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Solubility Enhancement of a Poorly Water-Soluble Drug Using Hydrotropy and Mixed Hydrotropy-Based Solid Dispersion Techniques

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Sachin B. T.*, Nagaraja T. S, Maruthi.N, Yogananda R

Sjm college of pharmacy chitradurga, NH 4 bypass Karnataka 577501 India.

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ABSTRACT

Solubility can be defined as the occurrence of dissolving a solute in a solvent to make a homogenous solution. In order to achieve the necessary concentration in the systemic circulation and to achieve the best possible treatment outcome, solubility is a crucial characteristic. 40% of medications have poor water solubility, which causes inadequate bioavailability and subpar drug delivery, effectiveness, and side effects. Numerous approaches are currently adaptable to enhance the solubilization of poorly water-soluble drugs and additionally enhance their bioavailability. Hydrotropic solubilization is one of them. Hydrotropy is a solubilization phenomenon in which the addition of large amounts of a second solute increases the aqueous solubility of another solute and increases solubility by many folds with the use of hydrotropes such as sodium citrate, sodium benzoate, urea, and so on; and This technique has several advantages, including being highly selective, non-flammable, environmentally friendly, and cost-effective. Drug carriers could be hydrotropic agents. These can be used in the development of formulations for oral, parenteral, and topical use. This review focuses on the use of hydrotherapy as a solubility enhancement technique, providing a concise overview, mechanism, and various advances in drug delivery.

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 current main problem in the pharmaceutical industry is related to strategies that augment the aqueous solubility of drugs, as almost 70% of the newly discovered drug candidates suffer from poor aqueous solubility[1].

Solubility is one of the prime features to accomplish the desired pharmacological response. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately is attributed to solubility of drug moiety.[2]

Presently number of methodologies can be adapted to improve solubilization of poor water-soluble drug and further to improve its bioavailability. The techniques generally employed for the solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc.[3]

In addition to these technologies, 'hydrotropy' is one of the recognized techniques available for resolving solubility issues. This review will elaborate on various hypothetical and investigational mechanisms, geometrical features and applications of hydrotropic agents in the pharmaceutical field which will aid the researchers to explore hydrotropy for progress in drug delivery[4].

HYDROTROPIC AND HYDROTROPIC AGENTS

Neuberg was the first to institute the term hydrotropic agent in 1916, to designate anionic organic salts that, at high concentrations, significantly increase the aqueous solubility of poorly soluble solutes[5].

Later Booth and Everson showed that concentrated aqueous solutions of organic salts, such as sodium benzoate, salicylates, benzene sulfonate and cumin sulfonate can increase the solubility of many compounds[6].

Booth and Everson were the primary to point out that the solubility increase in the hydrotropy solution does not occur in a linear fashion, but with the increase in the concentration of hydrotrope. This fact has an important bearing on understanding the mechanism of the hydrotropy[7].

Hydrotropy is a solubilization phenomenon whereby addition of large amount of second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions 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 drugs. The chemical structure of the conventional Neuberg's hydrotropic salts [sodium benzoate, proto-type] consists generally of two essential parts, an anionic group and a hydrophobic aromatic ring or ring system. The type of anion or metal ion appeared to have a minor effect on the phenomenon.

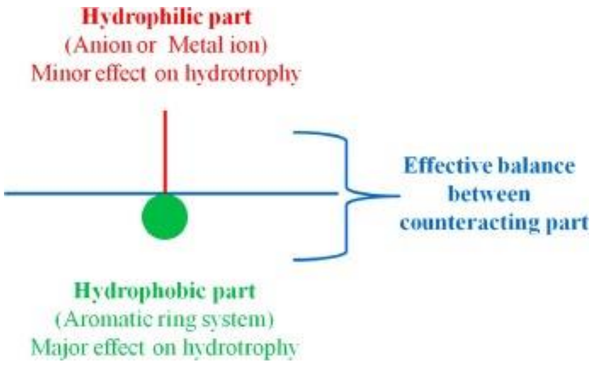
Hydrotropic agents are stated as ionic organic salts which help to increase or decrease the solubility of solute in a given solvent via 'salt in' or 'salt out' effects, respectively. Salts which show 'salt in' of non-electrolytes are called "hydrotropic salts" and the phenomenon is known as "hydrotropism". They do not exhibit any colloidal properties, but they improve solubility by forming weak interactions with solute molecules.[9]

A hydrotropic molecule interacts with a less water-soluble molecule via weak van der Waals interactions such as π–π or attractive dipole–dipole interaction.[10]

