World Journal of Pharmaceutical and Life Sciences

www.wjpls.org

Impact Factor: 8.21 Coden USA: WJPLA7

A REVIEW ON APPLICATION OF HYDROTROPIC SOLUBILIZATION IN THE ESTIMATION OF POORLY SOLUBLE DRUGS IN BULK AND PHARMACEUTICAL DOSAGE FORM BY SPECTROPHOTOMETRY

Remi S. L.[1], Abhijith Jayan*[2], Amegha C. S.[3], Devika B. S.[4], Muhammed Shan C. V.[5], Sivanandini S. Babu[6]

[1,2,3,4,5,6]College of Pharmaceutical Sciences, Government Medical College, Thiruvananthapuram.

***Corresponding Author: Abhijith Jayan**

College of Pharmaceutical Sciences, Government Medical College, Thiruvananthapuram.

DOI: https://doi.org/10.5281/zenodo.18656951

How to cite this Article: Remi S. L.[1], Abhijith Jayan*[2], Amegha C. S.[3], Devika B. S.[4], Muhammed Shan C. V.[5], Sivanandini S. Babu[6] (2026). A Review On Application Of Hydrotropic Solubilization In The Estimation Of Poorly Soluble Drugs In Bulk And Pharmaceutical Dosage Form By Spectrophotometry. World Journal of Pharmaceutical and Life Science, 12(3), 348–357.

Article Received on 05/01/2026 **Article Revised on 25/01/2026** **Article Published on 01/02/2026**

ABSTRACT

Solubility of different drug formulations depends on various factors like temperature, pressure, degree of ionization, partition coefficient, nature of solvents, etc. Solubility is a vital factor for the estimation of drugs or any chemical entity. Estimation of poorly soluble drugs depends upon their solubility in different solvents. Literature survey tells us that spectroscopic estimation of poorly soluble drugs is mostly done by using organic solvents. The main limitation of using organic solvents for the estimation is that they are highly toxic, expensive, cause pollution and result in bias due to their volatile nature. Hence different methods of solubilization techniques can be utilized to improve the solubility of poorly soluble drugs in water. One such cost-effective and novel method is hydrotropic solubilization technique, which involves increasing the solubility of poorly soluble drug candidate in water by the addition of hydrotrope. The review emphasizes the mechanism of hydrotropic solubilization, what are the novel methods employed, different hydrotropes used, advantages over conventional techniques and also validation of the method by ICH guidelines. By utilizing hydrotropic solubilization technique, spectroscopic estimation of poorly soluble drugs can be easily analyzed.

KEYWORDS: Hydrotrope, Minimum hydrotropic concentration, structure breaker and maker, chaotropes, Kosmotropes.

INTRODUCTION

Currently the gap faced by many researchers in development of a new drug candidate is poor water solubility. Solubility of a substance is the maximum amount of solute that can be dissolved in a given solvent at a particular temperature and pressure. Since the number of poorly water-soluble drugs developed are increasing steadily to meet the current medical requirements, their quality control and estimation is essential. So, a novel method of estimation is to be established for the quality control of such formulations.[1]

Over the last few years, the concern of scientists and the public towards environmental protection, human health, and safety have dramatically increased. Owing to this, more attention has been paid to the development of new analytical techniques to reduce the consumption of hazardous organic solvents. Moreover, the operators handling toxic chemicals face serious health issues due to accidental inhalation of toxic chemicals during their work. Therefore, a need for green analytical chemistry is essential.[2]

The combination of green chemistry and analytical chemistry leads to the origin of green analytical chemistry. The core of green chemistry depends on the design and analysis of products with less consumption of hazardous chemicals and minimum generation of toxic waste materials.

Analytical chemistry is concerned with determining the identity, strength, quality and purity of drugs, synthetic intermediates, and the final drug product.[3] The therapeutic effectiveness of a drug depends upon the

bioavailability and ultimately upon the solubility of drug molecules. Solubility is expressed in the form of descriptive terms in Indian Pharmacopoeia (IP) as parts of solvent required for part of solute.[4]

Table 1: Solubility Classification as per Indian Pharmacopoeia.

DESCRIPTIVE TERMS	PARTS OF SOLVENT REQUIRED FOR PART OF SOLUTE
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Practically insoluble, or insoluble	10,000 or more

Currently only 8 % of new drug candidates have both high solubility and permeability. Nearly 40 % of the new chemical entities currently being discovered are poorly water-soluble, and more than 1/3 of the drugs listed in the United States Pharmacopeia (USP) fall into poorly water-soluble or water-insoluble categories.[5]

So, the challenge is to solubilize these new chemical entities as it necessitates the use of organic solvents like chloroform, dinitro benzene, dinitro toluene, etc. These solvents are listed in Class II (solvents to be limited) of ICH Q3C (R6) guideline.[6]

These solvents have been reported to be hazardous to human beings and most of them are volatile and cause bias in analysis.[7] Based on the above-mentioned facts, researchers are trying to replace these hazardous solvents with green solvents which are more acceptable and safer as well as cost-effective and eco-friendly.

One such method is hydrotropic solubilization techniques and the application of hydrotropic solubilization has not been explored to appreciable extent in various fields of pharmaceutical sciences.

BACKGROUND

Shriram et al. developed a simple UV-spectrophotometric method for estimating Olmesartan Medoxomil, a poorly water-soluble drug, by using 0.05 M sodium acetate as a hydrotropic solubilizing agent. Olmesartan showed a clear λ_{max} at 256 nm, with no interference from the hydrotropic agent or tablet excipients. The method obeyed Beer–Lambert's law in the range 2–14 µg/mL with a high correlation coefficient (r = 0.9987). Precision and recovery studies (%RSD < 2 %) confirm good accuracy and reproducibility. Tablet analysis showed results close to the label claim, indicating no placebo interference. Overall, the method was found to be simple, rapid, economical, and suitable for routine quality control of Olmesartan Medoxomil in tablets.[8]

Maheshwari R. K. et al. reported a novel, eco-friendly UV-spectrophotometric method for the estimation of indomethacin in capsule dosage forms using niacinamide as a hydrotropic solubilizing agent. In their study, a 2 M aqueous solution of niacinamide was employed to enhance the solubility of the poorly water-soluble drug, eliminating the need for organic solvents. Preliminary solubility studies revealed more than a five-fold increase in aqueous solubility at 28 ± 1 °C compared with distilled water. The hydrotropic agent showed no interference at the analytical wavelength (320 nm), ensuring method specificity. The proposed method was validated and demonstrated good linearity, accuracy, precision, and reproducibility, with assay results comparable to official methods. The authors concluded that hydrotropic solubilization using niacinamide is a simple, economical, and environmentally safer approach for routine quality-control analysis of indomethacin capsules and highlights the broader applicability of hydrotropy in pharmaceutical analysis.[9]

Remi S. L. et al. developed an eco-friendly and cost-effective RP-HPLC method for the estimation of Ornidazole using a 5 % urea hydrotropic solution as the mobile phase, eliminating organic solvents. The method produced a sharp peak at 3.996 min (Photodiode array detection at 320 nm) and showed excellent linearity (10–50 µg/mL; R^2 = 0.9990), high accuracy (99.36% recovery), good precision (%RSD < 2 %), and high sensitivity (LOD 0.01577 µg/mL; LOQ 0.04779 µg/mL). The validated method is robust, green, and suitable for routine quality control analysis.[10]

Ruchi Jain et al. developed two novel UV-spectrophotometric methods for the simultaneous estimation of Metronidazole (MTR) and Furazolidone (FZ) using mixed hydrotropic solubilization (2 M sodium acetate: 8 M urea, 50:50 v/v). Metronidazole and Furazolidone showed λmax at 319 nm and 364 nm, with no hydrotrope interference above 240 nm. Both drugs obeyed Beer's law (MTR: 10–50 µg/mL; FZ: 5–25 µg/mL; $r^2 > 0.999$). Method A (simultaneous equation) and Method B (absorption ratio) showed good accuracy, precision, and recovery (~98–99%). The validated methods were simple, safe, and suitable for routine quality control of bulk drugs and tablet formulations.[11]

A. P. Sherje and K. J. Desai developed a UV-spectrophotometric method for rosiglitazone maleate using urea as a hydrotropic solubilizing agent. A 6 M urea solution enhanced drug solubility by more than 14-fold. The drug obeyed Beer's law over 5–300 µg/mL

with good linearity across 80–120% of label claim. The method showed satisfactory accuracy and precision in tablet analysis and was simple, eco-friendly, economical, and suitable for routine quality control.[12]

Remi S. L. et al. developed an ecofriendly, simple, accurate, and reproducible UV spectrophotometric method for the estimation of paliperidone using a mixed hydrotropic system containing 20% sodium benzoate and 20% niacinamide. The method enhanced drug solubility by more than 87-fold compared to distilled water. Paliperidone showed maximum absorbance at 286 nm with no interference from excipients. The method was linear over the concentration range of 10–50 µg/mL (r^2 = 0.9990). The assay of two marketed tablet formulations showed mean percentage label claims of 99.48 ± 0.292 and 98.01 ± 0.326, confirming the accuracy and reliability of the method.[13]

Remi S L et al. also reported an ecofriendly and cost-effective RP-HPLC method for the simultaneous estimation of paracetamol and diclofenac sodium using 5% urea solution as the mobile phase. Chromatographic separation was achieved on a Shimadzu Shim-pack C18 column (4.6 × 250 mm) at a flow rate of 1.0 mL/min with detection at 268 nm. Retention times were 3.272 min for paracetamol and 1.772 min for diclofenac sodium. The method showed good linearity in the range of 100–500 µg/mL for paracetamol and 10–50 µg/mL for diclofenac sodium. Percentage recoveries of 99.97 % and 99.79 % respectively demonstrated the accuracy and suitability of the method as per ICH guidelines.[14]

HYDROTROPY

The term hydrotropy was first introduced by Carl Neuberg in 1916, to designate anionic organic salts, at high concentrations considerably increasing the aqueous solubility of poorly soluble solutes. It is a solubilization technique in which the addition of a large amount of hydrotropic agent increases the aqueous solubility of poorly soluble drug.[15] Hydrotropic agents or hydrotropes are ionic organic salts that help to increase the solubility of the solute in a given solvent via salting-in phenomenon. Salts which show salting-in of non-electrolytes are called “hydrotropic salts” and the phenomenon is known as “hydrotropism”. They do not exhibit any colloidal properties, but they improve solubility by forming weak interactions with solute molecules.[16] A hydrotropic molecule interacts with a less water-soluble molecule via weak van der Waals interactions such as π–π or attractive dipole–dipole interactions.[17]

Neuberg studied the term hydrotropy by adding increased amounts of alkali metal salts of different organic acids to describe the increased solubility of the solution. He mentioned that some aqueous saline solutions have the power to dissolve certain substances that are not soluble in water.[33] In the pharmaceutical industry, this phenomenon has been demonstrated. It was used to define non-micellar, liquid or solid, organic or inorganic substances that are capable of solubilizing insoluble compounds.

Hydrotropes contain both hydrophobic and hydrophilic fractions in them. In comparison to surfactants, they contain a very small hydrophobic fraction.[18] The efficiency of hydrotrope solubilization depends on the balance between hydrophobic and hydrophilic parts of a hydrotrope.[19] The larger is the hydrophobic part of an additive, the better the hydrotropic efficiency. The presence of the charge on the hydrophilic part is less significant.[20] These are freely soluble organic compounds which enhance the aqueous solubility of organic substances by forming stack-type aggregation.[15,21]

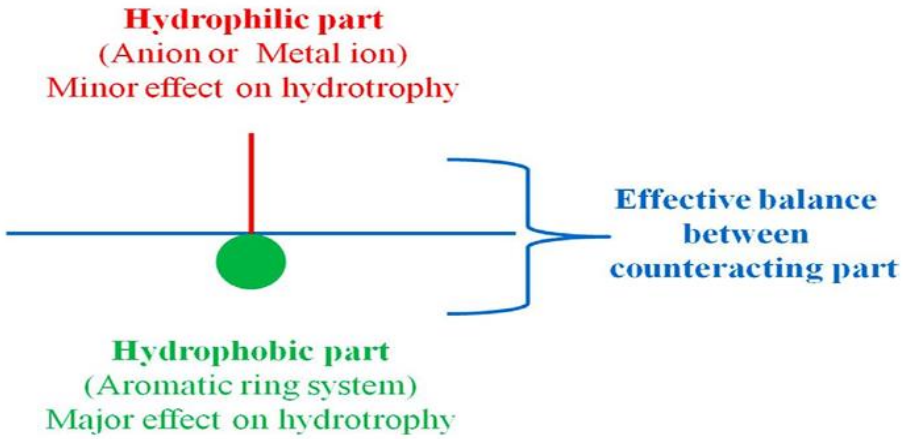

Figure 1: The structure of a hydrotropic agent.[22]

Citric acid, Benzoic acid, Sodium salicylate, sodium benzoate, Sodium citrate, Sodium acetate, Sodium ascorbate, Sodium caprylate, Potassium citrate, Urea, N, N-dimethylurea, Caffeine, Nicotinamide, N, N-diethyl nicotinamide, N, N-dimethyl benzamide, Resorcinol, Pyrogallol, Catechol, Sodium dodecyl sulphate, Procaine hydrochloride, Para-amino benzoic acid, etc. were used as hydrotropic agents.[23]

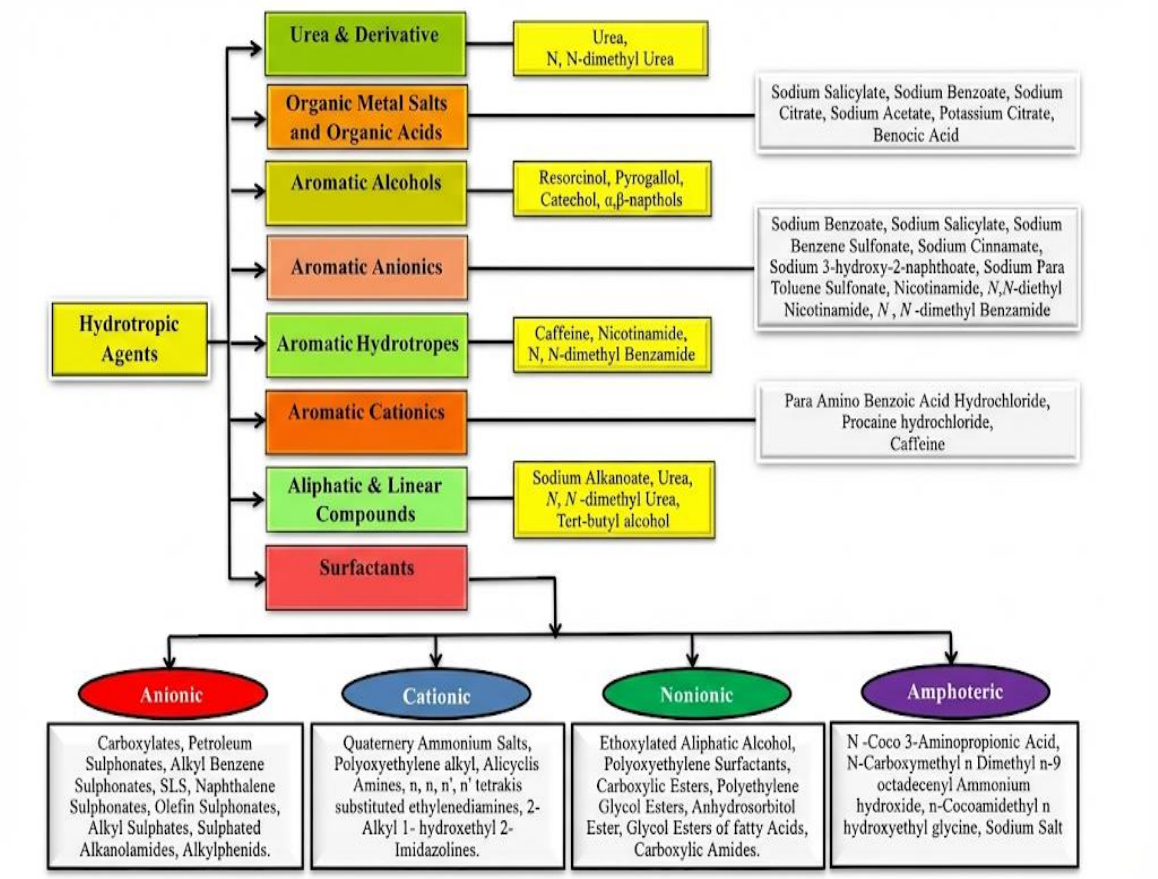

Figure 2: Arbitrary classifications of hydrotropes.[24]

The properties of hydrotropes are.[25]

- Upon dissolution in water, the hydrotropic agent does not produce any significant change in temperature, indicating the absence of appreciable exothermic or endothermic interactions.
- It exhibits complete miscibility/solubility in water, ensuring the formation of a homogeneous aqueous system.
- The hydrotrope is economically feasible due to its low cost and wide commercial availability.
- It is non-toxic and chemically inert under normal experimental conditions, thereby ensuring safety and compatibility with pharmaceutical formulations.
- The solvent characteristics of the hydrotropic system remain largely independent of pH within the working range, providing robustness to the analytical method.
- It demonstrates high selectivity by preferentially enhancing the solubility of poorly water-soluble drugs without significantly affecting other formulation components.

The enhancement in solubility of the poorly soluble drug by the hydrotrope is based on two facts

• The molecular self-association of the hydrotrope.

• The association of hydrotrope molecules with the solute.

