Research on Application of Hydrotropy: A Review

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Abstract— **Hydrotropy is an increase in solubility of solute in water by adding an agent termed as hydrotrope. Increasing the solubility of various drugs in water is very important aspect of hydrotropy. Various formulations needs some substances or drugs to solubilize in water. Also it is very important to analyze the drug formulations. Hydrotropy can be incorporated with spectrophotometric and chromatographic analysis for accurate, rapid, easy and precise analysis. The present review summerizes the investigations carried out for use of various hydrotropes for various drugs and compounds . Most of the investigations concluded that hydrotropy was most efficient tool for solubility enhancement. Also the trend of increase in solubility with hydrotrope concentration was found common in many investigations. Solubility enhancement in excess of 100 fold was observed in some investigations.**

***Index Terms*—hydrotropes, solubility, enhancement, analysis.**

I. INTRODUCTION

Hydrotropy is the term used for enhancement in solubility of insoluble solute in water by adding the agent called as hydrotrope. Hydrotropes are micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds. The formation of molecular structure in the form of complexes can be reason for the solubility enhancement. Increase of solubility is important factor in determining the therapeutic effectiveness of drug.

The methods used for solubility enhancement includes micronization, nanonization, sonocrystallization, super critical fluid method, evaporative precipitation into aqueous solution, use of surfactant, use of co solvent, hydrotropy method, use of salt forms, solvent deposition, solubilizing agents, modification of the crystal habit, spray freezing into liquid and lyophilization. Investigations show that hydrotropy is very effective technique for increasing solubility. Various methods are developed for analysis of the purity of drugs, which are water insoluble by combining spectrophotometric and chromatographic methods with hydrotrpy. The presents review summarizes these investigations with respect to the hydrotropes used, methods use and the results obtained.

Manuscript received Sep, 2014.

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II. RESEARCH ON APPICATION OF HYDROTROPY

Citric acid, sodium benzoate and urea were used as hydrotropes for investigation on mass transfer coefficients and solubility by Arunodaya et.al [1]. They prepared the samples with wide range of hydrotrope concentrations. They determined minimum hydrotrope concentration (MHC) at which there was significant increase in concentration. They observed that for urea, the MHC remained unaltered with change in temperature. There is a limit beyond which there is no significant change in the solubility. This was termed as maximum hydrotrope concentration (C_{max}).Similar trend was observed by them for all the three hydrotropes. Also they observed that mass transfer coefficient increased with increase in hydrotrope concentration. They concluded that the increase in solubility was effect of the formation of organized aggregates at particular concentration. Pandey and Maheshwari invented new spectrophotometric method for estimation of ketoprofen using hydrotropy [2]. They observed that there was 210 times increase in the solubility because of hydrophilic stabilization phenomenon. They found that the concentrations determined by this method were in agreement with the manufacturer specification. It was concluded that the proposed method was accurate, easy and economical.

A review was carried out on hydrotropy for enhancement of solubilization and bioavailability of poorly soluble drugs Tyagi et.al [3]. Various methods used for enhancement of solubility included nanonization, sonocrystallization, spray freezing into liquid and lyophilization, hydrotropy method, use of salt forms, solvent deposition, solubilizing agents, modification of the crystal habit etc. They concluded that, The there are various methods for alteration of the solubility and hydrotrpy can be used very effectively for the purpose. The use of specific method depends on factors like drug property, site of absorption, and required dosage form and characteristics. Investigation was carried out for determination of dexibuprofen concentration by spectrophotometric method by Vijayaraj et.al [4]. The solubility of dexibuprofen in water was very less. During the selection of additives, they found that urea and sodium benzoate caused sedimentation of drug. Based on the performance of additives, they selected tri sodium citrate for increasing solubility. They observed that the solubility increased with concentration of the additive. They concluded that new technique was fast and accurate. Ali and Choudhary discussed the importance of hydrotropy in solubility enhancement [5].Their study reveals that about 40 percent drugs are water insoluble. It is very important to use easy and applicable method for increasing the solubility of drugs. Their review highlighted the importance of hydrotropy in the pharmaceutical and therauptic applications. The investigation on application of hydrotropy for poorly soluble drugs was

ISSN: 2278 – 7798

done by Kim et.al [6].They carried out studies on solubility characteristics of N, N-diethylnicotinamide (DENA) and N, N-dimethylbenzamide (DMBA) in poorly soluble drugs. The solubility enhancement of 1000 to 10000 times was observed by them during their investigation. They studied the solubility characteristics of five model drugs (probucol, paclitaxel, progesterone, nifedipine, and griseofulvin) in water. The solubilization curves exhibited a sigmoidal profile for two most hydrophobic solutes, probucol and paclitaxel. As the results were encouraging, they tried these hydrotropes successfully for many other solutes like felodipine, fenofibrate, and coenzyme Q10. According to the, self-aggregation properties of the two agents was the reason for self-aggregation properties.

