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Review Article

SOLUBILITY ENHANCEMENT TECHNIQUES WITH SPECIAL EMPHASIS ON HYDROTROPHY

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Abstract

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. 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 increasing efficiency and/or reducing side effects for certain drugs. This is true for parenterally, topically and orally administered solutions. Hydrotropy is one of the solubility enhancement techniques which enhance solubility to many folds with use of hydrotropes like sodium benzoate, sodium citrate, urea, niacinamide etc. and have many advantages like, it does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system etc.

Keywords: Solubility,Solubility enhancement techniques,Hydrotropy,Hydrotropes.

Introduction

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction.

Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. The drug solubility in saturated solution in a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate [1].

The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to 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 (table1.1).

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Table 1.1 Expression for approximate solubility[2]

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

Need Of Solubility

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. Currently only 8% of new drug candidates have both high solubility and permeability [3].

As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. It was reported a couple of decades ago that more than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility, while it was still indicated recently that about 50% failure of drug candidates was due to poor "drug-like" properties. It is commonly recognized in the pharmaceutical industry that on average more than 40% of newly discovered drug candidates are poorly water-soluble. Poor "drug like" properties of lead compounds led to ineffective absorption from the site of administration, which has been designated as an important part of the high clinical failure due to poor pharmacokinetics [4].

The basic aim of the further formulation & development section is to make that drug available at proper site of action within optimum dose.

As Solubility & permeability is the deciding factor for the in-vivo absorption of the drug, these can be altered or modified by enhancement techniques like [5]:

Techniques For Solubility Enhancement

1.Micronization :

The process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of attrition methods (fluid energy or jet mill).The process is also called micro-milling.

Vogt M. et al. [6], compared several techniques for improving the dissolution of fenofibrate, a poorly soluble drug and particle size reduction was realized by jet milling (micronization; cogrinding with lactose, polyvinylpyrrolidone or sodium lauryl sulphate) and by media milling using a bead mill (nanosizing) with subsequent spray-drying. Micronization of fenofibrate enhanced its dissolution rate in biorelevant media (8.2% in 30min) compared to crude material (1.3% in 30min). Coground mixtures of the drug increased the dissolution rate further (up to 20% in 30min). Supersaturated solutions were generated by nanosizing combined with spray-drying, this process converted fenofibrate to the amorphous state. Fenofibrate drug products commercially available on the German and French markets dissolved similarly to crude or micronized fenofibrate, but significantly slower than the coground or spray-dried fenofibrate mixtures. The results suggest that cogrinding and spray-drying are powerful techniques for the preparation of rapidly dissolving formulations of fenofibrate, and could potentially lead to improvements in the bioavailability of oral fenofibrate products.

Tamer B. et al. [7], prepared and evaluated an enteric coated dosage form of nicardipine hydrochloride (NCH)-loaded microspheres for delivery over a 12-hr period. Microspheres containing Eudragit RS and L with different ratios were prepared by solvent evaporation method. The change in the diameters of microspheres with time in simulated intestinal fluid (pH 7.5) at 37°C has been studied. Release of NCH from microspheres increased with Eudragit L amount, but no controlled-release pattern was observed. Q values ≥18.88 caused a slow initial release followed by an accelerated release. Microspheres with an Eudragit RS-L ratio of 1:5.7, Q value of 38.71, and drug release rate of 0.155% min^{-1} exhibited a remarkable delayed time for erosion to begin (120 min). Thus, microspheres prepared from this formulation may provide an effective enteric dosage form, releasing NCH at a predetermined rate.

2.Nanonisation :

It's a process whereby the drug powder is converted to nanocrystals of size 200-600nm, e.g. amphotericin B. The main production technologies currently in use to produce drug nanocrystals yield as a product a dispersion of drug nanocrystals in a liquid , typically water (called nanosuspension). There are three basic technologies currently in use to prepare nanoparticles:

i. Pearl milling
ii. Homogenisation in water (wet milling as in a colloid mill)
iii. Homogenization in non aqueous media or in water with water-miscible liquids.

Zhang Z.B. et al.[8], prepared megestrol acetate (MA) nanoparticles via a liquid precipitation technique. The as-prepared MA particles had a mean size of 208 nm, and 90% of the particles were distributed in the range of 100−300 nm, whereas the raw MA had a mean particle size of about 3.02 μm, ranging widely from 0.2 μm to 30 μm. The freeze-dried MA nanoparticles exhibited improved wettability as demonstrated by the contact angle measurement result proving that particles were covered by a hydrophilic layer. In dissolution rate tests, the nanoparticles achieved 100% drug dissolution within 5 min, while the raw MA did not dissolve completely after 120 min, suggesting that the dissolution property of MA nanoparticles was significantly enhanced.

3.Supercritical Fluid Recrystallization :

Supercritical fluids (e.g. corbon dioxide) are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure(tp), allowing it to assume the properties of both o liquid and a gas. At near-critical temperatures , SCFs are highly compressible , allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power . Once the drug are solubilised within SCF , they may be recrystallization at greatly reduced particle sizes.

4.Spray freezing into liquid and lyophilization :

This technique involves atomizing an aqueous, organic, aqueous-organic cosolvent solution, aqueous organic emulsion

or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. co2, helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon or hydrofluroethers). The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders use of acetonitrile as the solvent increases drug loading and decreases the drying time for lyophilization. The dissolution rate is remarkably enhanced from the SFL powder containing amorphous nanostructured aggregates with surface area and excellent wettability.

Wang et al.[9] reported the challenges associated with lyophilization of solid protein pharmaceuticals. He identified and discussed many critical issues like drying, stresses, instability and stabilization of the lyophilized formulation.

Betageri et al.[10], Topalogh et al.[11], Badry et al.[12] and Fathy et al.[13] have successfully investigated the potential applications of lyophilization in manufacturing of SD(s). Drooge et al[14] suggested spray freeze-drying as a potential alternative to the above-mentioned process to produces 9-tetrahydrocannabino containing inulinbased solid dispersions with improved incorporation of - tetrahydrocannabino in inulin.