Table 2: List of hydrotropes used and drugs analysed.

Sr. No.	Hydrotropic Agent(s) Used	Type	Drug(s) Analysed / Formulated	Ref. No.
1	Niacinamide	Single hydrotrope	Indomethacin	9
2	Sodium salicylate	Single hydrotrope	Theophylline	28
3	Urea + Sodium citrate + Sodium benzoate	Mixed hydrotropy	Aceclofenac (Injection)	15
4	Urea + Sodium benzoate + Sodium salicylate	Mixed hydrotropy	Aceclofenac	5
5	Sodium benzoate + Urea	Mixed hydrotropy	Metronidazole, Furazolidone	11
6	Sodium benzoate + Sodium salicylate	Mixed hydrotropy	Olmesartan Medoxomil	8
7	Sodium benzoate	Single hydrotrope	Rosiglitazone	12

8	Sodium benzoate + Urea	Mixed hydrotropy	Paliperidone	13
9	Sodium benzoate + Sodium salicylate	Mixed hydrotropy (mobile phase)	Paracetamol, Diclofenac sodium	14
10	Sodium benzoate–based hydrotropic solution	Single / RP-HPLC application	Ornidazole	10
11	Hydrotropic polymeric micelles (aromatic hydrotropic segments)	Advanced hydrotropy	Paclitaxel	32
12	Sodium salicylate (alone & in blends)	Single / Mixed hydrotropy	NSAIDs (various)	38
13	Polymeric micelles + hydrotropic excipients	Mixed / advanced	Capecitabine	44
14	Hydrotropic salt (tromethamine)	Mixed / crystalline salt formation	Indomethacin	45
15	Saquinavir + hydrotropic aqueous solution	Mixed hydrotropy	Saquinavir (Injection)	46
16	Dabigatran Etexilate + cocrystallization with hydrotrope	Mixed / solubility enhancement	Dabigatran Etexilate Mesylate	43

MECHANISM OF HYDROTROPIC SOLUBILIZATION

The proposed mechanism is given by.[26]

(a) Self-aggregation potential,

(b) Structure-breaker and structure-maker,

(c) Ability to form micelle-like structures.

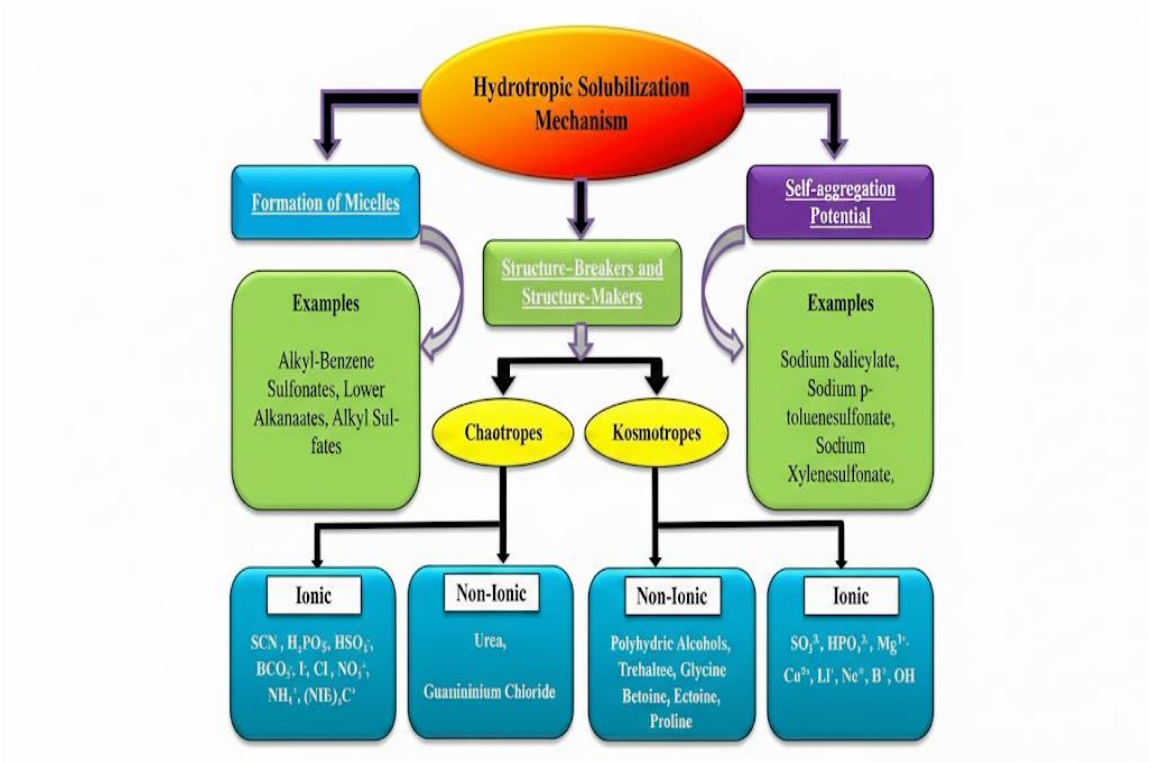

Figure 3: Flow diagram of Hydrotropic Solubilization.[24]

Self-Aggregation Potential

Minimum hydrotropic concentration (MHC) is a critical concentration at which hydrotrope molecules starts to aggregate, i.e., self-aggregation potential.[16] The solubilization power of hydrotropic agents is governed by their self-aggregation potential.[19] This potential depends upon their amphiphilic features and the nature of a solute molecule. They mainly show the volume-fraction-dependent solubilization potential.

