REVIEW ARTICLE

Hydrotropy: Recent Advancements in Enhancement of Drug Solubility and Formulation Development

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ABSTRACT

Solubility can be defined as the phenomenon of dissolving a solute in a solvent to prepare a homogenous system. It is essential to get a required drug concentration in plasma to get a desired pharmacological response. More than 40% of new chemical entities developed by the pharmaceutical industry are insoluble in water practically. Low plasma concentration can be a challenge for formulation scientists to deliver drugs with low aqueous solubility. This, in turn, will affect the dissolution process and, lastly, the bioavailability of drug molecules. Dissolution may be a rate-limiting step for Bio Pharmaceutics Classification System (BCS) class II and IV drugs. Several techniques to enhance solubility like particle size reduction, micro-ionization, nano-ionization, solid dispersion, complexation, pH adjustment, hydrotropy etc. have been studied and successfully applied for the last decade. Solubility enhancement is done by hydrotropy deals using anionic organic salts (hydrotropic agents) to improve the solubility of poorly soluble solutes by forming weak interactions. This technique possesses various advantages like it is highly selective, non-flammable, environment-friendly, and cost-effective. Hydrotropic agents may act as drug carriers. Along these can be used in formulation development for oral, parenteral, and topical use. This review focuses on using hydrotropy as a solubility enhancement technique through a concise overview, mechanism, and different advancements towards drug delivery.

Keywords: Bioavailability, Drug delivery, Formulation development, Hydrotropy, Solubility.

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INTRODUCTION

Solubility can be called the property of a substance, whether a solid, liquid, or gas which is described as a "Solute" to be dissolved in a solid, liquid or gaseous solvent to form a homogeneous one-phase system. The physical parameters on which the solubility of a substance depends are temperature and pressure. Solubility also depends on the choice of solvent. If the addition of a solute does not increase its concentration in a particular solvent, it is called saturation concentration.[1] The term insoluble is generally applied to poorly or very poorly soluble compounds.[2] Solubility must not be misunderstood with the substance's ability to dissolve or liquefy another substance since it can occur by chemical reaction and not from the dissolution process. For instance, zinc does not solubilize in hydrochloric acid but gets dissolved in it by a chemical reaction and gets converts into zinc chloride and hydrogen, where zinc chloride gets dissolve in hydrochloric acid. Different pharmacopoeias classify the solubility in quantification and do not consider the solvents used (Table 1).

Oral administration is the most common drug delivery route as it is convenient, has good patient acceptability. Also, It is cost-effective with no sterility requirement and is flexible

Table 1: Solubility criteria as per the Pharmacopoeia[3,4]

	Part of solvent required per part of solute
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10- 30
Sparingly soluble	30 - 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

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to be designed as a dosage form, because of which, many drug companies with generic products are willing more to produce oral drug products showing bioequivalence.[5] The major issue lies with the design of oral dosage forms' poor bioavailability of the drugs. The per oral bioavailability of a drug depends upon numerous factors like solubility, permeability, dissolution rate, hepatic first-pass metabolism, and its susceptibility to efflux the mechanisms. The most recurrent causes of low oral bioavailability are referred to low solubility and poor permeability. Besides oral dosage forms, solubility also plays an essential role in other forms like parenteral formulations.[6] To achieve a desired pharmacological response, the desired amount of concentration in plasma is required, which depends upon the solubility of the drug. Poorly soluble drugs are required in high doses orally to achieve the required therapeutic plasma concentrations. A significant problem formulation scientists face during formulation development is the low solubility of the drug.[7] A drug is required to be present in a solubilized form at the site of absorption. Water is a choice of solvent for liquid pharmaceutical formulation. The majority of the poorly soluble drugs are either weak acids or weak bases. More than 40% of new chemical entities developed by pharmaceutical companies are practically insoluble in a solvent like water. This insolubility of these drugs is the main reason for their variable bioavailability.

As per the Biopharmaceutical classification system, Class II drugs show low solubility and high permeability, and Class IV drugs show low solubility and low permeability; dissolution is the rate-limiting step, and bioavailability may be increased by enhancing the solubility.[5,7,8] Therefore, to improve the bioavailability, the solubility of the drug has to be improved, and this improvement of solubility may be a challenge during the drug development process, especially for oral drug delivery. Several approaches have been studied and found in various research works to enhance the solubility of poorly water-soluble drugs. The techniques are selected considering the properties of API understudy, excipients required, and the type of intended dosage form.

Different Techniques for Solubility Enhancement[9]

Solubility improvement techniques can be categorized into physical modification, chemical modifications of the drug substance, and other techniques.

Physical Modifications

Particle size reduction like micronization, nanosuspension, crystal habit modification like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions, and cryogenic techniques.

Chemical Modifications

Change of pH, use of buffer, derivatization, complexation, and salt formation.

Miscellaneous Methods

The supercritical fluid process uses adjuvants like surfactants, solubilizers, co-solvency, hydrotrophy, and novel excipients.