5.Evaporative precipitation into aqueous solution :

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophiic drugs. The drug is first dissolved in a low boiling point organic solvent. The solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution on the aqueous solution to optimize particle formation and stabilization.

6.Use of surfactants :

Surfactants are very useful as absorption enhancers and enhance both dissolution rate as well as permeability of drug. They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles. Seedhar N. et al[15], studied solubility enhancement of antimicrobial drug enrofloxacin using a series of co-solvents and surfactants. Aqueous solubility of enrofloxacin could be increased up to 26 times. Co-solvents alone produced only small increase in solubility. However, the combined effect of co-solvents and buffer was synergistic and a large increase in solubility could be attained. Ionic surfactants were found to be much better solubilizing agents than non-ionic surfactant. Amongst ionic surfactants, solubility was found to be very high in anionic surfactant, sodium dodecylsulphate as compared to the cationic surfactant, cetyltrimethylammonium bromide. Up to 3.8 mg/ml of enrofloxacin could be dissolved in sodium dodecylsulphate.

7.Use of salt forms :

Salts have improved solubility and dissolution characteristics in comparison to the original drug. It is generally accepted that a minimum difference of 3 units between the pKa value f the group and that of its counterion is required to form stable salts. Alkali metal salts of acidic drugs like pencillins and strong acid salts of basic drugs like atropine are water-soluble than the parent drug.

8.Use of precipitation inhibitors :

A significant increase in free drug concentration above equilibrium solubility results in supersaturation, which can lead to drug precipitation or crystallization. This can be prevented by use of inert polymers such HPMC,PVP,PVA,PEG etc.

9.Alteration of pH of the drug microenvironment:

This can be achieved in two ways- in situ salt formation, and addition of buffers to the formulation e.g buffered aspirin tablets.

10.Use of amorphs,anhydrates,solvates and metastable polymorphs:

Depending upon the internal structure of the solid drug, selection of proper form of drug with greater solubility is important. in general, amorphs are more soluble than metastable polymorhs, anhydrates are more soluble than hydrates and solvates are more soluble than non-solvates.

Rajebahadur M. et al[16], studied the mechanism responsible for solubility enhancement of Nifedipine solid dispesion, prepared using Vitamin E TPGS or Solutol HS-15, PEG_{1000}, and lipocol C-10 of varying drug/polymer ratios by a fusion method. The solubility enhancement was found to be in the order of vitamin E TPGS > solutol HS-15 > lipocol C-10 > PEG_{1000}. Based on these results,it can be concluded that enhanced solubility using vitamin E TPGS and solutol HS-15 resulted from a partial conversion of crystalline drug to the amorphous form, increase in wettability of the drug by water soluble polymers, better separation of drug particles, micellar solubilization of drug by high concentrations of surfactant polymers, and interaction between polymer and drug at the molecular level.

11.Solvent Deposition:

In this method,the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose by evaporation of solvent.

12.Precipitation:

In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nano size particles. The product so prepared is also called as hydrosol.

13. Selective Adsorption on Insoluble Carriers:

A highly active adsorbent such as the inorganic clays like bentonite can enhance the dissolution rate of poorly water soluble drugs such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient at its maximum. The two reasons suggested for the rapid release of drugs from the surface of clays are- the weak physical bonding between the adsorbate, and hydration and swelling of the clay in the aqueous media.

Karavas E. et al[17], studied the use of three modified celluloses, carboxymethyl cellulose sodium, hydroxyethyl cellulose (HEC), and hydroxypropylmethyl cellulose (HPMC) as carriers in felodipine solid dispersion systems. This study was concerned with solid dispersions, which were prepared following the dissolution method using a common solvent. The drug-polymer interactions were studied using DSC and IR techniques, as well as HPLC purity after storage in strength conditions. Neither significant interactions nor degradation of the active ingredient was observed after storage at 40 Â°C for 3 months. In addition, felodipine release from the solid dispersion systems was studied and the factors influencing release, such as the drug-polymer ratio, interactions, and polymer properties were investigated. HPMC was observed to promote a more significant retard and a more linear release of the active ingredient than HEC.

14. Solid Solution:

The three means by which the particle size of a drug can be reduced to submicron level are- Use of solid solution, Use of eutectic mixture, use of solid dispersion. A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the two compartments crystallize together in a homogenous one phase system, solid solutions are also called as molecular dispersion or mixed crystals. Because of reduction in particle size to the molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersion. They are generally prepared by fusion method whereby physical mixture of solute and solvent are melted together followed by rapid solidification. Such systems, prepared by fusion are called as melts.

15. Eutectic Mixtures:

These systems are also prepared by fusion method. Eutectic melts differ from solid solutions in that the fused melt of solute –solvent show complete miscibility but negligible solid-solid solubility, i.e. , such systems are basically intimately blended physical mixture of two crystalline components.

16. Solid Dispersions:

These are generally prepared by solvent or co-precipitation method whereby both the guest solute and the solid carrier solvent are dissolved in a common volatile liquid solvent such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which results in amorphous precipitation of guest in a crystalline carrier. Thus, the basic difference between solid dispersion and solid solution/eutectics is that the drug is precipitated out in an amorphous form in the former as opposed to crystalline form in the latter: e.g. amorphous sulphathiazole in crystalline urea. Such dispersions are often called as **co-evaporates** or **co-precipitaes** . The method is suitable for thermolabile substances but has a number of disadvantages like high cost of processing, use of large quantities of solvent, difficulty in complete removal of solvent.

Shukla M. et al.[18], prepared the solid dispersion and reported the solubility enhancement of Glipizide by different solubilization techniques. Solid dispersion was prepared by solvent evaporation method; PEG 4000, mannitol and urea were used as carriers. Hydrotropic studies were carried out using different hydrotropic agents (sodium acetate, sodium benzoate and salicylate) and Micellar solubilization was carried out using different surfactant solutions (sodium lauryl sulphate, tween 80 and cetrimide). The solubility enhancement of glipizide by different solubilization technique was observed in decreasing order as:

Hydrotropic solubilization > Solid dispersion > Micellar solubilization.

