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Review Article

A Review On Hydrotropy Technique Used In Solubility Enhancement

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ABSTRACT

Oral route is the most desirable and preferred method of administering therapeutic agents for their systemic effects, but poorly solubility of drug is major challenge for formulation scientist. About 40% of orally administered drugs suffer from formulation difficulties related to their water insolubility. Dissolution rate, absorption, distribution and excretion of a moiety depend upon its solubility characteristics. On the basis of solubility, drugs are classified into four classes of the BCS classification. Solubility challenges are faced in the Class II and Class IV of the BCS system. To improve solubility and bioavailability of poorly soluble drug we use various methods or techniques. The methods like solid dispersion, complexation, liquisolid, hydrotropy, sonocrystallization, self-emulsifying method, are commonly referred for solubility enhancement. In this review we concentrated on the hydrotrophy method used in solubility enhancement of poorly soluble drugs.

INTRODUCTION

A variety of approaches can be used to increase the solubilization and bioavailability of poorly water-soluble drugs [6]. Micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, and other procedures are often used for medication solubilization. Solubilization of poorly soluble pharmaceuticals is a common difficulty in novel chemical entity screening investigations as well as formulation design and development. The ultimate quantity of analyte that may be dissolved in a volume of solvent is known as solubility[8]. It can be characterised both quantitatively and qualitatively. In qualitative term, it can be defined as Spontaneous interaction of two or more substance to form a homogenous dispersion. In quantitative term, Concentration of a substance (solute) in a given volume of solvent at a certain temperature to form homogenous [17]. The solubility of drug may be expressed as percentage, parts, molality, molarity, mole fraction & volume fraction. In

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pharmaceuticals, solubility equilibria are very important. Drugs having poor water solubility (BCS class II and class IV) shows dissolution related problems [15].

Hydrotropy is defined as a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute and the chemicals which are used in hydrotropy are called hydrotropes. For example, sodium benzoate, urea, sodium salicylate and ibuprofen sodium etc. 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 Solubilization of poorly water – soluble drug. To carry out analysis of poorly water-soluble drug. The drawback of these organic solvent includes high cost. Volatility, pollution and toxicity such as nephrotoxicity or teratogenicity. So, these organic solvents are spectrophotometric analysis. Hydrotropic Solubilization concept is one of best choice to preclude the use of organic solvent.

[1] Hydrotropy report first in 1916 by Newberg 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]

Definition of 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 described in terms of solvent parts are required for one part of solute is explained in Indian pharmacopeia which as in table. [3]

Table No 1: Definition of solubility on the basis of particles dissolved in solvent

Definition	Parts of solvent required for one part of solute
Very Soluble	< 1
Freely soluble	1 – 10
soluble	10-30
Sparingly soluble	30-100
Slightly	100-1000
Veryslightlysoluble	1000-10000
Insoluble	> 10,000

The BCS is a scientific paradigm for categorising pharmaceuticals based on their water solubility and intestinal [11]. When paired with the drug product's in vitro dissolving properties, the BCS considers three important factors: solubility, intestinal permeability, and dissolution rate, all of which influence the rate and amount of oral drug absorption from sudden release solid oral-dosage forms [21].

According to the BCS which was classified by US Food & Drug Administration (FDA), pharmaceuticals are classified into four fundamental classes based on their solubility and permeability (Table 1). Drugs of class II & class IV are face solubility problem. [3,4] So, increase the solubility turns increase bioavailability of BCS Class II & Class IV drugs.[5].

Table No 2: Biopharmaceutical Classification System [15].

CLASS	SOLUBILITY	PERMEABILITY	ABSORPTION PATTERN	RATE L.S IN ABSORPTION
1	High	High	Well absorbed	Gastric emptying
2	Low	High	Variable	Dissolution
3	High	Low	Variable	Permeability
4	Low	Low	Poorly absorb	Case by Case

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 drugs 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]

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 involves 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.

