CHAPTER–3

REVIEW OF LITERATURE

Saleh AM et al\textsuperscript{32} described the term hydrotropic agents, which was first introduced by Neuberg (1916) to designate anionic organic salts which at high concentration, considerably increase the aqueous solubility of poorly soluble solutes. El-Khordagui LK\textsuperscript{33} studied some physicochemical properties of hydrotrope-gelled starch. A starch gel has been prepared without heat treatment or chemical modification, using a typical hydrotropic salt (sodium salicylate) as a gelling agent. This gel has the advantage of retaining the marked solubilizing capacity of sodium salicylate. Badwan AA et al\textsuperscript{34} investigated the influence of simple structural modification on the solubility of a series of poorly soluble benzodiazepines in sodium salicylate solution. Results of solubility and spectral studies indicate that an electrostatic force of the donor-acceptor type plays an important role in the solubilization of these compounds by hydrotrophy. The remarkable increase in the solubilizing effect of sodium salicylate was probably associated with aggregate formation. Inclusion of the benzodiazepine molecules in the sodium salicylate aggregates was thought to be the mechanism responsible for the solubilization of these poorly soluble drugs.

Pahala Simamora et al\textsuperscript{35} presented the solubilization of rapamycin, a poorly water soluble investigational immunosuppressive drug by facilitated hydrotropy. The results showed that the incorporation of hydrotropes (either individually or in combination) into the ethanol-propylene glycol solution yields substantially greater
drug solubility than that of the ethanol-propylene glycol solution alone. The use of hydrotrope combination yields higher rapamycin solubility than that of the simple hydrotrope concentration in the solution, the more drug can be solubilized. This technique yielded a dramatic (>1000 fold) increase in the aqueous solubility of rapamycin. Etman MA et al\textsuperscript{36} reported that etodolac (ETO) a non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic, antipyretic and anti-inflammatory activities and is practically insoluble in water. The solubility of ETO in two hydrotropic salts; sodium benzoate and sodium salicylate was investigated. The solubility of ETO by the use of hydrotropic solution (sodium salicylate) showed no effect on ETO solubility, while increase in the concentration of sodium benzoate resulted in an increase in the aqueous solubility of etodolac.

Shivakumar HN et al\textsuperscript{37} investigated hydrotropically gelled maize starch as granulating agent for preparing tablets of diclofenac sodium. Granular and tablet properties were determined and compared with those obtained using conventionally prepared starch paste. Hydrotropically gelled starch exhibited good stability as compare to that of conventionally prepared starch paste. Saida Khalil et al\textsuperscript{38} studied the solubility and stability of diazepam in sodium salicylate solution, it was observed that as the concentration of sodium salicylate increases, the solubility of diazepam (practically insoluble in water) also increases. Thus, the author believed that the mechanism of solubilization by hydrotropic salts may involve change in water structure; diazepam in sodium salicylate was completely stable against photodecomposition.
Shikha Agrawal et al\textsuperscript{39} had carried out the hydrotropic solubilization of nimesulide for parental administration. Nimesulide is a non-steroidal-anti-inflammatory drug that exhibits analgesic, antipyretic and anti-inflammatory activities, which is insoluble in water. The effect of various hydrotropes such as nicotinamide, sodium ascorbate, sodium benzoate, sodium salicylate on the solubility of nimesulide was investigated. The authors observed the solubility enhancement of nimesulide by the hydrotropes in decreasing order: piperazine$>$ sodium ascorbate$>$ sodium salicylate$>$ sodium benzoate$>$ nicotinamide.

Nifedipine, a drug practically insoluble in water has been solubilized employing sodium benzoate and sodium salicylate as hydrotropes. In 30\% w/v sodium benzoate the solubility of nifedipine increased 85 and 75 fold at 25±1°C and at 37±1°C respectively. The corresponding increase in solubility of nifedipine in 30\% w/v sodium salicylate solution was 135 and 107 fold respectively. For studying the mechanism of hydrotropic solubilization of nifedipine, the solution properties of sodium benzoate and sodium salicylate over a concentration range of nifedipine to 30\% w/v were undertaken. The probable mechanism reported involves a complexation type of interaction at a low concentration of hydrotrope, aggregation of the hydrotropic molecules and inclusion of nifedipine in these aggregates at high concentration and structural changes in water caused by hydrotropes\textsuperscript{40}.

