A Review on Novel Solubility Enhancement Technique Hydrotrophy

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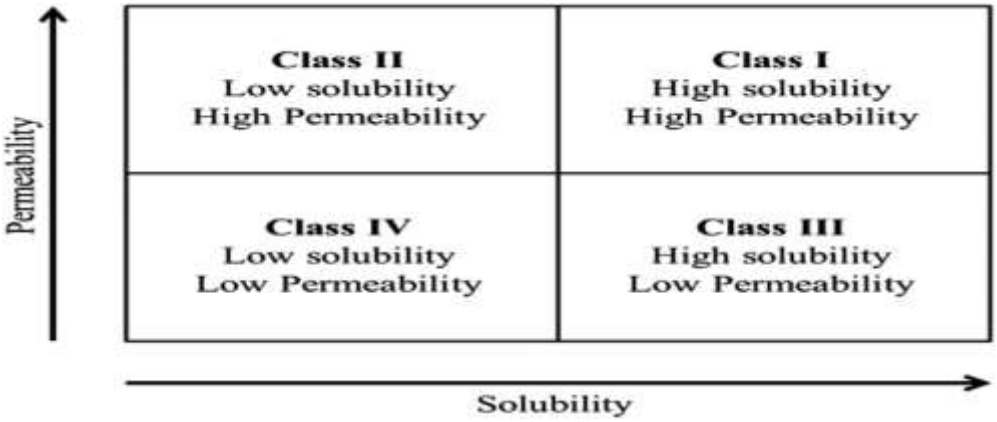
Abstract: Solubility is the most important physical characteristic of a drug for its oral bioavailability, formulation, development of different dosage form of different drugs and for quantitative analysis. The present review summarizes about solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. The applicability and effectiveness of drug depends to a considerable extent on solubility in water. The hydrotropic solubilization techniques can be used to enhance the solubility of the drug. In present scenario this method is getting lot of values and may be proved the best method in future. 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. Various drugs can be analyzed by combination of conventional analysis methods like spectrophotometer and chromatography with hydrotropes.

Key words: Solubility, Hydrotropy, Mechanism of hydrotropy, mixed hydrotropy

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.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[1]. 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.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 [2].

Table: Biopharmaceutical Classification System of drug.



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. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist. The improvement of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system[3].

Measure the solubility: Solubility determination of solid in liquid by using following steps-

Preparation of saturated solution: Solubility indicates maximum amount of a substance which can be dissolved in a solvent at given temperature also known as saturated solution. Solubility is measure either in g/100g of solvent or no of moles /L of the solution[4] (Table.1).

Table1. Expression for approximate solubility[5-6].

Descriptive term	Relative amount of solute to dissolve 1 part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Practically insoluble	>10000

Analysis of saturated solution: The saturated solutions are prepared for analysis of solubility. Solubility depends on the nature of solute & accuracy of method employed.

The following methods involve in the analysis of saturated solution-

- Evaporation method.
- Volumetric method.
- Gravimetric method.
- Instrumental method[7].

Process of solubilization: Hydrotropy is considered as one of the best solubility enhancement technique, used for novel, safe & accurate method for estimation of poorly soluble drug. The aqueous solubility of drug is the major Challenge in pharmaceutical industry; about 70% drugs suffer from low solubility. Enhancement of the aqueous solubility is major importance for insoluble and poorly soluble drug[8]. Solubility is the important parameter for desired concentration of drug. The following factors affect the solubility of drug such as temperature, nature of solvent, nature of solute, particle size, molecular size, pressure etc[9].**"Hydrotropy is defined as a solubilization process whereby addition of large amount of second solute result in an increase in the aqueous solubility of another solute and the chemical which are used in hydrotropy are called hydrotropes"**[10]. The following steps involve in the process of solubilization-

- Solubilization process involves the breaking of inter-ionic or intermolecular bond in solute.
- Separation of solvent molecules to provide space for the solute in solvent.
- Interaction between solvent and the solute molecule or ion[11].

