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HYDROTROPIC SOLUBILIZATION TECHNOLOGY AN ECOFRIENDLY ANALYSIS TO IMPROVE SOLUBILITY, DISSOLUTION AND BIOAVAILABILITY OF VARIOUS POORLY WATER SOLUBLE ANTIVIRAL DRUGS

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ABSTRACT

Solubility is one of the most essential parameter to achieve desired concentration of drug in the systemic circulation for pharmacological response to be shown. Drug efficacy can be severely limited by poor aqueous solubility of various drugs. Several drugs also show side effects due to their poor aqueous solubility. There are various techniques are used to enhance the aqueous solubility of poorly water-soluble drugs and hydrotropic solubilisation technique is one of them. A hydrotrope is one of the compound that solubilizes hydrophobic compounds in aqueous solution. Various antiviral drugs belongs to class iv in biopharmaceutics classification system (BCS). The major problem of this drug having poor solubility in biological fluid which result in poor bioavailability after oral administration. Hydrotropic solubilization technique is the best approach to increase the water solubility of poorly water-soluble drugs and overcome problem-related with organic solvents. This review investigates the characterstic of hydrotropy and hydrotropic agents and their different advance toward the pharmaceutical analysis. This review also provides the future prospective concerned with the green pharmaceutical analysis.

KEYWORDS: hydrotropy, Ecofriendly analysis, solubility, antiviral drugs.

INTRODUCTION

The current main problem in the pharmaceutical industry is related to the strategies that used to increase the aqueous solubility of drugs, as almost 40% of the newly discovered drugs suffering from poor aqueous solubility.[1] Solubility is one of the important substance to complete the desired pharmacological action. The therapeutic effectiveness of a drug depends upon the bioavailability and typically is attributed to the solubility of drug moiety.[2] Presently, new formulation technologies are available to increase solubility as well as dissolution profile to enhance oral bioavailability.[3] In addition to these technologies, "hydrotropy" is one of the recognized techniques available to solve the solubility issues. This review will complicated on various hypothetical and investigational mechanisms, geometrical features and applications of hydrotropic agents in the pharmaceutical field, which will use the researchers in exploring hydrotrophy for progress in drug delivery.

SOLUBILITY

Solubility is the phenomenon of dissolution of a solute in the given solvent to form a homogenous mixture or system. It is aso defined in quatitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion.[4] The pharmacopoeial list the solubility of drug in terms of a number of parts of solent required to dissolve one part of solute. For the drug substances where the exact solubilities are not known, the pharmacopoeia provides general terms to report a given range. These descriptive terms are listed in Table 1.

Table 1: Expression of Solubility.[5]

Solubility pattern	Parts of solvent required for one part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Insoluble	>10,000

Requirement of Solubility[6]: GIT drug absorption can be limited by a variety of factors. One of the most significant factors is poor aqueous solubility and poor permeability of the drug molecule. When an active agent is administered orally it must first dissolve in gastric or

intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation. Hence, these two areas of pharmaceutical research that focus to increase the oral bioavailability of active agents include; enhancing of solubility nd dissolution rate of poorly aqueous soluble drugs. The basic aim of the formulation and development section is to make that drug available at proper site of action within optimum dose.

Techniques of Solubility Enhancement[7, 8]

Following are various techniques used to enhance the solubility of poorly soluble drugs.

A. CONVENTIONAL TECHNIQUES

a. Physical Modification Techniques

1. Particle size reduction
2. Micronization
3. Nanosuspension
4. Other techniques
5. Modification of the crystal habit
6. Polymorphs
7. Pseudo polymorphs
8. Drug dispersion in carriers
9. Solid dispersions
10. Eutectic mixtures
11. Solid solutions
12. Complexation
13. Stacking complexation
14. Inclusion complexation
15. Solubilization by surfactants
16. Microemulsions
17. Self-micro emulsifying drug Co-solvency

b. Chemical Modification Technique

This approach is successful mostly in case of corticosteroids, e.g., By chemical modification, the solubility of betamethasone alcohol (poorly soluble drug having a solubility of 5.8 mg/100 ml) is increased 1500 times (10 g/100 ml) by its esterification with disodium phosphate.

