Journal of Pharma Research
Available online through
www.jprinfo.com

Review Article
ISSN: 2319-5622

A Review on Hydrotropy

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Received on: 25-04-2013; Revised and Accepted on: 04-05-2013

ABSTRACT

Solubility is one of the important parameter to achieve desired concentration of drug in systemic for pharmacological response to be shown. Drug efficacy can be severely limited by poor aqueous solubility and some drugs also show side effects due to their poor solubility. There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for certain drugs. This is true for parentally, topically and orally administered solutions. Use of the solubility characteristics in bioavailability, pharmacological action and solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. Hydrotropy 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.

Keywords: *Hydrotropy, Solubility, Hydrophobic drugs, Hydrotropes, Solubility enhancement.*

INTRODUCTION

The term hydrotropic agent was first introduced by Neuberg (1916), to designate anionic organic salts which, at high concentrations, considerably increase the aqueous solubility of poorly soluble solutes [1]. Hydrotropy is a solubilization phenomenon whereby addition of large amount of second solute results in an increase in the aqueous solubility of another solute. 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. The chemical structure of the conventional Neuberg's 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 ringing 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 [2]. 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 [3].

Hydrotropy:

Hydrotropy is a solubilization phenomenon whereby Addition of large amount of a 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 [4, 5].

Mechanism of Hydrotrope Action: [5]

A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous slutions. Typically, hydrotropes 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' starts to occur (as found for micelle - and vesicle -forming surfactants, which have a not necessarily anionic, can act as hydrotropic agents. Saleh critical micelle concentration or cmc and a critical vesicle concentration or cvc, respectively). 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 solubilisate has been added.

History of Hydrotropy and Basic Structure of Hydrotrope:

Hydrotropy is the term originally put forward by Neuberg [6] 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-in. 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 Gaikar et al [5, 6], investigated whether a drug with an amphiphillic structure can exhibit hydrotropic. properties. They sought to establish sodium ibuprofen as an effective hydrotrope. On the other hand, planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization [6, 7]. 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 soluble drugs. and El-Khordagui [8] 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 involve They used procaineHCl, PABAHCl and cinchocaineHCl as cationic salts and resorcinol and pyrogallol as neutral molecules in their studies.

Advantages of Hydrotropic Solubilization Technique: [9]

1. Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, cosolvency 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.

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Commonly used Hydrotropes:

The hydrotropes are known to self-assemble in solution [9]. 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 [9], aromatic alcohols like resorcinol, pyrogallol, catechol, a- and b-naphthols and salicylates, alkaloids like caffeine and nicotine [10], ionic surfactants like diacids [11], SDS (sodium dodecyl sulphate) [12] and dodecylated oxidibenzene [13]. 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 [14]. Besides enhancing the solubilization of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multi component systems with reference to nano dispersions and conductance percolation, clouding of surfactants and polymers, etc [8, 14].

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 [14].

Advantages of Mixed Hydrotropic Solubilization: [15]

1. 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.
2. 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 [16, 17].
3. It precludes the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost etc [18]. A list of drugs studied by hydrotropic solubilization and its solubility enhancement ratio is presented in **Table 1**.

Table No. 1: Hydrotropic solubilization study of various poorly water-soluble drugs [19]

S. No.	Drugs	Hydrotrope	Solubility Enhancement Ratio
1)	Ketoprofen	2M Potassium acetate	210
2)	Hydrochlorothiazide	8M Urea	70
3)	Olenzepine	1M Sodium benzoate	60
4)	Aceclofenac	40% Urea	25
5)	Nimsulide	2M Nicotinamide	150
6)	Nalidixic acid	2M Sodium benzoate	90
7)	Norfloxacin	2M Sodium benzoate	60

CONCLUSION

By this article we conclude that, Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. Solubility can be enhanced by hydrotropic solublization techniques and number of folds increase in solubility is reported too.

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Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil