Review Article

A Brief Review on Solubility Enhancement Technique: Hydrotropy

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ABSTRACT

In this review we have elaborated about number of hypothesis postulated to understand the mechanism of hydrotropic agents, although majority of the postulated hypothesis haven't justified the solubility enhancement mechanism. Further to it the articles focuses upon the parameters affecting enhancement of solubilizing ability. Hydrotropes are extensively used in drug solubilization, extraction agents for various phytoconstituents, separation agent used for pharmaceutical analysis, as well as for increasing the rate and yield of a chemical reaction due to their unique features. Because of this, hydrotropic solutions possess high industrial demand. While mixed hydrotropy is mostly used in enhancement of solubility, extraction of phytoconstituents and separation by the use of more than one hydrotropic agent. This review article also highlights the applications and future prospects with the employment of hydrotropes and hydrotropic agents in novel drug delivery or parental or oral or tropical systems to enhance solubility profile the drugsare also discussed.

Key words: Mixed Hydrotropy, Solubilizing agent, Mechanisms of hydrotropes, Application of Hydrotropes, Solubility, Bioavailability enhancement.

INTRODUCTION

Agents that are employed to enhance solubility of solutes which are poorly soluble in solvents are termed as hydrotropes or hydrotropic agents.[1] Solubilization is a process that involves molecular interactions that are balanced by various forces at molecular level, it cannot be explained as a simplex complication process or phenomenon that are greatly influenced by effect of medium comprising of salting-in or co-solvency.[2] To increase solubility, processes like salting-in and salting-out are majorly employed. Salts demonstrating process of 'salting in' of non-electrolytes are defined as "hydrotropic salts" and the event is described as "hydrotropism" this salting-in is contrasting to salting-out.[3] Hydrotropic salts intensify the solubilizing property of the solute by establishing a weak interaction with them, although no colloidal property is exhibited due to interaction.[4] Hydrotropes, resembles properties of surface active agents,[5] which enhances aqueous solubility of solutes that are sparingly water soluble under room temperatures. Hydrotropy has potential to develop itself as an industrial technique.[6]

The majority of studies on the mechanism of hydrotropic solubilization focuses on potential interactions between the hydrotropes and the solute which concludes that the solubilization is due to complexation between the two.[1] We can easily correlate hydrotropy as a solubilization process which enhances aqueous solubility of a solute which is dependent over the addition of another solute (hydrotropic agents).[1] Hydrotropes generally employed are tetraalkylammonium halides, urea, nicotinamide, aromatic sulfonates, guanidinium chloride, sodium thiocyanate etc.[7] Hydrotropic agents can be characterized as an ionic organic salts which on addition to the solvent may either cause increment in the solubility profile of

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a solute or may decrease solubility as well.[8] Numerous studies have proven that hydrotropes to be a reliable technique for enhancing solubility of drugs or any solute or organic solvents also that have poor aqueous solubility profile or are not at all soluble in aqueous solutions. Hydrotropes may be studied and investigated further as an additive as it has surfactant like property in both aqueous as well as oily phases; it can also act as a carrier for API. Further research may also deal with the capability of hydrotropes which leads to the formation of a aggregated structure in hydrophilic system due to non-covalent bonding.[9-11]

Various researchers concluded that hydrotropes are amphiphilic in nature as they have two-parts i.e. one polar and another nonpolar in one single molecule. Comparative study determined non-polar portion to be smaller than polar portion.[9] Other study demonstrated that properties of hydrotropes and surfactant were linked with a slight system variation in the molecular structure.[10] Hydrotropic agents are characterized structurally as short, bulky and compact moiety which differs them from surfactants that consists of long hydrocarbon chains.[12] Researcher also demonstrated that hydrotropes may be distinguished as cationic, anionic, or neutral molecule.[11]

The concept of mixed hydrotropy was developed cause of its cheapness, non-toxicity and eco-friendly nature which ultimately resulted in solubility enhancement miraculously due to synergistic action of the hydrotropic agents. This characteristic property of mixed hydrotropes give it an edge over simple hydrotropy, resulting in increased percent yield of constituents in the process of extractions as well as in separation techniques like that of chromatography.[14]

In this review we will be focusing over hydrotropes and hydrotropic agents, possible mechanisms by which they enhance solubility of the drug in solvent and various parameters of hydrotropes. We will also be lime lighting the importance of the technique in pharmaceutical industry and also discussing its advantages and disadvantages.

MECHANISM OF HYDROTROPE

Mode of action of hydrotropes are by far not clear, as it is still under debate and far behind from conclusive. Many researchers gave their own hypothesis about the possible mechanism of hydrotrope. Three hypothesis postulated to explain hydrotropic activity are as follows:

(a) Complex formation between solute and hydrotrope,

(b) Disintegrating or shattering tetrahedral complex of water molecules,

(c) Self-association of hydrotropes.

But, they haven't justified the mechanism of hydrotropes. Furthermore, several researchers postulated various hypothesis to understand mechanism of hydrotropes, some of which are explained below:

Hydrotrope self-aggregate formation

This theory postulates that the molecule of the hydrotropes self-aggregates themselves, which paves the way for the formation of organized clusters in the hydrophilic solution. It was also suggested that solutes molecules get entrapped in these organized clusters leading to enhancement of solute hydrophilicity.[16,17] While the critical concentration at which hydrotropes begins to aggregate themselves is described as Minimum Hydrotropic Concentration (MHC).[4] Presumptions were made that planar aromatic rings found in the molecular structure of the hydrotropes mounds one over the other for aggregation. As hydrophobic compound solubilization initiates, the phenomenon of aggregation also takes place simultaneously in the aqueous solvent, similarly to that of micellization process. The self-aggregation of the hydrotropes has been considered to be a pre-requisite for several applications in various meadows such as drug solubilization. Aggregation of hydrotropes is accompanied by change in enthalpy, entropy and free energy.[18,19]

Alteration of the water structure

Proposed by Frank and Evans, who explained that hydrotropes do not bind themselves directly with poorly or sparingly soluble solutes, but they break water structure which prevents formation of iceberg.[16,17]

Formation of solute-hydrotrope complexes

Solubilization takes place due to weak complexation between the non-polar compound and the hydrotrope, which results in higher aqueous solubility.[20] These complexation hypothesis claims low stoichiometry complexes (such as 1:1 or 1:2) as the origin of hydrotropy.[16,17]

Accumulation of hydrotrope around the drug

Several compounds have been employed to determine the mechanism of hydrotrope via different experimental studies employing additives which demonstrated strong interaction between solute and additive that leads to micelles formation thus, acting as a bridge and concentrating around hydrophobic solute without interaction.[7] some other mechanisms include:

(a) Formation of compound between hydrotropes and dissolved solute,

(b)Formation of molecule complex at low hydrotrope concentration,

(c)Molecular aggregation of hydrotrope due to electrostatic forces of donor-acceptor type between hydrotrope and solute molecule,

(d) Stake-type aggregation.[5]

PARAMETER OF HYDROTROPY

Minimum Hydrotropic Concentration (MHC)

MHC can also be explained as the hydrotropes concentration which significantly enhances the solubility of the poorly water-soluble solutes,[19] effective concentration of the hydrotropes can do miracles as it enhances solubility of solute many folds. It was also noted that above MHC hydrotropes tends to aggregates themselves similar to the phenomenon of micelle formation beyond CMC as seen in case of classical surfactants.[15]

Maximum Hydrotrope Concentration (C_{max})

C_{max} can be explained as the concentration of hydrotropes in hydrous phase, beyond which there will be no significant increase in the solubility of the solute.[22] The solubilization effect depend upon the concentration of individual hydrotropes.

Setschenow constant, Ks

Empirical formula which was established in 1889[18] helped to determine the efficiency of the hydrotrope at a particular concentration when introduced into the solvent.[6] "Salting constant" is also sometimes referred as Setschenow constant. It not only co-link solubility variation of a solute in correlation of a particular hydrotrope but also elaborates about the effect of combination of salts. Later, this model was suggested by Setschenow and further improvised by Gaikar and Pathak, who proposed an equation:

$$\text{Log}S/Sm = Ks\,[Cs - Cm]$$

Where S and Sm = solubility of compound at any hydrotrope concentration and Cs = Concentration of salt.[18]

Effect of temperature

Determining the effectiveness of the hydrotrope concerning the different range of temperature, is also measured in terms of Setschenow constant.

In Table 1, some of the hydrotropes are summarized with their MHC, C_{max}, Setschenow constant (Ks) and Maximum enhancement factor.