Following steps are involve in process of Solubilization

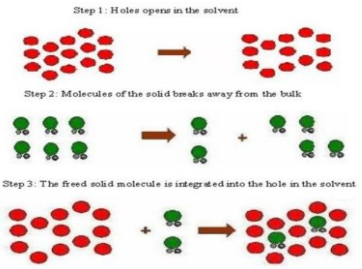

Fig No 1: Steps are involve in process of Solubilization

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]

Hydrotropy method:

Hydrotropy is mostly used for solubility enhancement of ALBENDAZOLE. Hydrotropy is a solubilisation process in which a high amount of a second solute is added to increase the aqueous solubility of a third solute [18]. The method by which it improves solubility is more directly associated with complexation, which involves a weak contact between hydrotropic agents such as sodium alginate, sodium acetate, sodium benzoate, urea and poorly soluble drugs. The "salting in" of non-electrolytes known as "hydrotropic salts" is caused by many salts with large anions or cations that are themselves extremely soluble in water, a process known as "hydrotropism."[22]. Hydrotropic solutions are non-colloid and have a weak contact between the hydrotropic agent and the solute [10]. Hydrotropy is a solubilization procedure, whereby expansion of a lot of the second solute, the hydrotropic operator brings about an expansion in the fluid solvency of first solute. Hydrotropic operators are ionic natural salts, comprises antacid metal salts of different natural acids [5]. Added substances or salts that expansion dissolvability in given dissolvable is said to “salt in” the solute and those salts that lessening 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 is known as “hydrotropism.” [18]. Hydrotropy assigns the expansion in dissolvability in water because of the nearness of enormous measure of added [14]. The instrument by which it improves dissolvability is all the more firmly identified with complexation including a powerless connection between the hydrotropic operators such as sodium benzoate, sodium acetic acid derivation, sodium alginate, urea, and the ineffectively solvent medications [18]. Hydrotropy is a developing ground-breaking drug solubilization procedure which has been appeared to fundamentally improve the dissolvability of numerous medications. Hydrotropy alludes to the procedure by which a lot of solute improves the dissolvability of another intensify (the

medication). They are as often as possible anionic sweet-smelling and non-sweet-smelling mixes and can be once in a while impartial [11]. The hydrotropes are known to self-collect in the arrangement. The order of hydrotropes based on atomic structure is troublesome since a wide assortment of mixes has been accounted for to show hydrotropic conduct. Explicit models may incorporate ethanol, sweet-smelling alcohols such as resorcinol, parallel, catechol, α and β-naphthols and salicylates, and alkaloids such as caffeine and nicotine, and ionic surfactants such as diacids, sodium dodecyl sulphate, and dodecyl oxydibenzene [1]. The fragrant hydrotropes with anionic head gatherings are for the most part contemplated mixes [7]. They are enormous in number in view of isomerism, and their successful hydrotrope activity might be due to the accessibility of intuitive pi (π) orbital [17].

Hydrotropy is an expansion in water dissolvability brought about by the expansion of a subsequent solute. A few hydrotropic operators, for example, urea, caffeine, sodium benzoate, sodium salicylate, and nicotine amide, have been recognized. The fundamental utilization of this wonder is to build the water solvency of insoluble or somewhat dissolvable medications; there are no reports of the advancement of a hydrotropic plan containing a percutaneous enhancer for the transdermal definition of a water-solvent medication [12]. Unsaturated fat liquor esters are usually utilized as adjuvants for beautifiers and pharmaceuticals. A few esters have been utilized as pervasion enhancers for medications. The hydrotropy acts as increase in the solubility of solutes by the addition of high concentration of alkali metal salts of different organic acids [15]. Which forward by Neuberg, there are several concentrated aqueous hydrotropic agents is available synthetically or naturally. Some of our hydrotropic agents describe as sodium benzoate, niacinamide, citric acid, tannic acid, piperazine, and caffeine have been observed to enhance the aqueous solubility of poorly water-soluble drugs.

