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Review Article

ROLE OF HYDROTROPIC SALT SOLUTIONS IN PHARMACEUTICAL RESEARCH: PAST PRESENT AND FUTURE

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ABSTRACT

Hydrotropic solubilization technique is a one of the most potential tool to solubilize poorly water soluble drug. Hydrotropy can be described by the increase in the solubility of a solute by the addition of fairly high concentrations of another solute, may it be an organic compound, salt, or amhiphile. Initially it was proposed for the solubilization of poorly water soluble drug but recently various facets of the technique has been discovered viz. for use in, solid dispersions, parenteral formulation, nanoparticlate delivery and extraction of bioactive materials and many of them are being critically assessed through active research. In this review attempts have been made to compile every aspect of the hydrotropic, its probable mechanism, its utilization in the estimation of poor water soluble drugs in their bulk drug and respective dosage to serve as a better replacement for the hazardous organic solvents like methanol, acetone, DCM, ethers etc which are more commonly used in the analytical estimation. Similarly the technique is also being progressively used in the formulation of poorly water soluble drugs to avoid the use of organic solvents. Salts involved in this technique present certain limitations which confine their use. In order to avoid such limitations of these salts, concept of mixed hydrotropy and mixed solvency has been introduced recently. The same is also discussed in this review.

Keywords: Poor water soluble drugs, Solubilization, Hydrotropy, Mixed hydrotropy,

INTRODUCTION

Poor aqueous solubility of a drug limits its efficacy and utility, since the solubility is one of the most important factors for the absorption of any drug administered through oral route. Consequently consequences several attempts have been made to develop techniques for enhancing the solubility of such drugs and hydrotropy is one of them. The term hydrotropy was first introduced by Neuberg in 1916 to describe the increase in solubility of a solute by the addition of high concentration of alkali metal salts of organic acids. The definition implies that the hydrotropes are metal salts of organic acids, which are responsible for increase in solubility of poorly water soluble compounds when the hydotrophes are added at fairly high concentrations. **[**1**]**

Saleh et.al. in 1985 extended the definition of hydrotrope and stated that it can be cationic, anionic or a neutral molecule having a hydrophobic as well as a hydrophilic group. Therefore, any aromatic solubilizing agent used in high concentration (i.e. in non-stoichiometric excess) can be termed a hydrotrope. **[**2]

A different view on hydrotropes states them as a special class of compounds which are known to possess distinct solution properties. They may self associate in aqueous medium which in turn can be compared to amphiphilic self-association or micellization. They are efficient solubilizers and can influence the formation of micelle and microemulsion **[**3**]**. In this review, the effect of hydrotropes on solution behavior of amphiphiles has been presented with a brief description of the important aspect of hydrotrope action**.** Hydrotropes are a class of compounds which are amphiphilic in character, having short hydrophobic regions and thus differ from classical surfactants, yet they display substantial ability to solubilise nonpolar compounds in water [4].

On the basis of above postulates it was proposed that hydrotropic agents are freely soluble organic compounds which at a concentration sufficient to induce a stack-type aggregation considerably enhance the aqueous solubility of organic substances, practically insoluble under normal conditions. These compounds may be anionic, cationic or neutral molecules. However, further characterization of hydrotropic agents is the subject of subsequent studies with respect to solubilization technique. [5]

Examples of hydrotropic agents used as excipients in literature are urea, sodium salicylate, sodium gentisate, sodium gluconate, sodium benzoate, sodium ascorbate, sodium citrate, sodium ibuprofen, pheniramine, lysine, tryptophan, sodium acetate, and isoniazid. 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, selection of appropriate hydrotropic agents for a poorly soluble drug requires screening a large number of hydrotropes.[6] Common hydrotropic agents that are used, include sodium benzoate, sodium salicylate, urea, caffeine as well as nicotinamide and its analogues. [6- 9] Among these hydrotropes, nicotinamide or vitamin B3 has two advantages which make it a very attractive agent when used as a hydrotrope. It has FDA approval status and has a very low toxicity. [7] Nicotinamide has been used to improve the solubility of anti-cancer [9], antitumor and anti-viral drugs, including nucleoside analogues, and antimetabolites [10]. Higuchi and Drubulis [11] studied the sodium salts of several aromatic and hydroxyaromatic acids (sodium benzoate, sodium o-hydroxybenzoate, sodium-hydroxybenzoate and sodium p-hydroxybenzoate) to see their influences on the solubilities of theophylline, hydrocortisone, prednisolone and phenacetin.

