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A REVIEW ON HYDROTROPY: A SOLUBILITY ENHANCING TECHNIQUE

[1]Miss. Pranali P. Hatwar, [2]Mr. Gaurav G. Hudekar,[3]Mr.Gajanan S. Hudekar, [4]Dr. Gajanan S. Sanap

[1]Assistant Professor, [2]Student, [3]Student, [4]Principal

[1]Pharmaceutics,

[1]Late Bhagirathi Yashwantrao Pathrikar College of Pharmacy Pathri, Aurangabad, Maharashtra, India.

Abstract: The current review is based upon the method used to enhancing the solubility by hydrotropy technique.Effectiveness on a drug depends upon the bioavailability and solubility of molecule. Solubility play very important role in drug concentration in systemic circulation for pharmacological response to be shown. Generally currently only 8% of new drug have both high solubility and permeability but, more than 40% of lipophilic drug fail to reach to market, due to poor bioavailability. The lipophilic drug can reaches market it required high dose to attain proper pharmacological action. Currently hydrotropic solution having high industrial demand due to their unique feature such as, easy availability, good recovery, absence of fire hazards, etc. Hydrotropy is one of solubility enhancing technique which enhance solubility using hydrotropes like sodium benzoate, sodium citrate, urea, etc.'Hydrotropy' is unique solubilisation technique used to describe in solubility of solute by addition of large amount of second solute result in increase in aqueous solubility of another solute.

Keywords- Hydrotropy, bioavailability, permeability, solubility, lipophilic drug.

1. INTRODUCTION:-

1.1 Hydrotropy:-

Solubilisation process of Hydrotropy in that addition of large amount of second solute it May lead to increase aqueous solubility of another solute.The drug more than one-third of the drug listed in I.P. and U.S.P fall into less water soluble or water insoluble categories. As almost 41% of the newly discovered drug candidates suffer from poor aqueous solubility mostly newly developed drug molecule are lipophilic nature and poor solubility is one of most difficult problem of these drug. [1]
Various organic solvent such as methanol, chloroform, dimethyl formide and acetonitrile have been employed for Solublization of poorly water – soluble drug. To carry out analysis of poorly water soluble drug. The drawback of these organic solvent include high cost. Volatility, pollution and toxicity such as nephrotoxicity or teratogenicity. So these organic solvent are spectrophotometric analysis. Hydrotropic Solublization concept is one of best choice to preclude the use of organic solvent. [1]Hydrotropy report first in 1916 by Neuberg when he dissolved various organic substance such as carbohydrate, lipid, ester and drugs in aqueous solution containing Hydrotropes. The process of hydrotropic solubilization includes intermolecular cooperation. Rather than a single complexation event or a process dominated by a medium effect, such as co-solvency or salting-in, interaction with many balancing molecular forces is more likely. Hydrotropic agents have been shown to improve the aqueous solubility of medications that are weakly water soluble.[2]Concentrated aqueous Hydrotropic solution of sodium benzoate, sodium salicylate, urea, Nicotinamide ,sodium citrate and sodium acetate have been observed to enhance the aqueous Solubility of many poorly water – soluble drug.[3,4]

1.2 Solubility:-

The solubility is defined as maximum amount of solute is dissolved in given amount of solvent. Quantitatively it is defined as concentration of the solute in a saturated solution at a certain temperature. In the qualitative terms, solubility may take place two or more substance of spontaneous interaction to form a homogenous dispersion molecular.[5, 6]
The International union of pure and applied chemistry (IUPAC) defined "solubility as analytical composition of a saturated expressed as a proportion of designated solute in the designated solvent."

The solubility of drug may express as the parts, percentage, molarity, mole fraction, molality, volume, fraction and other unit. Inadequate and variable bioavailability, as well as gastrointestinal mucosal toxicity, are the results of poorly water soluble medicines combined with sluggish drug absorption.[7]It is also describe in terms of solvent parts are required for one part of solute is explained in Indian pharmacopeia which as in table. [3]

Table 1:- solubilityclassification as per IP[8]

Descriptive term	Solvent part ate required for one solute part
Very soluble	Less than 1-10
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30 -100
Slightly soluble	From 100 -1000
Very slightly soluble	From 1000 -10000
Practically insoluble /insoluble	10000 or more

On the basis of solubility drug can also classified into four classes of biopharmaceutical classification system. The drug substance with respect to their aqueous solubility and membrane permeability. [4]

