

Review Article

A REVIEW ON SOLUBILITY ENHANCEMENT USING HYDROTROPIC PHENOMENA

V. SAMPATH KUMAR, C. RAJA, C.JAYAKUMAR*

Department of Chemical Engineering, A.C. College of Technology, Anna University, Chennai, India 600025.

Email: c_jayakumar71@yahoo.com

Received: 27 Jan 2013 Revised and Accepted: 25 May 2013

ABSTRACT

Solubilization of poorly water-soluble drugs has been a very important issue in screening studies of new chemical entities as well as formulation research. Various techniques are employed to enhance the aqueous solubility of poorly water-soluble drugs and hydrotropic solubilisation is one of them. A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solution. The problem of emulsification, which is normally encountered with conventional surfactant solutions are not found with hydrotrope solutions. Easy recovery of the dissolved solute and the possible reuse of hydrotrope solutions make this method the most effective one particularly at industrial levels. Besides, the advantage of certain properties like the solvent character independent of pH, high selectivity, non-flammability, cheap and easy availability of hydrotropes, makes this technique superior to other solubilization methods. To solubilize water insoluble drugs especially in case of oral formulation, solubility remains a critical factor, so for in this review various solubility enhancement techniques are highlighted and a brief review of hydrotrophy and its preparation are discussed.

Keywords: Hydrotrophy, Hydrotropes, Solubility, Solubility enhancement, Hydrophobic drugs, Bioavailability, Mixed hydrotrophy.

INTRODUCTION

Neuberg (1916) was the first to report hydrotrophy when he dissolved a variety of organic substances, such as carbohydrates, esters, lipids, drugs and oil in aqueous solutions containing hydrotropes [1]. Later Booth and Everson had shown that concentrated aqueous solutions of organic salts, such as sodium benzoate, salicylate, benzene sulfonate and cumene sulfonate, can increase the solubility of many compounds. Booth and Everson were the first to show that the solubility increase in the hydrotrophy solution does not occur in a linear fashion, but with the increase in the concentration of hydrotrope. This fact has an important bearing while understanding the mechanism of the hydrotrophy [2-4]. Balasubramanian and Friberg have reviewed most of the recent developments in the field of hydrotrophy, other than separations, emphasizing the similarities between aggregation behavior of hydrotropes and surfactants [5]. The emphasis on chemical engineering and industrial applications of hydrotropes started with an article by McKee who highlighted some important features and advantages of hydrotrophy. He noted that most hydrotropic solutions precipitate the solute on dilution with water and pointed out that this fact permits the recovery of the hydrotrope for further use [7].

An overview on hydrotrophy

Hydrotrophy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are mentioned to be ionic organic salts. Additives or salts that increase the solubility in a given solvent are said to "salt in" the solute and those salts that decrease the solubility are said to "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism" [8-11]. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs [12-15].

Hydrotrophy is a unique and unprecedented solubilization technique in which certain chemical components termed as hydrotropes can be used to effect a several fold increase in the solubility of sparingly

soluble solutes under normal conditions. This increase in solubility in water is probably due to the formation of organized assemblies of hydrotrope molecules at critical concentration [16-18]. Hydrotropes in general are water soluble and surface-active compounds, which can significantly enhance the solubility of organic solutes such as acids, esters, alcohols, aldehydes, ketones, hydrocarbons and fats. Hydrotropes are widely used in drug solubilization, detergent formulation, health care and household applications as well as for being an extraction agent for fragrances [19-23].

This potentially attractive technique can also be adapted to separate close boiling isomeric/non-isomeric mixtures. At the same time, the problem of emulsification, which is normally encountered with conventional surfactant solution, is not found with hydrotrope solutions [24-26]. Hydrotropes have been used to increase the rate of heterogeneous reactions and have also been used for the separation of close boiling mixture through extractive separation and liquid-liquid extraction [27]. The solubility enhancement of organic compounds through hydrotrophy could be due to the formation of the molecular structures in the form of complexes. Since this aggregation process is driven by hydrophobic interactions, the parameters associated with the hydrocarbon part of the hydrotrope, such as surface area and volume of the hydrophobic part, may play a significant role in the solubility change and perhaps in extractive separations [28-29]. In light of the similarity in amphiphilic structure of hydrotrope molecules and of conventional surfactants this comparison is unavoidable. The major difference between a hydrotrope and the micellar surfactant is in the solubility behavior. Some inorganic salts such as alkali iodides, thiocyanates, oxalates, bicarbonates have similar enhancement effect, the mechanism in this cases is clearly understood to be 'salting in' and therefore these compounds are not classified as hydrotropes. Hydrotropes have also been used to increase the rate of heterogeneous reactions also. Most compounds when dissolved in water decrease the solubility of the second component, some present opposite behavior, leading to considerable solubility increases [30-31]. The occurrence of such phenomena led to terminologies 'salting out', referring to reduced solubility, and 'salting in' for the reverse effect. Compounds that cause increase in aqueous solubility are called hydrotropes. Both salting in and salting out effects present many practical applications, for instance in separation processes (precipitation of proteins, separation of isomers using hydrotropes) development of pharmaceutical formulations increase of cloud points of detergent solutions changes in reaction rates among others [32].

Solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown [33-34]. The study on solubility yields information about the structure and intermolecular forces of drugs. Drug efficacy can be severely limited by poor aqueous solubility and some drugs also show side effects due to their poor solubility. There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a

valuable aid to increase efficiency and/or reduce side effects for certain drugs. This is true for parenterally, topically and orally administered solutions [35-36].