Proposed Mechanism of Action of Hydrotropic Salts

The exact mechanism of hydrotropic solubilization is still a point of debate among the scientists. Some workers have speculated that hydrotropy is simply another type of solubilization, with the solute dissolved in oriented clusters of the hydrotropic agents [12]. According to some workers, this phenomenon is basically related to complexation due to a weak interaction existing between the solute and hydrotropic agent. Higuchi and Drubulis [11] studied various hydrotropic agents and observed their influences on the solubilities of theophylline, hydrocortisone, prednisolone and phenacetin. In their study they concluded that majority of the interactions between these aromatic or hydroxyaromatic compounds and the substrates was of the “donor-acceptor” type and the contributions from hydrophobic bonding and hydrogen bonding were possibly of lesser magnitude. Poochikian and Cradock [13] had observed the effect of various hydroxybenzoates on the solubility of the water-insoluble cytotoxic agent, chartreusin and postulated a plane-to-plane

orientation of chartreusin and the ligand molecules brought together by electrostatic and hydrophobic interactions. Hydrotropic solutions do not show colloidal properties however another belief is that this phenomenon is more closely related to complexation involving a weak interaction between the hydrotropic agent and the solute. Still another theory state that the phenomenon must be due to a change in solvent character because of the large amount of additive is needed to bring about the increase in solubility.

Silva assumed that these additives (hydrotrope) act in a bridge like manner, concentrating themselves around the hydrophobic solute, but without any specific interaction with it. [14-15]

Some common examples of hydrotropic agents

➢ Benzoic acid and sodium salt	➢ Salicylic acid
➢ Brompheniramine maleate	➢ Sodium-2,4/2,5/2,6/2,4,6 hydroxy benzoate
➢ Butyl urea	➢ Urea,
➢ Chlorpheniramine maleate,	➢ 1-3-dimethyl urea
➢ Methyl urea	➢ Sodium ascorbate,
➢ Nicotinamide	➢ Sodium benzoate
➢ Nicotinamide derivatives	➢ Sodium gentisate
➢ Nipecotamide	➢ Sodium glycinate
➢ N-dimethyl acetamide	➢ Sodium salicylate
➢ N-methyl nicotinamide,	➢ Sodium salt of Ibuprofen
➢ N, N-dimethyl nicotinamide	➢ Sodium-m-hydroxy benzoate
➢ m-hydroxy benzoic acid	➢ Sodium-p-hydroxy benzoate
➢ p-hydroxy benzoic acid	➢ 4-sulphonic calix[n]arenes
➢ Pheniramine maleate	➢ sodium cumene sulphonate
➢ pyrogallol	➢ sodium alkyl benzene sulfonates
➢ Resorcinol	➢ sodium butyl monoglycol sulfate
➢ Penicillin potassium salt	

The influence of large concentration of sodium benzoate on the solubility of caffeine is a classic example of this phenomenon which is applied to a pharmaceutical system. Other example includes the solubilization of benzoic acid with sodium benzoate. [15]

Badwan et al. [16] showed that the phenomenon of hydrotropy could be correlated with a break in the solution properties of benzoate hydrotropic agents at relatively high concentration. Such a deviation has been attributed to a stacking-type association of the hydrotrope molecules favored by the planarity of their structure.

Some workers have proposed that nicotinamide undergoes stacking with drug molecules· [17] A complex is formed by the interaction between the planer hydrophobic regions of the complexing agent and the drug. The stacked arrangement represents an orientation wherein the hydrophobic regions are less exposed to water. This involves a passive process. In other words, the drug and the complexing molecules may not have a direct affinity towards each other but they interact with each other in order to minimize their exposure to water. Stacking may occur between the molecules of same species (self-association) or different species (co-association). Stacking occurs primarily between planar molecules for which the exposure to water can be efficiently minimized. A simple 1:1 complex consists of one molecule each of the drug and complexing agent. A 1:2 sandwich complex may be formed where the central molecule is surrounded on two sides with the complexing agent. [17-19]

Besides stacking, at least two other theories have been proposed to explain the mechanism of drug solubilization by nicotinamide. It has been postulated that nicotinamide acts like a chaotrope, i.e., breaks the self-associated structure of water. This results in higher drug solubility. [19]

Chaotropes reduce the surface tension of water by lowering its molecular cohesiveness. Surfactants on the other hand, do so by selectively accumulating at the air–water interface leading to the formation of micelles in the aqueous phase. The concentration at which this occurs is referred as critical micelle concentration (CMC). In a similar way aggregation of the hydrotopes and their drug loading has been reported and the concentration of the same has been reported to as “critical hydrotrope concentration” which is analogous to the term critical micellar concentration.[20] The term “critical hydrotrope concentration” has been proposed to refer to the concentration at which the aggregation starts. It has been reported in different studies that nicotinamide forms micellar aggregates in water, followed by the incorporation of drug into these aggregates. Roy et al., studied different hydrotropic agents viz. sodium salicylate, proline, pyrogallol, resorcinol, urea to find out any possible self aggregation of the hydrotopes. Viscosity measurements were in support of the possible self-aggregation of hydrotropes but on the other hand microcalorimetric measurements did not support the existence of the phenomenon. [3]

