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ROLE OF HYDROTROPES IN SOLUBILIZING DRUGS –A REVIEW

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ABSTRACT

Many existing drugs are poorly soluble in water, and this limits their clinical applications. A large number of newly developed drug candidates are frequently found to be poorly water soluble, making it difficult to test their bioefficacy and to produce formulations with sufficiently high bioavailability. The drug solubility in saturated solution is a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate. Increasing the aqueous solubility of poorly soluble drugs has been one of the most important issues in drug discovery and delivery, because the clinical applications of many drugs are limited by their poor water solubility. Hydrotropy is one of the solubility enhancement techniques that enhance solubility to many folds using hydrotropes like sodium benzoate, sodium citrate, urea, nicotinamide etc. They have many advantages like, does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system etc. The present review discusses literature available on drug solubilization using different hydrotropes. The mechanism of hydrotropy is also discussed in this review. Scope for future work is also presented.

Key Words: Hydrotropes, drug, mechanism, bioefficacy, formulations

Introduction

Poor water solubility of drugs often causes significant problems in producing formulations of sufficiently high bioavailability, preventing effective use of the drugs. It is commonly recognized in the pharmaceutical industry that on average more than 40% of newly discovered drug candidates are poorly water-soluble. Paclitaxel, which is one of the most successful chemotherapeutic drugs, is a good model drug for describing the problems with poorly water-soluble drugs[1]. Owing to its poor water solubility, the only commercial paclitaxel product (Taxol) is currently formulated in a concentrated solution containing 6 mg paclitaxel in 1 ml of Cremophor EL (polyoxyl 35 castor oil) and dehydrated alcohol, which must be further diluted 5- to 20-fold with 0.9% sodium chloride or other aqueous solutions before intravenous (IV) administration2. Despite excellent efficacy of the formulation, it resulted in serious side effects, such as hypersensitivity reactions, neurotoxicity, and nephrotoxicity, owing to the presence of Cremophor E[2].

Development of drug formulations for poorly soluble drugs is undoubtedly very important for producing

patient-friendly formulations with high bioavailability. The bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability[3] and is given by

$$\frac{dc}{dt} = \frac{AD(C_s - C)}{h}$$

where, dc/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, Cs is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t, h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound. The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions.

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature.

The aqueous solubility of organic non electrolytes is given by the following expression [4]:

$$\log X_w = -\frac{\Delta S_f (T_m - T)}{2.303RT} - \log \gamma_W$$

where Xw is the (mole fraction) aqueous solubility, Sf the entropy of fusion of the crystalline solute, Tm and T are the absolute melting and experimental temperatures, respectively, R is the gas constant and w is the activity coefficient of the solute in water.

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[5]. These descriptive terms are listed in table-1.

Table-1 : Expression for approximate solubility

S.No	Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
1	Very soluble	<1
2	Freely soluble	1-10
3	Soluble	10-30
4	Sparingly soluble	30-100
5	Slightly soluble	10-1000
6	Very slightly soluble	1000-10000
7	Insoluble or practically insoluble	>10000

The European Pharmacopoeia uses similar solubility definitions except the 'practically insoluble' characteristic, which is not specified (European Pharmacopoeia 5.0). Solubility and apparent solubility depends on several factors[6] and are listed in table-2 [when solubility becomes an issue]

The value of equilibrium solubility is often limited by test duration which is normally between 4 to 24 hours.

Some authors presented detailed review on different drug solubilization techniques[7]. They are pH adjustment, micronization, micellar solubilization, co solvency and salting in, hydrotropy etc. The authors

mentioned that hydrotropy is the superior technique due to the following reasons.

1. The solvent character is independent of pH
2. It has high selectivity and does not require emulsification 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.

This term hydrotropy was originally proposed to define a non-stoichiometric solubilization of a solute by high concentrations of anionic aromatic compounds[8]. Hydrotropic solubilization may be a result of stacking complexation; chaotropy, i.e., breakdown of water structure; or the formation of micellar aggregates [9]. It is suggested that a good hydrotrope should have high water solubility while maintaining hydrophobicity. In other words, an effective hydrotropic solubilization depends on the balance between these two counteracting effects. It is interesting to note that while the study of hydrotropes is pioneered by a biochemist, greater appreciation of their role and utility has happened in chemistry and chemical engineering than in biology. Easy recovery of dissolved solute and possible reuse of hydrotrope solutions makes this most attractive particularly at industrial level.