IMPORTANCE OF HYDROTROPY

Hydrotrope solution can be regarded as a green solvent as they are cheap, easy to handle, non-toxic and environmentally friendly. Averting the use of organic solvents is one step closer for increasing the solubility in hydrotrope i.e., avoiding the use of organic solvents; aqueous solutions of hydrotropes demonstrated the unique features of an alternative reaction media for organic synthesis, as organic solvents were frequently employed which may be sources of pollution while some of them may be toxic, costlier also. While volatility may also lead to inaccuracy.[13,25-27]

APPROACH

By use of different solubilization approaches such as solid dispersion that enhances the solubility, by thermodynamic as well as molecular approach. Various approaches are been targeted in the field of science like in pharmacognosy, here, hydrotropes are employed as solvent for extraction of drug, while in analytical field mixed hydrotropes helped in identification, novel separation technique, spectrometric analysis, HPLC and many other instrumental approaches and in the field of pharmaceutical science, hydrotropes are used in formulation and estimation processes. Mostly hydrotropes and mixed hydrotropy are effectively used in the chemistry for various purposes that are linked to thermodynamics, mass coefficient, temperature studies, concentration phenomenon, green solvent, pH-dependent study, micelle formation, etc. On the other hand industrial scenario of the hydrotrope is entirely different as it was used in cleaning and personal care product formulation but in pharmaceutical industry hydrotropes are used for "green synthesis" for the formulation of dosage form and various approaches in the formulations of dosage form (examples, parenteral, oral, transdermal, nasal, etc).

Pharmaceutical application

In the field of pharmaceutical science, hydrotropes have been used for the preparation of drug formulation as well as to stabilize them. Hydrotropes have found their application in manufacturing of parenteral, oral, topical as well as in novel drug delivery system also. It is mainly employed for drugs that have solubility issues. Some of the examples are described in Table 2 that showed increased solubility of drug, when employed with hydrotropes.

Analytical application

In analytical chemistry, to avoid or prevent use of organic solvents and enhance aqueous solubility of the

Table 1: Minimum hydrotropic concentration (MHC), Maximum hydrotropic concentration (C_{max}), Setschenow constant (Ks) and Maximum enhancement factor (Φs) of individual hydrotropes.

Hydrotropes	Compound	MHC	C_{max}	(Ks)		(Φs)	Reference
Diethyl nicotinamide	Aminonitrobenze	0.5	2.4	303k 313k 323k 333k	0.41 0.49 0.50 0.51	17.02 28.1 40.93 56.6	[23]
Sodium pseudocumene sulfonate	Aminonitrobenze	0.4	2.4	303k 313k 323k 333k	0.41 0.43 0.44 0.46	20.61 28.1 40.93 56.6	[23]
Sodium thiocyanate	Aminonitrobenze	0.3	2.2	303k 313k 323k 333k	0.43 0.47 0.55 0.59	21.01 29.01 60.75 93.95	[23]
Rea	Ethylbenzene	0.50	2.20	303k 313k 323k 333k	0.540 0.575 0.561 0.616	12.227 15.763 18.259 23.512	[18]
Nicotinamide	Ethylbenzene	0.40	2.20	303k 313k 323k 333k	0.598 0.667 0.661 0.668	17.482 22.968 27.254 32.591	[18]
Sodium Salicylate	Ethylbenzene	0.30	2.40	303k 313k 323k 333k	0.594 0.609 0.661 0.668	28.447 37.219 44.609 52.561	[18]
Citric acid	-	0.40	2.40	303k 313k 323k 333k	0.481 0.513 0.539 0.565	16.08 21.52 24.82 26.66	[22]
Tri-Sodium Citrate	Furfural	0.40	2.40	303k 313k 323k 333k	0.338 0.372 0.402 0.424	4.75 5.55 6.38 7.06	[6]
Sodium Toluate	Furfural	0.60	2.20	303k 313k 323k 333k	0.324 0.363 0.399 0.418	3.30 3.81 3.68 4.07	[6]
Sodium saccharin	Aminonitrobenze	0.4	2.4	303k 313k 323k 333k	0.41 0.43 0.44 0.46	20.61 32.19 54.18 74.64	[23]
Dimethylbenzamide	Aminonitrobenze	0.3	2.2	303k 313k 323k 333k	0.43 0.47 0.55 0.59	21.01 29.01 60.75 93.95	[23]
Sodium benzoate	Aminonitrobenze	0.5	2.4	303k 313k 323k 333k	0.41 0.49 0.50 0.51	17.02 28.1 40.93 56.6	[23]
Resorcinol	Benzamide	0.50	2.20	303k 313k 323k 333k	0.489 0.525 0.534 0.549	6.77 7.79 8.07 8.58	[24]
Sodium citrate	Benzamide	0.60	2.20	303k 313k 323k 333k	0.421 0.491 0.521 0.563	4.71 5.12 6.81 7.95	[24]