Expressing Solubility And Concentration

The Solubility is usually expressed by variety of concentration that is by Quantity per quantity, Percentage, Parts, Molarity, Molality, Mole fraction, Milliequivalents and normal solutions [37] This is also explained in term of parts of solvent required for 1 part of solute as explained in U. S pharmacopeia which is shown in Table 1.

Table 1: Expression for approximate solubility [38,-41].

Descriptive terms to dissolve 1 part of	Relative amounts of solvents to dissolve 1 part of solute	Examples of drugs
Very soluble	Less than 1	Metoprolol, Deltiazam
Freely soluble	From 1-10	Ipratropium bromide
Soluble	From 10-30	Cyclophosphamide, carmustine, Quinidine, Procainamide, Propranolol, Timolol
Sparingly soluble	From 30-100	Fluorouracil, Quinidine Sulphate, Labetolol, Ramipril
Slightly soluble	From 100-1000	Fludrabine, Atenolol, Valsartan
Very slightly soluble	From 1000-10,000	Busulphan, lomustine, Flecainide, Doxazocine
Insoluble or practically insoluble	More than 10,000	Chlorambucil, Melphlan, Lidocaine, Candesartan, Irbesartan, Nifedipine

Descriptive terms

General parameters affecting solubility are particle size, shape and surface area physicochemical properties of drugs, and physical forms of drugs, solvents, pH of the medium, temperature and use of surfactants. The pharmacopoeia lists solubility in terms of dissolve 1g of solute. If exact solubilities are not known, the pharmacopoeia provides general terms to describe a given range. These descriptive terms are listed in (Table 1).

Hydrotropes

Hydrotropes are compounds that are usually used as a media for promoting solubilization of sparingly soluble substances in aqueous solution, or providing appropriate media for specific reactions. The main property of the hydrotropes is related to the MHC (minimum hydrotrope concentration), which is defined as the critical concentration at which hydrotropes molecules begin to aggregate, i.e., forming new microenvironment with properties different those of the hydrotropes in relatively diluted solutions. Above MHC the solubility of the organic compound in aqueous phase increases significantly. The MHC of a hydrotrope may be as high as 0.8-0.9 mol/L. Determination of MHC was made initially by measuring the effect of hydrotropes concentration on chemical properties of these solutions, like solubility enhancement or increase in hydrolysis reaction rate [42].

Hydrotropes are amphiphilic substances composed mainly of hydrophilic functional group. Hydrotropes are organic salts that when present in aqueous solutions can substantially enhance the solubility of a variety of hydrophobic organic substances in the aqueous phase. These substances include aryl sulfonic acids, their potassium, sodium, calcium, and ammonium salts, sodium and potassium salts of benzoic acids and phenols etc. Some typical hydrotropes are hydroxybenzenes, hydroxybenzoates, and benzenesulfonates which, when present in significant concentration in water, can enhance the solubility of hydrophobic compounds. Above a certain characteristic concentration, compounds aggregate to offer non-polar micro-domains to solubilize hydrophobic solutes [43]. Hydrotrope assemblies have special geometrical features which enable them to distinguish among other solubilizers. For example: o-, m- and p- isomers differ in their action towards hydrotropy. This makes hydrotropy distinctly different from salting in and micellar solubilization. These features suggest that several balancing molecular forces are at work during hydrotropy. The hydroxybenzenes selected differ from each other in minute structural features in the number and position of hydroxyl groups. Hydrotropes comprises of hydrophilic and hydrophobic moieties with the hydrotropic moiety being typically too small to induce micelle formation. They self-associate to form aggregates that may act as micelles affecting the solubility and properties of the other

solutes [44]. Hydrotrope molecules are assumed to aggregate by a stacking mechanism of the planar aromatic ring present in their chemical structures. This type of aggregation is believed to be at the origin of the solubilization process of sparingly soluble hydrophobic compounds in water; in analogy to a micellization process hydrotrope assemblies have special geometrical features which enable them to distinguish among solubilizers [45]. Hydrotropes provide highly selective separation processes for industrial mixtures that are difficult to separate by conventional processes. Extractive separations, extractive distillation, and crystallization using aqueous solutions of hydrotropes are very efficient techniques of separations. The separation factors obtained with these techniques can be higher than those obtained even with reactive separations. Their high solubilization capacity has made hydrotropes very useful in many fields. Each hydrotrope has a selective ability towards a particular component in the mixture which facilitates easy recovery of the hydrotrope solution by controlled dilution with water. Solubility do not show any appreciable increase even after the addition of hydrotrope in the aqueous phase, but on subsequent increase in the concentration of hydrotrope, the solubility of the organic compound present in aqueous phase increases significantly. This solubility increase in the organic compound when present in water could be due to the formation of organized assemblies of hydrotrope molecules at critical concentrations. The critical concentration of hydrotrope is termed as the Minimum Hydrotrope Concentration (MHC) which is the minimum required hydrotrope concentration in the aqueous phase. This increase is presumably through a self-aggregation process because of their amphiphilic nature and varies with the nature of the organic compound. The increasing trend is maintained only up to a certain concentration of hydrotrope beyond which there is no appreciable increase in the solubility of organic compound in the aqueous phase. This concentration of hydrotrope is termed as the Maximum Hydrotrope Concentration (C_{max}) [46-49].