Mechanism of Hydrotropy:

Although definitive studies are yet to be made, the term hydrotropy does not imply a specific solubilization mechanism. The broad range and functionality of hydrotropes has led to various suggested hydrotropic solubilization mechanisms.

Some inorganic salts such as alkali iodides, thiocyanates, oxalates, bicarbonates have similar solubility enhancement effect; the mechanism in these cases is clearly understood to be 'salting in" and hence these are not classified as hydrotropes [10].

This claim is supported by Hamza and Paruta[11] in their work of dissolution of paracetamol using sodium glycinate, sodium gentisate, and sodium salicylate and nicotinamide hydrotropes. Ultra-violet spectral analysis, TLC, infra-red, and NMR techniques are utilized in order to elucidate the solubility mechanism. These tests indicated that no special bonding or complex formation exists for the sodium salt hydrotropes. There is some evidence from UV & TLC analysis that nicotinamide and paracetamol enter into complex formation. The other hydrotropic agents, indicated the mechanism of solubilization is one of "salting - in" by causing miscibility of two formally immiscible liquid phases of ternary systems.

Balasubramanian et al[12] opposed this claim and mentioned that hydrotropy is different from salting-in or mixing behaviour. It is found that these molecules self-aggregate in aqueous solution to form organized assemblies. The authors also mentioned that the cooperativity displayed by hydrotrope molecules in the aggregation process is low.

The formation of aggregates is further supported by some other Pal et al[13] during their study on the aggregation behaviour of a hydrotrope, sodium n-butyl benzene sulfonate (Na-NBBS), in aqueous solutions investigated by small-angle neutron scattering (SANS). Nearly ellipsoidal aggregates of Na-NBBS at concentrations well above its minimum hydrotrope concentration are detected by Small angle neutron scattering (SANS). The hydrotrope seems to form self-assemblies with aggregation number of 36-40 with a substantial charge on the aggregate. This aggregation number is weakly affected by the hydrotrope concentration.

Badwan et al[14] hypothesized that an electrostatic force of donor-acceptor type plays an important role

in solubilization by hydrotropes. The authors in their work on solubility of Benzodiazepines using sodium salicylate solutions mentioned that inclusion of the benzodiazepine molecules in the sodium salicylate aggregates is thought to be the mechanism responsible for the solubilization of these drugs. A donor-acceptor interaction between sodium salicylate and benzodiazepine molecules is assumed to stabilize such an inclusion and determine the degree of solubility of the benzodiazepines in sodium salicylate solution.

Subsequent development of phase diagrams[15] introduced a new solubilizing action. Instead of the earlier attempts to relate the increased solubility to the association of the hydrotrope molecules per se, the results showed that the superior solubilization in a hydrotrope comes of the hydrotrope action on the colloidal association structure of surfactants.

Roy and Moulik[16] in their work using Proline (Pr), Pyragallol (Pg), Urea (U), Sodium salicylate (NaS), procaine·HCl (PHCl) and resorcinal (Rc) mentioned that viscosity measurement support self aggregation where as micro calorimetric measurements have not supported it.

It is also shown, based on crystal structure analysis of several hydrotropes[17] that these compounds form open-layer assemblies, reminiscent of lamellar liquid crystals consisting of alternating hydrophobic clustering of the nonpolar regions adjacent to ionic or polar regions that are knitted together in a two-dimensional network. Stacking of aromatic rings is not seen. Two types of assemblies are seen, one with a more open and extended hydrophobic layer than the other. It is suggested that the solubilizates enter the hydrophobic layers of micro units producing a cooperative and mutual stabilizing effect. The observed open layer structure of hydrotropes might also account for the occasional ability of these compounds to solubilize even better than micelles. Layered structures seem preferred by hydrotropes, in contrast to the "oil drop with a polar coat" compact assembly preferred by surfactant micelles.

Ritesh Sanghvi et al[18] during their studies on drug solubilization claimed that during solubilization, complex formation takes place. They mentioned that the drug and the complexing molecules may not have a direct affinity towards each other but interact 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 planer 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.

Some authors mentioned that hydrotropes that interact favorably with the hydrophobic portion of the polymer have a more pronounced solubility[10]. The authors also mentioned in their review that some hydrotropes can function as pH probes and also are used for controlled release of drugs.

