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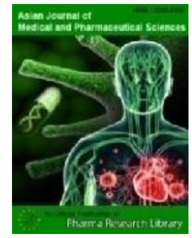

Review Article **Open Access**

A Review on Solubility Enhancement Using Hydrotropy

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A B S T R A C T

The effectiveness of formulation depends particularly on how efficiently is drug available at the site of action. Therapeutic effectiveness of a drug basically depends upon bioavailability and the solubility of drug moiety. Most of the chemical entities that are being discovered are lipophilic and have poor aqueous solubility. A more than 40% drug suffers from poor water solubility. Solubility is one of the important parameter to achieve desired concentration of drug in systemic for pharmacological response to be shown. Drug efficacy can be severely limited by poor aqueous solubility and some drugs also show side effects due to their poor solubility. There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and reducing side effects for certain drugs. This is true for parentally, topically and orally administered solutions. Use of the solubility characteristics in bioavailability, pharmacological action and solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. Hydrotropy is one of the solubility enhancement techniques which enhance solubility to many folds with use of hydrotropes like sodium benzoate, sodium citrate, urea, niacinamide etc. and have many advantages like; it does not require chemical modification of hydrophobic drugs, use of organic solvents or preparation of emulsion system.

Keywords: Bioavailability, Drug efficacy, Hydrotropy, Lipophilic, Solubility enhancement.

A R T I C L E I N F O

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1. Introduction

The important phenomenon in pharmaceutical formulation is "solubility" which plays very effective and significant role in the formulation of various dosage forms. Solubility of a compound in a particular solvent is defined as the concentration of a solute in a saturated solution at a certain temperature [1]. The solubility of a drug molecule may be critical factor determining its usefulness since the solubility dictates the amount of compound that will dissolve and therefore the amount available for absorption. If a compound has low water solubility it may be subject to dissolution rate limited absorption within the gastrointestinal residence time. In biopharmaceutical terms the solubility importance has been highlighted by Biopharmaceutical Classification System (BCS) described by Amidon in 1995 which classified the drugs into the four groups [2]. The key parameters on which BCS of a drug depends upon are solubility and permeability, solubility play an important role for the absorption of drugs [3].

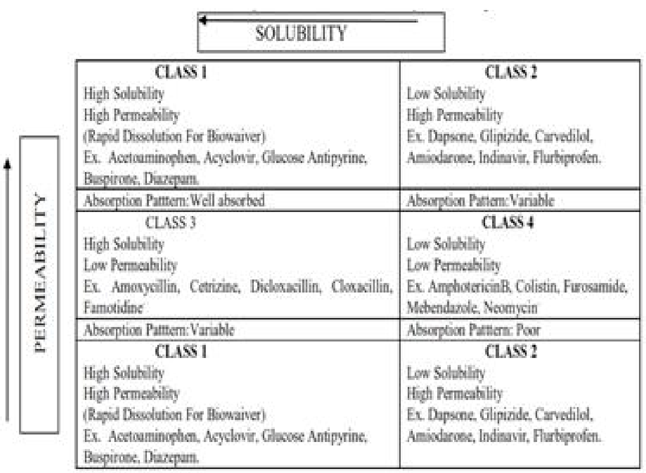

Figure 1: The Biopharmaceutical classification system for drugs [4]

Need of Solubility

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Due to advanced research &development, there are varieties of new drugs & their derivatives are available. But more than 40% of lipophilic drug candidates fail to reach market due to poor bioavailability, even though these drugs might exhibit potential pharmacodynamic activities [5]. The lipophilic drug that reaches market requires a high dose to attain proper pharmacological action. The basic aim of the further formulation & development section is to make that drug available at proper site of action within optimum dose.