Arias et al.[19] increased the dissolution rate of oxazepam by preparing solid dispersion with hydrophilic carriers (PEG 6000 and D-mannitol) by the o-fusion or the fusion carrier methods, were evaluated by DSC and HSM.

Varma et al.[20], observed the influence of urea and xylitol on the dissolution rate of flurbiprofen. Solid dispersion of flurbiprofen in urea and xylitol were prepared by fusion method and evaluated for dissolution rate in buffer (pH 1.2) and distilled water. Solid dispersions gave fast and rapid rate of dissolution of drug as compared with that of pure drug.

Mooter et al.[21], illustrated the mechanism of increased dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersions and concluded that mechanism involved was solubilization.

Madhusudhan et al.[22], enhanced the solubility of several poorly water-soluble drugs. Solid dispersions of various compositions were prepared using mannitol as carrier. An improvement in the solubility and dissolution rates of sulphamethaxazole from solid dispersions was observed.

Wong et al.[23] compared the SD(s) of felodipine prepared by conventional solvent evaporation (CSE) and supercritical antisolvent precipitation (SAS) methods. The particle sizes of the SD(s) from CSE process increased at 1h after dispersed in distilled water. However the particle sizes of the SD(s) from SAS process were maintained for 6 h due to the increased solubility of felodipine. Moreover, SD(s) form the SAS process showed a high dissolution rate of over 90% within 2 h showing the potential applications of SCE technology in preparation of SD(s).

17. Molecular Encapsulation with Cyclodextrins:

The beta- and gamma- cyclodextrins and several of their derivatives are unique in having the ability to form molecular inclusion complexes with hydrophobic drugs having poor aqueous solubility. These bucket shaped oligosaccharides produced from starch are versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophilic drug as guests; the outside of the host molecule is relatively hydrophilic. Thus the molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate. There are several examples of drugs with improved bioavailability due to such phenomenon- thiazide diuretics, barbiturates and a number of NSAIDs.

Rao et al.[24], improved the dissolution rate of naproxen using carriers such as PVP 4000, PEG6000, PEG 20000, methyl cellulose and β cyclodextrin with a view to develop fast release formulation of naproxen.

Acarturk F. et al.[25], studied the effect of some natural polymers on the solubility and dissolution characteristics of nifedipine. Comparison of such polymers was carried out by complexation with β-cyclodextrin. The interaction of nifedipine with these polymers both in aqueous solution and in the solid state was examined by performing solubility analysis, powder X-ray diffractometry and DSC measurements. Solid mixtures of nifedipine and polymer in various ratios were prepared by the kneading technique and their dissolution was carried out. It was found that water-soluble gelatin and β-cyclodextrin resulted in a significant increase in the rate of dissolution of nifedipine as compared to drug alone.

18. Use Of Cosolvent

Cosolvents system can increase the water solubility of a drug significantly. But the choices of biocompatible solvents are limited, such as to glycerine, propylene glycol, dimethylsulfoxide, ethanol and N, N dimethylformamide etc.

Etman et al.[26] studied solubility of etodolac in four different co-solvents; ethanol, propylene glycol, polyethelene glycol 400, and glycerol, three sugars sucrose, sorbitol and mannitol, two hydrotropic salts; sodium benzoate, sodium salicylate, and two enhancers; Tween 80, Brij 58. Based on the solubility data, a trial has been done to propose a formulation (100 mg/3ml) for parenteral use in an aqueous solvent blend and formulation was tested physically for color, turbidity, and precipitation.

19. Complexation

The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylene glycol, N methylglucamide. cyclodextrin are unique since they increase the water solubility of poorly soluble drugs by fitting them into the hydrophobic cavity of the cyclodextrin molecule.

Saha et al.[27], enhanced the solubility and dissolution rate of nimesulide and ibuprofen by solid dispersion techniques and complexation using various hydrophilic excipients. Solid dispersion of nimesulide with PEG-6000 enhanced the solubility of nimesulide by more than 1000%. Dispersion of ibuprofen in sorbitol showed maximum enhancement of solubility (upto 75%). Dispersion in combined carriers: PVP K-30-MCC and PVP K-30-PEG-6000 also markedly increased the solubility of ibuprofen. Inclusion complexes of nimesulide in β cyclodextrin also increased the solubility by 66.3%.

Raghavan K.S.S. et al[28], enhanced the aqueous solubility of DMP 840 by complexation with water-soluble and nontoxic agents, and to understand the nature of the interactions involved in complex formation using nuclear magnetic resonance (^{1}H-NMR). The solubility of DMP 840 in water, saline, acetate buffers, and cosolvent mixtures was determined by high-performance liquid chromatography, and the effect of nicotinamide and pyridoxine concentrations on the solubility of DMP 840 was examined by the phase solubility method. The aqueous solubility of DMP 840 was sensitive to the presence of chloride and acetate anions in solution, and did not improve in the presence of cosolvents. The solubilization appears to be due to formation of 1:1 complexes between DMP 840 and the bioorganic ligands. The NMR results indicate that the interaction is a result of vertical or plane-to-plane stacking and the complexation constants were in agreement with that obtained by phase solubility. The results suggest that the aqueous solubility of a poorly water soluble drug substance such as DMP 840 can be significantly enhanced by its complexation with water-soluble and nontoxic agents.

20. Hydrotropy

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs.[29]

Rasool A.A. et al.[30], enhanced the solubility of five poorly water-soluble drugs, diazepam, griseofulvin, progesterone, 17 β-estradiol, and testosterone, in the presence of nicotinamide and related compounds. All solubilities were found to increase in a nonlinear fashion as a function of nicotinamide concentration. Two aliphatic analogues of nicotinamide (nipecotamide and *N*,*N*-dimethylacetamide) were studied as ligands with diazepam and griseofulvin and were found to increase the solubilities of both drugs in a linear fashion. The aromatic analogue, *N*,*N*-diethylnicotinamide, showed a nonlinear solubilization relationship. These ligands were not soluble enough in water to be studied over the wide range of concentrations used for nicotinamide and *N*,*N*-diethylnicotinamide; however, in the concentration range studied, these ligands solubilized diazepam and griseofulvin to a degree similar to that observed with comparable concentrations of nicotinamide. These results suggest that the aromaticity (Pi-system) of the pyridine ring is an important

factor in complexation because the aromatic amide ligands were found to enhance the aqueous solubilities of the test drugs to a greater extent than the aliphatic amide ligands.