Hydrotrope as a true solubilizer [50]

A solubilizer is a surfactant. A solvent insoluble material is solubilized in the surfactant micelle. Factors that cause an increase in either the diameter of the micelle or its aggregation number generally increase solubilization. Some examples of regularly used solubilizers are fatty soaps, polyethoxylated nonionics and quaternary ammonium surfactants. Solubilization greatly increases once the CMC has been reached. Hydrotropes are effective only at high concentrations.

Difference between hydrotropy and other cosolvency methods [51-54]

Hydrotropy is different from simple phase mixing, or the cosolvency process, and also from salting-in action. While the self-aggregation

phenomenon of hydrotropes is reminiscent of surfactant self assemblies, there are important differences. Solubilization of hydrotropes is characterized by the relatively high concentrations of the hydrotrope needed and the larger amounts of solute solubilised, compared with that in micellised surfactants. Further, hydrotropes often exhibit selective ability to solubilise guest molecules than micellised surfactants. Surfactants have long hydrocarbon chains, whereas, hydrotropes are characterized by a short, bulky hydrocarbon groups. The aggregation numbers found in the case of hydrotrope aggregates is lower compared to those found in the case of micelles. Hydrotropes tend to form loose aggregates while long chain surfactants tend to form micelles by comparing the aggregation behaviors of two linear alkyl benzene sulfonates.

Need of solubility [55]

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Due to advanced research & development, there are varieties of new drugs & their derivatives are available. But more than 40% of lipophilic drug candidates fail to reach market due to poor bioavailability, even though these drugs might exhibit potential pharmacodynamic activities. The lipophilic drug that reaches market requires a high dose to attain proper pharmacological action. The basic aim of the further formulation & development section is to make that drug available at proper site of action within optimum dose.

Mechanism of hydrotropy [56-59]

Each hydrotrope has selective ability towards a particular component in the mixture, which facilitates easy recovery of the hydrotrope solution by controlled dilution with water. Solubility do not show any appreciable increase even after the addition of hydrotrope in the aqueous phase, but on subsequent increase in the concentration of hydrotrope, the solubility of the organic compound present in aqueous phase increases significantly.

This solubility increase in the organic compound when present in water could be due to the formation of organized assemblies of hydrotrope molecules at critical concentrations. The critical concentration of hydrotrope is termed as the minimum hydrotrope concentration (MHC) which is the minimum required hydrotrope concentration in the aqueous phase above which the solubility of the organic compound in aqueous phase increases significantly.

This increase is presumably through a self-aggregation process because of their amphiphilic nature and varies with the nature of the organic compound. The increasing trend is maintained only upto a certain concentration of hydrotrope beyond which there is no appreciable increase in the solubility of organic compound in the aqueous phase. This concentration of hydrotrope is termed as the maximum hydrotrope concentration. Few examples relevant to the mechanism of hydrotropy are presented below: The plant cell wall is made up of phospholipid bilayer. The hydrotrope destroys the phospholipid bilayer and penetrates through the cell wall into the inner structures. The water soaking shows very less effect on cork cells. The cellulose and suberin lamella are the cell wall component of cork cells. The suberin lamella makes the cork cell impermeable to water. But, the hydrotrope solutions break open the water impermeable suberin lamella and then the mature cork cells. The cork cell layers are disturbed by the hydrotrope and the aqueous solution penetrates through the cell wall. When the inner part is exposed to the hydrotrope solution, the cell swells, and frees the cells from closely bound structures. Hydrotropic solutions precipitated the solutes; out of the solution on dilution with water thus enable the ready recovery of the dissolved solutes. Hydrotropic agents can make the O/W and W/O microemulsion and the lamellar liquid crystal destabilized, which results in the 'phase transition' from lamellar liquid crystal phase to bi-continuous structure this is called as Hydrotrope- solubilization action. Vitamin C shows hydrotrope-solubilization action.

Hydrotropes are known as 'coupling agents'. When hydrotropes are added to a turbid liquid with relatively high water content causes the liquid to become transparent because of 'phase transition' [60].

Self-association of hydrotropes[61]

In recent years, self-aggregation of hydrotropes in aqueous medium has been reported by a number of workers. The term minimum hydrotrope concentration (MHC) has been used in consonance with the CMC of surfactants. Rath has emphasized the formation of intermolecular stack-type aggregation of hydrotropes. Like Rath, they have also considered stacking of hydrotropes as the process for self-association. From detailed physicochemical studies, Balasubramanian and co-workers, concluded that hydrotrope action is a collective molecular phenomenon involving the formation of non-covalent aggregates. According to them, there are

- Comparable micro environmental features of hydrotrope assemblies with micelles.
- Surface activity of hydrotrope solutions are similar to micelle forming surfactants.
- Sigmoidal solubilization curves show cooperativity in the process, and
- Open-layer assemblies of hydrotropes exist in their crystalline state.

The high concentration required for self-association of hydrotropes (i.e. high MHC values) strongly contrasts micelle formation and casts doubts on the formation of ordered assemblies as in micelles. Besides, the hydrotropes are essentially not efficient surface-active compounds, i.e. they do not appreciably lower the surface tension of water. The hydrotropes have produced monotonous change in the thermal behaviour, no sharp change has been observed. The self-association of hydrotropes yielding a break at higher solute concentration is thus doubtful; this can be a common occurrence of a measured property due to activity and other effects. Further work is required for a conclusive decision on hydrotrope association. Until then, the concept of hydrotrope association and MHC must not be discarded, but should be used with reservation.