In a study by Kumar et al. [21] it has been demonstrated that a ‘Minimum Hydrotrope Concentration’ (MHC) in the aqueous phase is required to initiate significant solubilization of furfural which is supported by the fact that the mass transfer coefficient was found to increase with increase in hydrotrope concentration accompanied by increase in solubilization of furfural. On one hand the increase in solubility has been attributed to the aggregation of the hydrotopes viz. in case of nicotinamide but on the other hand the most common proposed and accepted mechanism for solubilization with nicotinamide is complexation which occurs through a π –donor π –acceptor mechanism. [19, 22, 23]

Solubility of substrates at higher hydrotope concentration can be attributed to aggregation and other related reasons but solubility at lower concentrations can be understood through a study conducted by Jain A. K [24] which reveals that the solubility of indomethacin at lower hydrotrope concentration might occur due to to weak ionic interactions. Woolfson [25] has investigated the solubilisation of temazepam by hydrotropic complexation using Sodium salicyate and nicotinamide as hydrotropes. The former allowed appreciable solubilization of temazepam but the effect was less marked in the case of nicotinamide. The results of the study revealed that increased solubilisation with temazepam can be attributed to an increase in hydrogen bonding between drug and hydrotropic agent.

In another study it has been demonstrated that an electrostatic force of the donor-acceptor type plays an important role in the solubilization of benzodiazepines when sodium salicylate is used as hydrotope [16]. It has been assumed as per the study that a donor-acceptor interaction exists between sodium salicylate and benzodiazepine molecules to stabilize such an inclusion and enhance the degree of solubility of the benzodiazepines in sodium salicylate solution.

Use of the hydrotropic agent for the analytical estimation of poor water soluble drug

Solubility is the one of the critical factor during the analytical estimation of the poor soluble drug in aqueous media and this can be minimized by using thee hydrotropic solutions. Maheshwari[26] et al. analyzed cefixime (a poorly water-soluble drug) in tablet dosage

forms using urea, sodium acetate and sodium citrate as hydrotropic solubilizing agents. They also developed the titrimetric and spectrophotometric methods for frusemide [27, 28], ketoprofen and salicylic acid [29] using hydrotropic solution and also explored the use of hydrotropes as solubilizing agent to analyze a poorly water-soluble drug, cephalexin [30], ketoprofen[31] and Gatifloxacin[32]. Researchers have also explored the use of hydrotropic agent as solubilizing agent for the spectrophotometric estimation of amlodipine besylate [33] nalidixic acid, norfloxacin, tinidazole and metronidazole. [34]

Development of the various formulations using hydrotropes

It is well evident that the solubility is one of the most important limiting factors during the formulation of parentral and oral liquid dosage form of a poorly water soluble drug. It has been found that liquid formulation of poorly water soluble drugs can be prepared by increasing the solubility using hydrotropes. Khordagui et al [35] had studied release characteristics of riboflavin as a model solubilized drug from the prepared starch gel using a typical hydrotropic salt (sodium salicylate) as a gelling agent without heat treatment or chemical modification. They indicated consistent diffusion-controlled kinetics and concluded that hydrotrope-gelled starch may be a potent vehicle for topical drug delivery.

Agrawal et. al. ketoprofen [36] had prepared the parentral formulation of nimusulide by using different hydrotropes as piperazine, sodium benzoate, sodium ascorbate, nicotinamide etc. and reported piperzine as the best solubilizing agent for the preparation of parental formulation of nimusulide. Nahar et al [37] has prepared the injection of saquinavir by using nicotinamide and ascorbic acid and found that the nicotinamide was more promising. Rao et al [38] had prepared hydrotropic starch gels of terbinafine hydrochloride using corn starch and sodium salicylate as hydrotropic salt.