B. NOVEL TECHNIQUES

1. Nanotechnology approaches
2. Nanocrystals
3. Nanomorphs
4. Hydrotrophy
5. Co-crystallization
6. Co-solvency

Hydrotropy

The term hydrotropy was first coined by Scientist Carl Neuberg in 1916, but the practical suggestion were introduced as late as 1976 by Thoma and co-workers.[9] In this technique add a large amount of secondary solute to increase the aqueous solubility of the poorly soluble drug. However, the term has been used in the literature to nominate non- micelle forming substances, either liquid or solid, organic or inorganic, which is capable of insoluble solubilizing compounds.

Hydrotropic agent

The hydrotropic agents are known as non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of insoluble solubilizing compounds. The chemical structure of the racial Neuberg's hydrotropic salts (prototype sodium benzoate) having two essential parts one is anionic group, and second one is hydrophobic aromatic ring. The anionic group is involved in consider about high aqueous solubility, which is a prerequisite for a hydrotropic substance. The type if anion meta ion recignise to have a minor effect on phenomenon. On the other hand, the planarity of the hydrophobic part has been appreciated as an important factor in the mechanism of hydrotropic solubilization.[10] Several additives or salts that increase the solubility in a given solvent are known as "salt in" the solute and salts that decrease the solubility "salt out" the solute, Various salts have large numbers of anions and cations that are itself very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism". Hydrotropic solution does not show any colloidal properties and involve a weak interaction between the hydrotropic agent and solute.[11]

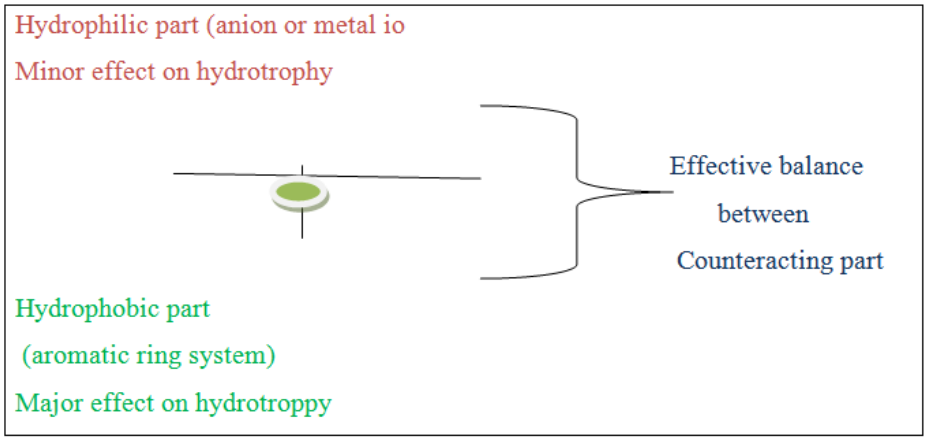

Fig. 1: Structure of hydrotropic agent.[12]

Mechanism of hydrotropic agents

The enhancement of solubility of the poorly aqueous soluble drug by using the hydrotrope which is based on the molecular self-association of the hydrotrope and on the association of various hydrotrope molecules with the solute. While the hydrotropic agents are widely used in various industial applications, only medicinal information on the mechanism of hydrotropy available. Various hypotheses and research efforts are reference to clarify the mechanism of hydrotrophy. The available proposed mechanism can be categorise according to three designs.[13]

(a) Self-aggregation potential,

b) Structure-breaker and structure-maker,

(c) Ability to form micelle-like structures.