Akhilesh Kumar Jain\textsuperscript{41} carried out work on solubilization of indomethacin using hydrotropes for aqueous injection. Indomethacin a non-steroidal anti-inflammatory drug, practically insoluble in water.
The author observed the effect of various hydrotropes such as urea, nicotinamide, sodium benzoate on the solubility of indomethacin, the solubility enhancement of indomethacin by the hydrotropes was in decreasing order as sodium benzoate > nicotinamide > urea. Saleh AM et al.\textsuperscript{42} studied that the solubilizing effect of sodium salicylate is greater than that of sodium benzoate pointing out the important role played by the (-OH) group in the salicylate ion. The author concluded that hydrotrophy was different from unicellular solubilization, the increased solubility of water in cyclohexanol in the presence of hydrotropic salts affects the structure of water in favor of a more hydrophobic mode.

The effect of sodium salts of hydroxy and amino derivatives of benzoic acid on the water-solubility of carbamazepine was investigated by Ammar HO and Omar SM\textsuperscript{43} in 1994. It was found that these hydrotropic agents enhanced the water-solubility of carbamazepine as a function of their concentration. The solubilizing power of these hydrotrops was shown to be highly dependent on their chemical structure. Woolfson AD et al.\textsuperscript{44} investigated the solubilization of temazepam by hydrotropic complexation. Sodium salicylate and nicotinamide were used as hydrotropes, sodium salicylate allowed appreciable solubilization of temazepam. Increased solubilization with temazepam was attributed to an increase in hydrogen bonding between drug and hydrotrope.

Rathore KS et al.\textsuperscript{45} studies showed that the enhancement of the solubility of nimesulide using hydrotropes such as sodium benzoate, sodium O-hydroxy benzoate and sodium p-hydroxy benzoate. The solubility of nimesulide was found to increase up to 93 times at
25±2°C in 2% w/v sodium benzoate solution by increasing the temperature from 25±2°C to 37±2°C, the solubility of drug was increased showing that the solubilization of nimesulide was endothermic. The solubility enhancement power of different hydrotropes is ranked in decreasing order as: sodium benzoate > sodium O-hydroxy benzoate > sodium p-hydroxy benzoate.

The influence of various hydrotropic agents, including urea, niacinamide (nicotinamide), sorbitol and fructose, on the complexation between clotrimazole and beta-cyclodextrin was investigated by constructing phase diagram of clotrimazole and beta-cyclodextrin in phosphate buffer pH 7.1 containing 0.5M of various hydrotropic agents. The water structure disrupters, urea and nicotinamide increased the intrinsic solubility of clotrimazole while the water structure forming agents sorbitol and fructose decrease the solubility. Roy BK and Moulik SP reviewed that the hydrotropes are a special class of compounds that exhibit distinct solution properties. They may self-associate in aqueous medium, comparable to amphiphile self-association or micellization. Hydrotropes are efficient solubilizers and can influence the formation of micelle and micro emulsion. The authors concluded that hydrotropes showed interesting solution properties. Maheshwari RK et al studied on the application of hydrotropic solubilization phenomenon in spectrophotometric analysis of hydrochlorothiazide tablets. Concentrated aqueous solution of various hydrotropic agents like sodium benzoate, sodium salicylate, sodium citrate, sodium acetate, and urea has been observed to enhance aqueous solubilities of a large number of poorly water-soluble drugs. Solubility of
hydrochlorothiazide was determined in distilled water and 10.0 M urea solution at 28±1°C. Solubility of the drug was more than 45 fold in 10.0M urea solution as compared to its solubility in distilled water. This tremendous enhancement in solubility was due to hydrotropy.

Maheshwari RK et al\textsuperscript{49} investigated the solubility studies of diclofenac sodium, a poorly water soluble drug, there was more than six-fold enhancement in aqueous solubility of diclofenac sodium by 8.0M urea solution (as compared to aqueous solubility). The results obtained by the proposed method were very close to the results obtained by the standard method (Indian Pharmacopoeial method) precluding the use of organic solvents. To gain insight into the mechanism of solubilization, the influence of structural variation in a hydrotrope molecule on the solubilization pattern of nalidixic acid was studied. Results indicated that the enhanced solubility of nalidixic acid in the presence of hydrotropes is due to complex formation. Possible mechanism of hydrotropic solubilization at lower hydrotrope concentration are ionic interactions, while at higher concentration the possible mechanism is the inclusion of drug molecules in the stacks formed by self-association of the hydrotrope molecules\textsuperscript{50}.