Table 2: BCS classification[9]

Classification	Property
BCS – I	Highly soluble , Highly permeable
BCS – II	Low soluble , Highly permeable
BCS – III	Highly soluble , low permeable
BCS – IV	Low soluble , low permeable

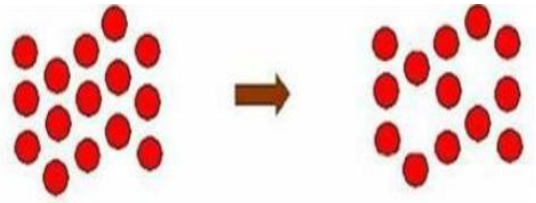
1.3 Need of Solubility:-

- Therapeutic effectiveness of drug it depends on the bioavailability and also depend on the solubility of drug molecule.
- Solubility is one of important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.
- Due to advance research and development, there are varieties of new drug and their derivatives are available. [3]
- More than 40% of lipophilic drug candidates fail to reach market due to poor bioavailability, even though these drug might exhibit potential pharmacodynamics activity.
- The lipophilic drug that reaches market required the high dose to attain proper pharmacological action.
- The basic aim of further formulation and development section is to make that drug available at proper site of action within optimum dose. [5]

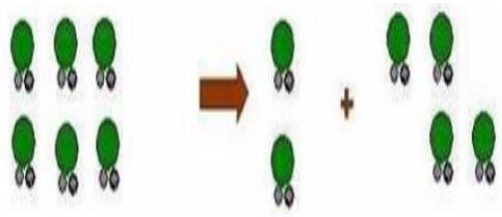
1.4 Mechanism of Solubility:-

- The term solubility is defined as maximum amount of solute that can be dissolve in given amount of solvent. It also defined as quantitatively as well as qualitatively.
- Quantitatively is defined as concentration of solute in saturated solution at certain temperature.
- In qualitative term solubility may be expressed as two or more substance of spontaneous interaction to form homogeneous molecule dispersion.[5]
- The process of solubilisation involve the breaking of inter ionic or intermolecular bond in the solute. The separation of the molecule of solvent to provide space in the solvent for the solute. [10]

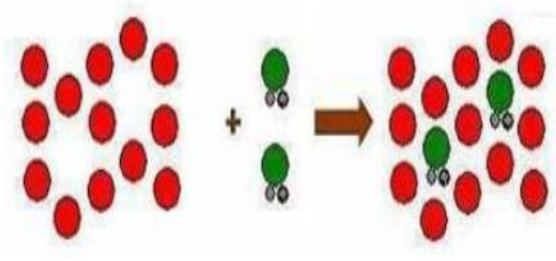
1.5 Following steps are involve in process of Solubilization[11,24]



Steps 1:- Hole open in the solvent.



Step 2:- Solid molecule breaks away from the bulk



Step 3:-Free solid molecule is Integrate into the hole in the solvent.

1.6 Factors Affecting Solubility:-

- Particle size
- Molecular size
- Temperature
- Polarity
- Pressure
- Polymorphs
- Temperature of the solute and solvent [10]

1.7 Different technique use in solubility Enhancement:-

To increase the solubility of poorly water soluble drug different solubilisation technique have been used which are –

I. Chemical Modifications:

1) Salt Formation
2) Co-crystallization
3) Co-solvency
4) Hydrotropy
5) Use of novel solubilizer
6) Nanotechnology

II. Physical Modifications:

1. Particle size reduction
a) Micronization
b) Nanosuspension
2. Modification of the crystal habit
a) Polymorphs
b) Pseudopolymorphs
3. Complexation
a) Physical mixture
b) Kneading method
c) Co-precipitate method
4. Inclusion Complex Formulation Based Techniques
a) Kneading method
b) Lyophilization/ Freeze- drying Technique
c) Microwave irradiation method
5. Solubilization by surfactants
a) Microemulsions
b) Self microemulsifying drug delivery system
6. Drug dispersion in carriers
a) Solid solutions
b) Solid dispersions