Jain A. K had investigated the effect of various hydrotropes such as urea, nicotinamide, resorcinol, sodium benzoate and sodium p-hydroxy benzoate on the solubility of indomethacin for the preparation of aqueous injectable formulations. In their study they found that solubility of indomethacin enhances in decreasing order as sodium p-hydroxy benzoate > sodium benzoate > nicotinamide > resorcinol > urea using sodium p-hydroxy benzoate. He also developed an injection formulation and studied its stability. [39]

Hydrotropes for extraction of bioactive compounds

It is well known that most of the extraction process for bioactive compounds includes organic solvent which are expensive and not safe for the environment, while such type of extraction also be done by using the various hydrotropic agents. Dandekar et al have shown that limonoid aglycones (0.65 mg/g seeds) can be extracted from sour orange by using the optimized concentration hydrotrope (sodium cumene sulphonate), extraction temperature and raw material loaded for extraction. **[**40] Similarly Raman et al. [41] had investigated that Hydrotropes, such as sodium alkyl benzene sulfonates and sodium butyl monoglycol sulfate, can be used for the selective extraction of piperine by cell permeabilization of *Piper nigrum* fruits. Significant effects of nature of the hydrotrope and its concentration, temperature, and the particle size on the extraction process have bee also shown.

Other Application

Hydrotropic polymers, dendrimers and micelles have been developed as nanocarriers for poorly water soluble drugs. The hydrotropic polymer micelles presents unique advantages over conventional polymer micelles in that the interaction between the polymer segment and drug is based on miscibility between the two, instead of the hydrophobic interaction alone. The hydrotropic polymer micelles in aqueous solution are more stable than the conventional polymer micelles. The new polymer systems based on hydrotropic polymers and dendrimers provide a new approach of designing nanocarriers for poorly soluble drugs. [42] Lee et al [9] have reported the ability of hydrotropes to dramatically alter the solubility of other molecules in a medium which can be exploited for the purpose of selective encapsulation and release. Cho et al reported the solubility enhancement of paclitaxel, using the hydrophobic core of poly (ethylenglycol)–poly (phenylalanine) copolymer micelles in water and then by the addition of one molar sodium salicylate to the micelle solution increases the water solubility of PTX by a factor of 100 without disrupting the polymer micelles and resulted in the controlled release of PTX into the bulk solution. [43] Some scientists reported the recent use of hydrotropes in the development of new hydrotropic polymer based on N, N-diethylnicotinamide and used it as a hydrophobic block for constructing amphiphilic block copolymers. In their further study they reported that these hydrotropic block copolymers get self-assembled to form micelles in the range of 30–50 nm in aqueous media leading to the increased paclitaxel loading (size of micelles-100–120 nm) facilitating the delivery of poorly water-soluble drugs such as paclitaxel[44]. Using similar approach Kim et.al have developed hydrophobic block copolymer using Poly ethylene glycol (PEG) *N,N*-diethylnicotinamide (DENA) and *N,N*-dimethylbenzamide (DMBA). They reported that the solubilizing capacity of polymeric hydrotropes reflects combined effects of the micellar solubilization by the hydrophobic micelle core and hydrotropic solubilization. [45, 46] Similarly, a polymeric nanoparticulate was developed Park and co-workers using copolymer consisting of PEG and poly (4-(2-vinylbenzyloxy-N-picolyl-nicotinamide) (PDENA). In their study they concluded that the prepared system provided efficient encapsulation of paclitaxel with high loading. [47]

Mixed Hydrotropy

Mixed hydrotropy involves the use of two or three hydrotropic agents in such way that the combination produces synergistic effects in terms of enhanced solubility of poorly water soluble drug and simultaniously the concentration of the hydrotropic salts is reduced. Maheshwari et. al have used the concept for the enhancement of solubility of a poorly water-soluble drug - aceclofenac, in bulk to carry out titrimetric estimation precluding the use of organic solvents.[47, 48] Maheshwari et. al also prepared the aqueous injection of acceclofenac by using the combination of urea and sodium citrate.[49]

CONCLUSION

Hydrotropic technique has proven its utility and importance in all most every area and can be effectively employed in the pharmaceutical field. It can be used for titrimetric and spectrophotometric estimations of poorly water-soluble drugs from their bulk drug samples and solid dosage forms precluding the use of organic solvents providing simple, economic, eco-friendly, safe (free from toxicity) and accurate analytical methods. It can also be used to prepare solid dispersions of poorly water-soluble drugs for improved dissolution rate, to develop liquid oral solutions (syrups) of poorly water-soluble drugs for improved bioavailability, to develop topical solutions of poorly water-soluble drugs having improved (probably) percutaneous absorption. Thus it can be concluded that by using hydrotropic technique one can be able to replace the use of organic solvents which are more costly and hazardous to our environment. Moreover certain experiments and formulations do not permit the use of such solvents. The hydrotropic solubilization technique is proving itself as a one of the most important tool for the formulation development of various water insoluble drugs but still there exists a room for the exploration of this technique.

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