 was the first to report Hydrotropy when he dissolved a variety of organic substances such as carbohydrates, esters, lipids, drugs and oils in aqueous solution containing hydrotropes. He designated that anionic organic salts which at high concentration considerably increase the aqueous solubility of poorly soluble solutes.

Booth and Everson were the first to show that the solubility of a hydrophobic drug increases with the increase in concentration of a hydrotrope in the solution. It does not occur in a linear fashion. This fact is important while understanding the mechanism of the Hydrotropy.

Hydrotropy is a solubilization phenomenon whereby addition of large amount of second solute results in an increase in the aqueous solubility of another solute. However the term has been used in the literature to designate non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds. Additives or salts that increase the solubility in a given solvent are said to be "salt in" the solute and those salts that decrease the solubility are said to be "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water results in salting in of nonelectrolytes called 'hydrotropic salts' and the phenomenon is known as "hydrotropism".

### PREPARATION OF HYDROTROPES

Hydrotropes are produced by sulfonation of an aromatic hydrocarbon solvent .e.g toluene, xylene or cumene. The resulting aromatic sulfonic acid is neutralized using an appropriate base e.g sodium hydroxide to produce the sulfonate or hydrotrope. The hydrotropes are pure substances but are produced and transported in either aqueous solutions at 30-60% level of activity, or in granular solids at 90-95% level of activity. Granular hydrotropes product is produced by spray drying that includes source control and dust collection. Hydrotropes are manufactured

for industrial, professional, and consumer use and are not used as intermediates or derivatives.

#### CHARACTERISTICS OF HYDROTROPES

- 1) Completely soluble in water.
- 2) They are surface active and aggregate in aqueous solution due to their amphiphilic structure.
- 3) They do not produce any temperature change when dissolved in water.
- 4) They are easily available and cheap.
- 5) They are Non-toxic and Non-reactive.
- 6) They are insensitive to temperature, when dissolved in water.
- 7) They are independent of high selectivity and pH of solvent.

#### FEATURES OF HYDROTROPES

- 1) Unprecedented increase in solubilization.
- 2) Easy recovery of solute from solution.
- 3) Economical and cost effective.
- 4) Absence of emulsion.
- 5) Absence of hazards present in other solvents used in extractive separation.

#### PROPERTIES OF HYDROTROPES

- 1) Hydrotropes are generally water-soluble and surface-active compounds that can significantly enhance the solubility of organic solutes such as esters, alcohols, aldehydes, ketones, hydrocarbons and fats.
- 2) All hydrotropes are non-reactive and non-toxic and do not produce any temperature effect when dissolved in water.
- 3) The solvent character being independent of pH, high selectivity, and the absence of emulsification are the other properties of hydrotropes.

#### MECHANISM OF SOLUBILITY

##### 1. Self association [stacking]

Self association of hydrotrope molecule forms an organized aggregate. It also attracts solute molecules inside the aqueous phase.

It also increases the solubilization effect with increase in hydrotropic concentration.

##### 2. Complex formation

Solute and hydrotropes interact strongly to form a higher aqueous soluble complex.

##### 3. Structure-breaker and Structure-maker

Changing the structure of the solvent by altering the ability of engaging in structure formation of intermolecular **H-bonding**.

#### 4. Hydrotropes act as a bridge

Hydrotropes act as a bridge to increase solubility by concentrating around the hydrophobic solute without interaction. (solubility increases due to decrease in Gibbs energy).

#### METHODS TO MEASURE THE SOLUBILITY

To determine solubility of solids in liquids following two steps are used

##### 1) Preparation of saturated solution

Solubility indicates the maximum amount of a substance that can be dissolved in a solvent at a given temperature. Such a solution is called saturated. Solubility is measured either in grams per 100 gm of solvent or number of moles per 1L of the solution.

##### 2) Analysis of saturated solution

Once the saturated solution is prepared its analysis is carried out to check the solubility. It depends upon the nature of the solute and accuracy of the method employed.

Following methods are used for analysis.

- 1) Evaporation method
- 2) Volumetric method
- 3) Gravimetric method
- 4) Instrumental method

#### ADVANTAGES OF HYDROTROPIC SOLUBILIZATION TECHNIQUE

- 1) Hydrotropy is suggested to be superior to other solubilization methods, e.g. miscibility, micellar solubilization, co-solvency, because the solvent character is independent of pH, selectivity, and does not require emulsification.
- 2) It only requires mixing the drug with the hydrotrope in water.
- 3) It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

#### MIXED HYDROTROPY

Mixed hydrotropic solubilization technique is the phenomenon to increase the solubility of poorly water soluble drugs in the presence of hydrotropic agents, which may give unprecedented increase in solubility of poorly water soluble drugs. Utilization of it in the formulation of dosage forms of water insoluble drugs and to reduce concentration of individual hydrotropic agent to minimize the side effect. i.e. in place of using a large concentration of one hydrotrope a blend of say, 5 hydrotropes

can be used as 1/5 th concentration reducing their individual toxicities.