The solubilizing ability of aromatic hydrotropes N,N-diethylnicotinamide (DENA) and N,N-dimethylbenzamide (DMBA), using a set of 13 poorly soluble, structurally diverse drugs is reported[19]. The authors observed that DMBA is more powerful solubilizer of hydrophobic drugs and DENA is powerful solubilizer of Paclitaxel, a highly hydrophobic compound. Paclitaxel has a large number of hydrogen bond donors (HBD=4) and acceptors (HBD=14) in its structure. The authors stated that the hydrogen bonding ability of the pyridine ring in DENA, absent in DMBA (which has a phenyl ring) is likely the reason for the remarkable ability of DENA to solubilize Paclitaxel. They further mentioned that solubilization of drugs by DENA and DMBA is not solely the result of

hydrophobic interactions. It is concluded that the aromatic nature of solute plays a strong role in hydrotropic solubilization so as to mask the effect of hydrophobicity. The authors also mentioned that hydrotropy and its resulting solubilization are no more than a mechanism of reduction of the free energy of mixing.

Coffman and Kildsig[20] elucidated the mechanism of hydrotropy by considering the interaction between nonionic surfactant (ethoxylated fatty alcohol containing between five and six oxyethylenic units) and sodium *p*-toluene sulfonate. Photon correlation spectroscopy studies showed that for this concentration of hydrotropes a drastic reduction in the surfactant micellar radius occurs. Furthermore the luminescence of the hydrotrope used as a fluorescence probe indicates that at low concentrations *p*-toluene sulfonate dissolves in the surfactant micelles but beyond the minimum concentration for hydrotropic solubilization the hydrotrope is present in the aqueous phase which suggests that the hydrotropic effect is related to alterations in the water structure induced by the hydrotrope molecules and to the presence of hydrotrope aggregates that furnish an appropriate niche for the surfactant amphiphile. The results of osmotic vapor pressure are interpreted as arising from the formation of dimers and trimers at the initial association of nicotinamide in water while at higher concentrations an aggregation number of 4.37 is found. As expected, the trimerization constant is found to be significantly greater, about two orders of magnitude, than the dimerization constant. It is hence tactically assumed that the association takes place through stacking of the molecules, an expected conclusion considering the molecular structure of this compound.

This assumption is to some extent cast in doubt by Srinivas et al [17], who determined the crystalline structure of sodium *p-tert*-butylbenzenesulfonate dihydrate, sodium cumenesulfonate semihydrate, sodium toluenesulfonate hemihydrate, and sodium 3,4-dimethylbenzenesulfonate. In none of these crystalline structures, stacking of the molecules is not found and hence it is concluded that stacking of the molecules during association in aqueous solutions should not be assumed a priori.

The determination of vapor pressure of the solubilizate phenethyl alcohol in sodium xylenesulfonate solutions[21] showed a constant vapor pressure at hydrotrope concentrations above the association concentration, indicating a colloid association without structure changes, once the association and solubilization take place.

Anitha[22] mentioned that hydrotropy is closely aligned with water structure breaking. The author mentioned that water structure modifiers are substances that cause a change in the structure of water by affecting the degree of hydrogen bonding. The degree of hydrogen bonding is decreased by structure breakers and increased by structure formers. They used urea and nicotinamide as hydrotropes to solubilize riboflavin. The authors also stated that the combined use of certain water structure modifiers can provide an even greater hydrotropic effect than is possible with one agent.

Use of hydrotropes for solubilization of insoluble drugs:

The literature available on various drugs using various hydrotropes is presented in the table (Table-2). The method of analysis reported for various drugs in the literature is also shown.