Hydrotropes contain both hydrophobic and hydrophilic fractions in them. In comparison to surfactant, they contain a very small hydrophobic fraction. [11]

The efficiency of hydrotrope solubilization depends on the balance between hydrophobic and hydrophilic part of hydrotrope.[12]

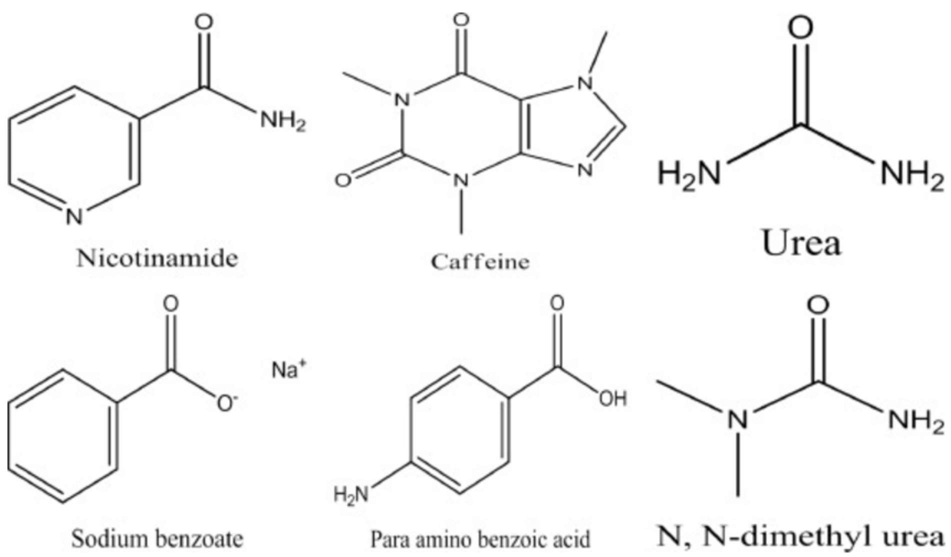
Hydrotropic agents can be anionic, cationic or neutral, organic or inorganic and liquids or solids in nature (Fig. 1). These are freely soluble organic compounds which enhance the aqueous solubility of organic substances by forming stack-type aggregation [13,14].



A few examples of hydrotropic agents are given in Table 1 and Fig. 2 [15,16].

Examples of hydrotropic agents.

Types	Examples
Aromatic anionics	Sodium benzoate, Sodium salicylate, Sodium benzene sulfonate, Sodium benzene di-sulfonate, Sodium cinnamate, Sodium 3-hydroxy-2-naphthoate, Sodium para toluene sulfonate, Sodium cumene sulfonate, nicotinamide, N,N-diethyl nicotinamide and N,N-dimethyl benzamide
Aromatic cationics	Paraaminobenzoic acid hydrochloride, Procaine hydrochloride and caffeine
Aliphatics and linear compounds	Sodium alkanoate, urea and N, N-dimethyl urea



MECHANISM OF HYDROTROPY

The enhancement of water solubility by hydrotrope is based on the molecular self-association of hydrotrope and on the association of hydrotrope molecules with the solute. Although 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

Self-Aggregation Potential

Minimum hydrotropic concentration (MHC) is a critical concentration at which hydrotrope molecules start to aggregate, i.e., self-aggregation potential. The solubilization power of hydrotropic agents is governed by their self-aggregation potential. This potential depends upon their amphiphilic features and the nature of a solute molecule. They mainly show the volume-fraction-dependent solubilization potential. Initially, hydrotrope molecules undergo primary association in a pair wise manner which is followed by consecutive steps to form trimers, tetramers, and so on and these complexes (trimers, tetramers) could then lead to higher aqueous solubility. These outcomes have evolved from the fluorescence emissions methods, crystallography analysis, molecular dynamics replication, and thermo-dynamic solubility experiments. Apart from these, they may act as bridging agents by reducing the Gibbs energy to increase the solubility of a solute. Simply, the structure of the hydrotrope water mixture around the drug molecule is the true key to understanding the origin of the self-aggregation potential.

Structure-breaker and Structure-maker

In the hydrotropic solubilization technique, an electrostatic force of the donor-acceptor molecule plays a vital role; hence, they are also termed as a structure-breaker and a structure-maker. Solutes which are capable both of hydrogen donation and acceptance help to enhance solubility. Hydrotropic agents, such as urea, exert their solubilizing effect by changing the nature of the solvent, specifically by altering the solvens ability to participate in structure formation or its ability to engage in structure formation via intermolecular hydrogen bonding. Structure-breaker hydrotropes are known as chaotropes while structure-maker hydrotropes are known as kosmotropes. Kosmotropes reduce the critical micelle concentration (CMC) by increasing the hydrophobic interaction which decreases the cloud point. A kosmotrope influences the cloud point in two ways, i.e., it helps

a. To form bigger micelles and

b. To decrease hydration.