Table 2: Application of hydrotropy and mixed hydrotropy technique in development of Pharmaceutical dosage forms.

Hydrotropes and Mixed Hydrotropes	Concentration and range	Drug	Solubility % w/v	Enhancement Ratio	References
Sodium benzoate + nicotinamide+ sodium citrate	40% = 20:15:5	Carvedilol	5.285	64.451	[20]
Urea+sodium benzoate+sodium citrate	40% =15:20:5	Furosemide	5.285	660.625	[14]
Sodium benzoate+ solvent system	40% = 15:20	Etodolac	-	275.65	[28]
Sodium benzoate+ sodium salicylate+ PEG 600+ Piperazine anhydrous	10%=2.5:2.5:2.5:2.5	Zaltoprofen	5.251	1875.35	[8]
Nicotinamide + sodium benzoate + sodium citrate	40% =15:20:5	Lurasidone	8.93	54.12	[11]
Urea	8M	Entacapone	7.97	67 fold	[29]
Piperazine anhydrous	30 %	Valsartan	0.021	30100.4	[30]
Meglumine	1:10	Glimepiride	1.6	24,000	[31]
Lactose+ citric acid;	15 : 25	Nevirapine	10.174	102.31	[32]
Urea+ PEG 4000+ PEG 6000	3.33 : 3.33 :3.33	Telmisartan	-	15737.5	[33]
Sodium salicylate.	4.0	Curcuminoids	$0.54x10^{-3}$ mol/L	144 times	[34]
Niacinamide	2 M	Indomethacin	-	More than five fold	[2]
Nicotinamide	10µg/ml	Paroxetine hydrochloride	-	26.02 and 19.78 l/mol	[12]
Sodium Gentisate	1M	Nimesulide	0.1 mg/ml	1173.408 and 747.65 l/moles	[35]

sample, this technique is used. Various methods where hydrotropes have been used are in -

- Titrimetric Analysis
- Spectrophotometric Analysis
- Thin-Layer Chromatography

The hydrotropic agent used in the above application are listed in following Table 3.

Chemistry application

To separate compound, solubility enhancement, extraction process etc, hydrotropes are employed. And because of it is eco-friendly, hydrotrope is also use for green synthesis. For example, determination of first principles of statistical thermodynamics of hydrotropes by gibbs phase rule,[27] hydrotropes used for determine the action in micro emulsion.[10] Some of the applications of hydrotrope solution in pharmaceutical chemistry are summarized in Table 4.

Pharmacognosy application

In the field of pharmacognosy various extraction process takes place in which hydrotropes assisted extraction enhances percent yield of the active constituents. For instance, reserpine which is isolated from the roots of *Rauwolfia vomitoria* yield was increased to that of conventional extraction when hydrotropic agent was introduced into the solvent. Three different hydrotropes, Na-CS, Na-PTS and NBBS were employed for the extraction of reserpine at the same concentration.[39] Hydrotropic salts such as sodium salicylate, sodium cumene sulfonate, sodium phenol sulfonate, sodium xylene sulfonate, used as a modified hydrotropes for Lignin extraction from Birch wood. Two treatments performed, namely as a conventional and a modified process.[40]

Computational application

Software are employed to predict the mechanism by which hydrotropes enhances solubility by using computer stimulations which is mostly likely predict results based on the classical molecular dynamic stimulation technique.[15]

Biochemistry application

Sodium xylene sulfonate (SXS) and formic acid both hydrotropes used for pretreatment as they enhance enzymatic activity. For example, reed when treated with these hydrotropic agents improvises it's digestibility.[31]

Table 3: Application of hydrotropes in Pharmaceutical Analytical technique.