Preparation of hydrotropes [62]

Hydrotropes are produced by sulfonation of an aromatic hydrocarbon solvent (i.e., toluene, xylene or cumene). The resulting aromatic sulfonic acid is neutralized using an appropriate base (e.g., sodium hydroxide) to produce the sulfonate or hydrotrope. The hydrotropes are 'pure' substances but are produced and transported in either aqueous solutions, typically at a 30-60 % level of activity, or in granular solids typically at 90-95 % level of activity. The other components of granular solids include sodium sulfate and water. Liquid product is produced in a closed system. Granular hydrotropes product is produced by spray drying that includes source control and dust collection. Hydrotropes are manufactured for industrial/professional and consumer use and are not used as intermediates/derivatives for further chemical manufacturing processes or uses.

Characteristics of hydrotropes [63]

1. Completely soluble in water and practically insoluble in system.
2. Hydrotropes are surface active and aggregate in aqueous solution because of their amphiphilic structure.
3. Should not produce any temperature when dissolved in water.
4. Cheap and easy availability.
5. Non toxic and non reactive.
6. Insensitive to temperature effects, when dissolved in water.
7. The solvent character being independent of pH, high selectivity, and the absence of emulsification are the other unique advantages of hydrotropes.

Features of hydrotropes [64]

1. Unprecedented solubilization increase.
2. Very high selectivity.

3. Easy recovery of solute from solution.
4. Economical and cost effective.
5. Absence of emulsion.
6. Absence of hazards present in other solvents used in extractive separation.

Other solubilization techniques [65-66]

1. Salting in.
1. Salting out.
2. Co-solvency.
3. Micellar solubilization.
4. Hydrotropy

Advantages of hydrotropic solubilization technique [67]

1. Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification
2. It only requires mixing the drug with the hydrotrope in water.
3. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

Properties of hydrotropes[68]

1. Hydrotropes in general are water-soluble and surface-active compounds that can significantly enhance the solubility of organic solutes such as esters, alcohols, aldehydes, ketones, hydrocarbons, and fats.
2. All are non reactive and nontoxic and do not produce any temperature effect when dissolved in water.
3. The solvent character being independent of pH, high selectivity, and the absence of emulsification are the other properties of hydrotropes.

Significance of hydrotropes

1. Hydrotropes have been used to solubilize organic compounds, dyes, drugs, and bio-chemicals.
2. Hydrotropes have been tested in the development of extractive separation processes in the separation of proteins and in distillation as an extractive solvent for separation of close boiling-point phenolic mixtures.
3. Aqueous hydrotrope solutions provide safe and effective media for the extraction of natural products and for conducting organic synthetic reactions.
4. Hydrotropes find wide applications in, detergent formulation, health care, and household purposes.
5. They have been used to increase the rate of heterogeneous reactions.
6. They are used as an extraction agent for fragrances.
7. As fillers and extenders in chemical formulations.
8. In the development of pharmaceutical formulations.
9. Hydrotropic solubilization in nanotechnology (by controlled precipitation).
10. Hydrotropy to give fast release of poorly water-soluble drugs from the suppositories.
11. Used in the preparation of drilling well fluids and the separation of water-oil emulsion.
12. It may used in the petroleum industry, in tertiary petroleum recovery as well as in other processes.

13. Hydrotropes modify the viscosity of surfactant formulations and increase the cloud point of detergents.

14. Aqueous hydrotrope solutions provide safe and effective media for the extraction of natural products and for conducting organic synthetic reactions.

15. Viscosity and cloud point (the temperature at which a clear product begins to become hazy upon cooling) of liquid detergents can be controlled by incorporating hydrotrope agents.

16. Hydrotropes improve the stability of the concentrated liquid detergents by enhancing the solubility of the surfactants and by regulating the gelling tendency which liquid detergents can exhibit upon dilution with water.

17. This process may be used to recover the solute in crystalline form at an improved purity, and the remaining mother liquor could be used to concentrate the hydrotrope for recycling.

18. Hydrotropes have been applied in, shampoos, degreasing compounds and printing pastes, as an additive for glues used in the leather industry.

19. The use of hydrotrope, sodium xylene sulfonate in paper pulp manufacturing industry gives excellent results.

Methods to measure the solubility [69]

To determine solubility of solids in liquids following two steps are used

Preparation of saturated solution: Solubility indicates the maximum amount of a substance that can be dissolved in a solvent at a given temperature. Such a solution is called saturated. Solubility is measured either in grams per 100 g of solvent (g/100 g) or number of moles per 1 L of the solution.

Analysis of saturated solution: Once the saturated solution is prepared its analysis is carried out to check the solubility. It depends upon the nature of the solute and accuracy of the method employed.

Following methods are used for analysis.

1). Evaporation method 2). Volumetric method 3). Gravimetric method 4). Instrumental method determination of interference of hydrotropic agents in the spectrophotometric estimation of drugs

A UV-Visible recording spectrophotometer with 1 cm matched silica cells was employed for spectrophotometric determinations. For determination of interference of hydrotropic agents in the spectrophotometric estimation of the standard solutions of drugs were determined in distilled water alone and in the presence of the maximum concentration of the hydrotropic agent employed for spectrophotometric analysis.