III. PH adjustment:
IV. Supercritical fluid process:
V.Liquisolid technique:
VI. Polymeric alteration: [12,13]

2. Hydrotropy:-

2.1 Hydrotropy and hydrotropic agent:-

Carl A. NeuCarl A. Neuberg, a physicist, created the term "Hydrotropy" in 1916. Hydrotropes with an amphiphilic molecular structure can increase the solubility of organic molecules that are only sparingly soluble in water. It is a chemical phenomenon in which the addition of a second solute (hydrotrope) aids in the aqueous solubility of poorly soluble solutes. Simply having a large amount of one solute increases the solubility of another solute. Many poorly water-soluble medications have been reported to benefit from concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate.[14]Hydrotropic agents are ionic organic salts that help to enhance or reduce the solubility of a solute in a particular solvent by causing'salt in' or 'salt out' effects. "Hydrotropic salts" are those that allow non-electrolytes to'salt in,' and the phenomena is known as "hydrotropism." They don't have any colloidal qualities, but they do help with solubility by forming weak interactions with the solute molecules. Weak van der Waals interactions, such as – or attractive dipole – dipole interaction, allow a hydrotropic molecule to connect with a less water-soluble molecule.

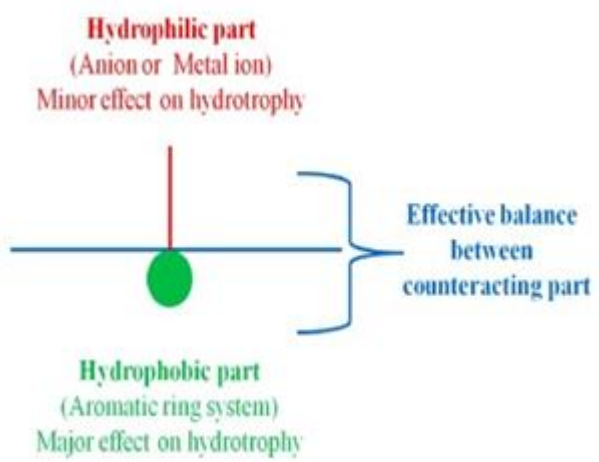


Fig.2 .the structure of a hydrotropic agent

Both hydrophobic and hydrophilic fractions exist in hydrotropes. They have a very minimal hydrophobic proportion when compared to surfactant. The balance between the hydrophobic and hydrophilic parts of the hydrotrope determines the efficacy of hydrotrope solubilization. The hydrotropic efficiency of an addition improves as the hydrophobic part grows larger; the presence of a charge on the hydrophilic part has less impact. In nature, hydrotropic agents can be anionic, cationic, or neutral, organic or inorganic, liquids or solids, and anionic, cationic, or neutral (Fig. 2). These are freely soluble organic compounds that form stack-type aggregation to increase the water solubility of organic molecules. Table 3 lists a few instances of hydrotropic agents.[15]

Hydrotropy is a process of solubility of soluble drug is improved with addition of the third substance with which the soluble molecular complex or compound salt of the drug can be formed. [4]

table.3: classification of hydrotropic agents [4]

S. No.	Hydrotropes
1	Urea and its derivatives
2	Aromatic alcohols
3	Organic metal salts and organic acids
4	Aromatic hydrotropes
5	Surfactants

2.2 Mechanism of Hydrotropy:-

The term "hydrotrophy" refers to the increase in water solubility caused by the presence of a large amount of additives.[16] The enhancement of water-solubility by Hydrotrope is based on molecular self-association of hydrotrope and on the association of hydrotrope molecules with the solute. They are widely used in various industrial applications, only sporadic information is available about the mechanisms of hydrotropism. Various hypothetical and investigational efforts are being made to clarify the mechanisms of hydrotrope. The available proposed mechanisms can be abridged according to three designs.

1. Self-aggregation potential
2. Structure-breaker and structure-maker
3. Ability to form micelles like structure. [4]

2.2.1. Self-aggregation potential:

The minimum hydrotropic concentration (MHC) is the point at which hydrotrope molecules begin to aggregate, i.e. the self-aggregation potential. Hydrotropes' solubilization power is determined by their self-aggregation potential. This potential is determined by their amphiphilic properties as well as the solute molecule's composition. They primarily display the solubilization potential as a function of volume fraction. Hydrotropes form complexes with the solute through strong interactions, and these complexes contribute to increased aqueous solubility. Fluorescence emission methods, crystallographic analysis, molecular dynamics replication, and thermodynamic solubility studies all contributed to these findings. Apart from that, they can operate as bridging agents by lowering the Gibbs energy and therefore increasing the solute's solubility. Simply put, understanding the genesis of self-aggregation potential hinges on the structure of the hydrotrope–water mixture surrounding the drug molecule. [15]

2.2.2. Structure-breaker and structure-maker:

The donor–acceptor molecule's electrostatic force is so important in hydrotropic solubilization, they are also known as structure-breakers and structure-makers.