Fig No 2: Hydrotrophy method

Most of the drug is given through the oral route, and their solubility plays a crucial role in their absorption, so various techniques have been used to improve the solubility of hydrophobic drug 2. Highly soluble drugs show greater solubility in 250 ml of aqueous phase at pH of 1.0- 7.5 and highly permeable drugs show 90% permeability in intestinal membrane 3. Albendazole (ABZ) is a hydrophobic drug that comes under II class of biopharmaceutical classification system. It shows anthelmintic activities 4, used to inhibit or kill helminths species such as Ascaris Lumbricoides, A. sum, and Necator americanus 5. Enhancing the effectiveness of ABZ can be possible by improving its dissolution 6. To enhance the solubility of ABZ, the most desirable technique for solubility enhancement is mixed hydrotropy 7. The mixed hydrotropy technique has been used to enhance the hydrophobic drug's solubility by using hydrotropic blends of desirable hydrotropes, or we can say that a large concentration of secondary hydrophilic solute is added with a drug that enhances the aqueous solubility of the hydrophobic drug. Hydrotropes are those compounds that have been used to enhance in solubility of hydrophobic drugs[18] .

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.

Hydrotropes:

Hydrotropes are compounds that improve the solubility of surfactants in water, particularly those

structured to contain high levels of builders or alkalinity. They are usually incorporated into a formulation at levels of up to 5%. Hydrotropes are a special class of material to be used at relatively low levels for solubilization of surfactants. Builders and other electrolytes will depress cloud point temperature or solubility of surfactants in aqueous systems [12]. Hydrotropes are used to adjust the cloud point of the formulation. A higher concentration of hydrotrope generally leads to higher cloud points. Solvents and more-soluble surfactant classes can also be used to increase solubility. The choice of hydrotrope is based on the builder levels and requirements for each specific application. When formulating with a hydrotrope it is best to use a hydrotrope that will contribute to the overall desired effectiveness of the formulation.

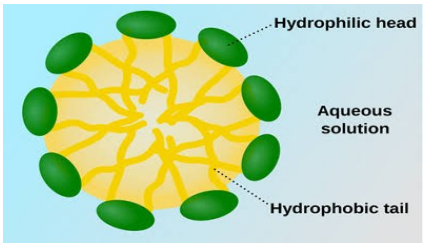

Fig No 3: Structure of Hydrotropes

Preparation of Hydrotrope:

Urea, guanidine chloride, nicotinamide, tetra-alkyl 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 hydrotropes are '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]

Advantages of Hydrotropes:

Hydrotropy is the most important tool for the other solubilization methods, such as micellar solubilization, spray drying, salting, and miscibility, because of the independent character of the solvent [17]. Chemical modification is not required in the hydrotropic method. It is efficient and simple for various pharmaceutical industries as organic transformations. They are easily available, having low cost. It reduces the chances of residual toxicity. Hydrotropes do not need any specific temperature when dissolved in water [10].

- Hydrotropy is important tool to the other solubilization methods, such as micellar solubilization, salting, and miscibility because of the independent character of solvent [16].
- Hydrotropes do not require any chemical modification of drugs.
- Hydrotrope should not produce any temperature condition when it dissolved in water [1].
- It only requires mixing the drug with the hydrotrope in water.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of the emulsion system [3].
- It provides an efficient, simple, and green platform for various pharmaceutical industries as organic transformations.
- They are easily available and having a low cost.
- Nontoxic and nonreactive [10].

Disadvantages of hydrotropes:

- This technique may have some disadvantages like cost, toxicity and environmental hazards. This can be overcome by using less costly hydrotropic agents.

- Nowadays hydrotropic agents are used to develop dosage forms in various forms such as solid dispersion, mouth dissolving tablets, injections.

classification of hydrotropic agents:

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

Characteristic of Hydrotropes:

- Completely dissolvable in water and essentially insoluble in the framework.
- 2 Hydrotropes are surface dynamic and total in watery arrangement in light of their amphiphilic structure [11].
- Should not create any temperature when disintegrated in water.
- Cheap and simple accessibility [10].

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.

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.
- Organic molecules, colours, medicines, and biochemical 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.
- 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.