Method	Dosage Form	Drug	Hydrotropes	Key Finding	Reference
Titrimetric Analysis	Bulk Drugs	Ibuprofen	8 M Urea	10 Folds Solubility Enhancement	36
Titrimetric Analysis	Tablets	Furosemide	15%Sodium Salicylate 5% Niacinamide,5% Sodium Acetate 5% Sodium Citrate	More Than 33 Folds Solubility Enhancement	37
Quantitative Analysis	Bulk Drugs	Salicylic Acid	Sodium Benzoate 2M Nicotinamide	98.90 ±0.475 98.97 ±0.375 Percentage Drug Estimate	38
Uv-Spectrophotometric Determination	Bulk Drugs And Tablets	Metronidazole	8 M Urea	AUC - 313-323nm Abs -318	25
Spectrophotometric	Bulk Drugs and Tablets	Gliclazide	2M Urea And 6M Trisodium Citrate	4µg/Ml –12µg/Ml Concentration Range 225 nm	39
Spectrophotometric	Bulk Drugs and Tablets	Amlodipine Besylate	Ammonium Acetate	Maximum Absorption at 362 nm	10
UV Spectrophotometer	Bulk Drugs	Amlodipine Besylate Celecoxib	2M Sodium Benzoate	32 And 26- Fold Solubility Enhancement	21
UV Spectrophotometry	Tablet	Ornidazole	25% Phenol And 15% Sodium Benzoate	Wavelength Maxima Of Ornidazole 319 nm	22
Spectrophotometry	Bulk Drugs and Tablets	Acyclovir	2% Sodium Benzoate 2% Urea	Solubility Increases 2mg/ml	13

Table 4: Application of hydrotropes solutions in Pharmaceutical chemistry.

Hydrotropes	compound	Extracted/separated from	Key finding	Reference
Sodium salicylate	Xanthones	Mangosteen Pericarp	1.14 to 4.69 mg/g yield	24
Sodium benzoate	Styrene	Styrene-ethyl benzene mixture	69.45 percentage Extraction	35
8 M urea	Etoposide	Etoposide tablet	more than 56- and 59-folds solubility	16
Nicotinamide, resorcinol, sodium citrate and sodium salicylate	Benzamide	-	Enhancement of solubility	24
Alkybenzene sulfonates	Lignin	bagasse	85 percent delignification	27
Cationic hydrotropes	Vanillin and Gallic acid.	-	40-fold solubility enhanced	38

In Asia, rice strawsare most preferred feedstock for production of fuel ethanol, are pretreated with hydrotropic agents NaCS and NaCS. Hydrotropes solution is a greener solvent and with several advantages, one of them been an attractive alternative for biomass refineries. Other advantages linked are quick recovery of the solute from hydrotrope solutions by simple dilution with water and reuse of the hydrotrope solution after recon centration. The various effect carried such as biomass loading, time, temperature 40 to 80°C and hydrotrope concentration 10% and 30% were study.[22]

Artificial neuronal application

In the pharmaceutical sciences, Artificial Neuronal Network (ANN) which are computational model by the application of machine learning is of relative important for the determination and prediction the quantitative assessment of various hydrotrope physicochemical properties. For the application of hydrotrope-enhanced property, use of computational model, predict by utilization of ANN to determine the role of hydrotropes in enhancing the solubility of poorly water-soluble drug.[21]

ADVANTAGES OF HYDROTROPY AND MIXED HYDROTROPY

- Less toxic compared to another organic solvent
- By the simple and cheap way solubilization done by using hydrotropes because, it only requires the mixing of drug substance and particular hydrotropes both together into the solvent.

- Answers to solubility problems in a wide variety of commercial and pharmaceutical applications.
- Widespread usage in today's increasingly complex formulas.
- Main positive aspects of hydrotropic technique is that it does not hinders with the chemical activity of the drug substances.
- Broad formulation, compatibility and effectiveness, inexpensive, greener solvent.
- Because of their high selectivity over the other solubilization technique hydrotropy suggested being superior as a point of safe, cheap, simple, accurate and precise method.
- Mixed hydrotropy preclude the use of an organic solvent to prevent the problem
- For optimum criteria, mixed hydrotropy is one of the best approaches.
- In the field of science hydrotropy having the role for example used as extraction, separation.
- Certain properties of hydrotropes, such as high selectivity, the solvent character being independent of pH, emulsification absence.
- Facile recovery of the solute from hydrotrope solutions by simple dilution.
- Main benefits of mixed hydrotropy are a combination of agents by lowering the individual concentration that should be effective as well as less toxic.
- For solubility of poorly water-soluble drugs mixed hydrotropy have a synergistic effect on the solubility of the substance.