These unique geometrical features and different association patterns of hydrotrope assemblies distinguish them from other solubilizers.[14,15]

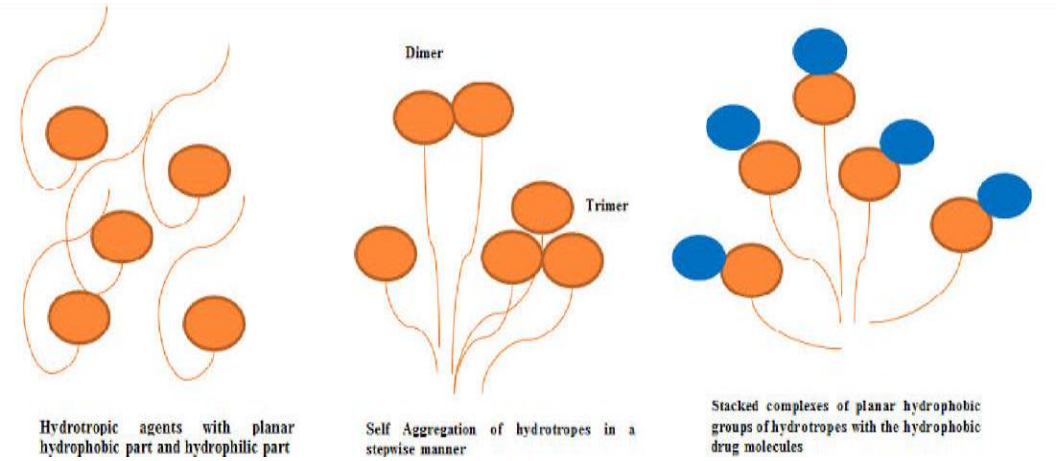

Fig no: Mechanism of hydrotrope.

Self-aggregation potential

Minimum hydrotropic concentration (MHC) is a critical concentration at which hydrotrope molecules start to aggregate, i.e., self-aggregation potential.[16] The solubilization power of hydrotropic agent is governed by their self-aggregation potential.[17] This potential depends upon their amphiphlilic features and the nature of a solute molecule.[14,18] They mainly show thw volume fraction –dependent soubilization potential 18. Initially, hydrotrope molecules undergo primary association in a pairwise manner which is followed by successive steps to form trimers, tetramers, and so on and these complexes (trimers, tetramers) could then lead to higher aqueous solubility. These outcomes have develop from tha fluorescence emission methods 19., crystallography analysis, molecular dynamics replication, and thermodynamic solubility experiments.[20,21,22] Aside from these, they may acts as bridging agents by reducing the Gibbs energy to increase the solubility of a solute.[23] Simply, the structure of the hydrotrope water mixture around the drug molecule is one of the very importat key for understanding the origin of the self-aggregation potential.[24]

Structure-breaker and Structure-make

In hydrotropic solubilization technique an electrostatic force of the donor-aceptor molecue plays a important role; hence, they are also known as a structure breaker and a structure-maker.[25,26] Solutes which are capable for the both hydrogen donation and acceptance which helps to enhance the solubility. Hydrotropic agents, eg.urea and sodium benzoate, apply their solubilizing effect by changing the nature of the solvent, specifically by altering the solvent's ability to participate in formation of structure or its ability to locate in structure formation via intermolecular hydrogen bonding.[27] Structure-breaker hydrotropes are known as "chaotropes" while structure –maker hydrotrope are known as "kosmotropes".[28] Kosmotropes reduce the critical micelle concentration (CMC) by increasing the hydrophobic interaction which decreses the cloud point. A kosomotrope influence influences the cloud point in two ways, i.e., it helps (i) to form bigger micelles and (ii) to decrease hydration. In the case of amphiphilic drugs, promazine hydrochloride (PMZ) and promethazine, cyclodextrin act as water structure-maker and reduce cloud point.[29]

Ability to form micelle-like structures

This mechanism is based on the self-association of hydrotropes with solutes into a micellar arrangement.[30] They form stably mixed micelles with a solute molecule decresing the electrostatic repulsion between the head groups.[31] Hydrotropic agents, that form micelle like

structure such as alkyl-benzene sulfonates, lower alkanoates, and alkyl sulphates, exhibit selfassociation with solutes and form micelles. Aromatic anions hydrotropic agent, i.e., nicotinamide, improve the solubility of riboflavin via a self-association mechanism.[32] In the case of PMZ, anionic hydrotropic agents, such as sodium salicylate, from stably mixed micelles by decreasing the electrostatic repulsion between the head groups of PMZ.