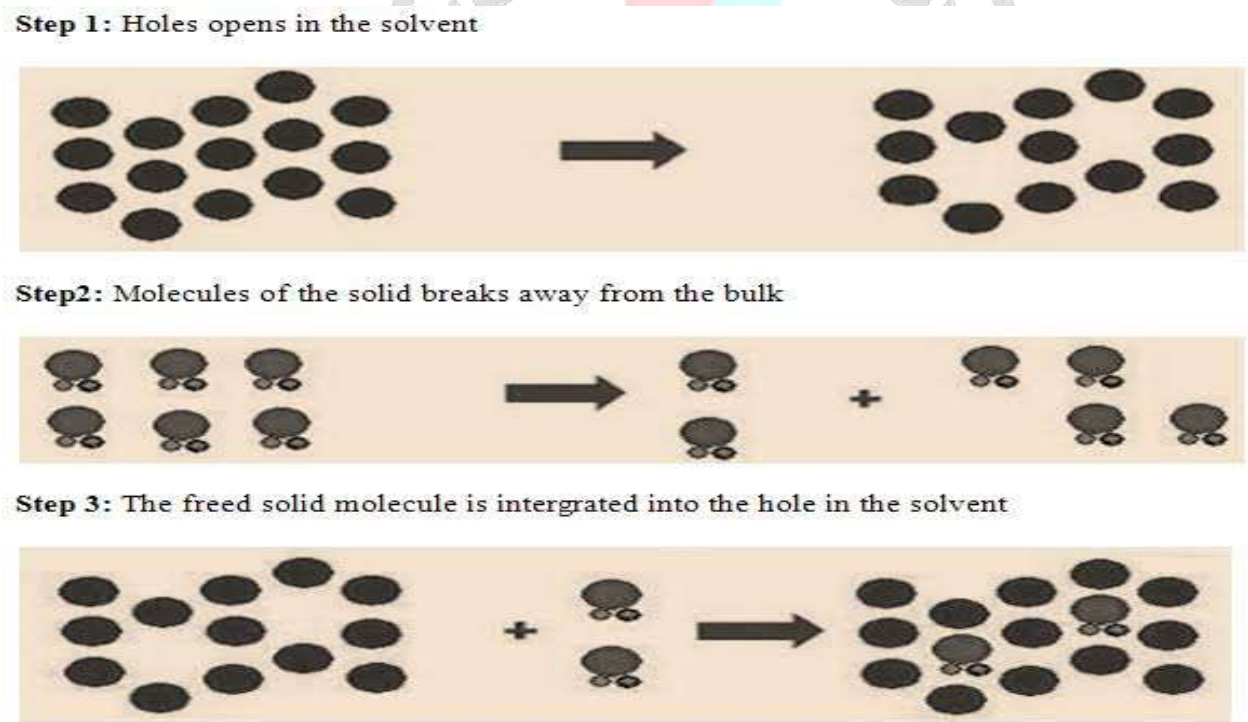


Fig. 1 Process of solubilisation

Some techniques used for Solubility Enhancement**,** solubility improvement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques.

Physical Modifications. Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques[12-13].

Chemical Modifications. Change of PH, use of buffer, derivatization, complexation, and salt formation[14].

Other Methods. Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy[15].

Hydrotropy: Neuberg first proposed the term Hydrotropy in 1916. Hydrotrope is a class of amphiphilic molecules they increase the aqueous solubility of organic compound[16].In the presence of large quantity of one solute enhances the aqueous solubility of another solute[17].Hydrotropic agents are ionic organic salt to increase the aqueous solubility of solute, several salts are ionic they mostly soluble in water which have "salting in" of non electrolytes called "hydrotropic salts" a phenomenon also known as "hydrotropism".