Advantages Of Hydrotropic Solubilization Technique

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.

History Of Hydrotropy And Basic Structure Of Hydrotrope

Hydrotropy is the term originally put forward by Neuberg[31] to describe the increase in the solubility of a solute by the addition of fairly high concentrations of alkali metal salts of various organic acids. However, the term has been used in the literature to designate non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds. Hydrotropic solubilization process involves cooperative intermolecular interaction with several balancing molecular forces, rather than either a specific complexation event or a process dominated by a medium effect, such as cosolvency or salting-in.

The chemical structure of the conventional Neuberg's hydrotropic salts (proto-type, sodium benzoate) consists generally of two essential parts, an anionic group and a hydrophobic aromatic ring or ring system. The anionic group is obviously involved in bringing about high aqueous solubility, which is a prerequisite for a hydrotropic substance. The type of anion or metal ion appeared to have a minor effect on the phenomenon[31].

Gaikar et al.[32], investigated whether a drug with an amphiphillic structure can exhibit hydrotropic properties. They sought to establish sodium ibuprofen as an effective hydrotrope.

On the other hand, planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization[33,34]. This should imply that hydrotropic agents are molecules having a planar hydrophobic structure brought into solution by a polar group. Hence, it seems rational to propose that molecules with a planar hydrophobic part and a polar group, which is not necessarily anionic, can act as hydrotropic agents. Saleh and El-Khordagui [35]suggested that the phenomenon of hydrotropy is not confined to the metal salts of organic acids, certain cationic salts and neutral molecules may be equally involved. They used procaineHCl, PABAHCl and cinchocaineHCl as cationic salts and resorcinol and pyrogallol as neutral molecules in their studies.

Rasool et al.[36], showed that the aromaticity (Л-system) of the pyridine ring which might promote the stacking of molecules through its planarity was an important factor in complexation because the aromatic amide ligands enhanced the aqueous solubility of the test drug to a greater extent than the aliphatic amide ligands.

Suzuki et al.[37], measured the aqueous solubility of nifedipine in presence of nicotinamide, urea, and their analogues and concluded that the significant contributor to the hydrotropic solubilization of nifedipine with nicotinamide was therefore the ligand hydrophobicity rather than the aromaticity of the pyridine ring.

As early as in 1916, Neuberg reported that the aqueous solutions of certain salts possess the power of dissolving certain substances, which are not soluble in pure water. This phenomenon has found an application in the chemical industry for the preparation of aqueous dye solutions but its pharmaceutical application was limited until the early sixties. Many workers have employed hydrotropic solubilization for increasing aqueous solubility of a variety of insoluble drugs using various organic compounds and studied the mechanism of hydrotropic solubilization.

Winsor[38], speculated that hydrotropy is simply another type of solubilization with the solute dissolved in oriented clusters of the hydrotropic agents. Some workers proposed that this phenomenon is more closely related to complexation with a weak interaction existing between the hydrotropic agent and the solute. The characteristic that hydrotropic agents share is the ability of self association in the aqueous solution, particularly at hydrotropic concentration more than 1 M.

As described by Kenneth C James[39], the process of salting-in has been known for many years and has acquired a description hydrotropism. It occurs with large ions such as phenate, alkyl sulfate and quaternary ammonium ions. It is probably due to a large extent to the expansion of water on the introduction of these ions. Ion-dipole interaction with polar non electrolyte is also a contributory factor.

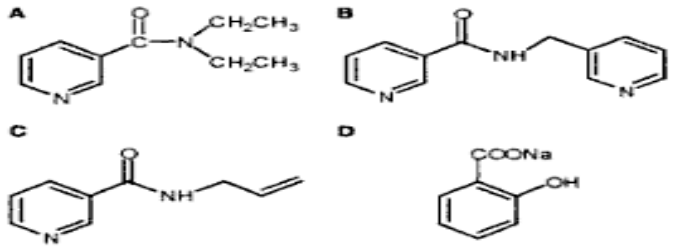
Commonly Used Hydrotropes

The hydrotropes are known to self-assemble in solution[40].The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol[41], aromatic alcohols like resorcinol, pyrogallol, catechol, *a*- and *b*-naphthols and salicylates, alkaloids like caffeine and nicotine[42], ionic surfactants like diacids[43], SDS (sodium dodecyl sulphate)[44] and dodecylated oxidibenzene[45]. The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of

isomerism and their effective hydrotrope action may be due to the availability of interactive pi-orbitals. Hydrotropes with cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride[46]. Besides enhancing the solubilization of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and polymers, etc.[40,46].

Table 1.2: Hydrotropic solubilization study of various poorly water-soluble drugs[48-68]