Rawat S et al\textsuperscript{51} carried out the hydrotropic solubilization of some COX-2 inhibitors like rofecoxib, celecoxib and meloxicam which are practically insoluble in water. The authors studied the effect of various hydrotropes such as nicotinamide, sodium benzoate and sodium salicylate on the solubility of these drugs. The solubility enhancement of these drugs by hydrotropes was observed as nicotinamide > sodium benzoate > sodium salicylate with celecoxib but it was sodium benzoate> sodium salicylate > nicotinamide with
meloxicam. The results indicated that the enhanced solubility of these drugs in the presence of hydrotrpopes in low concentration is due to weak ionic interaction. At higher hydrotrropic concentration, the formation of molecular aggregation seems to be the possible mechanism of solubilization.

Maheshwari RK$^{52}$ had analyzed piroxicam in solid dosage form, spectrophotometrically by use of sodium benzoate solution as solubilizing agent. Solubility of piroxicam was determined in distilled water and 2.0M sodium benzoate at 28±1°C, enhancement in solubility of the drug was more than 15 folds in 2.0M sodium benzoate solution as compared to its solubility in distilled water. Maheshwari RK et al$^{53}$ investigated the use of hydrotrropic solution 2.0M sodium benzoate to solubilize a poorly water-soluble drug, aceclofenac from fine powder of its tablets to carryout titrimetric analysis. The enhancement in the solubility of aceclofenac was more than 1000 fold in 2.0M sodium benzoate solution as compared to its solubility in distilled water.

Maheshwari RK et al$^{54}$ performed the solubility studies, 2M sodium benzoate solution was used as hydrotrropic solubilizing agent for three poorly water-soluble NSAIDs – ibuprofen, flurbiprofen and naproxen. There were more than 80, 110 and 120 fold enhancement in the solubilities of ibuprofen, flurbiprofen and naproxen respectively in 2M sodium benzoate solution as compared to solubilities in distilled water. The technique of hydrotrropic solubilization employed to formulate an aqueous injection of carbamazepine was observed in a 50% w/v solution of sodium salicylate. The amount of carbamazepine
solubilized increased with increasing concentration of sodium salicylate and sodium benzoate separately\textsuperscript{55}.

Maheshwari RK et al\textsuperscript{56} studied the solubility of poorly water soluble drugs like nalidixic acid, norfloxacin, tinidazole and metronidazole. Aqueous solubilities of these selected model drugs were enhanced to a 5, 6, 40 and 98 fold in 2M sodium benzoate solution in case of metronidazole, tinidazole, norfloxacin and nalidixic acid respectively. Similar enhancement in aqueous solubility in 2M niacinamide solution as compared to solubility in distilled water, were more than 10, 7, 5 and 21 folds.

Balaji NJ et al\textsuperscript{57} worked to enhance the solubility of albendazole in water by hydrotropic solubilization and to formulate an aqueous solution of albendazole for oral use. Sodium acetate, sodium benzoate, sodium salicylate and nicotinamide were used as hydrotropes. The solubility enhancement of albendazole by hydrotropes was in decreasing order of nicotinamide > sodium benzoate > sodium acetate > sodium salicylate. Initially increased solubility of albendazole was due to weak ionic interactions between the hydrotropes and albendazole molecules. Multifold increased in solubility at higher concentration of hydrotropes was due to molecular aggregation.

Maheshwari RK\textsuperscript{58} employed hydrotropic solution of urea (8 M) as solubilizing agent to solubilize poorly water-soluble drug, norfloxacin from fine powder of its tablets dosage forms for spectrophotometric determination. The solubility of norfloxacin in 8M urea solution was found to be more than 10-fold as compared to
its solubility in distilled water. Thus, the author concluded that enhancement in solubility of norfloxacin in 8M urea solution was due to hydrotropic solubilization phenomenon only. Maheshwari et al developed spectrophotometric estimation method, using hydrotropic solution of 2.0M sodium benzoate as the solubilizing agent for quick and complete solubilization of ofloxacin (a poorly water-soluble model drug) based on hydrotropic solubilization phenomenon. There was more than five-fold increase in solubility of ofloxacin in 2.0M sodium benzoate solution.