HYDROTROPY

The term hydrotropy was coined by the scientist Carl A, Neuberg in 1916. Hydrotropy is a method of solubility enhancement that involves addition of large amount of a second solute to enhance the aqueous solubility of another substance. The second solute is a usually ionic organic salt which are alkali metal salts of different organic acids. If they increase the solubility in a specific solvent, these additives or salts are said to be "salt in" the solute and vice versa. They are called to "salt out" the solute. These salts have large cationic or anionic groups, are very soluble in water, and cause "salting in" non-electrolytes. They are called "hydrotropic salts," and this phenomenon is called "hydrotropism" (Figure 1). Hydrotropic solutions do not show colloidal properties and involve a weak interactive force between the hydrotropic agent and the solute.[10] There are weak van der Waal interactions like $\pi\,\pi$ or attractive dipole-dipole between a hydrotropic molecule and a poorly soluble drug.[11] Both hydrophobic and hydrophilic portions are found in the hydrotropes. As compared to surfactants, they contain a very small portion of hydrophobic part. The balance between the hydrophobic part and the hydrophilic part determines their efficiency.[12] The more significant is the hydrophobic part, the better is the hydrotropic efficiency. The presence of charge on the hydrophilic part has no significance. Hydrotropic agents can be anionic, cationic, or neutral or can be solid or liquid and organic or inorganic.[13]

Neuberg used a prototype, sodium benzoate, a hydrotropic salt whose structure generally consists of two main parts, an anionic group, and a hydrophobic aromatic ring or ring system. The anionic group is mainly high aqueous solubility, which is the utmost requirement for a hydrotropic substance. The type of anion or metal ion has a minimal effect on this hydrotropic phenomenon.[14] The planarity of the hydrophobic part is an important factor in the mechanism of hydrotropic solubilization.[15,16] This exhibits that hydrotropic agents have a planar hydrophobic structure brought into solution by a polar group. Hence, it can be proposed that molecules with a planar hydrophobic part and a polar group, not necessarily anionic in nature, may act as hydrotropic agents.

Saleh and El-Khordagui suggested that this concept of hydrotropy is not restrained only to the metal salts of organic

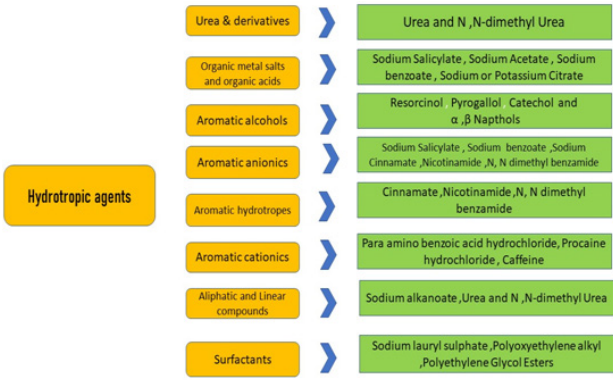

Figure 1: Classification of Hydrotropic agents

acids. Some cationic salts and neutral molecules can be found to be equally involved.[17] They used procaine hydrochloride, para-amino benzoic acid hydrochloride, cinchocaine hydrochloride as cationic salts, resorcinol, and pyrogallol neutral molecules in their research work.

In 1916, Neuberg reported that some salts in solution form in water own the power of dissolving some substances, which are poorly soluble in water of pure form. This concept was used in the chemical industry to prepare water-based dye solutions, but it has limited application in the pharmaceutical area until the early sixties. Many scientists have used the hydrotropic solubilization technique to enhance the aqueous solubility of numerous poorly soluble or insoluble drugs utilizing different organic compounds and tried to understand the mechanism of hydrotropic solubilization.

Winsor figured out that hydrotropy is simply one more type of solubilization where the solute gets dissolved in oriented clusters of the hydrotropic agents.[18] Some researchers have proposed that this phenomenon is strongly related to the complexation of hydrotropic agents and the solute with a weak interaction. The hydrotropic agents have a characteristic that shows their ability of self-association in the aqueous solution, particularly at hydrotropic concentrations of more than 1M. Kenneth C James has described that salting has been used for several years and is now called hydrotropism.[19] When large ions like phenate, alkyl sulfate, and quaternary ammonium ions are introduced, the expansion of water occurs. The other contributing factor may be Ion-dipole interaction with polar non-electrolyte.

Mechanism of Hydrotropy

The detailed literature review reflected various possible mechanisms of hydrotropic agent (HDA) responsible for the solubilization of poorly soluble drugs. The possible mechanisms that could be responsible for hydrotropic solubilization can be divided as Figure 2.[20,21]

- Potential of self-aggregation
- Micelles formation
- Structure breakers and Structure makers

The structure breakers and the structure makers are further classified into "Chaotropes" and "Kosmotropes."[22] Das and Paul studied the self-aggregation potential of sodium cumene sulfonate and used Flory-Huggins interaction parameter to justify the incorporation of griseofulvin into the core of sodium cumene sulfonate clusters.[23,24] Das and Paul have also determined solubilization of riboflavin by hydrotropy using self-association of nicotinamide as the hydrotropic agent. They also determined the orientation distribution and distance measurement for complexes of drug and hydrotrope and influence of complexation on drug-water, hydrotropic agent-water, hydrotropic agent-hydrotropic agent, hydrotropic agent drug, drug-drug H-bonding along with Van-der Waal's interactions were found to contribute. The electrostatic energy contributed to the solubilization process for drug and hydrotropic agent interaction.[25,26]