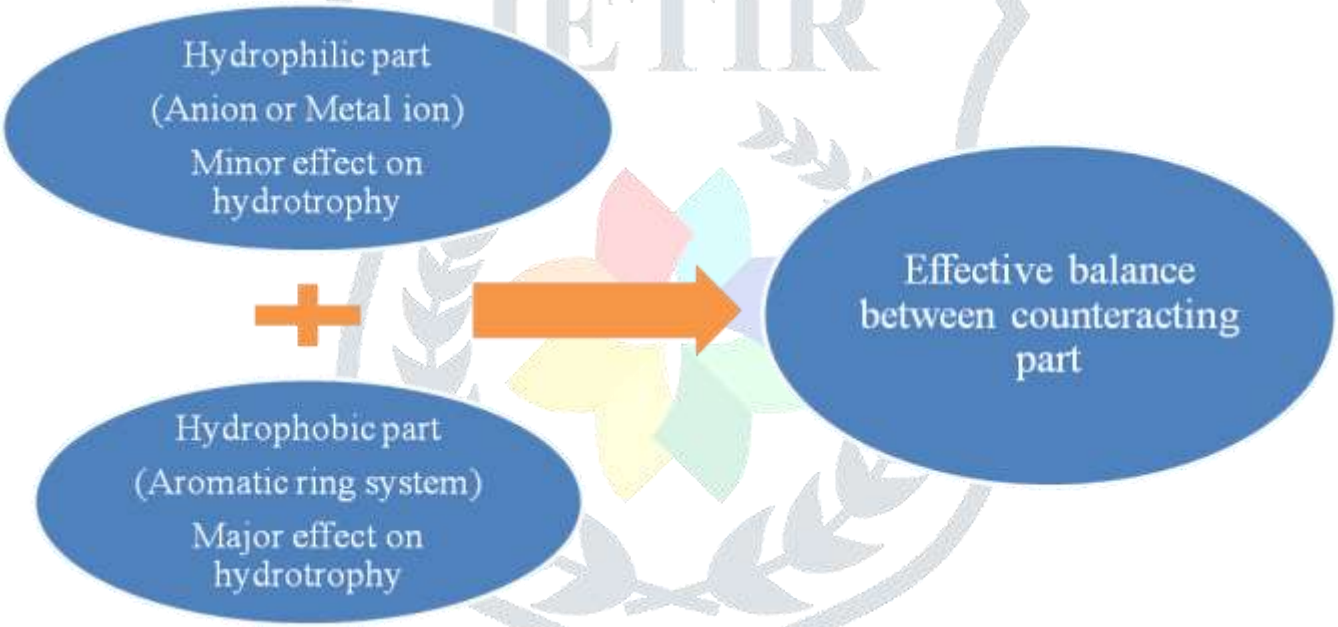


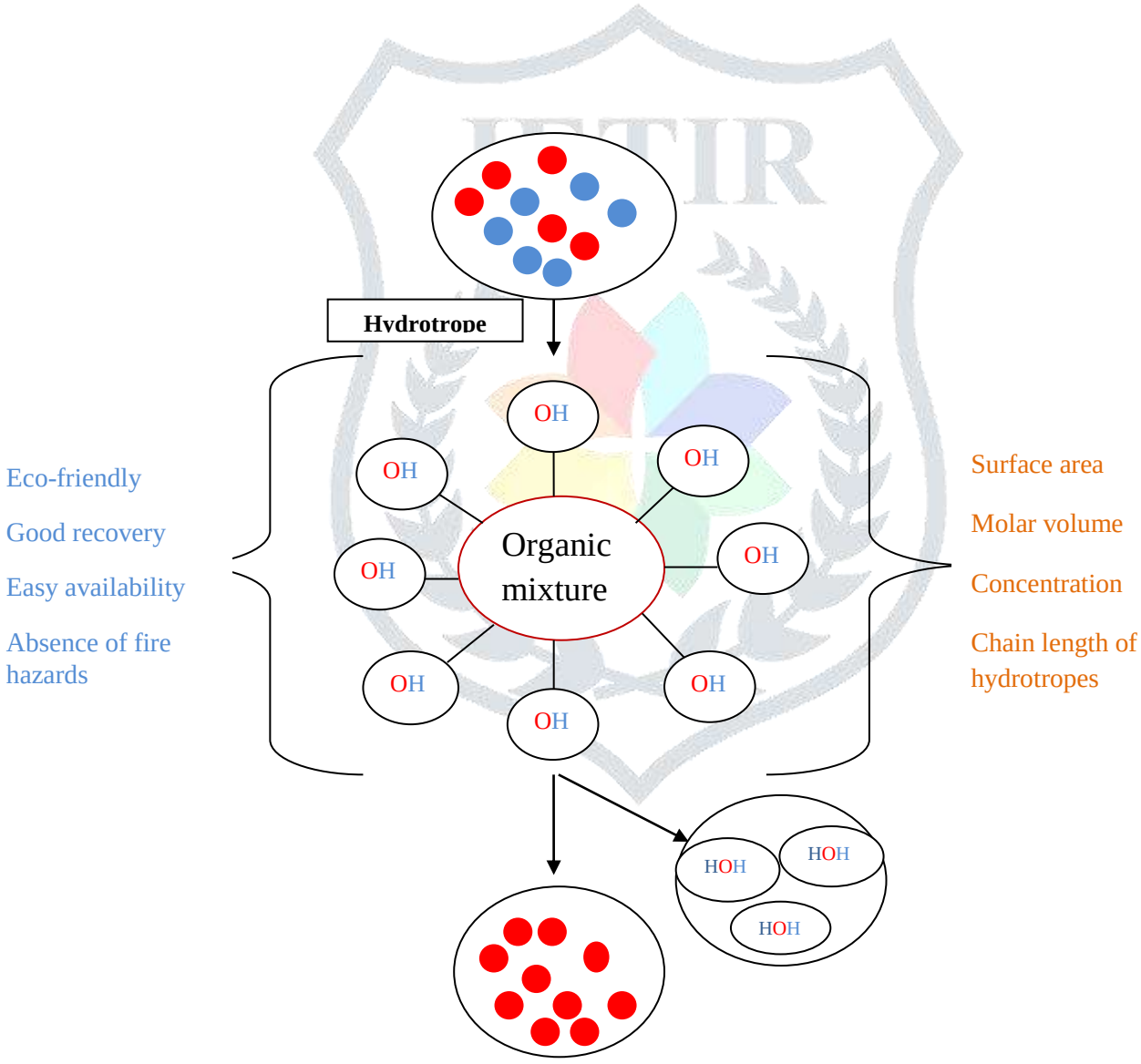
Fig.1. Structure of hydrotropic agent

They don't have any colloidal properties but increase aqueous solubility through weak interaction of organic salts and hydrotropic agents[18-19].The most popular example of hydrotropic agent is urea, Sodium benzoate, sodium salicylate, nicotinamide, urea, sodium ascorbate, sodium acetate, sodium citrate, niacenamide; N-dimethylurea[20].