Drug	**Hydrotropic agent**
Riboflavin	ProcaineHCl, PABAHCl, CinchocaineHCl, Resorcinol, Pyrogallol
Chartreusin	Sodium benzoate, Sodium p-hydroxybenzoate, Sodium m-hydroxybenzoate, Sodium o-hydroxybenzoate, Sodium 2,4-dihydroxybenzoate, Sodium 2,5-dihydroxybenzoate, Sodium 2,6-dihydroxybenzoate, Sodium 2,4, 6-trihydroxybenzoate
Diazepam, Medazepam, Oxazepam, Nitrazepam, Clonazepam	Sodium salicylate
Theophylline, Hydrocortisone, Prednisolone, Phenacetin	Sodium benzoate, Sodium o-hydroxybenzoate, Sodium m-hydroxybenzoate, Sodium p-hydroxybenzoate, Sodium 2,4-dihydroxy benzoate, Sodium 2,5-dihydroxybenzoate, Sodium 2,6-dihydroxybenzoate, Sodium 3,4-dihydroxybenzoate, Sodium 3,5-dihydroxybenzoate, Sodium 3,4,5 – trihydroxybenzoate
Progesterone, Testosterone 17- β Estradiol, Diazepam and Griseofulvin	Nicotinamide, Isonicotinamide, Nipecotamide,N-methylnicotinamide, N, N-dimethylnicotinamide
Paracetamol	Sodium salicylate, Sodium glycinate, Sodium gentisate, Nicotinamide
Saquinavir	Nicotinamide, Ascorbic acid, Dimethyl urea, Resorcinol
Benzoic acid, Salicylic acid	Urea, Methyl Urea, 1-3-dimethyl urea
Rofecoxib, celecoxib, melocoxib	Nicotinamide, Sodium benzoate, Sodium salicylate
Riboflavin	Nicotinamide
Temazepam	Sodium salicylate, Nicotinamide
Ibuprofen	Sodium salt of Ibuprofen
Nifedipine	Urea, Methyl urea, Ehhyl urea, Butyl urea, icotinamide, N-methyl nicotinamide, N, N-dimethyl nicotinamide
Ketoprofen	Sodium benzoate, Sodium o-hydroxybenzoate, Nicotinamide, Sodium m-hydroxybenzoate, Sodium ascorbate, Sodium 2,5-dihydroxybenzoate
icam	Sodium ascorbate, Sodium benzoate, Sodium o-hydroxybenzoate, Sodium m-hydroxybenzoate, Sodium 2,5-dihydroxybenzoate
Carbamazepine	Sodium salicylate, Sodium benzoate



Structure of some hydrotropes: (A) N,N-diethylnicotinamide ; (B) N-picolylnicotinamide ; (C) N-allylnicotinamide ; (D) sodium salicylate [47].

Each hydrotropic agent is effective in increasing the water solubility of selected hydrophobic drugs. No universal hydrotropic agent has been found effective to solubilize all hydrophobic drugs. Thus finding the right hydrotropic agent for a poorly water-soluble drug requires screening of large number of candidate hydrotropes. However, once the effective hydrotropic agent is identified for a series of structurally different drugs, the structure activity relationship can be established.

Agrawal et al.[69], investigated the effect of various hydrotropes such as sodium benzoate, sodium salicylate and piperzine on the solubility of nimesulide. The solubility enhancement of nimesulide by the hydrotropes observed in decreasing order as piperazine>sodium ascorbate> sodium salicylate> sodium benzoate> nicotinamide. Parenteral formulations using piperazine as a hydrotrope were developed and studied for physical and chemical stability.

Jain et al[70], investigated the effect of various hydrotropes such as urea, nicotinamide, resorcinol, sodium benzoate, sodium p-hydroxy benzoate on the solubility of indomethacin. The solubility enhancement of indomethacin by the hydrotropes was observed in decreasing order as sodium p-hydroxyl benzoate> sodium benzoate> nicotinamide> resorcinol> urea. Aqueous injectable formulations using sodium p-hydroxyl benzoate, sodium benzoate and nicotinamide as hydrotropes were developed and studied for physical and chemical stability.

Mechanism Of Hydrotrope Action

A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solutions. Typically, hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation. **Hydrotropes** do not have a critical concentration above which self-aggregation 'suddenly' starts to occur (as found for micelle- and vesicle-forming surfactants, which have a critical micelle concentration or cmc and a critical vesicle concentration or cvc, respectively). Instead, some hydrotropes aggregate in a step-wise self-aggregation process, gradually increasing aggregation size. However, many hydrotropes do not seem to self-aggregate at all, unless a solubilisate has been added.

Badwan et al.[48], studied the solubility of benzodiazepine in sodium salicylate solution. It was suggested that molecular aggregation takes place and benzodiazepine molecule were induced in these aggregates. A donor acceptor type of interaction between sodium salicylate and benzodiazepine molecules is assumed to stabilize such inclusions and determined the degree of solubility.

Hydrotropes are used in detergent formulations to allow more concentrated formulations of surfactants. Examples of hydrotropes include sodium p-toluenesulfonate and sodium xylene sulfonate.

Poochikian et al.[49], studied the solubilization of chartreusin by hydroxybenzoate. Plane to plane orientation of ligand molecules and chartreusin brought together by electrostatic and hydrophobic interactions was suggested as possible mechanism.

Jain et al.[63], investigated the solubilization of ketoprofen, by means of various physiologically active hydrotropic agents. In order to gain an insight into probable mechanism of solubilization, solubility, spectral, typical properties of hydrotropes, solution properties, gel formation, paste formation, TLC and IR spectral studies were carried out with structural variation in hydrotropes. The results indicated that the enhanced solubility of ketoprofen in presence of hydrotropes in low concentration is due to weak ionic interaction. At higher concentration, the formation of molecular aggregates seemed to be the possible mechanism of hydrotropic solubilization.

Rawat et al.[58], studied the effects of various hydrotrops such as nicotinamide, sodium benzoate, sodium salicylate in the solubility of rofecoxib, celecoxib and meloxicam, and were investigated to gain an insight into the mechanism of solubilization. The results indicated that the enhanced solubility of these drugs in the presence of hydrotropes in low concentration is due to weak ionic interaction. At high hydrotropic concentration the formation of molecular aggregation seems to be the possible mechanism of solubilization.

Coffman et al.[59], studied the effect of nicotinamide and urea on the solubility of riboflavin in various solvents. Their study examined the mechanism of hydrotropic solubilization. The most commonly proposed mechanism for hydrotropic solubilization is complexation.

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 $1/5^{th}$ concentrations reducing their individual toxicities.[71]

Maheshwari observed miraculous synergistic effect on enhancement in solubility of a poorly water-soluble drug (aceclofenac) by mixing two hydrotropic agents (urea and sodium citrate) and mixed hydrotropic blend was employed to solubilize a poorly water-soluble drug, aceclofenac from fine powder of its tablets to carryout spectrophotometric analysis precluding the use of organic solvents.

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.