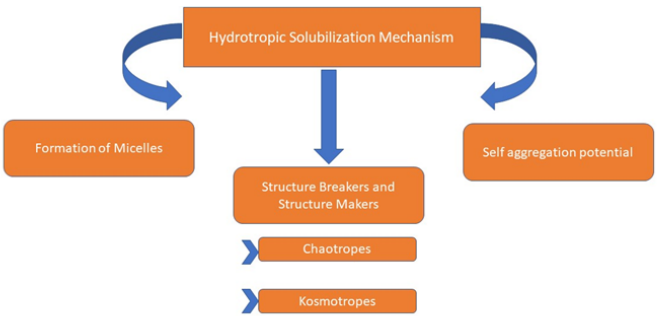

Figure 2: Mechanism of Hydrotropic solubilization

Young Cui used molecular dynamics simulation to examine the mechanism based on hydrotropy of numerous urea derivatives, e.g., urea, ethyl-urea, methyl-urea, and butyl-urea. A poorly water-soluble compound, nifedipine was used as the model solute to make it soluble. To investigates the solubilization mechanism, structural, dynamic, and energetic changes upon equilibration were analyzed. The study exhibited that nifedipine and urea derivatives undergo symbolic nonstoichiometric molecular aggregation in the aqueous solution. The reason may be the self-aggregation of derivatives under the same specified conditions. The investigation of hydrogen bonding and energy changes exhibited that the aggregation was caused by the partial restoration of normal water structure. The data of energy changes also determine the solubility of nifedipine is increased in the presence of urea and its derivatives.[27] Paul and his co-workers also carried out simulation studies on classical molecular dynamics of hydrophobic solute di-t-butyl-methane (DTBM) and hydrotrope sodium cumene sulfonate (SCS) in water with a system of SCS concentrations.[28] Their work demonstrated that the self-aggregation of SCS started when the minimum hydrotrope concentration (MHC) is achieved, and it created an environment of micelles in which the hydrophobic tail of SCS pointed inward. Its hydrophilic sulfonate group pointed outward to make good contact with water molecules. A hydrophobic core is formed of SCS cluster, which created a hydrophobic environment to encapsulate hydrophobic DTBM molecules. When average water-SCS hydrogen bonds were determined, it showed that the formation of an aggregate of SCS molecules has an imperceptible influence. Also, the calculations of Flory-Huggins interaction parameters also show supportive interactions between hydrotrope SCS and solute DTBM molecules. This study supports the enhanced solubility of hydrophobic molecules using hydrotropy.

Various Advantages of Hydrotropic Solubilization Technique[29]

- Hydrotropy is superior to other solubilization methods, e.g, micellar solubilization, miscibility, co-solvency and salting because the character of the solvent is independent of pH It is highly selective does not need any emulsification process.
- Mixing the drug with the hydrotrope is only required.
- It does not involve chemical modification of hydrophobic drugs, using organic solvents, or preparing any emulsion system.

Mixed Hydrotropic Solubilization

Mixed hydrotropic solubilization is a technique that is based on the use of blends of hydrotropic agents to increase the solubility of poorly water-soluble drugs.[30] This technique may give a synergistic effect in the enhancement of solubility of poorly water-soluble drugs. It can be utilized in the dosage form development of water-insoluble drugs, thus reducing the concentration of any singlel hydrotropic agent, which may help minimize the side effects of hydrotropes.[31] Maheshwari studied the use of a mixture of two hydrotropic agents (urea and sodium citrate) to enhance the solubility of a poorly water-soluble drug (aceclofenac). This blend of hydrotropic agents was employed to dissolve a poorly water-soluble drug, aceclofenac, taken as a fine powder from the tablets to carry out spectrophotometric analysis preventing the use of organic solvents. A miraculous synergistic effect of a blend of hydrotropic agents was seen.

Advantages of Mixed Hydrotropic Solubilization[32,33]

- It helps to lower the large total concentration of hydrotropic agents required to enhance solubility by utilizing a mixture of agents in lower concentrations.
- It is new technique that is simple, less costly safe, precise, accurate, and environmentally friendly method for the quantitative analysis of poorly water-soluble drugs minimizing the use of various organic solvents.[33]
- It excludes the use of organic solvents and therefore reducing residual toxicity.

APPLICATION OF HYDROTROPY

Hydrotropism has many applications in the engineering, biomedical, and pharmaceutical fields. The various uses are pharmaceutical formulation development, detergent solution, food-stuff, paint industry solute separation process, coating and plastic additives. We will discuss the various applications of hydrotropy in the formulation development of pharmaceuticals based on their role in solubility enhancement.

Solubility Enhancement

The mechanism of hydrotropy and mixed hydrotropy has been successfully used for enhancing the solubility of various drugs by utilizing a single or blend of hydrotropic agents (Table 2).

Formulation Development

Various formulations have been developed utilizing the concept of Hydrotropy. The mechanism behind the formulation development is the enhancement of solubility of the drugs. Various formulations like solid dispersions, oral, parenteral, and topical solutions have been developed.