Mechanism of Solubility

The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion [6-8]. A saturated solution is one in which the solute is in equilibrium with the solvent

Process of solubilization

The solubility of a solute is the maximum quantity of solute that can dissolve in a definite quantity of solvent or quantity of solution at a specified temperature. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Drug efficacy can be severely limited by poor aqueous solubility and some drugs also show side effects due to their poor solubility. Factors affecting solubility include molecular size, nature of solute and solvent, temperature, pressure, particle size and polarity. The process of solubilization involves the following steps Fig.2.

- Breaking of intermolecular or inter-ionic bonds in the solute
- Separation of the molecules of the solvent to provide space in the solvent for the solute
- Interaction between the solvent and the solute molecule or ion [9]

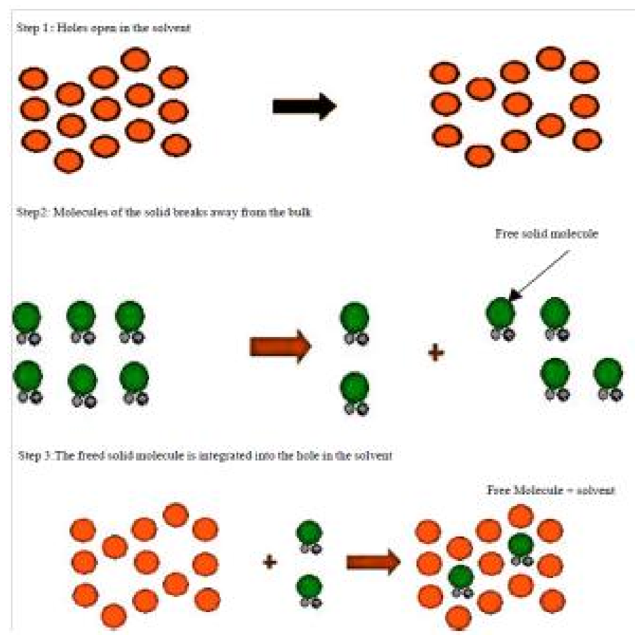

Figure 2: Process of solubilization

The term hydrotropic agent was first introduced by Neuberg (1916) to designate anionic organic salts which, at high concentrations, considerably increase the aqueous solubility of poorly soluble solutes[10]. 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. The chemical structure of the conventional Neuberg's hydrotropic salts (proto-type, sodium benzoate) consists generally of two essential parts, an anionic group and a hydrophobic aromatic ring or ring system. The anionic group is obviously involved in bringing about high aqueous solubility, which is a prerequisite for a hydrotropic substance. The type of anion or metal ion appeared to have a minor effect on the phenomenon [11]. On the other hand, planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism". Hydrotropic solutions do not show colloidal properties but they improve solubility by forming weak interactionswithsolute molecules **[**12**]**.

Table 1: Expression for approximate solubility [13]

Descriptive terms	**Relative amounts of solvents to dissolve 1 part of solute**
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1,000
Very slightly soluble	From 1,000-10,000
Insoluble or practically insoluble	More than 10,000

Hydrotropes contain both hydrophobicand hydrophilic fractions. In comparison to surfactant, they contain a very small hydrophobic fraction [14]. The efficiency of hydrotropic solubilization depends on the balance between hydrophobic and hydrophilic parts of the hydrotrope [15]. The larger is the hydrophobic part of an additive, the better is the hydrotropic efficiency; the presence of the charge on the hydrophilic part is less important [16]. Hydrotropes can be anionic, cationicor neutral, organic or inorganic, and liquidsor solids in nature (Fig. No.3), these are freely soluble organic compounds which enhance the aqueous solubility of organic substancesby forming stack-type aggregation [17].

2. Mechanism of Hydrotropy

The enhancement of water-solubility bythe hydrotrope is based on the molecular self-association of the hydrotrope and onthe association of hydrotrope molecules with the solute. Although they are widely used in various industrial applications, only sporadic information on the mechanisms of hydrotropism is available. Various hypotheses and research efforts are being made to clarify the mechanisms of hydrotropism. The available proposed mechanisms can be abridged according to three designs:

(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 hydro trope assemblies distinguish them from other solubilizers [18].