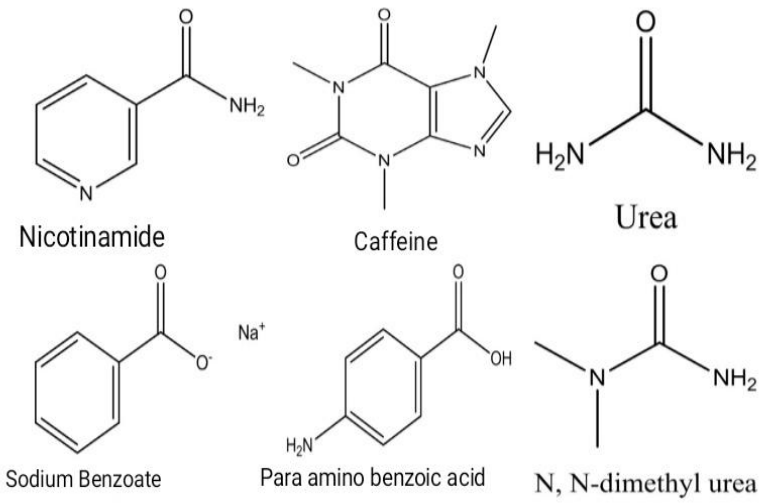


Fig: 3. hydrotropic compounds that are commonly used.

Increased solubility is aided by solutes that can both donate and accept hydrogen. Solutropic agents such as urea solubilize molecules by altering the nature of the solvent, specifically the solvent's ability to participate in structure formation or engage in structure creation via intermolecular hydrogen bonding. Chaotropes are structure-breaker hydrotropes, while kosmotropes are structure-maker hydrotropes. By strengthening the hydrophobic interaction, Kosmotrope lowers the critical micelle concentration, or CMC, and hence lowers the cloud point. Kosmotrope affects the cloud point in two ways: (a) it aids in the formation of larger micelles, and (b) it reduces hydration. Cyclodextrin acts as a water structure builder and lowers the cloud point of amphiphilic medicines including promazine hydrochloride (PMZ) and promethazine. [15]

2.2.3. Ability to form micelles like structure:

The self-association of hydrotropes with solutes into a micellar configuration is the basis for this mechanism. They essentially produce stable mixed micelles with a solute molecule, which reduces electrostatic repulsion between the head groups. Hydrotropes including alkylbenzene sulfonates, lower alkanoates, and alkyl sulphates self-associate with solutes to form micelles. Through a self-association process, nicotinamide, an aromatic anionic hydrotrope, boosts riboflavin solubility. Anionic hydrotropic agents like sodium salicylate reduce electrostatic repulsion between PMZ's head groups, resulting in stable mixed micelles.[15]

3. Selection of Hydrotrope:-

It is clear from previous studies that the aqueous solubility of poorly water soluble medicines increases as the concentration of hydrotrope rises. As a result, substantial concentrations of the hydrotropic agent should be utilised. Distilled water was used to make the hydrotropic solution. sodium benzoate, niacinamide solution, sodium salicylate, sodium acetate, urea, sodium citrate are some examples of hydrotropic solutions.

The hydrotropes should be selected appropriately utilising the proper solubility determination method for a sufficient increase in solubilization as shown in (fig.4), distilled water or hydrotropic solution was added to a glass bottle, and the gross weight, including the cap, was calculated. Then a few milligrammes of fine dry powder were added. The bottle was forcefully shaken by hand. When the medication has entirely dissolved. Repeat the technique until part of the surplus medication is not dissolved.

