



A NOVEL CONCEPT FOR ENHANCEMENT OF SOLUBILIZATION AND BIOAVAILABILITY OF POORLY SOLUBLE DRUGS: HYDROTROPY: A REVIEW



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Abstract

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Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include micronization, nanonization, sonocrystallization, supercritical fluid method, spray freezing into liquid and lyophilization, evaporative precipitation into aqueous solution, use of surfactant, use of co-solvent, hydrotropy method, use of salt forms, solvent deposition, solubilizing agents, modification of the crystal habit, co-crystallization, complexation and drug dispersion in carriers. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics. Hydrotropy is a solubilization phenomenon whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solution. To solubilize water insoluble drugs especially in case of oral formulation, solubility remains a critical factor so for in this review various solubility enhancement techniques are highlighted and a brief review of hydrotropy and its preparation are discussed.

INTRODUCTION:

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. The insufficient dissolution

rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble compounds¹.

The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. If exact solubilities are not known, the Pharmacopoeia provides general terms to describe a given range. These descriptive terms are listed in (table1)².

Table 1: Expression for approximate solubility^{2,3}

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 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

Hydrotropy is the term originally put forward by Neuberg to describe the increase in the solubility of a solute by the addition of fairly high concentrations of alkali metal salts of various organic acids. 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. Hydrotropic solubilization process involves cooperative intermolecular interaction with several balancing molecular forces, rather than either a specific complexation event or a process dominated by a medium effect, such as cosolvency or salting-in³.

The chemical structure of the conventional Neuberg 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^{3,4}.

On the other hand, planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization. This should imply that hydrotropic agents are molecules having a planar hydrophobic structure brought into solution by a polar group. Hence, it seems rational to propose that molecules with a planar hydrophobic part and a polar group, which is not necessarily anionic, can act as hydrotropic agents. Saleh and El-Khordagui suggested that the phenomenon of hydrotropy is not confined to the metal salts of organic acids, certain cationic salts and neutral molecules may be equally involved. They used procaine HCl, PABA HCl and cinchocaine HCl as cationic salts and resorcinol and pyrogallol as neutral molecules in their studies^{3,5}.

NEED OF SOLUBILITY⁶

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. 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 HYDROTROPE ACTION^{6,7}

A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solutions. Typically, hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation. Hydrotropes do not have a critical concentration above which self-aggregation 'suddenly' start to occur. Instead, some hydrotropes aggregate in a step-wise self-aggregation process, gradually increasing aggregation size. However, many hydrotropes do not seem to self-aggregate at all, unless a solubilise has been added. Maheshwari et al

enhanced the aqueous solubility of paracetamol, a poorly water-soluble drug by use of concentrated solution of urea (a hydrotropic agent). This hydrotropic phenomenon was employed to prepare solid dispersion (SD) and syrup of paracetamol. SD was evaluated for dissolution rate and a marked increase in dissolution rate was observed with SD. IR analysis revealed that there was no complexation/interaction between paracetamol and urea. Paracetamol syrups prepared with urea showed good chemical stabilities.

COMMONLY USED HYDROTROPES³

The hydrotropes are known to self-assemble in solution. The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behavior. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, *a*- and *b*-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene. The aromatic hydrotropes with anionic head groups are

mostly studied compounds. They are large in number because of isomerism and their effective hydrotrope action may be due to the availability of interactive pi-orbitals. Hydrotropes with cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilization of compounds

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in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and polymers, etc.

Table 2: Hydrotropic solubilization study of various poorly water-soluble drugs

Drug	Hydrotropic agent
Theophylline, Hydrocortisone, Prednisolone, Phenacetin	Sodium benzoate, Sodium o-hydroxybenzoate, Sodium m-hydroxybenzoate, Sodium p-hydroxybenzoate, Sodium 2,4-dihydroxy benzoate, Sodium 2,5-dihydroxybenzoate, Sodium 2,6-dihydroxybenzoate, Sodium 3,4-dihydroxybenzoate, Sodium 3,5-dihydroxybenzoate
Chartreusin	Sodium benzoate, Sodium p-hydroxybenzoate, Sodium m-hydroxybenzoate, Sodium o-hydroxybenzoate, Sodium 2,4-dihydroxybenzoate, Sodium 2,5-dihydroxybenzoate, Sodium 2,6-dihydroxybenzoate, Sodium 2,4,6-trihydroxybenzoate
Riboflavin	ProcaineHCl, PABAHCl, CinchocaineHCl, Resorcinol, Pyrogallol
Diazepam, Medazepam, Oxazepam, Nitrazepam,	Sodium salicylate