Ability to Form Micelle-like Structures

This mechanism is based on the self-association of hydrotropes with solutes into a micellar arrangement. They form stably mixed micelles with a solute molecule decreasing the electrostatic repulsion between the head groups. Hydrotropic agents, such as alkyl-benzene sulfonates, lower alkanoates, and alkyl sulfates, exhibit self-association with solutes and form micelles. Aromatic anionic hydrotropic agents, i.e., nicotinamide, improve the solubility of riboflavin via a self-association mechanism. In the case of PMZ, anionic hydrotropic agents, such as sodium salicylate, form stably mixed micelles by decreasing the electrostatic repulsion between the head groups of PMZ. [17-21]

Completely soluble in water but virtually insoluble in the framework.

Advantages of hydrotropic solubilization technique

1. Hydrotropy is suggested to be superior to other 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.

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.[22]

Significance of hydrotropes

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 distillation as an extractive solvent for the separation of close boiling-point phenolic 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 use 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 that 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 the paper pulp manufacturing industry gives excellent results.[23]

METHOD OF PREPARATION OF HYDROTROPIC SOLID DISPERSION

It is a relatively new technique in which the drug and selected hydrotropes are taken in different ratio in beaker, and distilled water is added at a temperature ranging between 80-85°C. Then the selected hydrotrope is taken and added to water. Then slowly add drug to the beaker and teflon coated magnetic bead is dropped in beaker, temperature is to be maintained for optimum stirring and stirring is continued until semisolid mass is obtained. This semisolid mass is spread on several watch glasses and is placed in oven maintaining a temperature of 60-65°C. Then the trituration is done with pestle and mortar and after drying passes it through sieve no.100 and kept in desiccators for 6 days[24-25]. Flow chart 1.

Preparation of hydrotropic solid dispersion

Distilled water (80-85°C)

Put ↓ Hydrotrope

Beaker

↓ Dissolve

Add Drug

↓ Stir

In Magnetic Stirrer

↓

Formation of Semisolid Mass

↓

Poured on watch glass

↓

Keep in Oven (60-65°C)

↓

To make it pulverizable

↓

Triturate in pestle mortar

↓

Kept in oven

↓

Drying

Mixed Hydrotropic Solubilization

Mixed hydrotropic solubilization is a technique that is based on the use of blends of hydrotropic agents to increase the solubility of poorly water-soluble drugs. This technique may have a synergistic effect in the enhancement of solubility of poorly water-soluble drugs. It can be utilized in the dosage form development of water-insoluble drugs, thus reducing the concentration of any single hydrotropic agent, which may help minimize the side effects of hydrotropes. Maheshwari studied the use of a mixture of two hydrotropic agents (urea and sodium citrate) to enhance the solubility of a poorly water-soluble drug (aceclofenac). This blend of hydrotropic agents was employed to dissolve a poorly water-soluble drug, aceclofenac, taken as a fine powder from the tablets to carry out spectrophotometric analysis preventing the use of organic solvents. A miraculous synergistic effect of a blend of hydrotropic agents was seen.

Advantages of Mixed Hydrotropic Solubilization

• It helps to lower the large total concentration of hydrotropic agents required to enhance solubility by utilizing a mixture of agents in lower concentrations.

• It is a new technique that is a simple, less costly safe, precise, accurate, and environmentally friendly method for the quantitative analysis of poorly water-soluble drugs minimizing the use of various organic solvents.

• It excludes the use of organic solvents and therefore reduces residual toxicity.

CONCLUSION

We conclude that drug solubility is the most important factor that controls drug formulation as well as therapeutic efficacy, and thus the most critical factor in formulation design and development. Because of their poor aqueous solubility, many useful drugs may be discontinued. There are various solubility enhancement techniques available to improve the solubility of poorly aqueous soluble drugs, but selecting the proper solubility enhancement technique is critical to ensuring good formulation features such as good oral bioavailability, reduced dosing frequency, improved patient compliance, and low production costs, all of which can be achieved by using the hydrotropic solubilization technique. In addition to this, hydrography is a novel, simple, and environmentally friendly method for improving the solubility of poorly soluble drugs. This technology is expected to accelerate progress toward improved therapeutic delivery of poorly soluble drugs as well as critical moieties with a narrow therapeutic index.

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