Maheshwari [71], investigated the application of mixed hydrotropy. There was miraculous synergistic effect on enhancement in solubility of a poorly water-soluble drug by mixing two hydrotropic agents. Solubility of aceclofenac in blends of two hydrotropic agents was much larger than the sum of the solubilities of aceclofenac in individual hydrotropic solutions.

Novel Pharmaceutical Applications Of Hydrotropic_Solubilization In Various Fields Of Pharmacy

1. Quantitative estimations of poorly water-soluble drugs by uv-visible spectrophotometric analysis precluding the use of organic solvents.

Maheshwari R.K.[72], performed, quantitative spectrophotometric determination of ornidazole tablet using 0.5M ibuprofen sodium as hydrotropic solubilizing agent. Ornidazole shows its maximum absorbance at 320 nm and Beer's law was obeyed in concentration range of 5-25 mcg/ml. Results of analysis were validated statistically and by recovery studies. The proposed method is new, simple, safe, environmentally friendly, accurate and cost-effective and can be successfully employed in routine to analyze ornidazole tablets. Hydrotropic agent and commonly used tablet additives did not interfere in the analysis.

Maheshwari R.K. et al.[73], performed the quantitative estimation of naproxen in tablets using 0.5M ibuprofen sodium as hydrotropic agent which showed more than 350 fold enhancement in the solubility of naproxen as compared to the solubility in distilled water**.** The naproxen has been successfully analyzed in tablets. The results of analysis obtained by proposed method compared well with those by corresponding British pharmacopoeial method involving the use of methanol. Presence of ibuprofen sodium and common excipients did not interfere in analysis.

Maheshwari R.K. et al.[74], developed an ecofriendly method of spectrophotometric estimation of Tinidazole (sparingly water soluble drug) in tablets using 1M lignocaine hydrochloride as hydrotropic solubilizing agent. Beer's law was obeyed in the concentration range of 5-25 ug/ml. Lignocaine hydrochloride does not interfere above 280 nm .There was more than six fold enhancement in the aqueous solubility of the tinidazole. The results of analysis obtained by the proposed method were comparable with the results of analysis obtained by Indian Pharmacopoeial method.

2. Quantitative estimations of poorly water-soluble drugs by titrimetric analysis
3. Preparation of hydrotropic solid dispersions of poorly water-soluble drugs precluding the use of organic solvents.

Maheshwari[75], enhanced the aqueous solubility of paracetamol, a poorly water-soluble drug by use of concentrated solution of urea (a hydrotropic agent). This hydrotropic phenomenon was employed to prepare solid dispersion (SD) and syrup of paracetamol. SD was evaluated for dissolution rate and a marked increase in dissolution rate was observed with SD. IR analysis revealed that there was no complexation/interaction between paracetamol and urea. Paracetamol syrups prepared with urea showed good chemical stabilities.

Preparation of ready to use syrups of poorly water-soluble drugs.

Agrawal et al.[68], studied the hydrotropic solubilization of carbamazepine, using sodium benzoate and sodium salicylate. No single mechanism could account for observed solubility. Injection and pediatric syrup were also formulated using 50% solution of sodium benzoate as the vehicle, with satisfactory stability.

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.
6. Prepration of injection of poorly water soluble drugs.

Jain et al.[66], evaluated aqueous injections of piroxicam in vitro (physical evaluation, heamolytic activity), and in vivo (pharmacokinetic studies), which were prepared by using hydrotropes and cosolvents earlier.

Jain et al.[67], studied physical and chemical stability of aqueous injection formulations of piroxicam, which were prepared by using hydrotropes and cosolvents earlier.

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 develope 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).

Xie Y. et al.[76], prepared solid dispersion of total flavones of *Hippophae rhamnoides* L.and a polymeric carrier, poloxamer 188 (PXM) by solvent evaporation method, and evaluated it by *in vitro* technique. A 3^2 full-factorial design approach was used for optimization wherein the amount of solvent (X_1) and the drug-to-polymer ratio (X_2) were selected as independent variables and the percentage of TFH dissolved in 10 min (Q_{10}) was selected as the dependent variable. Multiple linear regression analysis revealed that a suitable level of X_1 and X_2 was required for obtaining higher dissolution of TFH from PXM solid dispersions. Solid dispersions were characterized by DSC, XRD, FTIR, SEM and dissolution tests. Characterization studies revealed that solid dispersion of TFH–PXM showed enhancement of TFH dissolution due to the conversion of TFH into a less crystalline and/or amorphous form. In conclusion, dissolution enhancement of TFH was obtained by preparing its solid dispersions in PXM using solvent method.

Jin S.D. et al.[77], prepared solid dispersion of Rutaecarpine to improve its antihypertensive effect in spontaneously hypertensive rats. It was reported previously that rutaecarpine produced a hypotensive effect in phenol-induced and 2-kidney, 1-clip hypertensive rats. However, the same dose of crude rutaecarpine did not produce significant hypotensive effects when applied to spontaneously hypertensive rats (SHR). In this study, a different dose of rutaecarpine solid dispersion was administered intragastrically to SHR. The results showed that administration of the solid dispersion significantly increased the blood concentration of rutaecarpine, accompanied by significant hypotensive effects in SHR in a dose-dependent manner.

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 article we conclude that, Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. Solubility can be enhanced by many techniques and number of folds increase in solubility is reported too. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

References

1. Rathore K. S. et al, "A Review on Hydrotropes: Compounds for Solubility Enhancement of Poorly Water Soluble Substances", The Pharma Review ,Dec. 2007 – Jan. 2008.
2. Indian Pharmacopoeia, Goverment of India ministry of health and family Welfare, 4th ed., 1996, The Controller of Publication, Delhi, 332.
3. Shinde A.J. et al, "Solubilization of poorly soluble drugs: A Review", Pharmainfo.net, 2007, 5, 6.
4. Liu, R., Introduction, In: Liu, R., (Ed.), Water-Insoluble Drug Formulation, 2nd ed., 2008, CRS press, New York, 1.
5. Brahmankar D.M. et al, Biopharmaceutics and Pharmacokinetics 2009,349-357.
6. Vogt M. et al, "Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations.", Eur J Pharm Biopharm. ,Feb 2008, 68, 2, 283-8.
7. Tamer B. et al, Influence of swelling degree on release of Nicardipine hydrochloride from acrylic microspheres prepared by solvent evaporation method, Informaworld – Pharmaceutical Development and Technology, Feb 1998, 3, 1, 115-121.
8. Zhang Z.B. et al, "Nanonization of Megestrol Acetate by Liquid Precipitation", *Ind. Eng. Chem. Res.*, 2009, 48, 18, 8493–8499.
9. Wang W. et al, "Lyophilization and development of solid protein pharmaceuticals", Int. J. Pharm., 2000, 203, 24-30.