To improve the solubility of ketoprofen and investigate the mechanism of solubilization of hydrotropes, solubility, spectral, typical properties of hydrotropes, solution properties, gel formation, paste formation, temperature, TLC and IR spectral studies of various structural hydrotropes of ketoprofen were investigated. It was found that ketoprofen solubility was enhanced in the presence of hydrotropes in low concentration. Maheshwari RK carried out the work to enhance the aqueous solubilities of a large number of poorly water soluble drug (frusemide) by employing 2.0M sodium benzoate solution (a hydrotropic agent) to conduct its titration with sodium hydroxide solution. The pH of 2M sodium benzoate solution was found to be 8.2, buffer of pH 8.2 was made and the solubility of frusemide was determined in it. The solubility of frusemide in buffer of pH 8.2 and distilled water were nearly same. There was more than 90 fold enhancement in solubility of frusemide in 2M sodium benzoate as compared to solubility in distilled water. From this study, it was evident that the enhancement in solubility was due to hydrotropic phenomenon.
Maheshwari RK and Tewari A\textsuperscript{62} developed a spectrophotometric absorption method to estimate a poorly water soluble drugs, hydrochlorothiazide and indomethacin, in solid dosage forms with the use of aqueous solution of hydrotrropic agent, sodium benzoate, as solubilizing agent. The results of solubility studies indicated that enhancement in aqueous solubilities in 2M sodium benzoate solution as compared to solubility in distilled water were more than 39 fold in case of hydrochlorothiazide and 19 fold in case of indomethacin. This study proves that increase in solubilities of these drugs in hydrotrropic solution are not due to alteration in pH but are due to hydrotrropic solubilization phenomenon.

Maheshwari RK\textsuperscript{63} reported that the concentrated solution of urea (a hydrotrropic agent) was employed to enhance the aqueous solubility of paracetamol, a poorly water-soluble drug; this hydrotrropic phenomenon was employed to prepare solid dispersion and syrup of paracetamol. Solubilities of paracetamol in distilled water and 50\% w/v urea solution were found to be 1.23 g/100 ml and 6.32 g/100 ml at 27±1\(^\circ\)C respectively. There was about 5-fold enhancement in aqueous solubility of drug in urea solution. Saleh AM et al\textsuperscript{64} in 1986 investigated the effect of hydrotrropic salts on the solubility of water in 1-butanol and 1-hexanol. The hydrotrropic salts, sodium benzoate, sodium salicylate and sodium gentisate are shown to be the water solubilizers in 1-butanol, sodium salicylate showed the maximum solubilizing power. The effect of sodium benzoate, sodium salicylate and sodium lauryl sulfate on the solubility of water in 1-hexanol was also investigated, similar results were obtained.
Derle DV et al\textsuperscript{65} formulated microemulsion based gel for topical delivery of water insoluble antifungal agent ketoconazole with an aim to increase its penetration through skin and thereby its flux. The microemulsion based gels were evaluated for rheological behavior, in vitro permeation studies. The in vitro antifungal activity of ketoconazole was found to be significant with microemulsion based gel. Nayak SH et al\textsuperscript{66} developed and evaluated cosmetical hair styling gels of ketoconazole. Cosmetical antidandruff hair styling gel formulation containing 0.5 to 1.5\% ketoconazole were developed using carbopol 940, PEG 400, ethanol and water. All the formulation was characterized for viscosity, rheology, spreadability, pH, texture, drug content and antimicrobial activity. Formulation containing 1\% ketoconazole could be used as an effective antidandruff hair styling gel.

Ketoconazole is an imidazole antifungal which interferes with ergosterol synthesis and alters the permeability of the cell membrane of sensitive fungi. Ketoconazole available in the dose of 200 mg single dose. Ketoconazole incompletely absorbed after oral administration and extensively metabolized to inactive metabolized. About 13\% of a dose is excreted in the urine and 57\% is eliminated in the faeces\textsuperscript{67}.

