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A review: Hydrotropy a solubility enhancing technique

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Abstract
Therapeutic effectiveness of a drug depends upon the bioavailability and solubility of drug molecules. Solubility plays very important role to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability. Due to advanced research and development, there are varieties of new drugs and 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. The lipophilic drug that reaches market requires a high dose to attain proper pharmacological action. Hydrotropy is a unique solubilization technique used to describe the increase in the solubility of a solute by the addition of a large amount of second solute results in an increase in the aqueous solubility of another solute.

Keywords: Hydrotropy, solubility, solubilization, hydrophobic drugs, mixed hydrotropy

Introduction
More than one-third of the drug listed in Indian Pharmacopeia and US Pharmacopeia fall into the poorly water-soluble or water-insoluble categories. 41% of the failures in new drug development have been found due to poor biopharmaceutical properties mainly including water insolubility. Mostly newly developed drug molecules are lipophilic in nature and have poor solubility which is one of the most difficult problems of these drugs. Various organic solvents such as methanol, chloroform, dimethylformamide and acetonitrile have been employed for solubilization of poorly water-soluble drugs to carry out analysis of poorly water-soluble drugs. The drawback of these organic solvents includes high cost, volatility, pollution and toxicity such as nephrotoxicity or teratogenicity, So, these organic solvents are replaced by hydrotropic agent which are safe, eco-friendly, cost-effective solvent for spectrophotometric analysis. Hydrotropic solubilization concept is one of the best choices to preclude the use of organic solvents [1]. Neuberg (1916) was the first to report hydrotropy when he dissolved various organic substances such as lipids, carbohydrates, esters and drugs in aqueous solution containing hydrotropes [2]. 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 [3].

Solubility
The term solubility is defined as maximum amount of solute that can be dissolved in a given amount of solvent. 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 [4-5]. International Union of Pure and Applied Chemistry (IUPAC) define solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. A saturated solution is one in which the solute is in equilibrium with the solvent [6].

The solubility of a drug may express as Parts, Percentage, Molarity, Molality, Volume fraction, Mole fraction and other units. [7] This is also explained in terms of parts of solvent required for 1 part of solute as explained in Indian pharmacopeia which is shown as in Table 1. [8].

Table 1: Solubility as per I.P

Descriptive term	Parts of Solvent Required for One Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 or more

On the basis of solubility, drugs can also be classified into four classes of the Biopharmaceutical Classification System. The BCS Classification was introduced in the mid 1990's to classify the drug substances with respect to their aqueous solubility and membrane permeability [9-10].

Table 2: BCS Classification System

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

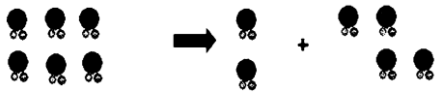
Requirement of Solubility

GIT drug absorption can be limited by a variety of factors. One of the most significant factors is poor aqueous solubility and poor membrane permeability of the drug molecule. When an active agent is administered orally it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing of solubility and dissolution rate of poorly water soluble drugs.[11-12] The basic aim of the further formulation and development section is to make that drug available at proper site of action within optimum dose [13].

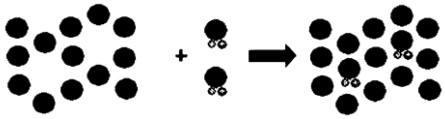
Process of Solubilization [14-16]

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute the 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.

Step 1: Holes opens in the solvent



Step 2: Molecules of the solid breaksaway from the bulk



Step 3: The freed solid molecule is integrated into the hole in the solvent

Fig 1: Process of solubilization

To increase the solubility of poorly water soluble drugs different solubilization techniques have been used which are: [17-24].

Physical Modifications

Particle size reduction

a) Micronization
b) Nanosuspension

Modification of the crystal habit

a) Polymorphs
b) Pseudopolymorphs

Drug dispersion in carriers

a) Eutectic mixtures
b) Solid dispersions

Complexation

a) Use of complexing agents

Solubilization by surfactants

a) Microemulsions

Chemical Modifications

a) Use of Buffers
b) Derivatization

Other Techniques

a) Co-crystallization
b) Co-solvency
c) Hydrotropy

Physical Modifications

Particle size reduction

a. Micronization- Micronization is a simple technique that refers to transfer of coarse drug powder to an ultrafine powder with the mean particle size in the range of 2-5 µm and only a very little fraction of the particles lie below 1 µm size range. The size reduction in these processes takes place by pressure, friction, attrition, impact or shearing. Jet mills, ball mills and high-pressure homogenization are commonly used for micronization of drugs and dry milling in a fluid energy mill (jet mill) is the most preferred Micronization technique. [19]

b. Nanosuspension- Nanosuspensions are colloidal dispersions and biphasic system consisting of drug particles dispersed in an aqueous medium in which the diameter of the suspended particles is less than 1 µm in size. Nanosuspensions can be prepared by two methods, namely, "bottom up technology" and "top down technology". [20]