Table-2: Details of drugs and hydrotropes used for their solubilization

S.No	Name of the drug	Hydrotrope(s) used	Concentration range (M)/ extent of increase in solubility	Analysis methods
1	Piroxicam[23]	Ibuprofen sodium	1.5 /50	Spectrophotometer at 358 nm
2	Ketoprofane[24]	Mixed hydrotropes of urea/sodium citrate/sodium acetate	30%urea, 11.6%sodium citrate and 13.6% sodium acetate/560	Titrimetric method
3a)	Aspirin[25]	Sodium salicylate	1M/-	Spectrophotometer in the range of 312-285 nm
b)	Aspirin[26]	Ibuprofen sodium	0.5M/5	Titrimetric method
4	Atenolol[27]	Metformin hydrochloride	1M/-	Spectrophotometer at 275 nm
5	Cefixime[28]	Sodium Tartarate	2M/-	Spectrophotometer at 288nm
6	Ketoprofen[29]	Mixed hydrotropes of urea and sodium citrate	30% Urea and 30% sodium citrate/700	Titrimetric method
7	Naproxen[30]	Niacinamide	2M/110	Spectrophotometer at 331 nm
8	Pramipexole Dihyrochloride[31]	Mixed hydrotropes of sodium acetate and urea	50:50 V/V of 2M sodium acetate and 8M urea solution/46	Spectrophotometer at 262 nm
9	Salicylic acid[32]	calcium disodium edetate	1M/45	Titrimetric analysis
10	Aceclofenac and Paracetamol[33]	Mixed hydrotropes of Urea and sodium citrate	30% urea with 20% sodium citrate/-	Spectrophotometer at 274.5 nm for Aceclofenac and 261.5nm Paracetamol
11	Benzoic acid[34]	Sodium benzoate and sodium salicylate	2M/14 with sodium benzoate and 2M/28 with sodium salicylate	
12	Cefixime[35]	Ammonium acetate, potassium acetate, potassium citrate, sodium citrate and urea	Ammonium citrate :6M Potasium acetate :5M Potasium citrate :0.5M Sodium citrate : 1.25 M Urea : 8M	Spectrophotometer at 269 nm and HPTLC with a mixture of methanol, ethylacetate and triethylamine (7:5:0.05 v/v) as developing solvent
13	Cefixime[36]	Sodium tartarate	2M/-	Spectrophotometer at 269 nm
14	Ketoprofen[37]	Potasium acetate	2M/210	Spectrophotometer at 260nm
15	Ketoprofen[38]	Mixed hydrotropes of urea, sodium acetate and sodium citrate	30% w/v of urea, 13.6% w/v of sodium acetate and 11.8 5 w/v of sodium citrate/570	Spectrophotometer at 260 nm
16	Aceclofenac[38]	Mixed hydrotropes of sodium citrate and urea	30% sodium citrate/5 and 30% urea solution/25 and mixed hydrotrope of 20% urea and 10% sodium citrate solution /250	Spectrophotometer at 275 nm.
17	Aceclofenac[39]	Mixed hydrotropes of sodium citrate and urea		Spectrophotometer at 275 nm
18	Aceclofenac[40]	Ibuprofen sodium	0.5M/120	
18	Griseofulvin[41]	sodium citrate, urea, sodium acetate, sodium benzoate and sodium salicylates	0.5,1 &2M/-	Spectrophotometer at 296.2 nm
19	Randitine Hydrochloride[42]	Urea	10M/-	Spectrophotometer at 299nm
20	Ibuprofen[43]	Sodium acetate, Sodium Benzoate, Sodium toluene sulfonate, Sodium Salicylate and Sodium toluate	1M Sodium acetate :1.9 times, Sodium benzoate :23 times, odium toluene sulfonate : 5 times, Sodium salicylate : 2.8 times Sodium toluate : 2.3 times	Spectrophotometer at 259 nm
21	Vitamin B2[44]	Mixture of Caffeine and Nicotinamide		NMR
22	Glipzide[45]	Sodium salicylate, Sodium benzoate and sodium acetate	2M/55 time with sodium salicylate sodium salicylate> sodium benzoate> sodium acetate	
23	Indomethacin, Captopril, Carvedilol[46]	Urea,Nicotinamide, Resorcinal, sodium benzoate and sodium p-hydroxy benzoate	2M sodium p-hydroxy benzoate>sodium benzoate> nicotinamide > resorcinol > urea solubility enhancement	Spectrophotometer at 319.5 nm