DISADVANTAGES OF HYDROTROPY AND MIXED HYDROTROPY

- There are chances of the weak interaction between the **hydrotropic** agent and drugs. As there is the use of water as a solvent, complete removal of water cannot be achieved.
- The use of hydrotropes is limited for some hydrotropic agent because of toxicity.

CONCLUSION

Various mechanisms of hydrotropes shows that how they work up to enhance solubility of a compound that have poor aqueous solubility, as well as their advantages and disadvantages have been described thoroughly in this review. This technique not only paved a way for the dosage development of the poorly water-soluble drugs but also helped in the enhancement of the extraction of the phytoconstituents which have potential pharmacological activity. Hydrotrope technique has the ability to replace major conventional techniques employed in the field of pharmaceuticals because they act as green solvents that causes less pollution, environmentally friendly and economically, as well as they are cheaper than organic solvents. As reviewed in the field of pharmacognosy this technique can be used to replace organic solvents and enhance percent yield of the constituents during isolation, separation and characterization of compounds. Similarly, in the field of pharmaceutics, this technique enhanced the aqueous solubility and increase the bioavailability of poorly solubilizing synthetic as well as isolated compounds. This review defines the application of hydrotropes in various field of science and thoroughly explains proposed mechanisms of hydrotropic agent. Above studies raises the use of hydrotropes in the field of pharmaceutics for further progress in hydrotropy, especially in formulation of drugs by utilization of hydrotropic agent towards the enhancement of solubility of poorly water-soluble drug to enhanced therapeutic delivery. However, many challenges remain with mechanisms of hydrotropes and these are still in debate. Basic approach involves interaction of hydrotropic agent with poorly water-soluble drug, which boosted solubility as well as bioavailability. Various experimental Studies have confirmed that hydrotropic technique can replace the use of organic solvents. This technology safe and eco-friendly in nature.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

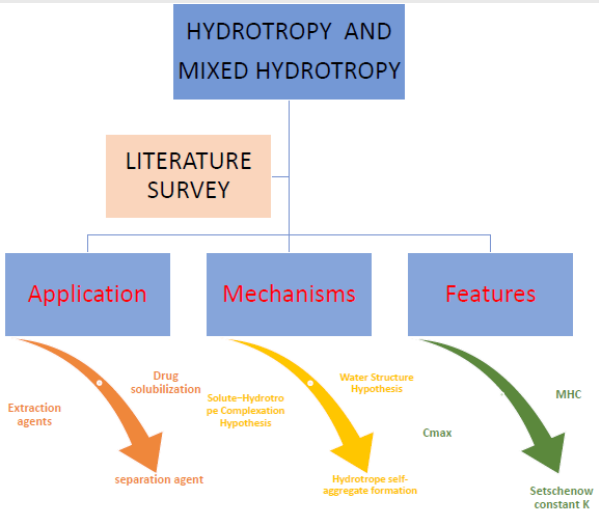
PEG: Polyethylene glycol; **Na-PTS:** Sodium p-toulenesulfonate; **NaCS:** Sodium cumene sulfonate; **NaeX:** Sodium xylene sulfonate; **ANN:** Artificial neural network; **MHC:** Minimum hydrotrope concentrations; **C_{max}:** Maximum hydrotrope concentration**; CMC:** Critical micelle concentration; **Ks:** Setschenow constant; Φs**:** Maximum enhancement factor; **M:** Molar concentration.

REFERENCES

1. The Coffman RE, Kildsig DO. Effect of nicotinamide and urea on the solubility of riboflavin in various solvents. J Pharm Sci. 1996;85(9):951–4.