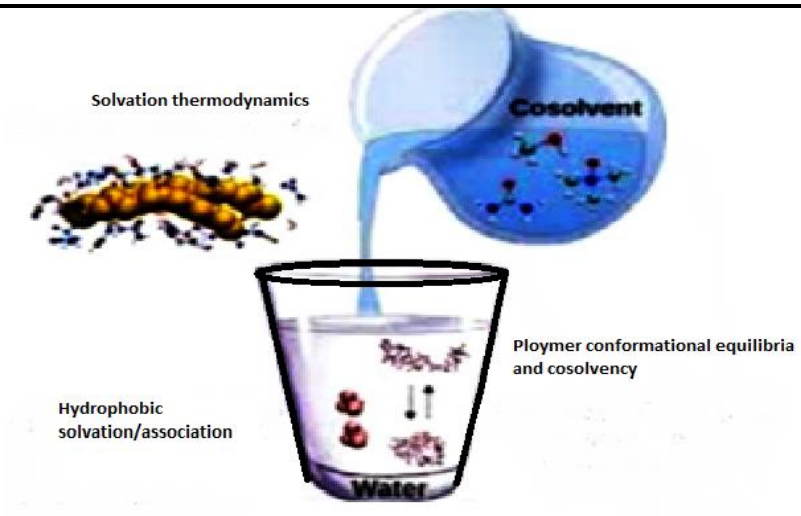


fig.4:- selection of hydrotropic agent.

The gross weight was taken once more. The difference between the two values was used to establish an approximate solubility and solubility enhancement ratio. All of the medications are subjected to the same computation. The hydrotropic solution with the lowest solubility enhancement ratio was chosen as a result. The results obtained should be comparable to those obtained using the IP method.[11]

4. Preparation of Hydrotrope:-

Urea, guanidinium chloride, nicotinamide, tetraalkyl ammonium halides, aromatic sulfonates, sodium thiocyanate, and other chemicals have all been employed as hydrotropes.[17]Hydrotropes are produced by sulphonation of an aromatic hydrocarbon solvent (i.e., toluene, xylene or cumin). The ensuing aromatic sulphonic acid is neutral mistreatment AN applicable base (e.g., atomic number 11 hydroxide) to supply the salt or hydrotrope. The hydrotropesar 'pure' substances however made and transported in either binary compound solutions, generally at a 30-60 the extent of activity, or in granular solids generally at 90-95 % level of activity. The other components of granular solids include sodium sulfate and water. Liquid product is produced in a closed system. 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/derivatives for further chemical manufacturing processes or uses. [3]

4.1. Experimentally Preparation of hydrotropic solutions:-

Hydrotropes (tri sodium citrate, urea, sodium acetate, sodium benzoate, and sodium salicylates) were dissolved in triple distilled water to achieve different molar concentrations of 0.5M, 1M, and 2M.

Study of saturation solubility:-

The method described by Higuchi and Connors was used to conduct saturation solubility studies in triplicate. Excess pure drug was added of varying molar hydrotrope solutions in a screwcap tube and shaken at room temperature for 24 hours in a rotary flask shaker. After reaching equilibrium, suitable aliquots were taken and filtered through filters. The filtrate was diluted with various molar solutions of hydrotropes and evaluated at different temperatures.

Formulation of suspensions:-

From the results of saturation solubility showed that sodium benzoate increases solubility more than other hydrotropes, formulations with sodium benzoate hydrotope as a structured vehicle in various molar concentrations, xanthan gum, acacia, and sodium alginate as a suspending agent were developed. negative coolant, sodium saccharin as a sweetener, and menthol as a flavouring ingredient. [18]

4.2 Commonly used hydrotropes:-

Urea, Sodium benzoate, Nicotinamide, Potassium citrate, Potassium acetate, Benzosulfonate, Polyethylene glycol 400 (PEG 400), Propylene glycol (PG), Caffeine, Sodium accurate, Sodium p-Benzoate, Sodium acetate, Sodium salicylate, Sodium citrate, Piperazine, Resorcinol, etc.[10]

5. The distinction between hydrotropy and other cosolvency techniques:

Simple phase mixing, or the cosolvency process, and salting-in action are not the same as hydrotropy. While the self-aggregation of hydrotropes is similar to that of surfactants, there are some significant distinctions. When compared to micellized surfactants, hydrotropesolubilization is defined by the comparatively high concentrations of hydrotrope needed, likewise because the larger amounts of fabric solubilized. Hydrotropes also have a better ability to selectively solubilize guest molecules than micellised surfactants. Long hydrocarbon chains describe surfactants, whereas short, bulky hydrocarbon groups characterise hydrotropes. When comparing hydrotrope aggregates to micelles, the aggregation numbers seen in hydrotrope aggregates are smaller. By comparing the properties of hydrotropes and long chain surfactants, it can be seen that hydrotropes tend to form loose aggregates while long chain surfactants tend to form micelles. [3]