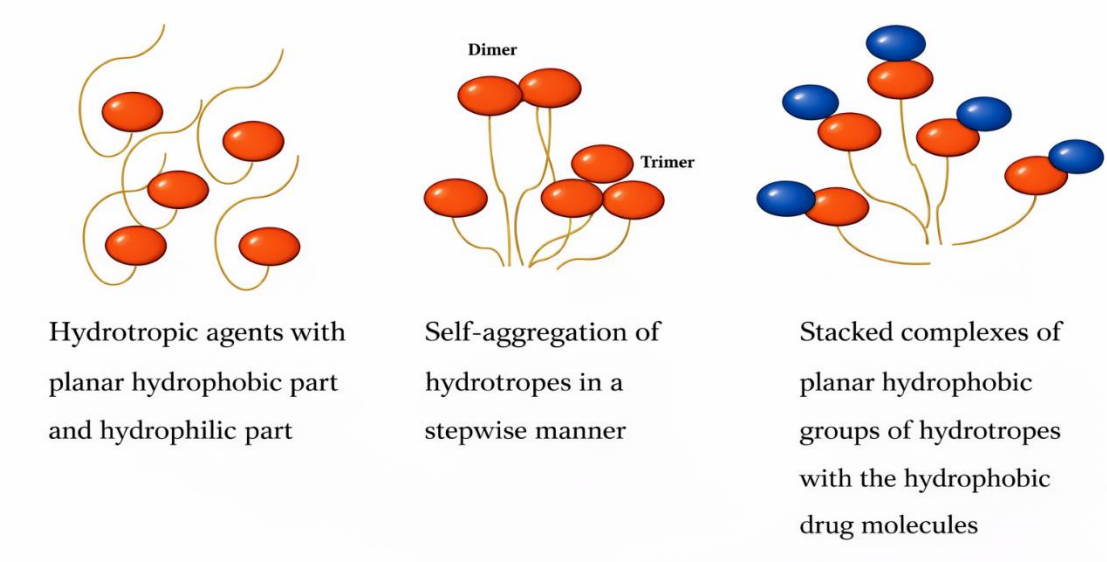

Figure 4: Mechanism of Hydrotrope.[27]

Initially, hydrotrope molecules undergo primary association in a pairwise manner which is followed by consecutive steps to form trimers, tetramers, and so on and these complexes (trimers, tetramers) could then lead to higher aqueous solubility.

- **Structure-breaker and Structure-maker**

In hydrotropic solubilization technique, an electrostatic force of the donor-acceptor molecule plays a vital role; hence, they are also termed as a structure-breaker and a structure-maker.[28,29] Solutes which are capable both of hydrogen donation and acceptance help to enhance solubility. Hydrotropic agents, such as urea, exert their solubilizing effect by changing the nature of the solvent, specifically by altering the solvent's ability to participate in structure formation or its ability to engage in structure formation via intermolecular hydrogen bonding.[30] Structure-breaker hydrotropes are known as chaotropes while structure-maker hydrotropes are known as kosmotropes.[31]

- **Ability to form Micelle-like Structures:**

This mechanism is based on the self-association of hydrotropes with solutes into a micellar arrangement.[32] They form stable mixed micelles with a solute molecule decreasing the electrostatic repulsion between the head groups. Hydrotropic agents, such as alkyl-benzene sulfonates and alkyl sulphates, exhibit self-association with solutes and form micelles.

ADVANTAGES OF HYDROTROPY OVER CONVENTIONAL METHODS[9,15]

- Simple and easy to use with minimal procedural steps.
- Cost-effective due to the use of inexpensive and easily available hydrotropic agents.
- Environment-friendly and compliant with green analytical chemistry principles.
- Eliminates or significantly reduces the use of toxic organic solvents.
- No chemical modification of the drug molecule is required.
- Enhances aqueous solubility of poorly water-soluble drugs.
- Avoids the need for emulsion systems, surfactants, or micelles.
- pH-independent solubilization compared to conventional methods.
- High selectivity toward target drug molecules.
- Minimal or no interference in UV–visible absorbance measurements.
- Simplifies sample preparation by eliminating extraction or derivatization steps.
- Improves accuracy and precision of analytical results.
- Increases method sensitivity by improving drug availability in solution.
- Reduced toxicity and health hazards to analysts.
- Non-volatile and non-flammable, enhancing laboratory safety.
- Produces stable drug solutions suitable for analysis.
- Compatible with UV, HPLC, HPTLC, and titrimetric analytical techniques.
- Can act as both solubilizing agent and mobile phase in chromatographic methods.
- Suitable for routine quality control of bulk drugs and pharmaceutical formulations.
- Regulatory acceptance when validated according to ICH guidelines.

APPLICATIONS[1]

- **Mixed Hydrotropy**

Mixed hydrotropic solubilization technique is the phenomenon used to enhance the solubility of poorly soluble drugs using blends of hydrotropic agents which may give synergistic enhancement effect on the solubility of poorly soluble drugs, and also reduce the side effects due to a reduction in the concentration of individual hydrotropic agents.[34]

Maheshwari et al. observed miraculous synergistic enhancement in solubility of a poorly water-soluble drug (Aceclofenac) by mixing two hydrotropic agents (urea and sodium citrate).[15] and this mixed hydrotropic blend was employed to solubilize Aceclofenac and carry out spectrophotometric analysis precluding the use of organic solvents.[35] Advantages of mixed hydrotropic solubilization technique include

- It may reduce the total concentration of hydrotropic agents necessary to produce a modest increase in solubility by employing a combination of agents in lower concentration.
- It is a new, simple, cost-effective, safe, accurate, precise, and eco-friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble drugs.
- It precludes the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost etc.

Solid Dispersion[36]

Solid dispersions in aqueous phase enhance the drug release rate and bioavailability of drugs. However, techniques used for preparation include solvent evaporation method by utilising organic solvent, but the limitation of residual solvent is its toxicity, cost and contamination of the product. This can be avoided by utilising hydrotropic solubilization technique.[15]

Liquid Oral Solutions (Syrup)[36,38]

The pharmacist faces many challenges in formulating and designing liquid dosage forms. Liquid oral solutions (syrups) have greater bioavailability compared to suspensions and a quicker onset of action. The proposed techniques are simple, practical, effective and less costly than the commercialized formulations using costly additives / excipients. Hydrotropic agents are safe and suggest suitability for large-scale production.