2. Maheshwari RK, Rathore A, Agrawal A, Gupta MA. New spectrophotometric estimation of indomethacin capsules with niacinamide as hydrotropic solubilizing agent. Pharm Methods [Internet]. 2011;2(3):184–8. Available from: http://dx.doi.org/10.4103/2229-4708.90359
3. McKee RH. Use of Hydrotropic Solutions in Industry. Ind Eng Chem. 1946;38(4):382–4.
4. Dhapte V, Mehta P. Advances in hydrotropic solutions : An updated review. St Petersbg Polytech Univ J Phys Math [Internet]. 2016;000:1–12. Available from: http://dx.doi.org/10.1016/j.spjpm.2015.12.006
5. Pandit A, Sharma MM. Intensification of heterogeneous reactions through hydrotropy: Alkaline hydrolysis of esters and oximation of cyclododecanone. Chem Eng Sci. 1987;42(11):2517–23.
6. Kumar CJ, Gandhi NN. Hydrotropic Study on Furfural - Comprehensive Design Expert Plot. Mod Appl Sci. 2009;3(4).
7. Da Silva RC, Spitzer M, Da Silva LHM, Loh W. Investigations on the mechanism of aqueous solubility increase caused by some hydrotropes. Thermochim Acta. 1999;328(1–2):161–7.
8. B A Kate. Solubility Enhancement of Poorly Water Soluble Drug Zaltoprofen by Mixed Hydrotropy Approach. Asian J Biomed Pharm Sci [Internet]. 2016;6(57):32–9. Available from: https://pdfs.semanticscholar.org/9123/7e97ed313ba8243ce4074c64bf2dbc016a24.pdf
9. Khan ZA. Effect of various cationic hydrotropes on association behaviour of imipramine hydrochloride at different temperatures. J Mol Liq [Internet]. 2019;281:333–43. Available from: https://doi.org/10.1016/j.molliq.2019.02.094
10. Yan C, Sagisaka M, James C, Rogers SE, Peach J, Eastoe J. Action of hydrotropes in water-in-CO2 microemulsions. Colloids Surfaces A Physicochem Eng Asp [Internet]. 2015;476:76–82. Available from: http://dx.doi.org/10.1016/j.colsurfa.2015.03.010
11. Madan J, Pawar K, Dua K. Solubility enhancement studies on lurasidone hydrochloride using mixed hydrotropy. Int J Pharm Investig. 2015;5(2):114.
12. Ujwala K, Babu PRS. Solubility enhancement of paroxetine hydrochloride by hydrotropy. Indian J Pharm Sci. 2017;79(4):591–8.
13. Hydrotropy K. Hydrotropic Solubilization : Tool for Eco-Friendly Analysis. 2018;(3).
14. Maheshwari RK, Jagwani Y. Mixed hydrotropy: Novel science of solubility enhancement. Indian J Pharm Sci. 2011;73(2):179–83.
15. Das S, Paul S. Computer Simulation Studies of the Mechanism of Hydrotrope-Assisted Solubilization of a Sparingly Soluble Drug Molecule. J Phys Chem B. 2016;120(14):3540–50.
16. Booth JJ, Abbott S, Shimizu S. Mechanism of hydrophobic drug solubilization by small molecule hydrotropes. J Phys Chem B. 2012;116(51):14915–21.
17. Das S, Paul S. Mechanism of Hydrotropic Action of Hydrotrope Sodium Cumene Sulfonate on the Solubility of Di-t-Butyl-Methane: A Molecular Dynamics Simulation Study. J Phys Chem B. 2016;120(1):173–83.
18. Morais AB, Jayakumar C, Gandhi NN. Hydrotropic effect and thermodynamic analysis on the solubility and mass transfer coefficient enhancement of ethylbenzene. Korean J Chem Eng. 2013;30(4):925–30.
19. Bauduin P, Renoncourt A, Kopf A, Touraud D, Kunz W. Unified concept of solubilization in water by hydrotropes and cosolvents. Langmuir. 2005;21(15):6769–75.
20. Chikhle H, Pandey V, Ganeshpurkar A, Dubey N, Bansal D. Solubility enhancement of Carvedilol using mixed hydrotropy Research Article. 2016;
21. Damiati SA, Martini LG, Smith NW, Lawrence JM, Barlow DJ. Application of machine learning in prediction of hydrotrope-enhanced solubilisation of indomethacin. Int J Pharm. 2017;530(1–2):99–106.
22. Nathan S, C. MJ, Nagendra Gandhi N. Effect of Hydrotropes on Solubility and Mass Transfer Coefficient of Methyl Benzoate. Mod Appl Sci. 2009;3(3).
23. M. DHINAKARAN, MORAIS AB, GANDHI NN. Enhanced Solubility and Reflection of Hydrotropy Technique in the Segregation of of m/p-Aminonitrobenze. Chem Sci Trans. 2012;1(2):261–8.