How to Prepare Hydrotopes[33]

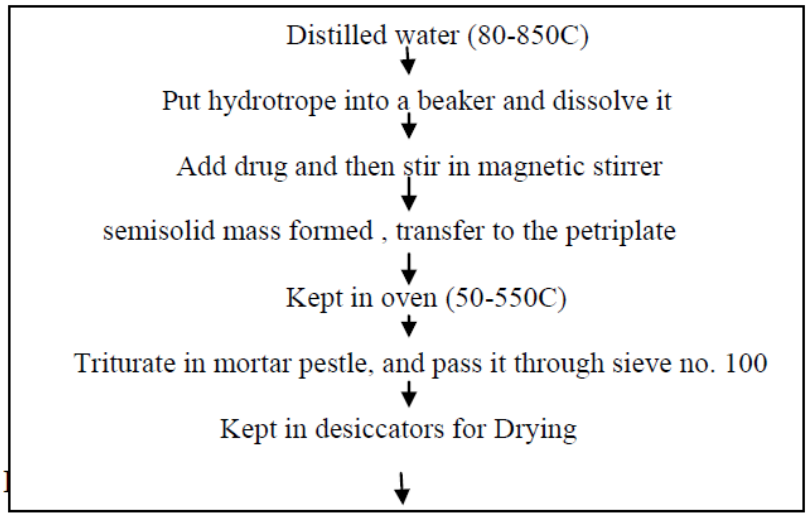

Fig. 2: Flow Chart for hydrotropes preparation.

How To Determining Solubility of Drug In Hydrotropic Agents[34]

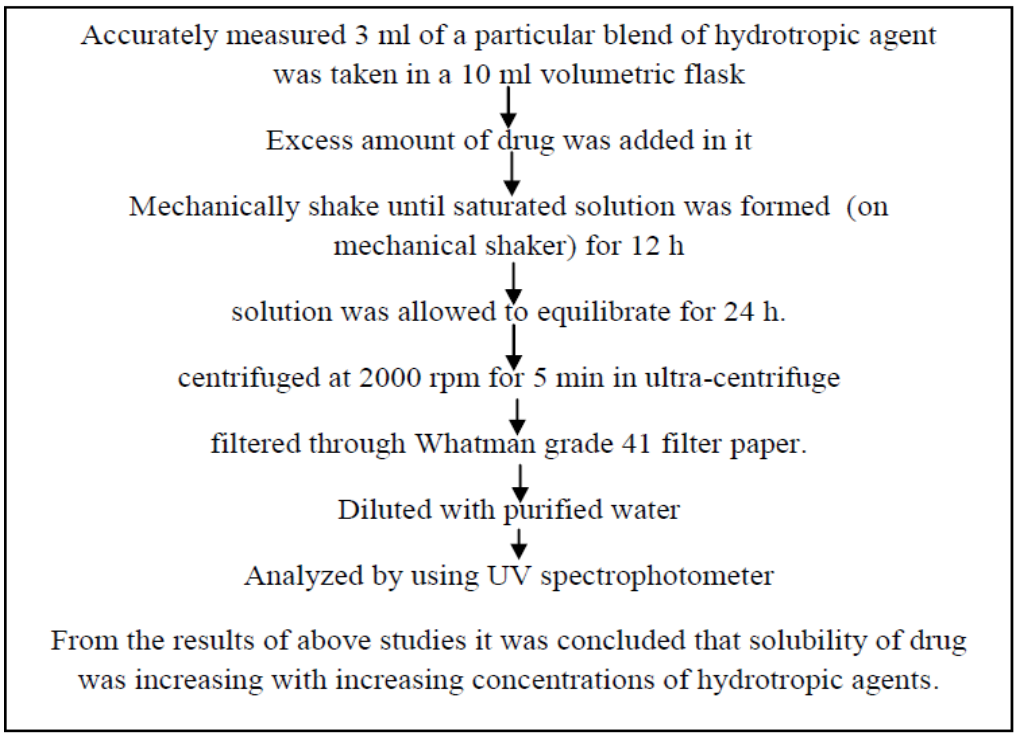

Fig 3: Flow chart for determine solubility of drug in hydrotope.

