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HYDROTROPHY: NOVEL SOLUBILITY ENHANCEMENT TECHNIQUE: A REVIEW

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ABSTRACT: Drug discovery and development plays a major role in the world and serves mankind. The major criteria to be considered and given importance in drug development is the solubility of a drug. Among all newly discovered chemical entities, about 40% of drugs fail to reach the market due to their poor aqueous solubility or lipophilicity. Poor solubility is not only a problem for formulation development and clinical testing but also an obstacle at the very beginning while screening new compounds for pharmacological activity. Nowadays oral route is considered as the preferred route of drug administration than other routes due to its convenience in terms of ease of administration and economy. The first requirement of drug which is supposed to be given by oral route is good aqueous solubility, as the poor solubility leads to low absorption, inadequate and variable bioavailability and also gastrointestinal mucosal toxicity. To prevent these crisis, several solubility enhancement techniques have been employed to enhance the solubility of poorly soluble drugs and hydrotropic solubilization is one of them. Besides, the advantage of certain properties like high selectivity, non-inflammability, environmentally friendly, easy availability and cost-effectiveness of hydrotropes makes this technique superior to other solubilization techniques. In the present review, an attempt has been made to discuss the hydrotropic solubilization technique and highlight the applications with this approach.

INTRODUCTION: The current main problem in the pharmaceutical industry is related to strategies that augment the aqueous solubility of drugs, as almost 40% of the newly discovered drug candidates suffer from poor aqueous solubility [1]. Solubility is one of the prime substance features to accomplish the desired pharmacological response. The therapeutic effectiveness of a drug depends upon the bioavailability and ultimately is attributed to the solubility of drug moiety [2]. Presently, numerous formulation technologies are available to enhance solubility as well as dissolution profile to enhance oral bioavailability [3].

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In addition to these technologies, 'hydrotropy' is one of the recognized techniques available for resolving solubility issues. This review will elaborate on various hypothetical and investigational mechanisms, geometrical features and applications of hydrotropic agents in the pharmaceutical field, which will aid the researchers in exploring hydrotrophy for progress in drug delivery.

Solubility: Solubility is the phenomenon of dissolution of a solute in the solvent to give a homogenous system. It is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion [4]. The pharmacopeia list the solubility of drugs in terms of a number of parts of solvent required to dissolve one part of solute. For substances where the exact solubilities are not

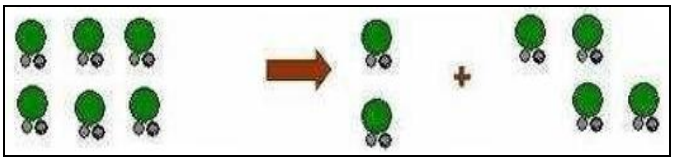
known, the Pharmacopoeia provides general terms to describe a given range. These descriptive terms are listed in **Table 1**.

TABLE 1: EXPRESSION OF SOLUBILITY [5]

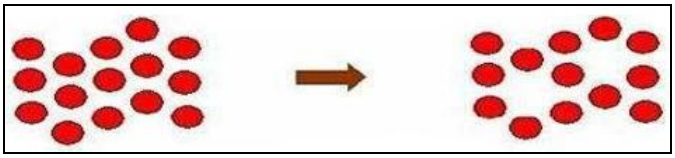
Definition	Parts of solvent required for one part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Insoluble	>10,000

The process of Solubility: The breaking of intermolecular or interionic bonds in the solute, separation of the solvent molecules which provide space for the solute in the solvent and then interaction between the solvent and the solute molecules or ions are known as solubilization process [6]. This gives rise to the concept of holes or cavities in liquids. The solubilization process may be divided into three steps: [7]

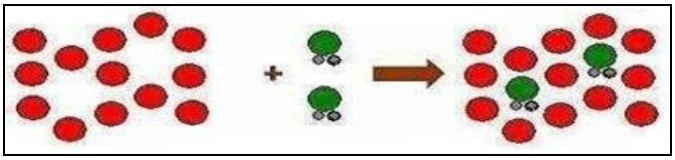
The total work as given by this extremely simplified scheme is thus (w22 + w11 - 2w12). The entire process is represented in **Fig. 1**.



Step I: Molecules of solute break away from the bulk



Step II: Holes open in the solvent



Step III: The freed solid molecules are integrated into the hole in the solvent

FIG. 1: DIAGRAMMATIC REPRESENTATION OF THE PROCESS INVOLVED IN THE DISSOLUTION OF A CRYSTALLINE SOLUTE [8]

1. The first step in the solubilization process involves the removal of a molecule from the solute phase at a definite temperature. The work is done in removing a molecule from a solute so that it is converted into the vapor phase requires breaking the bonds between adjacent molecules. The work involved in breaking the bond between two adjacent molecules is 2w22, in which the subscript 22 refers to the interaction between solute molecules. When the molecule escapes from the solute phase, however, the hole it has created closes, and one half of the energy is regained. The gain in potential energy or network for the process is thus w22.

