CHAPTER 2

LITERATURE REVIEW

2.1 ORIGIN OF HYDROTROPY

Neuberg (1916) was the first to report hydrotropy when he dissolved a variety of organic compounds in the aqueous solution containing hydrotropes. After this, there is hardly any publication in this promising field for three decades. The emphasis on chemical engineering and industrial applications of hydrotropes started with an article by Mckee (1946). Badwan et al (1983) later made significant contributions to hydrotropy.

2.2 SOLUBILIZING EFFECT OF HYDROTROPE SOLUTIONS

The literature available on the effect of hydrotropes on the solubility of solutes is rather limited.

Neuberg (1916) showed a substantial increase in the solubilities of cyclohexanone, cyclohexanol and furfural in the presence of hydrotropes such as urea and sodium toluene sulfonate in aqueous solutions.

Mckee (1946) demonstrated that solubilities of many sparingly soluble compounds like amyl chlorides could be increased 10-100 times using aqueous hydrotrope solutions of sodium xylene sulfonate. They visualized the easy recovery of the dissolved solute and the hydrotrope solutions by dilution with water.
Booth and Everson (1948) have found that increase in concentration of hydrotropes in aqueous solutions can increase the solubility of many sparingly soluble compounds by several fold. They were the first to show that the solubility increase in hydrotrope solution does not occur in a linear fashion with the concentration of the hydrotrope. They determined the solubility of a variety of solutes such as amyl alcohol, benzoic acid, butyl alcohol and chloroform in aqueous 40% sodium xylene sulfonate solutions at 25°C. They observed a pronounced increase in the solubility of solutes in hydrotrope solutions.

In further investigations, Booth and Everson (1949, 1950) observed a substantial increase in the solubility of solutes such as acetophenone, aniline and benzaldehyde in hydrotrope solutions of sodium-benzene sulfonate and sodium-xylene sulfonate. Their objective in this effort was to determine the relative effectiveness of these salt solutions as hydrotrope solvents at two different temperatures of 25°C and 60°C. The results obtained by them indicated that in general, sodium-xylene sulfonate was found to be effective for use even at lower temperatures.

The solubility of benzoic acid at 40°C in hydrotrope solutions as homologous series of derivatives such as sodium benzene sulfonate was determined by Licht and Wiener (1950). They observed a steep increase in the effect of hydrotrope with increase in temperature. Among the various salts used as hydrotropes for benzoic acid as the solute, sodium-p-cymene sulfonate was found to be the most effective. These researchers also compared and analyzed the hydrotropic effects of the various salts solutions on the solubility of benzoic acid.

Poochikian and Cradock (1979) have shown a significant increase in the solubility of ‘water-insoluble’ cytotoxic agent namely chartreusin in the presence of various hydroxybenzoates as hydrotropes. They observed a
significant increase in the solubility of chartreusin in aqueous phase in the case of sodium-tri-hydroxy benzoate as hydrotrope.

Badwan et al (1982) determined the solubility of poorly soluble benzodiazepine derivatives in the presence of sodium salicylate and sodium benzoate as hydrotropes in the aqueous phase. They were the first to point out the requirement of minimum hydrotrope concentration in the aqueous phase to initiate significant solubilization of the solute.

Pandit and Sharma (1987) found that potassium salts of butyl monoglycol sulphate, p-cumylphenol as hydrotropes were able to enhance the solubility of sparingly soluble organic compounds such as phenyl benzoate even by 100 fold. They exploited the solubilization efficiency of hydrotropes to increase the rates of heterogeneous reactions, involving such solutes.

Geetha et al (1991) have separated the isomers o- and p- chloronitrobenzenes (CNB) using the aqueous hydrotropes solution of sodium butyl monoglycol sulphate. o- CNB is highly solubilized as compared to p-CNB and can be precipitated out selectively on dilution with water. They also determined the solubility data for o-/p-CNB in aqueous solutions of sodium butyl monoglycol sulphate.