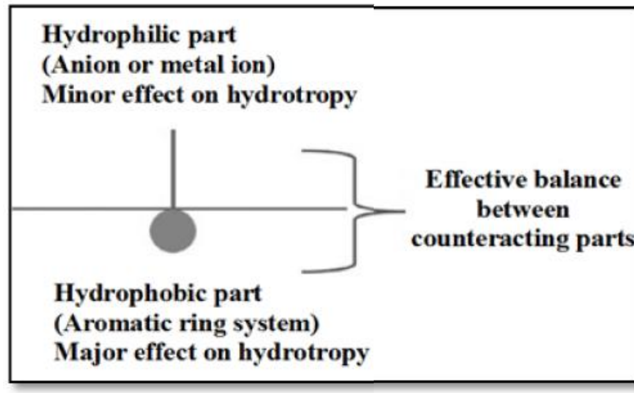

Figure 3: The internal effective structure of a hydrotrope

Table 2: Examples of hydrotropic agents

Type	**Example**
Aromatic anionic	Sodium benzoate, sodium salicylate, sodium benzene sulphonate, sodium benzene di-sulphonate, sodium cinnamate, sodium3-hydroxy 2-naphthoate, Sodium para-toluene sulphonate, sodium cumenesulphonate, nicotinamide, N, N-diethyl nicotinamide, N, N-dimethyl benzamide
Aromatic cationic	Paraaminobenzoic acid hydrochloride, procaine hydrochloride and Caffeine.
Aliphatic and linear compound	Sodium alkanoate, urea and N,N-dimethyl urea

Hydrotrope as a true solubilizer

A solubilizer is a surfactant. A solvent insoluble material is solubilized in the surfactant micelle. Factors that cause an increase in either the diameter of the micelle or its aggregation number generally increase solubilization. Some examples of regularly used solubilizers are fatty soaps, polyethoxylated nonionics and quaternary ammonium surfactants. Solubilization greatly increases once the CMC has been reached. Hydrotropes are effective only at high concentrations [19].

Difference between hydrotropy and other Cosolvency methods [20-23]: Hydrotropy is different from simple phase mixing, or the cosolvency process, and also from salting-in action. While the self-aggregationphenomenon of hydrotropes is reminiscent of surfactant self assemblies, there are important differences. Solubilization of hydrotropes is characterized by the relatively high concentrations of the hydrotrope needed and the larger amounts of solute solubilised, compared with that in micellised surfactants. Further, hydrotropes often exhibit selective ability to solubilise guest molecules than micellised surfactants. Surfactants have long hydrocarbon chains, whereas, hydrotropes are characterized by a short, bulky hydrocarbon groups. The aggregation numbers found in the case of hydrotrope aggregates is lower compared to those found in the case of micelles. Hydrotropes tend to form loose aggregates while long chain surfactants tend to form micelles by comparing the aggregation behaviors of two linear alkyl benzene sulfonates.

Preparation of hydrotropes

Hydrotropes are produced by sulfonation of an aromatic hydrocarbon solvent (i.e., 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, typically at a 30-60 % level of activity, or in granular solids typically 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 [24].

3. Characteristics of Hydrotropes

1. Completely soluble in water and practically insoluble in system.
2. Hydrotropes are surface active and aggregate in aqueous solution because of their amphiphilic structure.
3. Should not produce any temperature when dissolved in water.
4. Cheap and easy availability.
5. Non-toxic and non-reactive.
6. Insensitive to temperature effects, when dissolved in water.
7. The solvent character being independent of pH, high selectivity, and the absence of emulsification are the other unique advantages of hydrotropes [25].

Properties of hydrotropes [26]

1. Hydrotropes in general are 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 are non-reactive and nontoxic 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.