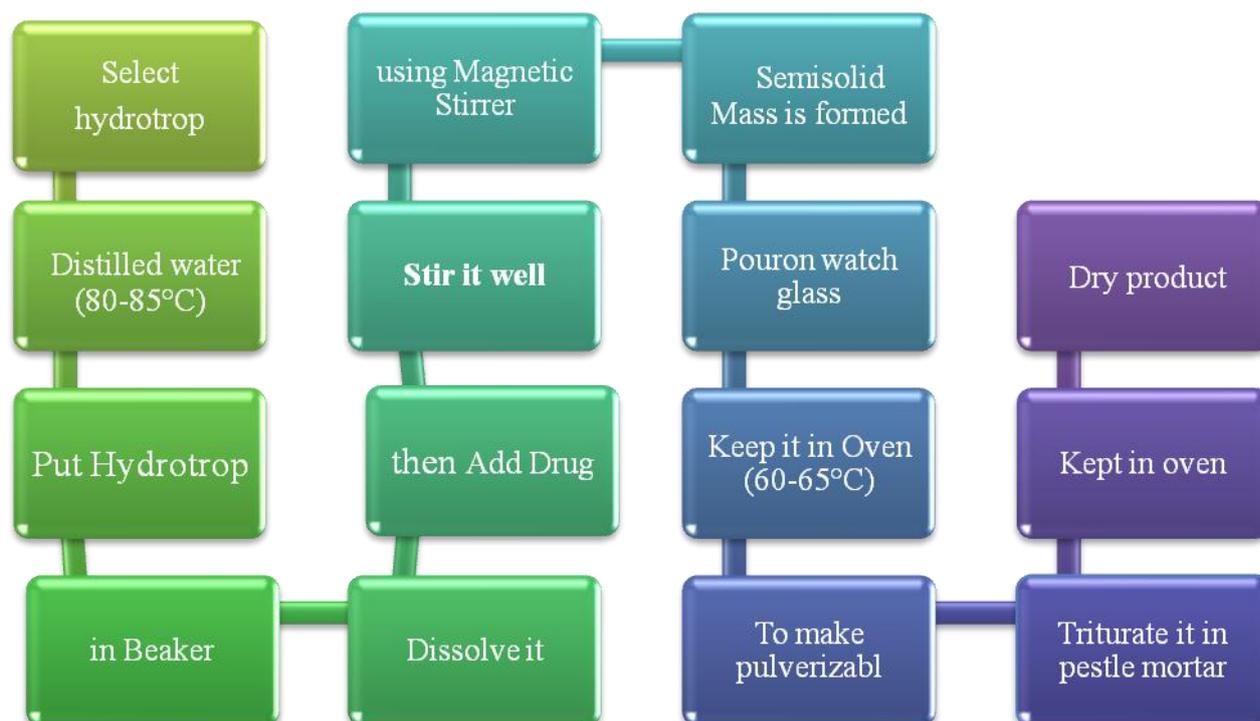
#### ADVANTAGES OF MIXED HYDROTROPIC SOLUBILIZATION

- 1) It reduces the large concentration of individual hydrotropic agents necessary to increase the solubility by employing combination of agents in lower concentration.

- 2) It is new simple , cost-effective , safe , accurate , precise and environmental friendly method for the analysis

- 3) It prevent the use of organic solvents and thus avoids the problem of residual toxicity , error due to volatility , pollution , cost etc .

#### METHOD OF PREPARATION



#### APPLICATION

- 1) Used in Solubility Enhancement.
- 2) Quantitative estimations of poorly water-soluble drugs by uv-visible spectrophotometric analysis, Titrimetric analysis precluding the use of organic solvents.
- 3) Used to enhance the Permeation.
- 4) Used in Preparations of dry syrups of poorly water-soluble drugs.
- 5) Used for extraction.
- 6) Preparation of Injection of poorly water soluble drugs.
- 7) Used in suppositories for fast release of poorly water –soluble drugs.

#### CONCLUSION

Hydrotropic agents are freely water soluble organic compounds which do not form well organized substance , such as micelles. They enhance the aqueous solubility of organic substances , practically which are insoluble under normal conditions . Enhancement of aqueous solubility is may be due to intercalation or co-aggregation of a solute with the hydrotrope aggregates , Complexation involving a weak interaction between the hydrotropic agents and the poorly soluble drugs , hydrotropes concentrating around the hydrophobic solute without interaction (act as bridge) , changing the structure of the solvent by altering ability of engaging in structure formation of intermolecular H bonding (structure-breaker and structure maker) . The

addition of the oppositely charged hydrotropic agents to aqueous ionic surfactant solution may alter the CMC, viscosity, solubility, surface tension, refractive index, specific conductance etc

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