Quantitative Analysis[37,39]

Quantitative study of drugs which have poor aqueous solubility utilizes different organic solvents. Recovery experiments and statistical evidence proved the precision, reproducibility, and consistency of the hydrotropy. Maheshwari et al. employed sodium benzoate as a hydrotropic agent to quantify drugs with poor aqueous solubility like norfloxacin, nalidixic acid, metronidazole, and tinidazole by spectrophotometric analysis and titrimetric aspirin analysis. High cost, instability and toxicity are the main disadvantages of organic solvents.

Parenteral Preparations[15,46,47]

Acquired immunodeficiency syndrome (AIDS) continues to be a major global health concern. The currently available formulations for its treatment exhibit low therapeutic efficiency due to poor bioavailability. To overcome this limitation, N. K. Jain and M. Nahar developed an aqueous injectable formulation of saquinavir that is expected to be more effective, safer, and associated with fewer adverse effects. Their study demonstrated that the solubility of saquinavir, which is inherently poorly water-soluble, was significantly enhanced by the use of hydrotropes and cosolvents. The increased solubility at low concentrations may be attributed to weak ionic interactions, while at higher concentrations, mechanisms such as complex formation and self-aggregation are likely to play a role.

Hydrotropic Nanocarriers[16,36,45]

Hydrotropic nanocarriers such as polymeric micelles and dendrimers enhance the aqueous solubility of poorly water-soluble drugs. Paclitaxel is often used as a model drug to demonstrate their solubilization efficiency. Hydrotropic polymers improve solubility by increasing local hydrotrope concentration, while hydrotropic polymeric micelles show greater stability than conventional micelles due to polymer–drug miscibility rather than only hydrophobic interactions. These systems offer high drug loading and long-term stability, making them promising carriers for poorly soluble drugs.

Pharmaceutical Industry[40]

Hydrotropes are highly useful in industrial applications because they enable rapid solubilization and easy recovery of solutes from solution. Unlike conventional surfactants, hydrotrope solutions do not cause emulsification problems. For instance, sodium toluene sulfonate possesses a strong polar ionic group and a smaller hydrophobic moiety compared to traditional surfactants. Due to their amphiphilic nature, both hydrotropes and surfactants are widely employed in aqueous systems.

Controlled Release Drug Delivery System[41,44]

Hydrotropy plays an important role in controlled release drug delivery systems (CRDDS) by improving the aqueous solubility of poorly water-soluble drugs, which facilitates their effective incorporation into controlled release formulations. The use of hydrotropic agents enhances drug loading and ensures uniform drug distribution within polymeric matrices or reservoir systems without the need for chemical modification of the drug. Hydrotropy also helps avoid the use of toxic organic solvents and surfactants, thereby reducing formulation-related toxicity. By increasing drug solubility and stability, hydrotropy supports the development of sustained and controlled release dosage forms with improved bioavailability and therapeutic efficacy.

SPECTROPHOTOMETRY[48]

Spectrophotometry is the measurement and interpretation of electromagnetic radiation (EMR) absorbed or emitted when the molecules or atoms or ions of a sample move from one energy state to another energy state. UV (Ultraviolet) spectroscopy is concerned with the study of absorption of UV radiation which ranges from 200-400 nm. Solvent plays an important role in UV spectra, since the compound peak could be obscured by the solvent

peak. Hence the solvent selected for the sample is that it neither absorbs in the region of measurement nor affects the absorption of the sample. Hydrotropes generally do not interfere with the absorption of the sample; hence, this method can be widely and successfully employed for the estimation of poorly soluble drugs making the method more economic, cost effective and eco-friendly by spectrophotometry.

VALIDATION AS PER ICH GUIDELINES[49,52]

The developed analytical methods are validated (Q2 (R1), ICH, 2005; Q2B, ICH, 1996) according to ICH guidelines. Method validation is a process of demonstrating that analytical procedures are suitable for their intended use. Various validation parameters include:

- System Suitability
- Accuracy
- Precision
- Linearity
- Specificity
- Robustness
- Ruggedness
- Limit of Detection
- Limit of Quantification

SUMMARY

Green Analytical Chemistry (GAC) focuses on developing environmentally friendly and safe analytical strategies that reduce risks to analysts and the environment. Enhancing the aqueous solubility of poorly soluble drugs is crucial in analytical techniques, as many modern drugs are highly lipophilic and commonly analysed using toxic, volatile, and expensive organic solvents. Hydrotropy offers a safe and green alternative for solubilizing poorly water-soluble drugs. It is a molecular phenomenon in which the addition of a hydrotropic agent increases drug solubility in water. Mixed hydrotropic systems further enhance solubility through synergistic effects while reducing the required concentration of individual hydrotropes. Hydrotropic agents—such as urea derivatives, organic salts, aromatic compounds, alcohols, and surfactants—improve solubility through weak interactions like van der Waals, π–π, and dipole–dipole forces. Due to the high number of poorly soluble drugs, hydrotropy has gained wide acceptance in spectroscopic methods as a cost-effective, eco-friendly replacement for organic solvents.

CONCLUSION

Hydrotropes are comparatively non-toxic, non-flammable, non-volatile, economical, and environmentally friendly when compared with organic solvents. Spectrophotometric methods based on hydrotropic solubilization eliminate the need for organic solvents, thereby avoiding errors associated with volatility, environmental pollution, and high cost. Owing to their simplicity, rapidity, reproducibility, eco-friendly nature, and cost-effectiveness, such methods are well suited for routine analytical applications. In the future, the discovery and application of new hydrotropic agents may further replace toxic, volatile, and expensive organic solvents in drug analysis. Hence, hydrotropic solubilization represents a promising approach for routine industrial analysis and large-scale method development of poorly water-soluble drugs.

ACKNOWLEDGEMENT

With utmost reverence, the authors express heartfelt gratitude to Almighty God, parents, and Dr. Remi S.L. (Guide, Assistant Professor of Pharmaceutical analysis, College of Pharmaceutical Sciences, Government Medical College, Thiruvananthapuram) for their blessings, valuable suggestions and constant encouragement.