The absorbances were recorded against respective reagent blanks at appropriate wavelengths. Titrimetric analysis method employed for determining equilibrium solubility at room temperature. Enhancement ratios in solubilities were determined by following formula - Enhancement ratio = Solubility in hydrotropic solution ÷ Solubility in distilled water Smita Sharma, Mukesh C. Sharma were investigate that hydrotropic solution of 8M urea has been employed as solubilizing agent to solubilization poorly water soluble drug Pseudoephedrine Sulphate, Desloratidine, from fine powder of its tablet dosage form for spectrophotometric determination in ultraviolet region.

Pseudoephedrine Sulphate, Desloratidine shows maximum absorbance at resulting solutions were measured at 274.4 nm and 289.1nm. R. K. Maheshwari, s. R. Bishnoi, d. Kumar, murali Krishna [70], in the present investigation, hydrotropic solution of ibuprofen sodium (0.5M) was employed as solubilizing agent to solubilize the poorly water-soluble drug, ornidazole from fine powder of its tablets for spectrophotometric determination. Ornidazole shows its maximum absorbance at 320 nm and Beer's law was obeyed in concentration range of 5-25 mcg/ml [71].

Mixed hydrotropy

Mixed hydrotropic solubilization technique is the phenomenon to increase the solubility of poorly water-soluble drugs in the blends of hydrotropic agents, which may give miraculous synergistic enhancement effect on solubility of poorly water soluble drugs, utilization of it in the formulation of dosage forms of water insoluble drugs and to reduce concentration of individual hydrotropic agent to minimize the side effects (in place of using a large concentration of one hydrotrope a blend of, say, 5 hydrotropes can be employed in 1/5th concentrations reducing their individual toxicities[27]. Veena Nair, Mithun S Rajput[28] were developed a novel, safe and sensitive method of spectrophotometric estimation in the ultraviolet region using a mixed hydrotropic solution, containing a blend of 30 % w/v urea, 13.6 % w/v sodium acetate and 11.8 % w/v sodium citrate for the quantitative determination of ketoprofen, a poorly water soluble drug, in tablet dosage form. Beer's law was obeyed in the concentration range of 4–20 µg/ml. There was more than 570-fold enhancement in aqueous solubility of ketoprofen in mixed hydrotropic solution as compared with the solubility in distilled water precluding the use of organic solvents. Nilesh Jain, Ruchi Jain, Navneet Thakur, Brahm Prakash Gupta, Jitendra Banweer and Surendra Jain[13] were developed Spectrophotometric method using 2 M sodium acetate and 8 M Urea solution as hydrotropic solubilizing agent for the quantitative determination of poorly water-soluble hydrochlorothiazide in tablet dosage form. There were more than 55 and 70 fold enhancements in the solubility of hydrochlorothiazide increases in 2 M sodium acetate and 8 M Urea solution as compared to solubilities in distilled water. Hydrochlorothiazide shows maximum absorbance at 272 nm. Sodium acetate and urea did not show any absorbance above 240 nm, and thus no interference in the estimation was seen. Hydrochlorothiazide is obeyed Beer's law in the concentration range of 10 to 50 µg/ml ($r^2=0.999$) in sodium acetate and 5 to 25 µg/ml ($r^2=0.999$) in urea with mean recovery 98.74 and 99.99% in sodium acetate and urea respectively [72-74].

Advantages of mixed hydrotropic solubilization

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

Vikas Pareek, Santosh Tambe, Santosh Bhalerao, Rupali Shinde, Lalit Gupta [75] were employed Conventional Spectrophotometric Estimation (Method I) and Area Under Curve Method (Method II) for quantitation of Cefprozil by using five different hydrotropic agents. These include Potassium acetate (6.0M), Potassium citrate (1.5 M), Sodium acetate (4.0 M), Sodium citrate (1.25 M) and Urea (10.0 M). All these agents do not show absorbance above 245 nm and hence do not interfere with absorbance of Cefprozil (λ_{max} 280 nm).

Novel pharmaceutical applications of hydrotropic solubilization in various fields of Pharmacy [76]

1. Quantitative estimations of poorly water soluble drugs by UV-Visible spectrophotometric analysis precluding the use of organic solvents.
2. Quantitative estimations of poorly water soluble drugs by titrimetric analysis such as ibuprofen, flurbiprofen and naproxen using sodium benzoate[29].
3. Preparation of hydrotropic solid dispersions of poorly water-soluble drugs precluding the use of organic solvents. Such as felodipine[30] using poly-ethylene glycol 6000 and poly-vinyl alcohol.

4. Preparation of dry syrups (for reconstitution) of poorly water-soluble drugs.
5. Preparation of topical solutions of poorly water-soluble drugs, precluding the use of organic solvents. Such as tinidazole, metronidazole and salicylic acid using sodium benzoate and sodium citrate.
6. Preparation of injection of poorly water soluble drugs.
7. The use of hydrotropic solubilizers as permeation enhancers.
8. The use of hydrotropy to give fast release of poorly water-soluble drugs from the suppositories.
9. Application of mixed- hydrotropy to develop injection dosage forms of poorly water-soluble drugs.
10. Application of hydrotropic solubilization in nanotechnology (by controlled precipitation).
11. Application of hydrotropic solubilization in extraction of active constituents from crude drugs (in pharmacognosy field).
12. Hydrotropic solutions can also be tried to develop the dissolution fluids to carry out the dissolution studies of dosage forms of poorly water-soluble drugs.