Pathak and Gaikar (1993) carried out a study on the solubility of chlorobenzoic acids at the temperatures of 303, 313, and 323 K in the presence of hydrotropes such as sodium p-toluene sulfonate and sodium-butyl monoglycol sulphate. They also reported Setschenow constant for these solute-hydrotrope systems. They observed a substantial enhancement in the solubility of o-chlorobenzoic acid. According to their findings, this effect may be due to the lower melting point of o-chlorobenzoic acid.
Raynaud-Lacroze and Tavare (1993) demonstrated the process of selectively precipitating 2-naphthol from a commercial mixture containing 1- and 2- naphthols using hydrotropes such as sodium cumenesulfonate and sodium butyl monoglycol sulfate. They have also determined the solubility data for 1- and 2- naphthols using the same hydrotropes at different system temperatures.

Ammar and Khalil (1995) have shown the enhancement in the aqueous solubility of oxamiquine, a potential drug by employing the hydrotropes such as sodium salts of hydroxyl and amino derivatives of benzoic acid. They also proposed the interactions between oxamiquine molecules being the background of hydrotropic solubilization mechanism.

Jadhav et al (1995) have exploited the solubilization efficiency of hydrotropes such as sodium butyl monoglycol sulphate, sodium cumenesulfonate, sodium xlyenesulfonate, sodium toluenesulfonate and ammonium xlyenesulfonate for the separation of close boiling isomeric and nonisomeric industrial mixtures such as m-/p-aminoacetophenones.

Tavare and Jadhav (1996) have found the solubilities of 6-aminopenicillanic acid (6-APA) and phenoxyacetic acid (PAA) at 25°C by using hydrotropes such as sodium butyl monoglycol sulphate, sodium cumenesulfonate, sodium xlyenesulfonate and potassium-sodium xylene sulfonate. An effective separation of 6-APA was carried out by using sodium butyl monoglycol sulphate as hydrotrope.

Colonia et al (1996) have observed the aqueous solubilities of o-/p-chlorobenzoic acids (o-/p-CBA) for different hydrotrope concentrations of sodium butyl mono-glycol sulphate at 25°C and 45°C. Further they have correlated the process variables for a series of batch experimentations.
Suzuki and Sunada (1998) have determined the hydrotropic solubilization of nifedipine, a poorly water-soluble drug by using the hydrotropes such as nicotinamide and urea. They also examined the mechanism for the hydrotropic solubilization of nifedipine.

Gaikar and Phatak (1999) demonstrated the selective solubilization of o-/p-chlorobenzoic acids and o-/p-nitroanilines in the presence of sodium butyl monoglycol sulphate as the hydrotrope. Hydrotrope concentration, system temperature and solute composition were found to have a significant contribution towards separation efficiency. The solubility of o-isomer in the hydrotrope solution was found more than that of corresponding p-isomer and hence the o-isomer can be selectively solubilized.

Tavare and Jadhav (1999) have proposed a novel technique of crystallizing 6-amino penicillanic acid (Reaction mixture 6-amino penicillanic acid and phenoxyacetic acid) in a typical hydrotrope environment using sodium butyl monoglycol sulphate as a hydrotrope.

Simmora et al (2001) have reported the unprecedented solubility increase of rapamycin, a negligibly water soluble drug by using hydrotropes such as benzyl alcohol, benzyl benzoate and benzoic acid.

Horvath et al (2001) observed the hydrotropic action of sodium xylene sulfonate on the solubility of Lecithin, an emulsifying fat. They also attempted to propose a model for the solubility of Lecithin.

Lee et al (2003) demonstrated that the solubility of paclitaxel, an anticancer drug can be increased several fold using nicotinamide derivative as hydrotrope.
Girija Raman and Gaikar (2003) have found that sparingly soluble boswellic acids can be selectively extracted by using alkyl benzene sulfonate solutions as hydrotrope. They further studied the effect of hydrotrope concentration on the solubility followed by kinetics of solubilization.

Agarwal et al (2004) determined the solubility of practically insoluble drug nimesulide in the presence of hydrotropes such as sodium ascorbate, sodium benzoate and sodium salicylate. They also attributed this solubility increase to molecular interactions of hydrotropes.

