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A REVIEW ON: NOVEL SOLUBILITY ENHANCEMENT TECHNIQUE HYDROTROPY

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ABSTRACT

Hydrotropy is one of the important solubility enhancement techniques that can be used to enhance solubilisation of poorly water soluble drugs in folds by using various hydrotropic agents. Hydrotropic agents such as sodium citrate, sodium acetate, sodium benzoate, urea, nicotinamide are commonly used. Mechanism of hydrotropic solubilisation is by salting in or by stacking complexation. Hydrotropic agents can be classified generally or on the basis of chemical structure. Hydrotropy is used in the analysis of active pharmaceutical ingredients to skip use of organic solvents that means it is eco-friendly method. It is used in solid dosage forms, injections and separation of closely boiling liquids, in novel systems. To achieve highest degree of solubility hydrotropes can be combined with polymers or co-solvents as in mixed hydrotropy.

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INTRODUCTION

Now a days 40% of new chemical entities which are synthesized are poorly water soluble or lipophilic in nature and hence their applicability remains limited. Knowledge of the solubility of a drug in water can be critical in formulating products, developing analytical methods, and evaluating drug transport or distribution problems.[1] Solubility of water insoluble or poorly soluble drugs can be enhanced by various techniques such as complexation with cyclodextrins, particle size reduction, solid dispersion, chemical modification, co-solvency, surfactants etc.[2]

Solubility

Solid drugs administered orally for systemic activity must dissolve in GI fluids prior to their absorption. Thus the rate of dissolution can influence rate of absorption. As rate of dissolution of a solid is a function of its solubility in dissolution medium, latter could influence absorption of insoluble drugs. Compounds with an aqueous solubility of greater than 1% w/v do not show dissolution related problems. Mainly BCS class II and Class IV drugs show solubilisation problems.

Dissolution is the transfer of molecules or ions from a solid state into solution. The extent to which the dissolution proceeds under a given set of experimental conditions is referred to as the solubility of the solute in the solvent. Thus, solubility is the amount of solute that passes into solution when equilibrium is established between the solution and excess (undissolved) solute. [7]

The pharmacopoeia lists solubility in terms of solvent required to dissolve 1g of solute. If exact solubilities are not known, the pharmacopoeia provides general terms to describe a given range as shown in table no. 1.

Description of solubility terms:[10]

Table No. 1: Description of solubility terms

Sr. No.	Descriptive term	Parts of solvent required for part of solute
1	Very soluble	Less than 1
2	Freely soluble	From 1 to 10
3	Soluble	From 10 to 30
4	Sparingly soluble	From 30 to 100
5	Slightly soluble	From 100 to 1000
6	Very slightly soluble	From 1000 to 10,000
7	Practically insoluble, or Insoluble	10,000 or more

Determination of solubility:

A semi-quantitative determination of solubility can be made by adding the solute in small incremental amounts to a fixed volume of solvent, after each addition system shaken vigorously and examined visually for undissolved particles. Following are the method used to determine the solubility,

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 solution. 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. Methods used for analysis of saturated solution are, evaporation method, volumetric method, gravimetric method, instrumental method.

Hydrotropy:

The phenomenon of hydrotropism was first put forth by the scientist Neuberg [3] [4] in 1916. He defined the term hydrotropy as enhancement in the solubility of a substance in presence of high concentrations of alkali metal salts of various organic acids.

Conventional Neuberg's hydrotropic salt consists of two groups. One is an anionic group which is responsible for high aqueous solubility. A hydrophobic ring system is responsible factor in the mechanism of hydrotropic solubilisation. Nature of anion or metal ion have a minor effect in solubilisation. [5]

Hydrotropic agent:

Hydrotropic agents are freely soluble organic compounds which at a concentration sufficient to induce a stack-type aggregation considerably increase the water solubility of organic substances, practically insoluble under normal conditions. These compounds may be anionic, cationic or neutral molecules.[53] A wide range of substances have been used as hydrotropes so it is difficult to classify hydrotropes. They have been classified on the basis of chemical structure. [54] Further they can be generally classified as given in table no. 2,

Table No. 2: Classification of hydrotropic agents.