Clonazepam

Paracetamol	Sodium salicylate, Sodium glycinate, Sodium gentisate, Nicotinamide
Progesterone, Testosterone 17- b Estradiol, Diazepam and Griseofulvin	Nicotinamide, Isonicotinamide, Nipicotinamide, N-methylnicotinamide, N, N-dimethylnicotinamide
Riboflavin	Nicotinamide
Saquinavir	Nicotinamide, Ascorbic acid, Dimethyl urea, Resorcinol
Benzoic acid, Salicylic acid	Urea, Methyl Urea, 1-3-dimethyl urea
Rofecoxib, celecoxib, melocoxib	Nicotinamide, Sodium benzoate, Sodium salicylate
Nifedipine	Urea, Methyl urea, Ethyl urea, Butyl urea, icotinamide, N-methyl nicotinamide, N, N-dimethyl nicotinamide
Temazepam	Sodium salicylate, Nicotinamide
Ibuprofen	Sodium salt of Ibuprofen
Carbamazepine	Sodium salicylate, Sodium benzoate
Ketoprofen	Sodium benzoate, Sodium o-hydroxybenzoate, Nicotinamide, Sodium m-hydroxybenzoate, Sodium ascorbate, Sodium 2,5-dihydroxybenzoate

Each hydrotropic agent is effective in increasing the water solubility of selected hydrophobic drugs. No universal

hydrotropic agent has been found effective to solubilize all hydrophobic drugs. Thus finding the right hydrotropic agent for a

poorly water-soluble drug requires screening of large number of candidate hydrotropes. However, once the effective hydrotropic agent is identified for a series of structurally different drugs, the structure activity relationship can be established.

METHODS TO MEASURE THE SOLUBILITY⁶

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To determine solubility of solids in liquids following two steps are used

1. Preparation of saturated solution: Solubility indicates the maximum amount of a substance that can be dissolved in a solvent at a given temperature. Such a solution is called saturated. Solubility is measured either in grams per 100 g of solvent (g/100 g) or number of moles per 1 L of the solution.
2. Analysis of saturated solution: Once the saturated solution is prepared its analysis is carried out to check the solubility. It depends upon the nature of the solute and accuracy of the method employed. Following methods are used for analysis.

a) Evaporation method

b) Volumetric method

c) Gravimetric method

d) Instrumental method

ADVANTAGES OF MIXED HYDROTROPIC SOLUBILIZATION^{6,7}

1. 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.
2. It precludes the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost etc.
3. 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.

NOVEL PHARMACEUTICAL APPLICATIONS OF HYDROTROPIC SOLUBILIZATION IN VARIOUS FIELDS OF PHARMACY^{6,13-15}

1. Preparation of dry syrups (for reconstitution) of poorly water-soluble drugs.
2. Quantitative estimations of poorly water soluble drugs by UV-Visible spectrophotometric analysis precluding the use of organic solvents.
3. Quantitative estimations of poorly water soluble drugs by titrimetric analysis. Such as ibuprofen, flurbiprofen and naproxen using sodium benzoate.
4. The use of hydrotrophy to give fast release of poorly water-soluble drugs from the suppositories.
5. 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.
6. 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. The use of hydrotrophy to give
- fast release of poorly water-soluble drugs from the suppositories.
7. Application of mixed- hydrotrophy to develop injection dosage forms of poorly water-soluble drugs.
8. 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.
9. The use of hydrotropic solubilizers as permeation enhancers.
10. Preparation of injection of poorly water soluble drugs.
11. Application of hydrotropic solubilization in nanotechnology (by controlled precipitation).
12. Application of hydrotropic solubilization in extraction of active constituents from crude drugs (in pharmacognosy field).

CONCLUSION:

Solubility can be enhanced by many techniques among them hydrotrophy is of very much importance. Hydrotrophy 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 etc.

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