6. Characteristics of hydrotropes:-

- Completely soluble in water and practically insoluble in system.
- Hydrotropes are surface active and aggregation in aqueous solution due to their amphiphilic structure.
- Should not produce any temperature when dissolved in water.
- Cheap and easy availability.
- Non toxic and non reactive.
- Insensitive to temperature effects, when dissolved in water.
- The solvent character being independent of pH, high selectivity, and the absence of emulsification are the other unique advantages of hydrotropes.[19]

6.1 Features of Hydrotropes:-

- Unprecedented solubilization increase.
- Very high selectivity.
- Easy recovery of solute from solution.
- Economical and cost effective.
- Absence of emulsion.
- Absence of hazards present in other solvents used in extractive separation. [3, 20]

6.2 Properties of Hydrotropes:-

- Hydrotropes are water-soluble, surface-active chemicals that can improve the solubility of organic solutes such esters, alcohols, aldehydes, ketones, hydrocarbons, and lipids.
- All are non reactive and nontoxic and don't manufacture any temperature result once dissolved in water.
- The solvent character being independent of pH, high selectivity, and the absence of emulsification are the other properties of hydrotropes. [3]

6.3 Advantages of hydrotropic Solubilization technique:-

- The solvent property is independent of pH, has excellent selectivity, and does not require emulsification, hydrotropy is seen to be preferable to alternative solubilization methods such as miscibility, micellar solubilization, cosolvency, and salting in. [21]
- It merely takes a few minutes to combine the medication and the hydrotrope in water.
- It does not necessitate modifying hydrophobic medicines chemically, using organic solvents, or preparing an emulsion system.
- It can be used to substitute organic solvents in titrimetric and spectrophotometric measurements of poorly water soluble medicines. Hydrotropic solutions can also be used for TLC of drugs that are weakly water soluble, eliminating the need for an organic solvent. As a result, it is a cost-effective, safe, and user-friendly method.
- By combining agents in lower concentrations, it may be possible to minimise the total concentration of hydrotropic agents required to produce a slight improvement in solubility.
- It's a new, easy, cost-effective, safe, accurate, precise, and environmentally friendly approach for analysing poorly water-soluble pharmaceuticals that doesn't require the use of organic solvents.
- It eliminates the need of organic solvents, avoiding issues such as residual solvent toxicity, inaccuracy owing to volatility, pollution, and cost, among others.[10, 22]

7. Mixed Hydrotropy:-

The principle of mixed hydrotropic solubilization was used to create solid dispersions of the medication. When compared to a pure bulk drug sample, solid dispersions containing a blend of urea and sodium citrate as water-soluble carriers show rapid drug release.[23] The mixed solubilisation technique is solubility of poorly soluble medications utilising blends of hydrotropic agents, which may have a synergistic enhancement effect on the solubility of poorly soluble drugs while also reducing adverse effects due to a decrease in the concentration of individual hydrotropic agents. [4]The inclusion of more than one hydrotropic agent improves the solubility of poorly soluble medicines. In addition to the additive impact, hydrotropic agents taken in combination may improve the solubility of poorly soluble medicines by a miraculous synergistic effect. [10]

7.1 Advantages of Mixed Hydrotropy Solubilization:-

- By combining agents in lower concentrations, it may be possible to reduce the huge total concentration of hydrotropic agents required to produce a modest improvement in solubility.
- It is new, simple, cost-effective, safe, accurate, precise and environmental friendly method for analysis (titrimetri & spectrophotometric) of poorly water-soluble drugs. [4]
- It precludes the use of organic solvents andthus avoids the problem of residual toxicity,error due to volatility, pollution, cost etc.[5]

7.2 Significance of Hydrotropy:-

- Organic molecules, colours, medicines, and biochemicals have all been solubilized with hydrotropes.
- Hydrotropes have been used in the development of extractive separation methods for protein separation and distillation as an extractive solvent for separation of phenolic mixtures with low boiling points.
- Aqueous hydrotrope solutions are a safe and efficient way to extract natural compounds and perform organic synthesis processes.

- Hydrotropes are used in a variety of applications including detergent formulation, health care, and domestic cleaning.
- They've been employed to make heterogeneous reactions go faster.
- They are utilised as a scent extraction agent.
- In chemical compositions, as fillers and extenders.
- Pharmaceutical formulations are being developed.
- In nanotechnology, hydrotropic solubilization is used (by controlled precipitation).
- Hydrotropy is used to allow poorly water-soluble medications to be released quickly from suppositories.

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