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]

MECHANISM OF HYDROTROPY:

Each hydrotrope has specific capacity toward a specific segment in the blend, which encourages simple recuperation of the hydrotrope arrangement by controlled weakening with water [6]. Dissolvability does not demonstrate any apparent increment even after the expansion of hydrotrope in the fluid stage, however on ensuing increment in the centralization of hydrotrope, the solvency of the natural compound present in watery stage

increments essentially. This solvency increment in the natural compound when present in water could be because of the development of sorted out gatherings of hydrotrope particles at basic focuses. The basic convergence of hydrotrope is named as the base hydrotrope fixation minimum hydrotropic concentration (MHC) which is the base required hydrotrope focus in the watery stage above which the dissolvability of the natural compound in fluid stage increments altogether [8]. This expansion is apparently through a self-collection process due to their amphiphilic nature and differs with the idea of the natural compound. The expanding pattern is kept up just up to a specific grouping of hydrotrope past which there is no calculable increment in the dissolvability of natural compound in the watery stage [9]. This convergence of hydrotrope is named as the greatest hydrotrope focus. Barely any models important to the system of hydrotropy are exhibited beneath: The plant cell divider is comprised of phospholipid bilayers [17]. The hydrotrope demolishes the phospholipid bilayer and infiltrates through the cell divider into the inward structures. The water drenching indicates exceptionally less impact on stopper cells. The cellulose and suberin lamellae are the cell divider part of plug cells. The suberin lamella makes the plug cell impermeable to water. In any case, the hydrotrope arrangements tear open the water-impermeable suberin lamella and after that the develop stopper cells [9]. The plug cell layers are bothered by the hydrotrope, and the watery arrangement enters through the cell divider. At the point when the inward part is presented to the hydrotrope arrangement, the cell swells and liberates the cells from firmly bound structures [18]. Hydrotropic arrangements accelerated the solutes; out of the arrangement on weakening with water in this manner empower the prepared recuperation of the disintegrated solutes. Hydrotropic operators can make the O/W and W/O microemulsion and the lamellar fluid precious stone destabilized, which results in the "stage change" from lamellar fluid gem stage to bi-constant structure this is called as hydrotrope-solubilization activity. Nutrient C demonstrates hydrotrope-solubilization activity [19]. Hydrotropes are known as "coupling specialists.". At the point when hydrotropes are added to a turbid fluid with generally high-water substance makes the fluid straightforward in light of stage change [10].

Hydrotropic solubilization study of various poorly water-soluble drugs

Sr. No.	Drugs	Hydrotrope
1	Ibuprofen	Sodium acetate, Sodium benzoate, Sodium toluene sulfonate, Sodium salicylate and Sodium toluate
2	Ketoprofen	Potassium acetate
3	Naproxen	Niacinamide
4	Piroxicam	Ibuprofen sodium
5	Olanzepine	Sodium benzoate, sodium acetate, sodium bicarbonate, sodium chloride, sodium gluconate, thiourea, trisodium citrate and urea.
6	Lornoxicam and Paracetamol	Urea
7	Aceclofenac	Urea and sodium citrate
8	Theophylline	Urea and sodium citrate
9	Glipizide	PEG (Polyethylene glycol) 4000, mannitol and urea
10	Escitalopram	Niacinamide
11	Chlorobenzene	Citric acid, sodium benzoate and urea
12	1,1/1,2-diphenylethane	Diethylnicotinamide, sodium pseudocumenesulfonate and sodium thiocyanate

13	L-Tyrosine	Caffeine, Nicotinamide, Sodium salicylate and Sodium Benzoate
14	m/p– amino nitrobenzene	Sodium benzoate, sodium saccharin, dimethyl benzamide
15	Methyl benzoate	Citric acid, urea and nicotinamide
16	Furfural	Urea, tri-sodium citrate, sodium toluate and sodium benzoate

CONCLUSION

By this article we conclude that, Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water-soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. Solubility can be enhanced by hydrotropic solubilization techniques and number of folds increase in solubility is reported too.

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