CONCLUSION

By this Study we can conclude that, Solubility is the most important physical characteristic of a drug for its oral bioavailability, formulation, development of different dosage form of different drugs and for quantitative analysis. Solubility can be enhanced by many techniques among them hydrotropy is of very much importance. Hydrotropy is defined as a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute and the chemicals which are used in hydrotropy are called hydrotropes. For example sodium benzoate, urea, sodium salicylate and ibuprofen sodium etc. In present scenario this method is getting lot of values and may be proved the best method in future.

REFERENCES

1. Neuberger C. Hydrotropy. *Biochem. Z.* 1916; 76: 107- 109.
2. Booth H.S, Everson H.E. Hydrotropic solubilities in aqueous sodium o-, m- and p-xylene sulfonate solutions. *Ind. Eng. Chem.* 1950; 42: 1536-1537.
3. Booth H.S, Everson H.E. Hydrotropic solubilities. *Ind. Eng. Chem.* 1949; 41: 2627-2629.
4. Booth H.S, Everson H.E. Hydrotropic solubilities in 40% sodium xylene sulfonate Solutions. *Ind. Eng. Chem.* 1948; 40: 1491-1493.
5. Balasubramanian D, Srinivas V, Gaikar V.G., and Sharma M. M. Aggregation behavior of hydrotropes in aqueous solutions. *Journal Physical Chemistry.* 1989; 93: 3865-3870.
6. Mckee R.H. Use of hydrotrope solutions in Industry. *Ind. Eng. Chem.* 1946; 38: 382.
7. Rodriguez A, Gracini M, Moya M.L. Effects of addition of polar organic solvents on micellization. *Langmuir.* 2008; 24: 12785-2790.
8. Badwan A.A, El-Khordagui L.K, Saleh A.M. The solubility of benzodiazepines in sodium salicylate solutions and a proposed mechanism for hydrotropic solubilisation. *Int. J. Pharm.* 1983; 13: 67- 74.
9. Pandit A, Sharma M.M. Intensification of heterogeneous reactions through hydrotropy. Alkaline hydrolysis of esters and oximation of cyclododecanone. *Chem. Eng. Sci.* 1987; 42: 2519-2523.
10. Chen X, Micheu J.C. Hydrotrope Induced auto catalysis in the biphasic alkaline hydrolysis of aromatic esters. *J. Colloid Interface Sci.* 2002; 249: 172-179.
11. Akhilesh Kumar Jain. Solubilization of indomethacin using hydrotropes for aqueous injection. *European Journal of Pharmaceutics and iopharmaceutics.* 2008; 68 : 701-714.
12. 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. *Indian J. Pharm. Sci.* 2007; 69: 101-105.
13. Dandekar D.V, Gaikar V.G. Hydrotropic extraction of curcuminoids from turmeric. *Sep. Sci. Technol.* 2003; 38(5): 1185-1215.