REFERENCES

1. Kuchekar AB, Gawade A, Boldhane S. Hydrotropic solubilization: an emerging approach. Journal of Drug Delivery and Therapeutics, 2021 Jan 2; 11(1-s): 200-6.
2. Tobiszewski, M., Mechlinska, A., Zygmunt, B. and Namiesnik, J., 2009. Green analytical chemistry in sample preparation for determination of trace organic pollutants. Trends in Analytical Chemistry, 28(8): 943-951.
3. Ewing GW. 2001. Introduction to Instrumental Methods of Chemical Analysis, 5th ed. McGraw Hill Book company, Singapore. 1-2.
4. Indian Pharmacopoeia Commission. Indian Pharmacopoeia 2018. Vol. I. Ghaziabad: Indian Pharmacopoeia Commission; 2018. 2.4.26 Solubility; 220.
5. Harish N, Sree Giri Prasad B. and Gupta VRM., 2012. Mixed co-solvency concept: A promising tool to enhance solubility of poor soluble drug Aceclofenac. International Journal of Pharmaceutical, Chemical, and Biological Sciences, 2(3): 338-342.
6. ICH guideline Q3C (R6) on impurities: guideline for residual solvents 2006; 4-39.
7. Brautbar, N. and Williams II, J., 2002. Industrial solvents and liver toxicity: risk assessment, risk factors and mechanisms. International Journal of Hygiene and Environmental Health, 205(6): 479-491.
8. Shriram N B, Swapnil JD, Manish BS, Sujata MJ. Novel Spectrophotometric Method for Estimation of Olmesartan Medoxomil from its Tablet Dosage Form using Hydrotropic Solubilization.
9. Maheshwari R K, Rathore A, Agrawal A, Gupta MA. New spectrophotometric estimation of indomethacin capsules with niacinamide as hydrotropic solubilizing agent. Pharmaceutical methods, 2011 Jul 1; 2(3): 184-8.
10. Remi S L, Varkey J, Nair AJ, Sanjeev VS. Application of an Eco-friendly, Cost-effective Hydrotropic solution as mobile phase for the estimation and validation of Ornidazole in bulk and Pharmaceutical Formulation by RP-HPLC. Asian

Journal of Research in Pharmaceutical Sciences. 2021 Feb 1; 11(1): 15-21.
11. Jain R, Jain N, Jain D K, Patel V K, Rajak H, Jain S K. Novel UV spectrophotometer methods for quantitative estimation of metronidazole and furazolidone using mixed hydrotropy solubilization. Arabian Journal of Chemistry, 2017 Feb 1; 10(2): 151-6.
12. Sherje A P, Desai K J. Spectrophotometric determination of poorly water-soluble drug rosiglitazone using hydrotropic solubilization technique. Indian Journal of Pharmaceutical Sciences, 2011 Sep; 73(5): 579.
13. Remi S L, Varkey J. An eco-friendly novel spectrophotometric estimation and validation of paliperidone in bulk drug and their dosage forms by mixed hydrotropic solubilisation method. Asian Journal of Pharmaceutical and Health Sciences, 2018; 8(4): 1996-2001.
14. Remi S L, Varkey J, Maheshwari RK, Nair A J. A Novel Eco-friendly, cost-effective mobile phase for HPLC-Simultaneous estimation and Validation of Paracetamol and Diclofenac sodium in Bulk and Pharmaceutical Formulation by RP-HPLC using Hydrotropic Solution as Mobile phase. Asian Journal of Pharmaceutical Research, 2020; 10(3): 163-70.
15. Maheshwari, R.K. and Indurkhya, A., 2010. Formulation and evaluation of Aceclofenac injection made by mixed hydrotropic solubilization technique. Iranian Journal of Pharmaceutical Research, 9(3): 233-242.
16. Kumar, V.S., Raja, C. and Jayakumar, C., 2014. A review on solubility enhancement using hydrotropic phenomena. International Journal of Pharmacy and Pharmaceutical Sciences, 6(6): 1-7.
17. Neumann, M.G., Schmitt, C.C., Prieto, K.R. and Goi, B.E., 2007. The photophysical determination of the minimum hydrotrope concentration of aromatic hydrotropes. Journal of Colloid and Interface Science, 315(2): 810-813.
18. Kapadiya, N., Singhvi, I., Mehta, K., Karwani, G. and Dhrubo, J.S., 2011. Hydrotropy: a promising tool for enhancement of solubility: a review. International Journal of Drug Development and Research, 3(2): 26-33.
19. Kim, J.Y., Kim, S., Papp, M., Park, K. and Pinal, R., 2010. Hydrotropic solubilization of poorly water-soluble drugs. Journal of pharmaceutical sciences, 99(9): 3953-3965.
20. Bauduin, P., Renoncourt, A., Kopf, A., Touraud, D. and Kunz, W., 2005. Unified concept of solubilization in water by hydrotropes and cosolvents. Langmuir, 21(15): 6769-6775.
21. Saleh, A.M. and El-Khordagui, L.K., 1985. Hydrotropic agents: a new definition. International Journal of Pharmaceutics, 24(2): 231-238.
22. Dhapte V, Mehta P. Advances in hydrotropic solutions: An updated review. St. Petersburg Polytechnical University Journal: Physics and Mathematics, 2015 Dec 1; 1(4): 424-35.
23. Gawai, M N., Aher, SS. and Saudagar, RB., 2015. Mixed hydrotropy technique for solubility enhancement- A review. International Journal of Institutional Pharmacy and Life Sciences, 442-452.
24. Patil M R, Ganorkar S B, Patil A S, Shirkhedkar AA, Surana SJ. Hydrotropic solubilization in pharmaceutical analysis: Origin, evolution, cumulative trend and precise applications. Critical reviews in analytical chemistry. 2021 May 7; 51(3): 278-88.
25. Ghogare, D. and Patil, S., 2018. Hydrotropic solubilization: Tool for eco-friendly analysis. International Journal of Pharmacy and Pharmaceutical Research, 11(3): 300-322.
26. Avinash, A., Sushma, A., Lalasa, K., Kumar, S.P., Gowthami, T. and Sreenivasulu, M., 2016. A Review on solubility enhancement using hydrotropy. Asian Journal of Medical and Pharmaceutical Sciences, 4(1): 33-38.
27. Shafi, M.S.M. and Saudagar, R.B., 2015. A review on Solubility enhancement technique hydrotropy. World Journal of Pharmaceutical Research, 4: 324-332.
28. Jayakumar, C., Kumar, D.K., Nesakumar, D. and Gandhi, N.N., 2010. Quantitative analysis of Theophylline bulk sample using Sodium salicylate hydrotrope. International Journal of Pharmacy and Pharmaceutical Sciences, 2(3): 124-125.
29. Nagarajan, J., Wah Heng, W., Galanakis, C.M., Naga Sundara Ramanan, R., Raghunandan, M.E., Sun, J., Ismail, A., Beng-Ti, T. and Prasad, K.N., 2016. Extraction of phytochemicals using hydrotropic solvents. Separation Science and Technology, 51(7): 1151-1165.
30. Cui, Y., 2013. Hydrotropic solubilization by Urea derivatives: A molecular dynamics simulation study. Journal of Pharmaceutics, 1-15.
31. Khanam, A., Sheikh, M., Khan, I. and Khabiruddin., 2014. Aggregational behaviour of alkanedinyl-α,ω-bis (tetradecyl dimethyl ammonium) dibromide series with ionic and non-ionic hydrotropes at different temperatures. Journal of Industrial and Engineering Chemistry, 20(5): 3453-3460.
32. Lee, S.C., Huh, K.M., Lee, J., Cho, Y.W., Galinsky, R.E. and Park, K., 2007. Hydrotropic polymeric micelles for enhanced Paclitaxel solubility: in vitro and in vivo characterization. Biomacromolecules, 8(1): 202-208.
33. Mehringer J, Kunz W. Carl Neuberg's hydrotropic appearances (1916). Advances in Colloid and Interface Science. 2021 Aug 1; 294: 102476.
34. Kadam, S.V., Shinkar, D.M. and Saudagar, R.B., 2013. Review on solubility enhancement techniques. International Journal of Pharmacy and Biological Sciences, 3(3): 462-475.
35. Polshettiwar, S. and Khorate, S.S., 2016. Mixed Hydrotropy: A rising tool for solubility enhancement of transdermal drug delivery and cosmeceutical