Sr. No.	Hydrotrope	Example
1	Urea and its derivatives	Urea, N, N-dimethyl urea
2	Aromatic alcohols	Resorcinol, pyrogallol, catechol, a,b-napthols
3	Organic metal salts and organic acids	Sodium salicylate, sodium benzoate, sodium citrate, sodium acetate, sodium ascorbate, potassium citrate, citric acid, benzoic acid
4	Aromatic hydrotropes	Caffeine, nicotinamide, N,N-diethylnicotinamide, N,N-dimethylbenzamide
5	Surfactants	Sodium dodecyl sulphate, dodecylated oxidibenzene
6	Soluble drugs	Ibuprofen sodium[57], metformin hydrochloride

Mechanism of hydrotropic solubilisation:

A hydrotrope solubilizes water insoluble or poorly soluble compounds in aqueous solutions. It consist of, hydrophilic part and hydrophobic part which is too small to cause spontaneous self-aggregation which is observed in surfactants. And the concentration at which self-association begins is denoted as the minimum hydrotrope concentration (MHC) and as it is often indicated by changes in solution properties such as viscosity, conductivity, surface tension, or solubility.[58] Association of hydrotrope molecules, in contrast to micellar association, initially takes place in a pair wise manner, and that this primary association is followed by consecutive steps to form trimers, tetramers, and so on. The dominant free energy component for the association was judged to be the entropy contribution from water molecules liberated from the structure shell around the negative ions.[9]

Nicotinamide a hydrotropic agent which has been studied extensively shows stacking type of complexation.In an aqueous environment the aromatic planar structure and the hydrotrope favour stacking of aromatic rings, which is considered to be the main factor contributing to the solubilizing effect of these hydrotropes. The degree of aromaticity in the hydrotropic agent is important for its solubilizing power.[11] Nicotinamide forms 1:1 complexes at low concentration and 1:2 complexes at higher concentrations with drug molecules. [12]

Hydrotropic agents such as sodium benzoate, urea, sodium citrate are ionic organic salts. And used as additives which can either increase or decrease the solubility of a solute in a given solvent [6]. Several salts with large anions or cations that are themselves very soluble in water results in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism [13]. The mechanism can be presented as given in fig. no. 1

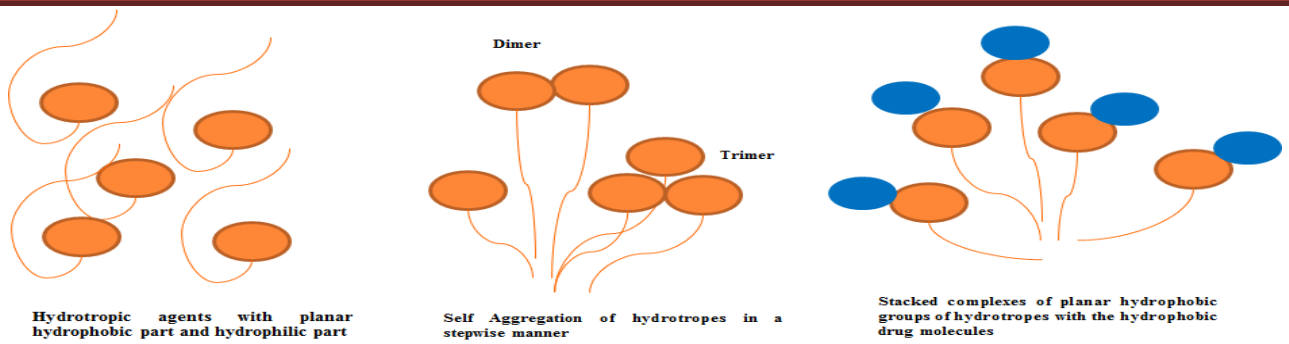

Figure 1: Mechanism of stacking complexation and self -association

Advantages: [61]

- Hydrotropy is superior to other solubilisation methods [8] such as miscibility, micellar solubilisation, co- solvency and salting in as solvent character is not dependent on pH.
- It has simple mixing of the drug with the hydrotrope in water.
- Use of organic solvents is not required so it is eco-friendly.
- No need to prepare emulsion system.
- The hydrotropes are known to self-assemble in solution.