Mechanism of Hydrotropy: The enhancement of water-solubility by the hydrotrope is based on the molecular self-association of the hydrotrope and on the association of hydrotrope molecules with the solute.Various hydrotropic agents have their individual properties for a particular component in mixture[21].Hydrotropic agent consists of hydrophilic and hydrophobic properties such as surfactant but have spontaneous self-aggregation ability caused by hydrophobic surfactant[22].The following steps involved in the machanism of hydrotropy-

Self-aggregation potential: Self aggregation of hydrotropic molecules forms aggregates, which depend on the amphiphilic properties and nature of solute. It also attract the molecules inside the aqueous phase[23-24].Hydrotropic agent interact with solute to form a complex and thus the complex formed has higher aqueous solubility. These outcomes evolved from fluorescence emission method[25]. Hydrotropes may act as binding agent by reducing Gibbs energy to increase aqueous solubility of solute. Finally the structure of hydrotropes around the dry molecules is a true key of understanding the origin of self aggregation potential[26].

Structure breaker & structure maker: Changing the structure of solvent through altering the ability of structure formation in intro-molecule H-bonding[27]. Hydrotropes play a vital role in hydrotrophy solubilization like an electrostatic force of the donor and acceptor molecule. They also called structure breaker and structure maker[28]. Solutes are capable for both hydrogen donor and acceptor helps to increase the solubility[29].



Ability to form micelles like structure: This mechanism is based on the self-association of hydrotropes with solutes into a micellar arrangement[30]. Basically they form stable mixed micelles with a solute molecule decreasing electrostatic repulsion between the head groups. Hydrotropes like alkyl- benzene sulfonates, lower alkanoates and alkyl sul fates exhibit self-association with solutes and form micelles. Aromatic anionic hydrotrope i.e. nicotinamide, improve solubility of riboflavin via self-association

mechanism. In case of PMZ, anionic hydrotropic agents like sodium salicylate forms stable mixed mi- celles by decreasing electrostatic repulsion between the head groups of PMZ[31].

Features of Hydrotropes:

- Hydrotropes increase unprecedented solubilization.
- Hydrotropic agenthave very high selectivity.
- Easy recovery of solute from solution.
- Economical & cost effective.
- Absence of emulation.
- Absence of hazard present in other solvent used in extracted separation[32-33].

Advantage of hydrotropic solubilization:

- Hydrotropic solubilization technique is superior to other solubilization method like Micellar solubilization salting in and co-solvency because solvent independent of pH has high selectivity.
- Hydrotropic solubilization only require for mixing the drug with hydrtope in water.
- It does not require chemical modification of hydrophobic drug use of organic solvent or preparation of emulsion system[34].

Mixed Hydrotropy:

Mixed hydrotropic solubilization technique is the phenomenon to increase the solubility of poorly water-soluble drugs in the blends of hydrotropic agents, which may give miraculous synergistic enhancement effect on solubility of poorly water soluble drugs, utilization of it in the formulation of dosage forms of water insoluble drugs and to reduce concentration of individual hydrotropic agent to minimize the side effects (in place of using a large concentration of one hydrotrope a blend of, say, 5 hydrotropes can be employed in 1/5th concentrations reducing their individual toxicities.[35]

Advantage of mixed hydrotropic solubilzation.

- 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.
- It is new, simple, cost-effective, safe, accurate, precise and environmental friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble drugs titrimetric and spectrophotometric precluding the use of organic solvents.
- It precludes the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost etc[36].

Conclusion: Solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Solubility can be enhanced by many techniques among them hydrotropy is of very much importance. Various drugs can be analyzed by combination of conventional analysis methods like spectrophotometer and chromatography with hydrotropes. The present review summarizes the application of hydrotropy in increasing the solubility of drugs in water. Hydrotropic agents enhance the aqueous solubility of organic substances , practically which are insoluble under normal conditions. Enhancement of aqueous solubility is due to intercalation or co-aggregation of a solute with the hydrotrope aggregates, complexation involving a week interaction between the hydrotropic agents and the poorly soluble drugs , hydrotropes concentrating around the hydrophobic solute without interaction, changing the structure of the solvent by altering ability of engaging in structure formation of intermolecular H bonding. The addition of the oppositely charged hydrotropic agents to aqueous ionic surfactant solution may alter the CMC,viscosity,solubility,suracetension,refractiveindex.

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