Pranjothy KLK\textsuperscript{68} reviewed that the active ingredients in gel based formulation were better percutaneously absorbed than cream or ointments base. Lei Wang, Xing Tang\textsuperscript{69} prepared a bioadhesive effervescent vaginal tablet formulation of ketoconazole against candida albicans. The in vivo studies indicated that the profile of ketoconazole retained in vagina followed a one-order pattern. Magdy
C. Mohammed have studied optimization of chlorphenesin emulgel formulation and evaluated emulgel for various parameters like rheological study, in vitro release study, antifungal activity and stability studies.

Sanghavi NM, Mahalaxmi D determined in vitro release of clobetasol propionate from topical bases like gels, creams and ointment using cellophane membrane and hairless mouse skin. The drug followed diffusion controlled release kinetics. By using the cellophane membrane, drug diffusion was fastest from the gel, slower from the cream and ointment bases. The gel formulation had given maximum release of drug using hairless mouse skin. It was concluded that the in vitro release of clobetasol from topical bases was fastest from a gel formulation.

Sanghavi NM and Puri RD determined the effect of absorption promoters on the transdermal delivery of ibuprofen from topical bases like gels, ointment and creams using albino rat skin. Canadian formulary cream with 5% urea showed optimum diffusion.

Chowdary KPR and Appan Kumar studied release and antimicrobial activity of ciprofloxacin from topical drug delivery systems. Gels were prepared with anhydrous, cream, water soluble and gel bases with drug and evaluated for drug release, antimicrobial and antifungal activity. Uma Devi S et al carried out the work on tetracycline gels and evaluated for pH, consistency, drug content, drug release, extrudability and skin irritancy. Loganathan V et al studied effects of polymers and permeation enhancers on released of flurbiprofen from gel formulation. The formulated gels were
evaluated for drug content, pH, viscosity and in vitro release through the sigma dialysis membrane.

Panigrahi LK et al\textsuperscript{76} reported formulation and evaluation of lincomycin hydrochloride gels. Gels were prepared using different gel forming agent. The formulation were evaluated for drug content, viscosity, pH, extrudability, homogeneity, skin irritation test, spreadability and gel strength.

Sanjay et al\textsuperscript{77,78} developed and evaluated a fluconazole gel. The formulated gels of antifungal drug fluconazole were evaluated for various physicochemical parameters like pH, viscosity, rheology, drug content, spreadability, skin irritation test and antifungal activity.

Venkatesan S and Ravi V\textsuperscript{79} investigated the \textit{in vitro} antifungal activity of eclipta alba against Candida albicans by using cup-plate method. Manvi FV et al\textsuperscript{80} investigated the effect of permeation enhancers like dimethyl sulfoxide and propylene glycol at different concentrations from the \textit{in vitro} diffusion study and concluded that there was increase in permeation rate with increase in permeation enhancer concentration. Panigrahi L et al\textsuperscript{81} formulated lincomycin hydrochloride gel by using dimethyl sulfoxide as permeation enhancer and evaluated for drug content, viscosity, pH, extrudability, homogeneity, skin irritation test, spreadability and gel strength.

Sankar SV et al\textsuperscript{82} has formulated and evaluated stability of diclofenac sodium ophthalmic gels. The gels were formulated and assessed for various parameters. Around 96\% of drug was released from the HPMC formulation within 9 hours and HPMC gels were more stable at the ambient, refrigerator and incubator temperature. Suppasrivasuseth J et al\textsuperscript{83} has studied permeability and retention.
studies of Epicatechin gel-formulation in human cadaver skin and concluded that ulcerz 10 promoter penetration and retention in upper layer of human cadaver viable skin of up to 3% of dose in 48 hours. Satyanarayanana M, Bert O and Lars-Olof\textsuperscript{84} studied on diffusion and concentration profiles of drugs like acetaminophen, ibuprofen, indomethacin, theophylline and chlorpheniramine in gels. Y Ozsoy, Gungor S, Cevher E\textsuperscript{85} studied the effect on \textit{in vitro} release of tiaprofenic acid from different topical formulation and concluded that carbopol 940-gel base was a good candidate for topical delivery of tiaprofenic acid.