14. Colonia E.J, Dixit A.B, Tavare N.S. Separation of o- and p-chlorobenzoic acids: hydrotropy and precipitation. *J.Cryst. Growth*.1996; 166: 976-980.
15. Coffman R.E, Kildsig D.O. Hydrotropic solubilization--mechanistic studies. *Pharmaceutical Research*.1996; 13(10): 1460-1463.
16. Dharmesh Varade, Pratap Bahadur. Effect of hydrotropes on the aqueous solution behavior of surfactants. *Journal of Surfactants and Detergents*.2004;7(3): 257-261.
17. Dharmendra Kumar M, Nagendra Gandhi, N. Effect of hydrotropes on solubility and mass transfer coefficient of amyl acetate. *Bio process. Eng*.2000; 23: 31-36.
18. Dharmendra Kumar M, Nagendra Gandhi N. Effect of hydrotropes on solubility and mass transfer coefficient of methyl salicylate. *J.Chem. Eng*. 2000; 45 : 419-423.
19. Deno N.C, Spink C.H. The Mc-Devit long equation for salt effects on non-electrolytes. *J.Phys. Chem*.1963; 67: 1347-1349.
20. Friberg S.E. Hydrotropes. *Surf. Sci. Z*.1997; 2: 490-494.
21. Gaspar Gonzalez, Eduardo J, Nassar, Maria Elizabete D, Zaniquelli. Examination of the Hydrotropic Effect of Sodium p-Toluenesulfonate on a Nonionic Surfactant (C12E6) Solution. *Journal of Colloid and Interface Science*.2000;230(2): 223-228.
22. Iqar Ahmad Khan, Ahmad Jahan Khanam, Mohmad Shafi Sheikh, Kabir-ud-Din. Influence of ionic and nonionic hydrotropes on micellar behavior of a cationic gemini surfactant butanediyl-1,4-bis(dimethyl cetyl ammonium bromide). *Journal of Colloid and Interface Science*. 2011;359(2): 467-473.
23. Jadhav V.K, Dixit B.A, Tavare N.S. Solubilities of m- and P-aminoacetophenones in hydrotrope solutions. *J. Chem. Eng. Data*. 1995; 40: 669-673.
24. Paul O, Raynaud-Lacroze, Narayan S, Tavare. Separation of 2-Naphthol: Hydrotropy and Precipitation. *Ind. Eng. Chem. Res*.1993;32: 685-691.
25. Travis K, Hodgdon, Eric W. Kaler. Hydrotropic solutions. *Current Opinion in Colloid and Interface Science*.2007; 3 : 121-128.
26. Maheshwari R.K, Gupta HM, Singh M, Ramchandani U, Pandey S. A novel application of hydrotropic solubilization in the spectrophotometric analysis of gatifloxacin in solid dosage form. *Asian J Chem*.2008;20 (1): 241-4.
27. Raynaud-Lacroze P.O, Tavare N.S. Separation of 2-naphthol: Hydrotropy and Precipitation, *Ind. Eng.Chem.Res*.1993;32: 685-691.
28. Friberg S.E, Yang Y, Huang T.A. Reversible extraction process of phenyl ethyl alcohol a fragrance. *Ind.Eng.Chem.Res*.1996;35: 2856-2859.
29. Jain P, Goel A, Sharma S, Parmar M. Solubility Enhancement Techniques with Special Emphasis On Hydrotropy. *International Journal of Pharma Professional's Research* July 2010; 1(1): 34-45.
30. Behera AL, Sahoo SK, Patil SV. Enhancement of solubility: a pharmaceutical overview. *Der Pharmacia Lettre*.2010; 2(2): 310-318.
31. Sharma R, Pathodiya G, Mishra PG. A novel application of hydrotropic solubilization indevelopment and validation of spectrophotometric method for simultaneous estimation of paracetamol and diclofenac sodium in solid dosage form *International Journal of Pharma and Bio Sciences* 2010; 1(3): 1-9.
32. Sara Nicoli, Franca Zani, Stefania Bilzi, Ruggero Bettini & Patrizia Santi. Association of nicotinamide with parabens: Effect on solubility, partition and transdermal permeation *European Journal of Pharmaceutics and Biopharmaceutics*.2008; 69(2): 613-621.
33. Deepak V, Dandekar, Jayaprakasha G.K, Bhimanagouda S. Patil. Hydrotropic extraction of bioactive limonin from sour orange (*Citrus aurantium L.*) seeds *Food Chemistry*.2008;109(3): 515-520.
34. Gibson. *Pharmaceutical preformulation and formulation*. 2nd ed. Interpharm Press. 2001: 28-29.
35. Martin A. *Micromeritics in physical pharmacy*. 2nd ed. Phikadelphia PA.1988:273.
36. Goel A, Sharma M, Sharma S, Haffez A, Arora J. Pharmacokinetic data and solubility profile of antihypertensive drugs. *Int J Pharma Prof Res*. 2010;1: 61-77.
37. Goel A, Saini S, Chowdhry V, Haider SA, Singh RK. Pharmacokinetic solubility and dissolution profile of anticancer drugs. *Int J Pharma Prof Res*. 2011; 2(4): 502-539.
38. Goel A, Aggarwal S, Partap S, Saurabh A, Choudhary V. Pharmacokinetic solubility and dissolution profile of antiarrhythmic drugs. *Int J Pharma Prof Res*. 2012;3(1): 592-601.
39. Sanjay P. Mishra ; V. G. Gaikar. Aqueous Hydrotropic Solution as an Efficient Solubilizing Agent for Andrographolide from *Andrographis paniculata* Leaves. *Separation Science and Technology*.2006;41: 1115-1134.
40. Pahala Simamora, Joan M, Alvarez, Samuel H, Yalkowsky . Solubilization of rapamycin Pahala Simamora . *International Journal of Pharmaceutics* .2001; 213: 25-29.
41. Gaikar,V.G. and P.V. Phatak, 1999. Selective solubilization of isomers in hydrotrope solutions: o-/p-chlorobenzoic acids and o-/p-nitroanilines. *Sep . Sci. Technol.*, 34(3): 439-459.
42. Yiyang Lin, Yan Qiao, Xinhao Cheng, Yun Yan, Zhibo Li Jianbin Huang. *Journal of Colloid and Interface Science*.2012; 369 : 238-244.
43. Ankit Mangal, Sandeep Singh Bhadoriya, Sorabh Joshi, Gaurav Agrawal, Amit Gupta, Narendra Mandoria . Extraction Of Herbal Drugs By Using Hydrotropy Solubilization Phenomenon. *Int. Res j pharm. App sci.*, 2012; 2(1):63-74.
44. Friberg E, Brancewicz C. O/W Microemulsions and hydrotropes: The coupling action of a hydrotrope. *Langmuir*. 1994; 10: 2945-2949.
45. Jouyban A, Chew NY, Chan HK, Sabour M, Acree WE Jr. A unified cosolvency model for calculating solute solubility in mixed solvents. *Chem Pharm Bull (Tokyo)*. 2005; 53(6):634-7.
46. Senthilnathan M, Jayakumar C, Nagendra Gandhi N., Effect of Hydrotropes on the solubility and Mass Transfer Coefficient of Methyl Salicylate, *Canadian Journal of Modern Applied Science*, 2009; 3:101-11.
47. Jayakumar C., Nagendra Gandhi N., Hydrotropic study on Furfural-Comprehensive Design Expert Plot, *Modern Applied Science*. 2009; 3:117-130.
48. Jayakumar C, Deepakkumar K, Nesakumar D, Nagendra Gandhi N, Quantitative analysis of Theophylline bulk sample using Sodium salicylate hydrotrope. *Indian J.Pharm.Sci*. 2010; 0975-1491.
49. Shinde A.J. Solubilization of poorly soluble drugs. A Review. *Pharmainfo.net*. 2007; 5: 6.
50. Hydrotropes .*Technical Bulletin: Pilot chemical company*.
51. Tirucherai G S, Mitra A K. Effect of hydroxypropyl beta cyclodextrin complexation on aqueous solubility, stability, and corneal permeation of acyl ester prodrugs of ganciclovir. *AAPS Pharm. Sci. Tech*.4:2003: E45.
52. Strickley R.G. Solubilizing excipients in oral and injectable formulations. *Pharm.Res*.2004;21:201-230.
53. Nema S, Washkuhn RJ, Brendel RJ. Excipients and their use in injectable products. *Pharm.Sci.Technol*.1997;51:166-171.
54. Rubino J T, Yalkowsky S H. Co-solvency and deviations from loglinear solubilization. *Pharm.Res*.1987;4:231-236.
55. Shiv M. Solubility Enhancement: *Need.pharmainfo.net*.2009.
56. Trease and Evanse: *Pharmacognosy*. Rajkamal Electric press Delhi 526 15th edition 2005.
57. Jain P, Goel A, Sharma S, Parmar M. Solubility Enhancement Techniques with Special Emphasis On Hydrotropy. *International Journal of Pharma Professional's Research*. 2010; 1(1): 34-45.
58. Zaheer A, Naveen M, Santosh MK, Imran K, Solubility enhancement of poorly water soluble drugs, *Int J PharmTech* .2011; 3 (1): 807-823.
59. Nidhi K, Indrajeet S, Khushboo M, Gauri K, Sen DJ, Hydrotropy: a promising tool for solubility enhancement, *Int J Drug Dev Res* .2011; 3(2) 26-33.
60. Rong Guo, Qiqing Zhang, Junhong Qian, Aihua Zou. Hydrotrope and hydrotrope -solubilization action of penicillin - K in CTAB/n -C 5H11OH/H2O system. *Physicochemical and Engineering Aspects*. 2002;196: 223-234.
61. Subir Kumar Das, Shrabani Das B. Nandi Ganguly, Amarnath Maitra. Self association of sodium salicylate system. *Chemical Physics*. 2003; 293: 211-216.
62. Shete A S, Yadav AV, Dabke A.P. Sakhare S. S. Formulation and Evaluation of Hydrotropic Solubilization Based Suspensions of