10. Betageri G .V. et al, "Enhancement of dissolution of Glyburide by solid dispersion and lyophilization techniques", Int. J. Pharm., 1995, 126, 155-160.
11. Yalcin T. et al, "Inclusion of ketoprofen with skimmed milk by freeze-drying" Il Farmaco, 1999, 54, 648-652.
12. Bandry M.B. et al, "Enhancement of the dissolution and permeation rates of meloxicam by formation of its freeze-dried solid dispersions in polyvinylpyrrolidone K-30", Drug Dev. Ind. Pharm., Feb 2006, 32, 2, 141-150.
13. Fathy M. et al, " In vitro and in vivo evaluation of an amylobarbitone /hydroxypropyl-betacyclodextrin complex prepared by a freeze-drying method", Pharmazie., Jul 2000, 55, 7, 513-517.
14. Drooge D.J.V. et al, " Spray freeze drying to produce a stable 9- tetrahydrocannabino containing inulin based solid dispersion powder suitable for inhalation", Eur. J. Pharm. , 2005, 26, 231-240.
15. Seedhar N. et al, "Various solvent systems for solubility enhancement of enrofloxacin", Indian J Pharm. Sci., 2009, 71, 1, 82-87.
16. Rajebahadur M. et al, "Mechanistic study of solubility enhancement of Nifedipine using Vitamin E TPGS or Solutol HS-15", Informaworld – Drug Delivery, May 2006, 13, 3, 201-206.
17. Karavas E. et al, "Hydrophilic matrices as carriers in Felodipine solid dispersion systems", European Colloid and Interface Science XV, 2001, 118, 149-152.
18. Shukla Meenakshi et al, "Enhanced solubility study of Glipizide using different solubilization techniques", International Journal Pharmaceutical Sciences, 2010, 2, 2, 46-48.
19. Arias M. J. et al, "Study by DSC and HSM of the oxazepam-PEG 6000and oxazepam-D mannitol system: Application to the preparation to the preparation of solid dispersion", Thermochimica Acta., 1998, 33-41.
20. Varma M.M. et al, "Influence of urea and xylitol on the dissolution rate of flurbiprofen", Indian Pharmacist, 2005, 97-99.
21. Mooter G.V. et al, "Mechanism of dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersion", Int. J. Pharm. , 2002, 249, 45-48.
22. Madhusudhan, "Studies on sulphamethoxazole solid dispersion and their tablets", Indian J. Pharm. Sci., 2000, 64, 233-238.
23. Dohrn R. et al, "Melting point depression by using supercritical CO2 for a novel melt dipersion micronization process", J of Molecular Liquids ,2007, 131- 132, 53-59.
24. Rao M.G. et al, "Preparation and evaluation of solid dispersion of naproxen", Indian J. Pharm. Sci., 2005, 67, 26-29.
25. Acarturk F. et al, "The effect of some natural polymers on the solubility and dissolution characteristics of Nifedipine", International Journal of Pharmaceutics, Sept 1992, 85, 1-3, 1-6.
26. Etman M.A. et al, "Solubilization of etodolac for pareteral administration", Indian J. Pharm. Sci., 2001, 63, 459- 467.
27. Saha R N. et al, "Solubility enhancement of nimesulide and ibuprofen by solid dispersion technique", Indian J. Pharm. Sci., 2006, 64, 529-534.
28. Raghavan K.S.S. et al, "Solubility Enhancement of a Bisnaphthalimide Tumoricidal Agent, DMP 840, Through Complexation", Pharmaceutical Development and Technology,1999, 1, 3, 231-38.
29. Maheshwari R.K., "A novel application of hydroscopic solubilization in spectrometric estimation of Frusemide in tablets", Pharma Rev. 2006, 4, 148.
30. Rasool A.A. et al, "Solubility enhancement of some water-insoluble drugs in the presence of Nicotinamide and related compounds", Journal of Pharmaceutical Sciences, 2006, 80, 4, 387-393.
31. Neuberg, C., Hydrotropy, Biochem. Z., 1961, 76, 107-109.
32. Gaikar V.G. et al, "Hydrotropic properties of sodium salts of ibuprofen", Drug Dev. Ind. Pharm., 1997, 23, 309-312.
33. Poochikian G.K. et al, "Enhanced chartreusin solubility by hydroxybenzoate hydrotropy", J. Pharm. Sci., 1979, 68, 728-729.
34. Badwan A.A. et al, "The solubility of benzodiazepines in sodium salicylate solution and a proposed mechanism for hydrotropic solubilization", Int. J. Pharm., 1983, 13, 67-73.
35. Saleh A.M. et al, "Hydrotropic agents: a new definition", Int. J. Pharm., 1985, 24, 231-238.
36. Rasool A.A. et al, "Solubility enhacement of some water-insoluble drugs in presence of nicotinamide and related compounds", J. Pharm. Sci., 1991, 80, 387-394.
37. Suzki H. et al, "Mechanistic studies on hydrotropic solubilization of nifedipine in nicotinamide solution", Chem. Pharm. Bull., 1998, 46, 125-130.
38. Winsor P.A. et al, "Hydrotropic solubilization and related emulsification process", Trans Faraday Soc., 1950, 54, 762-772.
39. Kennth C.J., Aqueous solubilities, In: Kennth, C. J., (Ed.), Solubility & Related Properties, 1986, Published by Informa health care, Inc., New York, 355.
40. Balasubramanian, D. and Friberg, S. E., in Surface and Colloid Science (ed. Matijevic, E.), Plenum Press, New York, 1993, vol. 15.
41. Friberg S.E. et al, "Colloids Surf. A: Physicochem", Eng. Aspects, 1999, 156, 145–156.
42. daSilva R. C. et al, Thermochim. Acta, 1999, 328, 161–167.
43. Robinson P.L. , J. Am. Oil Chem. Soc., 1992, 69, 52–59.