Winsor studied hydrotropy, solubilisation and related emulsification processes[7]. Their emphasis was use of active solvent for hydrophilic and liphophic liquids. In case of former the affinities depend on hydrogen bonding and for later it depends on Vandewaals forces of attraction. An investigation on enhancement of solubilization of Fenofibrate hydrotropic solubilization, mixed hydrotropy and hydrotropic solid dispersions was performed by Badjatya et.al.[8]. They used urea and sodium citrate as hydrotropic agents for the purpose. They also used blends of urea and sodium citrate. For both urea and sodium citrate, there was increase in the solubility enhancement. They used two blends, Blend A(15 % urea with 15% sodium citrate solutions) and Blend B(20% urea and 10% sodium citrate solutions). They observed that the solubility enhancement ratio was found to .be 73.56 times and 233 times in blend A and in blend B respectively. They concluded that the solubility enhanced to a great effect by the synergistic effect of different hydrotropic agents together. Prakash et.al investigated the solubility enhancement and mass transfer studies for benzoic acid[9].They used sodium salicylate, sodium benzoate, and nicotinamide for the purpose. As expected, the solubility and mass transfer coefficients increased with increase in hydrotrope concentration. They observed that the solubility of benzoic acid enhanced to 19.98 times in the presence of 2.5 mol/L concentration of sodium salicylate hydrotrope at 333K. According to the investigation, sodium salicylate was the most effective hydrotrope for benzoic acid. The mixture of hydrotropes(20%N,N-dimethyl urea + 20% sodium citrate) was used for the enhancement of solubility of aceclofenac by Maheshwari et.al[10]. By using this, they achieved 1155 times increase in the solubility. They concluded that mixed hydrotropes are very useful for formation of aqueous solutions of poorly soluble drugs. Mixed hydrotropism was used for spectrophotometric determination by Mehrotra et.al[11]. They observed that there were significant enhancements in aqueous solubility of frusemide in urea, sodium acetate and sodium citrate solutions respectively, compared to its solubility in water. Also, it was observed that the solubility enhancement, in the blend of hydrotropic agents was 15 fold compared to water. The UV method developed was accurate, simple and rapid.

Dhinakaran et.al. carried out investigation in order to study separation of m/p-aminoacetophenone using hydrotropy[12]. They used diethyl nicotinamide,sodium pseudocumene sulfonate and sodium thiocyanate solutions as hydrotropes in their research. They observed percentage separation of m-aminoacetophenone from m/p-aminoacetophenone increased with increase in concentration of hydrotropes. The percentage extraction of m-aminoacetophenone didn't show appreciable increase up to certain hydrotrope concentration. Minimum Hydrotrope Concentration (MHC) was observed to be 0.30 mol/l. They observed similar trend for other hydrotropes. Maximum hydrotrope concentration (Cmax) for sodium thiocyanate hydrotrope was 2.2 mol/l. They concluded that sodium thiosulphate was the best hydrotrope which can be used for enhancement of solubility of poorly soluble m-aminoacetophenone. Mangal et.al. produced thin layer chromatographic method for estimation of poorly water soluble Omeprazole in bulk form[13]. They used solvents such as methanol, chloroform, dimethyl formamide and acetonitrile for thin layer chromatographic analysis. Their study also emphasized the importance of hydrotropic agents in determination of the concentration of the substances which are poorly soluble in water.Thin layer chromatography with hydrotropes was promising analysis method. A review on importance and application of hydrotropy was carried out by Kapadiya et.al[14]. They reported the use of hydrotropes by various investigators for various non soluble solutes. Their study also highlighted the importance of hydrotropic agents in increase in the solubility of various formulations. The analysis methods for saturated solution included evaporation method, volumetric method, gravimetric method, instrumental method. Kumar and Gandhi used hydrotropes such as sodium salicylate, sodium benzoate, nicotinamide and urea under a wide range of hydrotrope concentrations (0 to 3.0) mol/L[15]. They investigated effect of hydrotropes on solubility of acetylsalicylic acid. Usual trend of increase in the solubility with concentration of hydrotropes was observed. Maximum solubilization enhancement factor of acetylsalicylic acid was highest for salicylic acid and least for urea. Also the solubility increased with temperature. At 333 ^{o}K, about 88 fold increase in solubility was observed. Spectrophotometric and chromatographic estimation of cefixime was studied by Pareek et.al.[16]. Their study dealt with conventional spectrophotometric estimation and area under curve method and a chromatographic method for estimation of Cefixime. They used five hydrotropic agents namely ammonium acetate (6M), Potassium acetate (5M),Potassium citrate (0.5 M), Sodium citrate (1.25 M) and Urea (8M). According to them the hydrotropic agents have not interfered the analysis above 245nm. In determining peak area of Cefixime in chromatographic methods , it didn't show any interference.

III. CONCLUSION

The present review summarizes the application of hydrotropy in increasing the solubility of drugs in water. The applicability and effectiveness of drug depends to a considerable extent on solubility in water. Various drugs can be analyzed by combination of conventional analysis methods like spectrophotometer and chromatography with hydrotropes. Most of these methods were proven to be accurate, rapid and precise. The solubility enhancement of 100-200 fold was observed in some cases. In most of the investigations, the solubility increased with concentrations.

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ISSN: 2278 – 7798

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ISSN: 2278 – 7798