applications. Indo American Journal of Pharmaceutical Research, 6(10): 6680-6690.
36. Brahmankar, D., Jaiswal, S., Biopharmaceutics and Pharmacokinetics: A Treatise. Third ed., Vallabh Prakashan, India, 2017; 347-366.
37. Maheshwari, R. K., Chaturvedi S. C., Jain, N.K. Novel application of hydrotropic solubilization in the quantitative analysis of some NSAIDs and their solid dosage forms. Ind. J. Pharm. Sci., 2007; 69(1): 101-105.
38. Ansari K, Gaikar V, Green hydrotropic extraction technology for delignification of sugarcane bagasse by using alky benzene sulfonates as hydrotropes. Chem. Eng. Sci. 2014; 115: 1157– 1166.
39. Gaikar, V., Sharma, M. Separations with hydrotropes, Sep. Technol. 1993; 3: 2–11.
40. Rub, M., Azum, N., Kumar, D., Khan, F., Asiri, A. Clouding phenomenon of amphiphilic drug promazine hydrochloride solutions: Influence of pharmaceutical excipients., J. Ind. Eng. Chem. 2015; 21: 1119–1126.
41. Kamble, S., Kumbhar, A., Jadhav, S., Salunkhe, R., Micheal, A. Reaction in glycerol as a sustainable hydrotropic medium. Mater. Today: Proc. 2015; 5: 1792–1798.
42. Jyoti J., Nidhi, N. S. Vikas, A. S., A review on hydrotropy: a potential approach for the solubility enhancement of poorly soluble drug. Asian J Pharm Clin Res, 2019; 12(10): 19-26.
43. Gawade, A. R., Boldhane, S. P. Solid Dosage Form Development of Dabigatran Etexilate Mesylate with Increased Solubility and Dissolution Using Cocrystallization. IJPSR, 2020; 11(5): 2899 2905.
44. Kuchekar, A. B., & Pawar, A. P. Capecitabine loaded polymeric micelles: Formulation, characterization and cytotoxicity study. International Conference on Advanced Nanomaterials & Emerging Engineering Technologies. 2013; 412-415.
45. Thipsay, M.P., Ross, S., Zhang, F., Bandari, S., Repka, M.A. Preparation of a crystalline salt of indomethacin and tromethamine by hot melt extrusion technology. Eur. J. Pharm Biopharm. 2018; 131(10): 109–119.
46. Nahar, M., Jain, N. K. Formulation and evaluation of Saquinavir injection. Ind. J Pharm. Sci. 2006; 10: 608- 614.
47. Agrawal, S., Pancholi, S.S., Jain, N.K., Agrawal, G.P. Hydrotropic solubilization of nimesulide for parenteral administration. Ind. J. Pharm. 2004; (274): 149–155.
48. Ravi Sankar S. Textbook of Pharmaceutical Analysis. 5th ed. India: RX Publication; 2019; 1(3): 53–1.
49. ICH Guidelines, 2013, Guidance for industry: Bio analytical method validation., US Department of Health and Human Services, 4-15.
50. ICH Guidelines, 1996. Guidance for industry: Q2B validation of analytical Methodology, 1-8.
51. ICH Harmonized Tripartite Guidelines., 2005.Validation of analytical Procedures: Text and Methodology; Q2 (R1), Geneva, 1-13.
52. ICH Guidelines, 1994. Q2A Validation of analytical procedure- Guidelines, Methodology, Geneva, 6-13.