Disadvantages:

- There are issues related to toxicity associated with excess use of hydrotropic agents.
- The relatively high concentrations required to reach the MHC limits the commercial application of hydrotropes.
- There are chances of weak interaction between hydrotropic agent and drugs.
- As there is use of water as a solvent, complete removal of water cannot be achieved.

Methods of preparation of hydrotropic solid dispersion:

There are two methods for preparation of hydrotropic solid dispersion as,

1. Hot melt method [33]:
   In this method the hydrotropic carriers are taken in a petridish kept on magnetic stirrer having temperature control so as to melt the carriers, then drug is added to molten mass. Blend is heated for 5 min. followed by instant cooling on an ice-bath. This method is used for drugs with high melting points.
2. Solvent evaporation method [45]:
   In this method hydrotropic carriers are dissolved in water at high temperature in a beaker, &then hydrophobic drug is added. Then beaker is kept on magnetic stirrer with magnetic bead inserted in it and heated at required temperature so as to evaporate water. Cessation of bead rotation indicates formation of solid dispersion, which is a semisolid mass. This mass is removed and spread on watch glasses. Kept in oven for drying.

Applications of hydrotropism in various fields of pharmacy:

1. In Analytical Chemistry:

There has been raising questions about use of organic solvents which cause harm to environment. Many drugs are soluble in organic solvents but are poorly water soluble. For such drugs hydrotropy method has been used for their estimation as shown in table no. 3.

Table 3: Drugs estimated using hydrotropy.

Sr. No.	Drug	Hydrotropic Agent	Increase in solubility	Method of estimation
1	Hydrochlorothiazide [14]	2M Nicotinamide	43 times	UV
2	Salbutamol sulphate[15]	2M Nicotinamide	17 times	Titrimetric
3	Cefixime*[16]	6M Ammonium acetate , 5M Potassium acetate , 0.5 M Potassium citrate, 1.25M Sodium citrate, 8M Urea.	-	UV, Chromatography
4	Ketoprofen[17]	2M Potassium acetate	210 times	UV
5	Lovastatin[18]	4M Sodium acetate	6 times	UV
6	Ornidazole [19]	0.5M Ibuprofen sodium	8 times	UV
7	Amlodipine besylate[20]	2M Sodium acetate	75 times	UV
8	Atenolol HCl[21]	1M Metformin hydrochloride	3 times	UV
9	Theophylline [22]	2M Sodium salicylate	18 times	Titrimetric
10	Eprosartan Mesylate, Hydrochlorothiazide* [23]	2M Sodium acetate, 8M Urea	56 times 74 times	UV
11	Aceclofenac [46]	2.5 M Sodium salicylate	400 times	Titrimetric
12	Diacerein*[47]	8M Urea, 0.5M Potassium citrate	-	UV
13	Frusemide*[48]	5M Urea, 1M Sodium acetate, 0.4M Sodium citrate	15 times	UV
14	Aspirin [49]	0.5M Ibuprofen sodium	5 times	Titrimetric
15	Atorvastatin [50]	2M Urea	6-7 times	UV
16	Famotidine [51]	2M Sodium salicylate	25 fold	Titrimetric
17	Cefadroxil [59]	6M Urea	10 times	UV
18	Naproxen[60]	0.5M Ibuprofen sodium	350 times	Titrimetric
19	Gatifloxacin[64]	20% N,N dimethyl urea, 20% Sodium citrate solution	15 times	UV
20	Lamotrigine [68]	5% Urea, 5% Sodium benzoate, 10% Nicotinamide.	15 times	UV

*Mixed hydrotropy for solubility enhancement

2. **Solubility enhancement:**
Many poorly water soluble drugs have been solubilised by using hydrotropy effectively. Following is the list of drugs and hydrotropic agents (Table No. 4).