24. Jayakumar C, Gandhi NN. Thermodynamic study on hydrotropic aggregation behavior of benzamide. J Chem Eng Data. 2010;55(10):4362–8.
25. Masthannamma S, Sravani K, Sridhar T, Siva sankar Naik B. Uv-Spectrophotometric Determination of Metronidazole in Bulk and Pharmaceutical Dosage Form Using Hydrotropic Solubilization Technique. J Glob Trends Pharm Sci J. 2015;6(1):2365–71.
26. Nidhi1 K, Indrajeet1 S, Khushboo1 M, Gauri1 K, Sen2 and DJ. HYDROTROPY: A PROMISING TOOL FOR SOLUBILITY ENHANCEMENT: A REVIEW. Int J Drug Dev Res. 2011;3(2):26–33.
27. Shimizu S, Matubayasi N. Unifying hydrotropy under Gibbs phase rule. Phys Chem Chem Phys [Internet]. 2017;19(35):23597–605. Available from: http://dx.doi.org/10.1039/C7CP02132A
28. Pande V V. Exploration of Mixed Hydrotropy Strategy in Formulation and Development of Etodolac Injection. J Nanomedicine Res. 2016;3(4).
29. Jain R, Jain N, Jain DK, Jain SK. A novel approach using hydrotropic solubalization technique for quantitative estimation of entacapone in bulk drug and dosage form. Adv Pharm Bull. 2013;3(2):409–13.
30. Agrawal S, Kasturi M. Hydrotropic solubilization technique to challenge the solubility of poorly water soluble drug. World J Pharm Res. 2016;5(8):833–45.
31. Li H, Ma L, Li X, Cui X, Yang W, Shen S, et al. A simple and effective method to improve bioavailability of glimepiride by utilizing hydrotropy technique. Eur J Pharm Sci [Internet]. 2015;77:154–60. Available from: http://dx.doi.org/10.1016/j.ejps.2015.06.016
32. AWASTHI R, Madan J, Kamate V, Dua K. Improving the solubility of nevirapine using a hydrotropy and mixed hydrotropy based solid dispersion approach. Polym Med. 2017;(2):83–90.
33. Citrate S, Acetate S. Solubility Enhancement of Telmisartan Using Mixed Hydrotropy Approach. Asian J Biomed Pharm Sci. 2015;5–7.
34. D.Sreenivasan CJ and NNG*. Effect of hydrotropes on solubility and mass transfer coefficient of Curcuminoids. J Pharm Res 2010,. 2010;3(9):2170–1.
35. Gopaiah V, Rao K, Chowdary S. Hydrotropic Technique : A Promising. 2018;2018(4):4–12.
36. Pradnya AP, Preeti PM. Titrimetric analysis of ibuprofen bulk drug sample by using urea as a hydrotropic solubilizing agent. Int J Curr Pharm Res [Internet]. 2015;7(3):76–7. Available from: http://innovareacademics.in/journals/index.php/ijcpr/article/download/7931/pdf_50
37. Maheshwari RK, Gupta J. New eco-friendly titrimetric analysis of frusemide tablets using mixed hydrotropic solubilisation. Indian Drugs. 2018;
38. Patil S, Mehta P, Chavan B. Quantitative analysis of salicylic acid bulk sample using hydrotropic solubilizing agents. Asian J Pharm Clin Res. 2016;9(2 M):168–9.
39. Kumar GS, Kumar DA, Babu MN, Debnath S, Ishwarya B, Jyothi G, et al. Eco-Friendly Spectrophotometric Estimation of Gliclazide using Hydrotropic Solubilization Technique. Asian J Pharm Anal. 2019;
40. Waghmare A, Taware G, Baokar S, Undare S. Ecofriendly Validated Spectrophotometric Method for the Estimation of Amlodipine Besylate by using Hydrotropic Solubilization Method. Asian J Pharm Anal. 2019.

PICTORIAL ABSTRACT



SUMMARY

The topic covered in this review article were summarized after extensive search over hydrotropic agents. Various applications identified are unique enough, which can be used in pharmaceutical industries for drug development which could be made environment friendly as well as can be cost effective with better results. The key aspect of this review article was to bring light over hydrotropic agents and their application in various pharmaceutical divisions. This article may help researchers in their work to get better result in more eco-friendly way.

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