Koparkar and Gaikar (2004) have shown a significant increase in the solubility of o-/p-hydroxy acetophenones in the presence of various sodium sulfonates as hydrotropes. These researchers also reported that the solubility enhancement of o-isomer was predominant compared to that of p-isomer.

A comprehensive investigation on the effect of hydrotropes on the solubility and mass transfer coefficient of benzyl benzoate has been undertaken by Meyyappan and Nagendra Gandhi (2005). The solubility and mass transfer studies were carried out using hydrotropes such as tri-sodium citrate, urea, sodium benzoate and sodium salicylate.

Nagendra Gandhi et al carried out a series of hydrotropic study (1998a,b, 2000, 2004, 2009 and 2010). They were the first to exploit the solubilization effect of hydrotropes to increase the mass transfer coefficient of a series of organic esters and petro products.

Evstigneev et al (2006) estimated the effect of Caffeine (CAF) and Nicotinamide (NMD) on the solubility of Vitamin B₂ derivatives (FMN).
Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic, antipyretic and anti-inflammatory activities. It is practically insoluble in water. The effect of various hydrotropes such as urea, nicotinamide, resorcinol, sodium benzoate and sodium p-hydroxy benzoate on the solubility of indomethacin was investigated by Jain (2008). In order to elucidate the probable mechanism of solubilization, various solution properties of hydrotropes such as viscosity, specific gravity, surface tension, refractive index and specific conductance of hydrotropic solutions were studied at 25°C.

Neumann et al (2007) proposed a method based on the aggregate to monomol emission ratio and it was used to determine the minimum hydrotropic concentration (MHC) of aromatic hydrotropes.

Maheshwari et al (2008) conducted an experiment using hydrotropic solubilization phenomenon to enhance the aqueous solubility of a large number of poorly water-soluble drugs. They have employed various organic solvents like methanol, chloroform, dimethyl formamide and ethanol for the solubilization of poorly water-soluble drugs.

Desai and Parikh (2009) investigated the aggregation behavior of sodium salicylate and sodium cumene sulfonate in aqueous solution at different temperature. Specific conductivity and relative viscosity were measured at different temperatures to find minimum hydrotropic concentration. The thermodynamic parameters (free energy, enthalpy and entropy) were also evaluated in the temperature range of 30°C and 35°C.

Concentrated aqueous solutions of a large number of hydrotropic agents viz. sodium benzoate, sodium salicylate, niacinamide, urea, sodium citrate, and sodium acetate have been employed to enhance the aqueous solubilities of poorly water-soluble drugs. This study was conducted by
Maheswari et al. (2010). The method used by them is more rapid and involves direct titration.

The effect of various hydrotropes such as citric acid, urea, sodium benzoate and sodium salicylate on the solubility and mass transfer coefficient of benzene was determined by Marimuthu et al. (2011). They also reported that the solubility and mass transfer coefficient of benzene increases with increase in hydrotrope concentration and also with system temperature.

Jayakumar et al. (2010, 2012a,b) carried out hydrotropic study on poorly water soluble drugs and organic compounds. They have used hydrotrope for quantitative spectrophotometric determination of sparingly soluble drugs. They also reported effect of hydrotropes to increase the mass transfer coefficient of organic compounds.

2.3 EFFECT OF HYDROTROPES ON EXTRACTION AND SEPARATION

A report on possible extractive separations using hydrotrope solutions was published by Gaikar and Sharma (1986).

Gaikar and Sharma (1993) reviewed the field of separations using hydrotrope solutions.

Raman and Gaikar (2002) have exploited the ability of hydrotropes such as alkyl benzene sulfonate and alkyl glycol sulphate for selective extraction of piperine from pipernigrum fruits by cell permeabilisation.

Dandekar and Gaikar (2003) have carried out the extraction of curcuminoid from turmeric using hydrotropic phenomenon. Sodium cumene sulfonate was found to be an effective hydrotrope in this case. By using this
Hydrotropic solubilization of total boswellic acids from Boswellia serrata gum resins has been undertaken with aqueous solutions of alkylbenzene sulfonate hydrotropes by Raman and Gaikar (2003). These researchers reported that the solubility of boswellic acids was increased by two orders of magnitude in the presence of hydrotropes in aqueous solutions.