- Griseofulvin. *International Journal of Pharma Sciences and Research (IJPSR)*.2010;1(1):51-57.
63. Marios Hopkins Hatzopoulos, Julian Eastoe, Peter J. Dowding, Isabelle Grillo, Bruno Demé, Sarah E. Rogers, Richard Heenan, and Robert Dyer. Effects of Structure Variation on Solution Properties of Hydrotropes: Phenyl versus Cyclohexyl Chain Tips. *Langmuir*. 2012; 28: 9332–9340.
64. Sharma D, Soni M, Kumar S, Gupta GD. Solubility enhancement—eminent role in poorly soluble drugs. *Research Journal of Pharmacy and Technology*. 2009;2(2):220–224.
65. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. *International Journal of Pharmaceutical Sciences Review and Research*. 2010;5(1):41–51.
66. Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancement techniques for hydrophobic drugs. *Pharmacie Globale*. 2011;3(3):1–7.
67. Jain P, Goel A, Sharma S, Parmar M. Solubility Enhancement Techniques with Special Emphasis on Hydrotrophy. *International Journal of Pharma Professional's Research*. 2010; 1(1): 34-45.
68. Marios Hopkins Hatzopoulos, Julian Eastoe, Peter J. Dowding, Isabelle Grillo, Bruno Demé, Sarah E. Rogers, Richard Heenan, and Robert Dyer . Effects of Structure Variation on Solution Properties of Hydrotropes: Phenyl versus Cyclohexyl Chain Tips. *Langmuir*, 2012; 28 (25): 9332–9340.
69. More HN, Hajare AA. Practical physical pharmacy. Career publication, 2010: 230.
70. Maheshwari RK. Analytical techniques using hydrotropic solubilization [Thesis]. Department of Pharmacy, Shri G.S. Institute of Technology and Science, Indore.2008; 61-62.
71. R. K. Maheshwari, S. R. Bishnoi, D. Kumar, Murali Krishna . Quantitative spectrophotometric determination of ornidazole tablet formulations using ibuprofen sodium as hydrotropic solubilizing agent *Digest Journal of Nanomaterials and Biostructures*.2009; 4(4): 751 – 754.
72. Maheshwari RK, Sharma S, Rai N, Rajput M. Simple titrimetric method to estimate ketoprofen in bulk using mixed hydrotropy. *Journal of Pharmacy Research* 2010; 3(3): 442-443.
73. Jain N, Jain R, Thakur N, Gupta B, Banweer J, Jain S. Novel spectrophotometric quantitative estimation of hydrochlorothiazide in bulk drug and their dosage forms by using hydrotropic agent. *IntJ. Appl. Pharma*. 2010; 2(3): 1114.
74. Sharma R, Pathodiya G, Mishra PG. A novel application of hydrotropic solubilization in development and validation of spectrophotometric method for simultaneous estimation of paracetamol and diclofenac sodium in solid dosage form *International Journal of Pharma and Bio Sciences* 2010; 1(3): 1-9.
75. Santosh Bhalerao, Santosh Tambe, Vikas Pareek, Rup ali Shinde, Lalit Kumar Gupta. A solid-liquid extraction and high performance thin layer chromatographic determination of diacerein and aceclofenac in pharmaceutical tablet dosage form. *Asian journal pharmaceutical and clinical Research*.2010; 3(1): 25-30.
76. Jain P, Goel A, Sharma S, Parmar M. Solubility Enhancement Techniques with Special Emphasis on Hydrotrophy. *International Journal of Pharma Professional's Research* July 2010; 1(1): 34-45.