Modification of the crystal habit

a. Polymorphs- It is defined as that crystallinity of substance which exists in more than one form. Polymorphism shown by pharmaceutical substance is of two types i.e. Enantiotropic (one form of polymer can change in other form) and Monotropic (no reversible transition is possible). Amorphous substance have greater hydration energy than crystalline substances, due to this greater hydration energy they tends to shows more solubility than crystalline substances. Metastable state is a state in between the crystalline state and amorphous

state of powder. Therefore order of solubility for Pharmaceutical powders is:

Amorphous > Metastable > Crystalline

b. Pseudopolymorphs- When crystalline form of drug is incorporated in solvent, it is called as solvates, and when water is used as solvent to incorporate a crystalline lattice then it is called hydrate. Existence of this solvate or hydrates in different crystalline forms is called pseudo polymorphism.[21]

Drug dispersion in carriers

a. Eutectic mixtures- Eutectic mixture consist of two compounds which are completely miscible in liquid state but to a limited extent in solid state. When the mixture is cooled both crystallize out spontaneously. Solid eutectic mixtures are usually prepared by cooling of co-melt of two compounds in order to obtain fine mixture of both compounds. When eutectic mixtures are exposed to gastrointestinal fluids, the soluble carrier dissolves rapidly. The large surface area should result in enhanced dissolution rate thereby improved bioavailability. Eutectic mixture prepared with hydrophilic agent also increase solubility of drugs.

b. Solid dispersions- The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most commonly used hydrophilic carriers for solid dispersions include polyethylene glycols (PEGs), Plasdone- S630. Various techniques to prepare the solid dispersion of hydrophobic drugs with an aim to improve their aqueous solubility are Fusion Process, Solvent Method, Fusion-Solvent Method.[22]

Complexation

a. Use of complexing agents- Is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry.

There are two type of complexes: Stacking complexes: It is driven by association of non-polar area of drug and complexes agent this results in exclusion of the non-polar area from contact with water. Stacking can be homogeneous or mixed, but results in clear solution.

Inclusion complexes: It is formed by the inserting the nonpolar molecule, region of one molecule into the cavity of another molecule or group of molecules. Cyclodextrine and their derivatives commonly used in Complexation.

Solubilization by surfactants

a. Micro emulsions- Generally it is four component systems which consist of an external phase, internal phase, surfactant and co-surfactant. Surfactant is soluble with internal phase of the system which makes a clear, isotropic and thermodynamic stable system called micro emulsion. Droplet diameter of internal phase of micro emulsion is < 0.1μm.[23]

Chemical Modifications

a. Use of Buffers- Generally dilution of GIT fluid may have an effect on the solubility of drug. If precipitation of drug occurs by dilution of GIT fluid then solubility of drug will be reduced. This problem may be overcome by use of buffers, which maintain the pH of GIT even in dilution conditions and solubility of drug will be maintained

b. Derivatization- In this technique parent form of poorly soluble drug is to be modified into a derivative of poorly soluble drug. Derivatization may be achieved by two methods; either by forming a prodrug or forming or changing the salt form of drug.

Other Techniques

a. Co-crystallization- In this technique drug is mixed with an inert (lacking of pharmacological activity) substance in equal molar ratio followed by adding the aqueous solvent in small amount followed by slowly evaporation of aqueous solvent and resultant product will be co-crystals and by which solubility of drug substance is enhanced.

b. Co-solvency- This method is employed for poorly water soluble drugs. Any external aqueous solvent is to be added in mixture of drug and water and that external solvent increases the solubility of drug in water. This process is called co-solvency and aqueous solvents which are used to enhance solubility are called co-solvents e.g. Poly-ethylene glycol (PEG-400), propylene glycol (PG) and glycerol are used as well-known co-solvents.[24]

c. Hydrotropy- Hydrotropy is a solubilisation process, whereby addition of a large amount of second solute results in an increase in the aqueous solubility of first solute.

Hydrotropy

Hydrotropy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are mentioned to be ionic organic salts. Additives or salts that increase the solubility in a given solvent are said to "salt in" the solute and those salts that decrease the solubility are said to "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".[25-28] Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotropy designate the increase in solubility in water due to the presence of large amount of additives.

Table 3: Classification of hydrotropic agents [29]

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

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 towards understanding the origin of the self-aggregation potential.

Structure-breaker and Structure-maker

In 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 solvent‟s 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 41. Hydrotropic agents, such as alkyl-benzene sulfonates, lower alkanoates, and alkyl sulphates, 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 [30-34]

Mixed hydrotropic

Mixed hydrotropic solubilization technique is the phenomenon to enhance the solubility of poorly soluble drugs using blends of hydrotropic agents, which may give synergistic enhancement effect on the solubility of poorly soluble drugs, and also reduces the side effects due to a reduction in the concentration of individual hydrotropic agents [35].

Advantages of Mixed Hydrotropic Solubilization

a. It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentration.
b. It is new, simple, cost-effective, safe, accurate, precise and environmental friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble drugs. [36]

Conclusion

By this article we can conclude that, solubility is one of the most important characteristics of a drug and can be enhanced by different solubilization techniques among which hydrotropy technique has boosted its use in various operational fields by adding a second solute which results in aqueous solubility of another solute.

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