Solid Dispersions

During the formulation development of new drug molecules, low aqueous solubility is a major problem formulation scientists face. Madan and co-workers prepared solid dispersions of Lurasidone to formulate them as a fast dissolving oral dosage form.[44] Lurasidone HCl was found to have low aqueous solubility and is practically insoluble in aqueous solution. Therefore it has poor bioavailability and exhibits slow onset of action. It cannot be administered in emergency clinical situations as an antipsychotic agent in conditions like schizophrenia. The concept of mixed hydrotropy was used, which can provide quick onset of action. Various hydrotropic agents like sodium citrate, nicotinamide, sodium benzoate, and urea were used at strengths of 10, 20, 30, and 40% weight by volume aqueous. 40% sodium benzoate solution exhibited the highest solubility. To reduce the concentration of individual hydrotrope mixture of various hydrotropic agents was used. The mixture that showed the highest solubility was obtained using 15:20:5 ratios of nicotinamide + sodium benzoate + sodium citrate. This optimized combination was then used to prepare the solid dispersions by using distilled water as a solvent. X-ray diffraction (XRD), differential scanning calorimetry (DSC), and Fourier-transform infrared (FTIR) were used to evaluate the solid dispersions, which showed no interaction between drug-hydrotropes. Fast dissolving tablets were prepared by compressing this solid dispersion. The prepared tablets showed 88% cumulative drug release within 14 minutes in the dissolution studies, and in vitro dispersion time was 32 minutes. The study proves the enhancement in solubility of Lurasidone by using hydrotropy.

Kamble *et al.* prepared Norfloxacin-loaded solid dispersions by a solvent evaporation technique using a mixture of urea, sodium benzoate, and niacinamide as hydrotropes.[45] They evaluated the formulated solid dispersions for the parameters like mean particle size, solubility, in vitro release, and oral bioavailability. The optimized batch showed a

Table 2: Solubility enhancement of various drugs by hydrotropy

S.No	*Drug*	*Hydrotropic agent (s)*	*Reference*
1	Diazepam,	Nipecotamide and N, Ndimethylacetamide	[34]
2	Progesterone,	Nipecotamide and N, N-dimethylacetamide	[34]
3	Griseofulvin,	Nipecotamide and N, N-dimethylacetamide	[34]
4	17 beta-estradiol,	Nipecotamide and N, N-dimethylacetamide	[34]
5	Testosterone	Nipecotamide and N, N-dimethylacetamide	[34]
6	Riboflavin	Nicotinamide, Urea	[25,35]
7	Nifedipine	Nicotinamide	[36]
8	Dexibuprofen	Sodium Citrate dihydrate, Urea	[37]
9	Telmisartan	Urea, PEG 4000, PEG 6000 ,Sodium Benzoate Sodium Salicylate	[38]
10	Glimepiride	Meglumine	[39]
11	Zaleplon	Sodium Benzoate, Resorcinol	[40]
12	Paroxetine HCl	Nicotinamide, Citric Acid, Tartaric Acid	[41]
13	Gliclazide	p-toluidinium chloride	[24]
14	Ibuprofen	Urea	[42]
15	Lovasatin	Arginine	[43]

high percentage yield of 99.04%, and a mean particle size of 132.91 μm. Optimized solid dispersions Exhibit 96.48% drug release. The oral bioavailability of prepared solid dispersions and marketed formulation were compared in Wistar rats at a dose of 20.0 mg/kg. Compared to the drug alone, around 6.90- and 5.0-fold increases in area under the curve (AUC) and maximum concentration (Cmax) were observed from hydrotropy based solid dispersions of Norfloxacin.

Madan and co-workers formulated a fast-dissolving oral dosage form of Gliclazide utilizing the concept of mixed hydrotropy. They determined the solubility of Gliclazide individually in sodium salicylate, nicotinamide, lactose, sodium acetate, urea, sodium benzoate, and trisodium citrate in 40% sodium benzoate solution[46] showed the highest solubility. Mixed hydrotropic agents were used to reduce the amount of the individual hydrotrope. Among the various combinations of the drug and hydrotropes, the combination of 25:15 of sodium salicylate and sodium benzoate showed maximum solubility. Solid dispersions were formulated by using this optimized combination. These were evaluated for any interaction between drug and hydrotrope using techniques like Xray diffractometry, DSC, and Fourier-transform infrared. The A 86% cumulative drug release was exhibited by batch G3 tablets within 14 minutes with an *in vitro* dispersion time of 33 seconds.

A fast-dissolving solid dispersion of nevirapine, an antiviral drug, was prepared by Madan *et al.*[47] It is prescribed in combination with nucleoside analogs to treat HIV type-1 (HIV-1) infection and AIDS. Nevirapine comes under biopharmaceutical clasification system (BCS) class II, where dissolution is the rate-limiting step. The solubility of nevirapine was determined individually in four hydrotropic agents, i.e., urea, lactose, mannitol, and citric acid, at a concentration of 10, 20, 30, and 40% w/v solutions in purified water as a solvent. The 40% citric acid solution showed the highest solubility. Different combinations of two and three hydrotropic agents in different ratios were studied to determine solubility so that the total concentration of hydrotropic agents should not exceed 40%. A solution of lactose and citric acid prepared at an optimum ratio of 15:25 showed the highest solubility. Solid dispersions were prepared using this optimized combination using distilled water as a solvent. These were evaluated for any interaction between drug and hydrotrope using techniques like X-ray diffractometry, DSC, and Fourier-transform infrared. The study reported enhancement in solubility of nevirapine using hydrotropy, which proves the significance of mixed hydrotropy to be used in the future for other poorly water-soluble drugs in which low bioavailability is a significant problem.