Significance of hydrotropes [27]

1. Hydrotropes have been used to solubilize organic compounds, dyes, drugs, and bio-chemicals.
2. Hydrotropes have been tested in the development of extractive separation processes in the separation of proteins and in distillationas an extractive solvent for separation of close boiling-pointphenolic mixtures.
3. Aqueous hydrotrope solutions provide safe and effective media for the extraction of natural products and for conducting organic synthetic reactions.
4. Hydrotropes find wide applications in, detergent formulation, health care, and household purposes.
5. They have been used to increase the rate of heterogeneous reactions.
6. They are used as an extraction agent for fragrances.
7. As fillers and extenders in chemical formulations.
8. In the development of pharmaceutical formulations.
9. Hydrotropic solubilization in nanotechnology (by controlled precipitation).
10. Hydrotropy to give fast release of poorly water-soluble drugs from the suppositories.
11. Used in the preparation of drilling well fluids and the separation of water-oil emulsion.
12. It may used in the petroleum industry, in tertiary petroleum recovery as well as in other processes.
13. Hydrotropes modify the viscosity of surfactant formulations and increase the cloud point of detergents.
14. Aqueous hydrotrope solutions provide safe and effective media for the extraction of natural products and for conducting organic synthetic reactions.
15. Viscosity and cloud point (the temperature at which a clear product begins to become hazy upon cooling) of liquid detergents can be controlled by incorporating hydrotrope agents.
16. Hydrotropes improve the stability of the concentrated liquid detergents by enhancing the solubility of the surfactants and by regulating the gelling tendency which liquid detergents can exhibit upon dilution with water.
17. This process may be used to recover the solute in crystalline form at an improved purity, and the remaining mother liquor could be used to concentrate the hydrotrope for recycling.
18. Hydrotropes have been applied in, shampoos, degreasing compounds and printing pastes, as an additive for glues used in the leather industry.
19. The use of hydrotrope, sodium xylene sulfonate in paper pulp manufacturing industry gives excellent results.

Novel pharmaceutical applications of hydrotropic solubilization in various fields of pharmacy [28]

1. Quantitative estimations of poorly watersoluble drugs by UV-Visible spectrophotometric analysis precluding the use of organic solvents.
2. Quantitative estimations of poorly water soluble drugs by titrimetric analysis. such as ibuprofen, flurbiprofen and naproxen using sodium benzoate.
3. Preparation of hydrotropic solid dispersions of poorly water-soluble drugs precluding the use of

organic solvents. Such as felodipine using polyethylene glycol 6000 and poly-vinyl alcohol.

4. Preparation of dry syrups (for reconstitution) of poorly water-soluble drugs.
5. Preparation of topical solutions of poorly water-soluble drugs, precluding the use of organic solvents. Such as tinidazole, metronidazole and salicylic acid using sodium benzoate and sodium citrate.
6. Preparation of injection of poorly water soluble drugs. The use of hydrotropic solubilizers as permeation enhancers.
7. The use of hydrotropy to give fast release of poorly water-soluble drugs from the suppositories.
8. Application of mixed- hydrotropy to develop injection dosage forms of poorly water-soluble drugs.
9. Application of hydrotropic solubilization in nanotechnology (by controlled precipitation).
10. Application of hydrotropic solubilization in extraction of active constituents from crude drugs (in pharmacognosy field)
11. Hydrotropic solutions can also be tried to develop the dissolution fluids to carry out the dissolution studies of dosage forms of poorly water-soluble drugs.

4. Conclusion

Solubility is the most important physical characteristic of a drug for its oral bioavailability, formulation, development of different dosage form of different drugs and for quantitative analysis. Solubility can be enhanced by many techniques among them hydrotropy is of very much importance. The present review summarizes the application of hydrotropy in increasing the solubility of drugs in water. The applicability and effectiveness of drug depends to a considerable extent on solubility in water. Various drugs can be analyzed by combination of conventional analysis methods like spectrophotometer and chromatography with hydrotropes. Most of these methods were proven to be accurate, rapid and precise. The solubility enhancement of 100-200 fold was observed in some cases. In most of the investigations, the solubility increased with concentrations.

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