Formula For Determine Solubility In Hdrotropic Agent[35]

$$\text{Enhancement ratio} = \frac{\text{solubility of drug in hydrotropic solution}}{\text{Solubility of drug in water}}$$

Advantages of Hydrotropic Solubilization Technique[36]

- It is a new, simple, cost-effective, safe, accurate and ecofriendly method for the analysis of poorly water –soluble drugs by and spectrophotometrically preventing the use of organic solvents.
- It only requires mixing of drugs with the hydrotrope in water.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of the emulsion system.
- It prevent the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution cost, etc.
- Hydrotropy technique is suggested to be superior as compared to another solubilization method, 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.

Disadvantages of Hydrotropic Solubilization Technique[37]

- There are issue related to toxicity which is associated with excess use of hydrotropic agents.
- The relatively high concentrations required to achieve the MHC limits the commercial application of hydrotropes.
- There are chances of the weak interaction between the hydrotropic agent and drugs.
- As there is the use of water as a solvent, complete removal of water cannot be achieved.

Mixed Hydrotropy

Mixed hydrotropic solublization technique is the phenomenon to enhance the solubility of poorly soluble drugs using mixture (blend) of various hydrotropic agents, which may give combined enhancement effect on the solubility of poorly soluble drugs, and also reduce the side effects due to a reduction in the concentration of individual hydrotropic agent.[38]

Advantages of Mixed Hydrotropic Solubilization Technique[39]

- It is a new, simple, cost-effective, safe, accurate, precise and eco-friendly method for the analysis (titrimetric and spectrophotometric) of poorly aqueous -soluble drugs.
- It may reduce the large total concentration of hydrotropic agents necessary to produce a complicated increase in solubility by employing a combination of hydrotropic agents in lower concentration.
- It prevent the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution cost, etc.

Table no. 2: Hydrotropic solubilization study of various poorly water soluble antiviral drugs.

Sr.No	Drug name	Hydrotropic agent	Reference No.
1	Dolutegravir sodium	8M urea	[40]
2	Neviripine	Citric acid, lactose, mannitol, Urea.	[41,42]
3	Saquinavir	Nicotinamide, Ascorbic acid. Dimethyl urea, Resorcinol.	[43]
4	Tenofovir disoproxil fumerate	2 M Sodium benzoate	[44]
5	Lamiudine	5M sodium benzoate	[45]
6	Acyclovir	4M urea & 4M sodium acetate, 5M urea	[46,47]
7	Etravirine	Citric acid, sodium salicylate, sodim benzoate.	[48]

Novel Pharmaceutical Applications Of Hydrotropic Solubilization In Various Fields Of Pharmacy[49]

- Quantitative estimations of poorly water soluble drugs by UV –visible spectrophotometric analysis preventing the use of organic solvents.
- Quantitative estimation of poorly water soluble drgs by titrimetric analysis.
- Preparation of hydrotropic solid dispersions of poorly watersoluble drugs precluding the use of organic solvents.
- Preparation of dry syrup (for reconstitution) of poorly water soluble drugs.
- Preparation of topical solutions of poorly water-soluble drugs, precluding the use of organic solvents.
- Preparation of injection of poorly aqueous soluble drugs.
- The use of various hydrotropic solubilizers as a permeation enhancers.
- The use of hydrotropy to give fast release of poorly aqueous-soluble drugs from the suppositories.

- Application of mixed- hydrotropy to prepare injection dosage forms of poorly water-soluble drugs.
- Used in the extraction of active constituents from crude drugs (in pharmacognosy field).
- Hydrotropic solutions can also be tried to prepare the dissolution fluids to carry out the dissolution studies.

CONCLUSION

By this review, we conclude that the solubility is the most critical factor in the formulation design and development. Many useful antiviral drugs may be deserted due to their poor aqueous solubility. There are various solubility enhancement techniques to enhance the solubility of poorly aqueous soluble antiviral drugs. Hydrotropy solubilization technique and mixed solvency concept are the best approaches to increase water solubility of poorly water soluble antiviral drugs and use successfully in analysis of drug. In addition to this hydrotrophy is the novel, simple and ecofriendly method for solubility enhancement of poorly soluble antiviral drugs. It is now possible that to increase the solubility of poorly aqueous soluble antiviral drugs with the help of various techniques as mentioned above.

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