Rajpoot and his co-workers formulated a fast disintegrating tablet of Gliclazide by hydrotropic solid dispersion technique.[48] Gliclazide is an anti-diabetic drug with poor aqueous solubility, which results in decreased bioavailability and insufficient therapeutic effect. In this investigation, a mixed hydrotropy technique was used to enhance the solubility and rate of dissolution of a poorly soluble drug Gliclazide by using hydrotropic solutes, such as sodium citrate sodium salicylate, and sodium benzoate. Different ratios were prepared by solid dispersion technique, and then an optimized batch was selected for final tablet formulation. Some super disintegrants such as crospovidone and sodium starch glycolate are used to increase the disintegration of the tablet formulation. Tablets were prepared by direct compression and evaluated. This study proved the influence of hydrotropic agents in the improvement of solubility of Gliclazide.

Dhere *et al.* utilized an aqueous solvent to develop hydrotropic solid dispersion to avoid the utilization of organic solvent and thus reducing their toxicity.[49] Sold dispersion of Eluxadoline was prepared using new hydrotropic agent sodium caprylate at various ratios utilizing this new technology. The prepared solid dispersions were evaluated using solubility study, Fourier transforms infrared spectroscopy, X-ray diffractometry, drug content analysis, and in-vitro drug release study. An improvement in the solubility and dissolution of Eluxadoline was clearly seen.

Oral Dosage Forms

Maheshwari employed a concentrated urea solution as a hydrotropic agent to enhance the aqueous solubility of a poorly water-soluble drug, paracetamol.[50] He used the concept to prepare solid dispersion and syrup of paracetamol. When the solid dispersion was evaluated for dissolution rate, a noticeable increase in dissolution rate was observed. No complexation or interaction was found between paracetamol and urea, as shown by IR studies. Syrup with good chemical stability was prepared using paracetamol and urea.

Maheshwari and his co-worker prepared the oral solution (syrup) of poorly water-soluble drug tinidazole.[51] For this, they employed mixtures containing solubilizers from the list of hydrotropes, co-solvents, and water-soluble solids. The blends of solubilizers were randomly selected used for solubility studies. Based on the solubility studies, few blends which showed the greatest solubility were used to formulate the syrup. This might minimize the individual concentration of solubilizers and so reduce their toxicity potential. The prepared syrups were found relatively stable when subjected to accelerated stability studies.

Maheshwari *et al.* utilized the hybrid hydrotropy approach for solubility enhancement of poorly water-soluble drugs, Naproxen, and Furosemide.[52] They prepared 16 blends with a total strength of 40% w/v, containing various solubilizers like urea, sodium benzoate, and sodium citrate; co-solvents (glycerin, ethanol, propylene glycol, PEG 600, and PEG 400), and water-soluble solids (PEG 4000 and PEG 6000) to study the influence on the solubility of Naproxen and Furosemide individually. Most of the hydrotrope mixtures were found to increase the solubility of both drugs and can be formulated as an oral solution (syrup) for the increased onset of action and bioavailability.

Topical Dosage Forms

Starches are essential for gel-forming material. It has been found that hydrotropic salts cause swelling and gelatinization of starch at low temperatures, but at high concentrations, they

also enhance the solubility of poorly soluble drugs in water. Nazim *et al.* investigated the possibility of hydrotropic gelled corn starch as a good vehicle for drug delivery through topical route and determined the effect of change in starch/ hydrotropic salt concentration on the rheological character of the gel.[53] They also studied the in vitro release of the drug Rofecoxib from the formulated gel. Various batches of hydrotrope gelled starches were formulated using 32 factorial designs. They used corn starch along with hydrotropic salts sodium benzoate and sodium salicylate. After the evaluations, it was found that hydrotropic salt sodium salicylate caused better gelling than sodium benzoate. These formulations prepared also showed much exponential release compared to some marketed formulations whose percent release was between 15.81% to 4.77% in 6hrs.

Herbig *et al.* studied the application of hydrotropic solubilization with regards to the topical dosage form.[54] They used the concept of log D value of drugs. After studying 12 hydrotropic agents, they were able to demonstrate the hydrotropic effect of urea. All the compounds which showed log D values between 2 to 4.5 exhibited a solubility enhancement factor (EF) of >5 in 40% aqueous urea solutions. For values of log D below 2 or above 5, only EF<5 were found. Certain compounds like diclofenac (pH 4) and prednicarbate can be achieved only EF >5 at 5% urea and EF>250 at 20% urea.