Aqueous solutions of aromatic hydrotopes were investigated for cell permeabilization and extraction of dioscin from dioscorea rhizomes by Mishra and Gaikar (2004). They also observed that the sodium cumene sulfonate was the most effective hydrotope for the extraction of dioscin and also for its hydrolysis to diosgenin at 353 K.

Jayaprakasha et al (2005) have carried out an extensive research on the chemical constituents on volatile oil, isolation, identification and analytical methods of curcuminoids and biological activities of curcuminoids.

An aqueous solution based extraction process for Andrographolide from Andrographis paniculata leaves has been developed using alkyl benzene sulfonates and carboxylates as hydrotropes by Mishra and Gaikar (2006). Sodium cumene sulfonate (NaCS) shows the most effective solubilization of Andrographolide amongst the hydrotropes studied. Thus they conclude that solubility of andrographolide was increased by two orders of magnitude in Na-CS aqueous solutions and ~96% Andrographolide extraction was achieved in just 20 min.

Latha (2006), proposed an alternate strategy for the extraction of embelin from Embelia ribes. The hydrotropes such as sodium n butyl benzene
sulfonate (NaNBBS), and sodium cumene sulfonate (NaCS) were found to be effective for the selective extraction of embelin with 95% recovery.

Dandekar et al. (2008) investigated hydrotropic extraction of limonoid aglyconed from sour orange seeds. Among the two hydrotropes used, sodium cumene sulfonate was found to give maximum limonin yield. Response Surface Analysis (RSA) of data was performed to study the effect of parameters on extraction efficiency.

Mishra and Gaikar (2009) have exploited the ability of hydrotropes such as alkyl benzene sulfonate and arboxylates for selective extraction of forskolin from coleus forskohlii roots by cell permeabilisation. They concluded that the solubility of forskolin is increased by 350 times in the hydrotrope solutions and it is possible to recover 85% pure forskolin from the hydrotropic solutions by simple dilution with water.

2.4 OTHER EFFECTS OF HYDROTROPE SOLUTIONS

The work of Janakiraman and Sharma (1985) shows that the rates of heterogeneous reactions can be enhanced considerably in the presence of hydrotropes. They studied the effect of various hydrotropic agents on the solid-liquid alkaline hydrolysis of phenyl benzoate, ethyl nitrobenzoate and 2,4 dichlorophenyl benzoate. The hydrotropic action of urea on the solid-liquid oximation of cyclododecanone was also reported.

Dhananjay and Sharma (1994), Vikas G. Sadvikar et al. (1995) obtained significant enhancement in the rates of some heterogeneous reactions due to the consequent solubilization effect of hydrotropes.

Hodgdon and Kaler (2007) studied the aggregation behavior of hydrotropes. They observed the strong synergistic effects when hydrotropes
are added to aqueous surfactants or polymer solutions. The effects of hydrotropes on phase behavior, aggregation, surface tension, viscosity, solubility and microstructure formation are reviewed. They also observed the hydrotropes are a class of amphiphilic molecules which has a special function of increasing the aqueous solubility of organic molecule. But it cannot form a well-organized structure such as micelles in water.

The effect of various hydrotopes such as sodium salicylate, sodium benzoate, and nicotinamide on the separation of close boiling mixture, o-/p-xylene has been undertaken by Ramesh et al (2009). They reported that the percentage extraction of p-xylene from o-/p-xylene mixtures increases with an increase in hydrotrope concentration and also with system temperature.

2.5 COMPARISON WITH OTHER SOLUBILIZATION METHODS

In the light of some similarities in the behavior of hydrotropes and other solubilizers particularly micellar surfactants, this comparison is unavoidable.

Srinivas et al (1997) observed that the behavior of hydrotropes differ from that of micelles in displaying a higher and somewhat more selective ability to solubilize solutes.

Gaikar and Sharma (1993) pointed out that the problem of emulsification normally encountered with micellar solutions is not found with hydrotrope solution.