44. Guo R. et al., J. Disp. Sci.Technol., 1996, 17, 493–507.

45. Lomax, E. G. (ed.), Amphoteric Surfactants, Marcel Dekker, Inc,New York, 1996, 2nd edn.

46. Roy, B. K. and Moulik, S. P., Colloids Surf. A: Physicochem. Eng.Aspects, 2002, 203, 155–166.

47. Encyclopedia of pharmaceutical technology, Volume 5, By James Swarbrick, 2918.

48. Poochikian G.K. et al, "Enhanced chartreusin solubility by hydroxybenzoate hydrotropy", J. Pharm. Sci., 1979, 68, 728-729.

49. Badwan A.A. et al, "The solubility of benzodiazepines in sodium salicylate solution and a proposed mechanism for hydrotropic solubilization", Int. J. Pharm., 1983, 13, 67-73.

50. Saleh A.M. et al, "Hydrotropic agents: a new definition", Int. J. Pharm., 1985, 24, 231-238.

51. Winsor P.A. et al, "Hydrotropic solubilization and related emulsification process", Trans Faraday Soc., 1950, 54, 762-772.

52. Kennth, C. J., Aqueous solubilities, In: Kennth, C. J., (Ed.), Solubility & Related Properties, 1986, Published by Informa health care, Inc., New York, 355.

53. Higuchi T. et al, "Complexation of organic substances in aqueous solution by hydroxyaromatic acids and their salts", J. Pharm. Sci., 1961, 50, 905-909.

54. Rasool A.A. et al, "Solubility enhacement of some water-insoluble drugs in presence of nicotinamide and related compounds", J. Pharm. Sci., 1991, 80, 387-394.

55. Hamza Y.E. et al, "Enhanced solubility of paracetamol by various hydrotropic agents", Drug Dev. Ind. Pharm., 1985, 11, 1577-1580.

56. Nahar M. et al, "Formulation and evaluation of saquinavir injection", 2006, 68, 608-614.

57. Feldman S. et al, " Effect of urea on solubility", J. Pharm. Sci. 1967, 56, 370-375.

58. Rawat S. et al, "Hydrotropic solubilization of some cox-2 inhibitors", Indian Drugs., 2006, 43, 565-573.

59. Coffman R.E. et al, "Effect of urea on the solubility of riboflavin in various solvents", J. Pharm. Sci.,1996, 85, 951-954.

60. Woolfson A.D. et al, "Stabilization of hydrotropic temazepam parenteral formulation by lyophilization", Int. J. Pharm., 1986, 34, 17-22.

61. Gaikar V.G. et al, "Hydrotropic properties of sodium salts of ibuprofen", Drug Dev. Ind. Pharm., 1997, 23, 309-312.

62. Suzki H., "Mechanistic studies on hydrotropic solubilization of nifedipine in nicotinamide solution", Chem. Pharm. Bull.,1998, 46, 125-130.

63. Jain N.K. et al, "Hydrotropic solubilization of ketoprofen", Pharmazie., 1996, 51, 236-239.

64. Singhai A.K. et al, "Evaluation of an aqueous injection of ketoprofen", Pharmazie., 1997, 52, 149-152.

65. Jain N.K.et al, "Enhanced solubilization and formulation of an aqueous injection of piroxicam", Pharmazie., 1997, 52, 942-151.

66. Jain N.K. et al, "Evaluation of piroxicam injection", Indian J. Pharm. Sci., 1997, 59, 306-309.

67. Jain N.K. et al, "Stability studies on aqueous injection of piroxicam", Indian Drugs, 1998, 35, 440-443.

68. Agrawal R.K. et al, "Formulation of aqueous injection of carbamazepine", Pharmazie., 1990, 45, 221-222.

69. Agrawal S. et al, "Hydrotropic solubilization of nimesulide for parenteral administration", Int. J. Pharm., 2007, 274, 149-155.

70. Jain A. K. et al, "Solubilization of indomethacin using hydrotropes for aqueous injection", Eur. J. Pharm. Biopharm., 2007, 30, 1-13.

71. Maheshwari R.K. "Mixed hydrotropy in spectrophotometric analysis of poorly water-soluble drug", Indian Pharmacist., 2007, 6, 66-67.

72. Maheshwari R.K. et al, "Quantitative spectrophotometric determination of Ornidazole tablet formulations using ibuprofen sodium as hydrotropic solubilizing agent", Digest Journal of Nanomaterials and Biostructures, March 2010, 5, 1, 97-100.

73. Maheshwari R.K. et al, "Quantitative estimation of Naproxen in tablets using ibuprofen sodium as hydrotropic agent", Indian Journal of Pharmaceutical Sciences, 2009, 71, 3, 335-337.

74. Maheshwari R.K. et al, "Ecofriendly spectrophotometric estimation of Tinidazole in tablets using Lignocaine hydrochloride as hydrotropic solubilizing agent", Asian Journal of Pharmaceutics, 2009, 319-321.

75. Maheshwari R.K., "Solid dispersion and syrup formulation of poorly water-soluble drug by hydrotropy", Indian Pharmacist., 2006, 5, 87-90.

76. Xie Y. et al, "Preparation and *in vitro* evaluation of solid dispersions of total flavones of *Hippophae rhamnoides* L.", American Association of Pharmaceutical Scientists-Pharm Sci Tech, June 2009, 10, 2, 631-640.

77. Jin S.D. et al, "Solid dispersion of Rutaecarpine improved its antihypertensive effect in spontaneously hypertensive rats", Wiley Interscience, Nov 2008 29, 9, 495-500.