TableNo. 4: List of poorly soluble drugs and hydrotropes

Sr. No.	Drug	Hydrotropic Agent	Increase in solubility
1	Diclofenac sodium *[24]	Urea, Sodium citrate	250 times
2	Albendazole *[25]	Nicotinamide (max. solubilisation)	17 times
3	Ibuprofen[26]	Sodium benzoate	About 100 times
4	Thioquanine[27]	Nicotinamide	-
5	Rapamycine[28]	Benzyl alcohol,Benzyl benzoate, Benzoic acid	1000 times
6	Riboflavin [29]	Caffeine	-
7	Carbamazepine[30]	Nicotinamide	2.5 times
8	Halofantrine *[31]	Nicotinamide, Caffeine	100 times
9	Nifedipine [32]	4-Sulphonic calix[8]arene	3 times
10	Rafecoxib *[33]	Urea, Nicotinamide	-

*Mixed hydrotropy

3. **Hydrotropic separation of closely related compounds:** Hydrotropes have been successfully used for separation of liquids which have close boiling points. (table no. 5).

Table 5: List of closely boiling liquids

Sr. No.	Separation of	Hydrotropes used
1	1, 1/1, 2-diphenylethane[34]	Diethylnicotinamide, Sodium pseudocumene sulfonate and Sodium thiocyanate
2	m/p- Aminoacetophenone[35]	Diethylnicotinamide, Sodium pseudocumene sulfonate and Sodium thiocyanate
3	m/p – Aminonitrobenzene[36]	Sodium benzoate, Sodium saccharin, Dimethyl benzamide
4	p-cresol/2, 6-xylenol and phenol/o-chlorophenol[37]	Sodium toluate, Sodium toluene sulfonate, Sodium cymene sulfonate, Sodium mesitylene sulfonate, and Sodium pseudocumene sulfonate
5	6-aminopenicillanic acid (6-APA) and phenoxyacetic acid(PAA)[38]	Sodium butyl monoglycol sulphate

4. Hydrotropy is also used to extract bioactive limonin from its source;sodium salicylate and sodium cumene sulphonate were used as hydrotropes.[39]
5. Hydrotropy also have been used to enhance solubility and mass transfer coefficient of sodium salicylate [40] using sodium acetate, sodium salicylate, citric acid, urea and acetyl salicylic acid [41] using sodium salicylate, sodium benzoate, nicotinamide, urea. Mass transfer coefficient of ethyl acetate in water has been enhanced using tri-sodium citrate, urea, sodium benzoate, and sodium salicylate. [42]
6. Applications in novel drug delivery systems, as hydrotropic solubilisation method has been used in novel systems as polymer micelles [43, 66], self- micro emulsifying systems [44], in transdermal

formulations to enhance hydrotropic solubilisation of polyol fatty acid monoesters[52], to form in situ gel [65]of poorly soluble drug.

7. In tablet dosage forms:Using hydrotropic solubilisation method nifedipine hydrotropic solid dispersion tablets [45] have been prepared.
8. Hydrotropic solubility enhancement have been employed for preparation of aqueous injections of Indomethacin [55], Aceclofenac [56], Temazepam [67]

Mixed Hydrotropy

Theconcentrated solutions made by taking several hydrotropes(sodium benzoate, sodium ascorbate, sodium citrate, niacinamide, urea) in small concentrations shows additive or synergistic enhancement in solubility. This is called mixed hydrotropy. When it is used to prepare the concentrated combined aqueous solutions of various water soluble additives, then it is called mixed solvency.[62, 63]

It is advantageous as when single hydrotrope is used it requires much higher concentration of that hydrotrope to achieve MHC, but when combination of hydrotropes are used then much lesser concentrations of individual hydrotropes are required and they show synergistic effect. This may help in widening the applicability of hydrotropes.

CONCLUSION

Hydrotropic solubility enhancement is simple, cost effective, eco-friendly, and novel method. Previously nicotinamide, sodium benzoate, sodium acetate, urea have been utilised most frequently but nowadays novel hydrotropes such as metformin hydrochloride, ibuprofen sodium have been utilised, and many of their kind can be exploited as hydrotropes. Hydrotropy method haven't yet been commercialised as there are issues related to use of higher concentration of hydrotropic agent for formulation. But it can be used for analysis of APIs and finished dosage forms. It is a cost effective method because it does not contain organic solvents.

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