Parenteral Dosage Forms

Woolfson *et al.* investigated the solubility of temazepam by complexation with Sodium salicyate and nicotinamide as hydrotropes.[55] It was found that the enhanced solubilization with temazepam was associated with a rise in hydrogen bonding between drug and hydrotrope. An unacceptable yellow color was developed on storage in the solutions of temazepam solubilized with sodium salicylate developed. This problem was overcome by lyophilization. Lyophilised injections were readily reconstituted, and the pharmacological response was evaluated in rabbits and was found satisfactory. The formulation prepared by lyophilization exhibited excellent storage characteristics. Jain *et al.* formulated an aqueous injection of Ketoprofen using various hydrotropes and cosolvents.[56]

Flurbiprofen is an analgesic, antipyretic and anti-inflammatory agent which is practically insoluble in water. Gupta and co-workers studied the aqueous solubility of flurbiprofen using various hydrotropes.[57] It was found that the solubility increased up to 63 using sodium benzoate as a hydrotropic agent. They developed aqueous injections of flurbiprofen using various selected hydrotropes. Formulations were studied for physical and chemical stability. The formulations were also evaluated for anti-inflammatory and analgesic activity and showed good results.

Agrawal *et al.* studied the effect of some hydrotropes like sodium ascorbate, nicotinamide, sodium benzoate, sodium salicylate, and piperazine on the solubilization of the drug nimesulide.[58] The enhancement in the solubility of nimesulide by the hydrotropes was observed to a greater extent in piperazine, followed by sodium ascorbate, sodium salicylate, sodium benzoate, and sodium benzoate nicotinamide. Physicochemical parameters of hydrotrope solutions like specific gravity, viscosity, refractive index, surface tension, and specific conductance of hydrotropic solutions were also studied at 25+/-2ºC to determine the probable mechanism of solubilization. Techniques like ultraviolet, infrared, powder X-ray diffraction, and differential scanning calorimetry were used to characterize each solubilized product. It was found that weak ionic interactions and molecular aggregation may be responsible for solubility enhancement. They also formulated aqueous injectable formulations using piperazine as hydrotrope and determined their physical and chemical stability.

Jain determined the effect of various hydrotropes such as nicotinamide, urea, sodium benzoate, resorcinol and sodium p-hydroxy benzoate on the solubility character of indomethacin.[59] The enhancement in the solubility of indomethacin by the hydrotropes was observed maximum in sodium p-hydroxy benzoate followed by sodium benzoate, nicotinamide, resorcinol, and urea. Various physicochemical properties of hydrotropes such as viscosity, specific gravity, surface tension, refractive index, and specific conductance of hydrotropic solutions were also studied at 25+/-2ºC to find out the probable mechanism of solubilization. Techniques like ultraviolet, infrared, powder XRD, and differential scanning calorimetry were used to characterize each solubilized product. It was found that weak ionic interactions and molecular aggregation may be responsible for solubility enhancement. He also developed aqueous injectable formulations using sodium benzoate, sodium p-hydroxy benzoate, and nicotinamide as hydrotropes and studied their stability.

Aceclofenac is a non-steroidal anti-inflammatory drug that exhibits analgesic, antipyretic and anti-inflammatory activities. It is found to be practically insoluble in water. Maheshwari *et al.* formulated injection of aceclofenac using mixed hydrotropy.[13] They investigated the effect of hydrotropes such as sodium citrate and urea and blends of sodium citrate and urea on the solubility of aceclofenac. The enhancement in the solubility of aceclofenac was more than 25 folds in 30% urea solution and 5 folds in 30% sodium citrate solution compared to its solubility in purified water. In a mixed hydrotropic solution which contained ≥20% urea and 10% sodium citrate solution, the enhancement in the solubility of aceclofenac was found exceeding 250 folds as compared to its solubility in purified water. This shows an enhancement in solubility of a poorly water-soluble drug due to mixed hydrotropy due to the synergistic effect.

Etodolac is a non-steroidal anti-inflammatory drug used for treating mild to moderate pain, osteoarthritis, or rheumatoid arthritis, and it is prescribed as a tablet. Pande *et al.* developed an effective and stable parenteral formulation for the drug for acute pain management.[60] Etodolac comes under BCS class II drug, associated with solubility. Therefore, enhancement of solubility and dissolution rate were carried out by using various combinations of hydrotropic blends. Etodolac was combined with various hydrotropic agents like sodium benzoate, sodium acetate, sodium citrate, etc., and other

co-solvents in different proportions. The drug was formulated as an injectable parenteral dosage form using an optimized hydrotropic combination as solvent. Various evaluation tests and accelerated stability studies were carried out for the optimized batches. Among the trial batches, formulations containing 15% sodium benzoate and 25% solvent system and 10% sodium acetate, 5% sodium citrate, and 25% solvent system were more stable and passed all tests.