However, a clear and undisputed distinction between hydrotropy and other solubilization methods was brought to light by Balasubramanian et al (1989). For this purpose, they have compared the increase in the solubility of the solute, perylene, brought about by sodium-p-toluene
sulfonate, a hydrotrope with that of guanidinium thiocyanate, a salting-in agent and in the presence of poly-ethylene glycol, a co solvent or phase mixing agent.

The solubility increase of perylene was seen to be monotonic and gradual in the case of salting in and cosolvency process. In neither case was seen the sigmoidal pattern of solubility increase of perylene observed with sodium-p-toluene sulfonate, a hydrotrope. Based on their experimental findings, they concluded that hydrotropy is a process which goes beyond miscibility or cosolvency or salting-in or any other solubilization methods. They have also shown that the solubilization effected by hydrotrope was higher and more selective compared to other solubilization methods.

The requirement of minimum hydrotrope concentrations in the aqueous phase to show significant increase in the solubilities of solutes was observed by them. However, they demonstrated that the MHC of a hydrotrope is not analogous to the critical micellar concentration required in the case of micellar surfactants.

2.6 ARTIFICIAL NEURAL NETWORK APPROACH FOR SOLUBILITY PREDICTION

Theoretical prediction of the aqueous solubility of organic compounds assumes important for the development of chemical process and drug formulations. There are various empirical modeling approaches to predict the solubility of organic compounds. Among these methods, ANN approach is used as a powerful tool to estimate the solubilities of organic compounds with more accuracy.

Huuskonen et al (1998) developed a method for predicting the aqueous solubility of drug compounds based on topological indices and ANN
modeling. They have used structural parameters such as atom-type
electrotopological indices and other topological indices to predict the
solubility of drug compounds.

Ran et al (2001) used revised General Solubility Equation (GSE)
along with four different methods including Huuskonen’s ANN and three
Multiple Linear Regression (MLR) methods to estimate the aqueous solubility
of pharmaceutically and environmentally interesting compounds. They have
reported that the GSE and ANN predictions are more accurate than MLR
methods. Their study provides evidence for the GSE being a convenient and
reliable method to predict aqueous solubilities of organic compounds.

The application of ANN to calculate the solubility of drugs in water-
cosolvent mixtures was shown by Jouyban et al (2004). The neural network
was optimized and the architecture 6-5-1 was used to predict the solubilities
of drugs. They have compared the results obtained with multiple linear
regression model and reported that the ANN model showed excellent
superiority to the regression model.

Bakhbakhi (2011) developed a back-propagation multi-layer neural
network to predict the solubility of solute in supercritical carbon dioxide with
/ without co-solvent. He further investigated the solubility of anthracene in
CO$_2$ with co-solvents, acetone, ethanol and cyclohexane using ANN model.
The result shows that the ANN model predicts the solubility of solid solute in
ternary systems with more accuracy.

A list of previous works done on the effect of hydrotropes on the
solubility of various solutes is given in Appendix 1(Table A1.1).
2.7 SUMMARY

From section 2.2 and 2.3, it can be seen that a certain amount of work has been carried out on the hydrotropic effect on the solubility and extraction of some organic compounds. However, a comprehensive study on the effect of different hydrotropes on the solubility of a series of solutes like organic acids and alizarin and extraction of mangiferin has not been carried out so far.

It is therefore necessary to study the effect of hydrotropes on solubility, mass transfer coefficient and extraction of organic compounds.

Data on the effect of hydrotrope under a wide range of hydrotrope concentrations is absent. Hydrotropic study at increased system temperatures will be additional information in the selection of a hydrotrope with respect to a particular solute.

Special emphasis needs to be given to the easily available chemical compounds in the selection of hydrotropes.

The literature provides some information on the requirement of certain Minimum Hydrotrope Concentration (MHC) in the aqueous phase to show significant increase in the solubility of solutes. However, this aspect requires extensive experimental investigations for different solute-hydrotrope systems to gather additional information of MHC.

It is beneficial to ascertain the hydrotropic effect on the mass transfer coefficient of acids in order to explore the possibility of using them as a suitable reaction medium/component.