			order 117.5/64.5/49.4/30.0/9.3	
24	Nimesilide[47]	nicotinamide, sodium ascorbate, sodium benzoate, sodium salicylate and piperazine	2M piperazine > sodium ascorbate > sodium salicylate > sodium benzoate > nicotinamide 3248 > 156 > 68 > 58 >12	Spectrophotometer at 393 nm
25	Orindazole[48]	ibuprofen sodium	0.5M	Spectrophotometer at 320 nm
26	Orindazole[49]	Urea	10M/10	Spectrophotometer at 320 nm
27	Tenfovir disoproxil fumerate[50]	Sodium Benzoate	2M/121	Spectrophotometer at 317 nm
28	Theophylline[51]	Sodium salicylate	2M/18	Titrimetric estimation
29	Rapamycine[52]	5% Benzoate buffer consisting of an equal amounts of benzoic acid and sodium benzoate hydrotropes with co-solvents like 10%ethanol, 40% propylene glycol)	>1000	A Beckman Gold HPLC system equipped with a model no. 168 detector at 277 and mobile phase composed of 80% (v:v) of methanol in water
30	Frusemide[53]	Urea +sodium acetate+sodium citrate	5M+1M+0.4M/15	Titrimetric method
31	Nifedipine[54]	Sodium salicylate	40%/-	Spectrophotometer at 350 nm
32	Acetaminophen[55]	Urea solution	8M /18	Spectrophotometer at 244nm
33	Chlorzoxazone[55]	Urea solution	8M /5	Spectrophotometer at 244nm
34	Aceclofenac[55]	Urea solution	8M /10	Spectrophotometer at 244nm
35	Budesonide[56]	45% Urea and 5% Sodium citrate	20/-	Spectrophotometer at 244.8 nm
36	Etoricoxib[57]	Sodium Benzoate		Spectrophotometer at 282 nm
37	Fenofibrate[58]	Urea Sodium citrate Urea Sodium citrate Blend of urea and sodium citrate	5%/ 4.45 5%/1.41 10%/5.86 10%/3.16 15% each of urea and sodium citrate : 74 times 20% of urea and 10% of sodium citrate : 233 times	Spectrophotometer at 286 nm
38	Meloxicam[59]	Tri sodium citrate		Spectrophotometer at 269 nm
39	Cefprozil[60]	Potassium acetate, Potassium citrate , Sodium acetate, Sodium citrate and Urea.	6M, 1.5M, 4M, 1.25M and 10M	Spectrophotometer at 280 nm
40	Griseofulvin[19], Clofibrate, Nifedipine, Glybenclamide, Progesterone, Dihydroanthracene Felodipine, Anthracene, Fenofibrate, Itraconazole, Probucol, Coenzyme Q10 and Paclitaxel.	N,N-diethylnicotinamide (DENA) and N,N-dimethylbenzamide (DMBA)	1000- to 10,000-fold	HPLC using C18 RP analytical column 293 nm 223 nm 240 nm 233 nm 254 nm 250 nm 237 nm 251 nm 280 nm 263 nm 254 nm 275 nm 227 nm

Facilitated hydrotropy is a unique strategy for solubilization in which one or more completely-water-miscible co solvents are used to solubilize a partially water miscible (often aromatic) solute which in turn acts to further solubilize the drug[47].

Conclusions

Hydrotropes are powerful solubilizing agents of hydrophobic drugs. They are also versatile in the sense that make it possible to take advantage of structural aspects of the solute such as the presence

of aromatic rings, hydrophobicity, hydrogen bonding ability and specific interaction properties. Furthermore, solubility enhancement with the use of hydrotropes can achieve several orders of magnitude. Despite these advantages, however, the use of hydrotropic agents poses an important pharmaceutical hurdle. In order to be effective, hydrotropes need to be present at non negligible concentrations. A situation that may lead to hydrotrope induced toxicity[61]. Hydrotropes are effective only when a particular concentration is reached and this is known as minimum hydrotrope concentration (MHC). The relatively high concentrations required to reach the MHC imposes restrictions as to the type and number of hydrotropic structures acceptable in pharmaceutical applications. However, it is reasonable to expect that the use of plain hydrotropic agents as solubilizing excipients in pharmaceutical formulations is bound to present serious challenges at best. Therefore, for hydrotropy to become a fully exploitable phenomenon in pharmaceutical applications, it is necessary to address the potential risks associated with the systemic absorption of the free hydrotrope, while still taking advantage of its solubilization properties. In other words, a system is needed where the hydrotrope is let to exert its solubilizing effect while being effectively prevented from being systemically absorbed.

A viable approach for such a system is one where the hydrotrope is turned non bioavailable through covalent linkage to a polymeric matrix. The development of polymeric hydrotropic micelles [62-64], whose hydrophobic core hosts a covalently linked hydrotrope is likely to serve this purpose.

An alternative approach for reducing is the addition of salts, n-alcohols, or urea[65] or use of mixed hydrotropes[55] to take advantage of their synergic effect.

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