Hydrotropy for Enhancing Drug Permeation

Nicoli *et al.* studied the effect of nicotinamide on the permeation of methyl, ethyl, propyl, and butyl parabens through the skin.[61] They measured in-vitro parabens flux in the presence and absence of different amounts of nicotinamide. It was found from solubility studies that nicotinamide complexed with methyl, propyl, and butylparaben in water, even though with low stability constants. Due to the hydrotropic effect, nicotinamide enhances paraben dissolution in aqueous media (solutions, gels), thereby decreasing partitioning of parabens in the oily phase, thus providing a reasonable concentration in the water phase in emulsion and reducing penetration through the skin, which results in lower toxicological risk. Saravanakumar *et al.* synthesized a potential drug carrier for delivery of paclitaxel.[62] This carrier was hydrotropic oligomer-glycol chitosan (HO-GC) prepared by chemical conjugation of the N, N-diethyl-nicotinamide-based oligomer, which was designed uniquely for increasing the aqueous solubility of paclitaxel to the backbone of glycol chitosan. Because of its ampiphillic nature, the conjugate formed self-assembled nanoparticles with a mean diameter of 313+/-13nm in phosphate-buffered saline of pH 7.4 at body temperature. The structure of these nanoparticles remained maintained for up to 50 days in PBS. They had high encapsulating efficiency that could encapsulate around (20% by weight) of paclitaxel (PTX) with almost 97% drug loading efficiency due to the presence of hydrotropic inner cores. A sustained release of PTX was found when HO-GC-PTX particles were exposed to the 0.1M sodium salicylate solution in a phosphate buffer solution of pH 7.4. The HO-GC-PTX nanoparticles showed lower cytotoxicity than free PTX formulation in 50%/50% Cremophor EL/ethanol mixture, which was proved by cytotoxicity test. It was found by optical imaging that near-infrared fluorescence dye (Cy5.5)-labeled HO-GC-PTX showed exceptional tumor specificity in SCC7 tumor-bearing mice because of the enhanced permeation and retention effect.

A hydrotropic formulation containing a percutaneous enhancer for the transdermal formulation of a water-soluble drug 5-fluorouracil (5-FU).[63] They used sodium benzoate (BA) and Sodium salicylate (SA) as hydrotropic agents and polyol fatty acid ester as a percutaneous enhancer. The solubilizing mechanisms were investigated. The solubility enhancement was also compared with the hydrotropic formulation and the other formulations using propylene glycol, ethanol, or mixed micelles. The *in-vitro* skin permeation of 5-FU was evaluated using Franz-type diffusion cell. Also, the accumulation of propylene glycol monocaprylate, which is one of the monoesters of polyol fatty acid ester, in the skin from the hydrotropic formulation or the other formulations was determined in the same way. It was found that the hydrotropic formulation showed an enhanced skin permeation of 5-FU when it was compared with the other formulations. Sodium benzoate and Sodium salicylate solubilized the monoesters of POFE in water. The hydrotropic formulation, which was prepared, significantly enhanced skin permeation of 5-FU as compared to the other formulations. Pan and his co-workers developed a hybrid system based on nicotinamide and nanoparticles encapsulating tacrolimus, for facilitating percutaneous delivery, utilizing the synergetic effect of both nicotinamide and nanoparticles.[44] After determining the solubility studies, the percutaneous permeation studies were also carried out. It was found that nicotinamide increased the solubility and permeability of tacrolimus. Nicotinamide at a concentration of 20% (w/v) also enhanced tacrolimus permeability and was thus chosen as the hydrotropic solution to solubilize tacrolimus and prepare tacrolimus -nanoparticles complexed with nicotinamide.

Application in Herbal Extraction

The concept of hydrotropic solubilization can also be effectively used for extracting phytoconstituents from various plant sources. Raman *et al.* used hydrotropes, like sodium alkyl-benzene sulfonates and sodium butyl mono-glycolsulfate, to select piperine of Piper nigrum fruits by using cell permeabilization.[65] It was assumed that when the hydrotrope molecules penetrate into the cellular structures, cell permeabilization takes place. This could be responsible for the enhanced extraction rates of aqueous hydrotrope solutions. After being adsorbed on cell wall, hydrotrope molecules disrupt the structure and causes rapid extraction of piperine in the bilayered cell membrane. The hydrotrope solution exhibited selective and speedy extraction of piperine from black pepper. The recovered piperine showed 90% purity and was found free from oleoresins.

Raman and co-workers studied hydrotropic solubilization of total boswellic acids from Boswellia serrata gum resins with aqueous solutions of alkylbenzene sulfonate hydrotropes.[66] As the hydrotropes are amphiphilic in their structures, the hydrotropes form microassemblies in aqueous solutions and thus cause the solubilization of water-insoluble organic substances. The solubility of boswellic acids was found to increase two times in the presence of hydrotropes in aqueous solutions. The effect of hydrotrope concentration on the solubility was determined in detail along with the solubilization kinetics.

Dandekar *et al.* investigated a new hydrotropy-based extraction method for selective extraction of curcuminoids from Curcuma longa.[67] Study showed that the degree of extraction depends on a hydrotrope's effect on the cellular structure and interactions between hydrotrope and the curcuminoids. Curcuminoids are made more accessible across the cell wall or membrane as hydrotropes affect the cell structure, either by dissolving the cell membrane/

wall constituents or disorganizing the cell wall structure. Curcuminoids were efficiently extracted using Sodium cumene sulfonate as an efficient hydrotrope. This process consisted of two steps, initially hydrotropic solubilization then dilution using water with or without pH adjustment. It yielded curcuminoids with high purity.

Mishra *et al.* investigated the use of aqueous solutions of aromatic hydrotropes to permeabilize the cell and extract dioscin from rhizomes of dioscorea.[68] The exact hydrotropic solutions were used to further hydrolyze the extracted dioscin to diosgenin without any decomposition to the product called 3,5-diene, compared to the conventional process. The optimizing parameters which affected the extraction of dioscin were the nature and concentration of the hydrotrope, the temperature, and the particle size. Sodium cumene sulfonate was found to be the most effective hydrotrope for the extraction of dioscin and its hydrolysis to be converted to diosgenin at 353 K. Latha proposed a different strategy of the extraction of embelin from Embeliaribes. She used aromatic hydrotropes such as sodium cumene sulfonate and sodium n butyl benzene sulfonate for the extraction process.[69] They were effective for the selective extraction of embelin at a high recovery rate of 95% using an aqueous solution of hydrotropes. The extract was found to be highly pure. The optimization variables were the concentration of hydrotropes and the temperature of extraction.

Hydrotropic Agents as Drug Carrier

Hydrotropic agents were found to be potential carriers for drugs. They create non-covalent assemblies, which are clusters in aqueous solutions. When hydrophobic compounds are present, these clusters stabilize by forming highly stable and long-living mesoscopic droplets by the phenomenon known as mesoscale solubilization. These materials can be used to process various pharmaceuticals, agrochemicals, and cosmetics.[70] These micellar solutions may have a role in tissue engineering and a modifier for drug delivery.[71]

Al-Shaikh and co-workers used Niacin as a hydrotropic carrier for fenofibrate, an antihyperlipidemic drug with low and variable oral bioavailability due to erratic dissolution characteristics.[72] The rationale behind this is the chemical structure of both drugs. This structure provides an opportunity for interaction during co-processing due to complementary hydrogen bonding sites. The hydrotropic effect of niacin along with size reduction resulted in a high dissolution rate of fenofibrate.

Application in Nanotechnology

A unique concept of applying hydrotropy with nanotechnology was also studied by various formulation scientists. De Souza *et al.* investigated using the hydrotrope method in the lamellar system precursor of the Lyotropic liquid crystal nanoparticles.[73] Curcumin with great pharmacological potential has limited bioavailability due to poor water solubility. It has high chemical instability and metabolic susceptibility. Sodium lauryl sulfate and Poloxamer 407 were used as hydrotropes. The LLC-NPs were evaluated for stability, dissolution rate, and other physicochemical properties. It was found that hydrotropes increased the stability of Lyotropic liquid crystal nanoparticles and the release profile of curcumin was modified.

Saravanakumar *et al.* synthesized amphiphilic hyaluronic acid conjugates as a possible drug carrier by conjugating an amine-terminated hydrotropic oligomer, chemically.[74] These conjugates have an exclusive ability to enhance the solubility of paclitaxel to a hyaluronic acid (HA) backbone utilizing carbodiimide chemistry. HydroHA conjugates formed self-assembled nanoparticles in a water-based medium due to hydrophobic interactions among hydrotropic oligomers. The prepared conjugates were evaluated. These results suggest that HydroHA nanoparticles can be used as a promising carrier for cancer therapy using paclitaxel.

Miscellaneous

In inclusion complex of MeT-2-HP-beta-CD, 2-hydroxypropyl-beta-cyclodextrin (2-HP-β-CD) was used to cover methyl testosterone (MeT) moiety. The solubility of MeT was increased due to various intermolecular hydrogen bonding between MeT and 2-HP-β-CD. The developed MeT-2-HP-beta-CD complex showed 7 times improvement in oral bioavailability of MeT.[75] Paclitaxel-β-cyclodextrin functionalized hyperbranched polyglycerol (HPG) micelles were formulated in order to enhance the solubility. The formulated micelles exhibited a multi-molecular spherical nature with a 200 to 300 nm particle size and showed good dispersity. It exhibited an initial burst release followed by an extended release in continuation.

Furthermore, MTT analysis supported good biocompatibility and a useful drug delivery system for hydrophobic moieties.[76] Shete *et al.* prepared griseofulvin suspensions using an aqueous phase of sodium benzoate. The particle size of the prepared suspension was found between 10 and 20 μm. It showed a drug release of 75% by the end of 45 minutes.[77] Rathod *et al.* prepared floating microspheres of furosemide using niacinamide and Eudragit RSPO by a solvent evaporation method. The encapsulation efficiency in the optimized formulation was 98.2%, and the mean particle size of 145 nm. The microspheres had a hollow spherical structure with a smooth outer surface. The study concluded that the enhanced drug solubility of furosemide was due to conversion in the amorphous form and an intermolecular hydrogen bonding between the drug and hydrotropes.[78]

Using the same approach Kim *et al.* developed hydrophobic block co-polymer using Poly-ethylene glycol (PEG) N, N-diethylnicotinamide (DENA), and N,N-dimethylbenzamide (DMBA). Their study reported that the capacity of solubilization of polymeric hydrotropes is due to joined effects of the micellar solubilization by the hydrophobic micelle core and also by hydrotropic solubilization.[79,80]

Current and Future Developments

Due to recent progress in hydrotropic solubilization in enhancing solubility, it has found its role in various fields. Especially its role in formulation development is extensively recognized. Various experimental studies have confirmed their role in solubility studies and quantitative estimation of

numerous drugs using non-toxic, non-flammable, and eco-friendly procedures. The challenges which are still crucial are the proper study of their structure-based mechanism and toxicity profiling since normal cells may also be affected while targeting. When used along with other novel delivery techniques, this technique is expected to transform the delivery of drugs with poor aqueous solubility and critical moieties with a narrow therapeutic range.

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