2. The creation of a cavity in the solvent is just large enough to accept the solute molecule. The work required for this step is w11, in which the subscript 11 refers to the energy of interaction between solvent molecules.

3. The placing of a solute molecule in the hole in the solvent. The gain in work or decrease of potential energy in this step is -w12. The subscript 12 stands for the interaction energy of solute with the solvent. The hole or cavity in the solvent created in step 2 is now closed, and an additional decrease in energy, -w12, occurs, involving network in this final step of -2w12.

Factors Affecting Solubility: The solubility depends on the physical form of the solid, the composition and character of the solvent medium as well as temperature and pressure of system [9].

Particle Size: The particle size of the solid influences the solubility because a decrease in the particle size results in an increase in surface area to volume ratio. The larger surface area allows greater interaction with the solvent which increases solubility [10].

Temperature: Temperature will affect solubility. The solubility will be increased as the temperature is increased if the solution process absorbs energy while as if the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increase [11].

Pressure: For solids and liquids, a change in pressure have practically no effect on solubility, but for gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decreases the solubility [11].

Nature of the Solute and Solvent: The nature of solute and solvent depends on the concentration of solute in a specific quantity of solvent at a specific temperature. Example: 1 g of lead (II) chloride can be dissolved in 100 g of water at room temperature where 200 g of zinc chloride can be dissolved in the same condition. The difference in the solubility of these two substances is the result of differences in their natures [12].

Molecular Size: Molecular size can affect solubility. The larger the molecular size or, the higher its molecular weight, the less soluble is the substance. Larger molecules are more difficult to surround with solvent molecules to solvate the substance. In the case of organic compounds, the amount of carbon branching will increase the solubility as more branching will reduce the molecular size (or volume) and make it easier to solvate the molecules with solvent [13].

Polarity: Solubility will be affected by the polarity of the solute and solvent molecules. Generally, non-polar solute molecules will dissolve in non-polar solvents, and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules.

This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules [14].

Techniques of Solubility Enhancement: There are various techniques available to enhance the solubility of poorly soluble drugs. Some of the approaches to enhance the solubility are [15]:

TABLE 2: TECHNIQUES OF SOLUBILITY ENHANCEMENT

Conventional Techniques		Novel Techniques
Physical Modification Techniques	**Chemical Modification Technique**	
Particle size reduction Micronization Nanosuspension Other techniques Modification of the crystal habit Polymorphs Pseudo polymorphs Drug dispersion in carriers Solid dispersions Eutectic mixtures Solid solutions Complexation Stacking complexation Inclusion complexation Solubilization by surfactants Microemulsions Self-micro emulsifying drug	This approach is successful mostly in case of corticosteroids, *e.g*., By chemical modification, the solubility of betamethasone alcohol (poorly soluble drug having a solubility of 5.8 mg/100 ml) is increased 1500 times (10 g/100 ml) by its esterification with disodium phosphate. However, this approach has severe practical limitations because new derivatives are required to be subjected to essentially the same testing protocol as the parent compound [16]	Nanotechnology approaches Nanocrystals Nanomorphs Hydrotrophy Co-crystallization Co-solvency

The approaches mentioned in **Table 2** have been used widely in the fields of pharmacy. However, applications of 'hydrotropic solubilization' and 'mixed solvency' haven't been explored to a considerable extent in various fields of pharmacy.

Hydrotropy: The term hydrotropy was first coined by Scientist Carl Neuberg in 1916, but the practical implications were introduced as late as 1976 by Thoma and co-workers [17]. In this technique by adding a large amount of secondary solute increase the aqueous solubility of the poorly soluble drug. However, the term has been used in the literature to designate non- micelle forming substances, either liquid or solid, organic or inorganic, capable of insoluble solubilizing compounds.

Hydrotropic Agent: The hydrotropic agents are non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of insoluble

solubilizing compounds. The chemical structure of the conventional Neuberg's hydrotropic salts (prototype sodium benzoate) usually consists of two essential parts, anionic group, and a hydrophobic aromatic ring or ring system. The anionic group is 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. On the other hand, the planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization [18]. Additives or salts that increase the solubility in a given solvent are said to "salt in" the solute and salts that decrease the solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism". Hydrotropic solutions don't show colloidal properties and involve a weak interaction between the hydrotropic agent and solute [19].

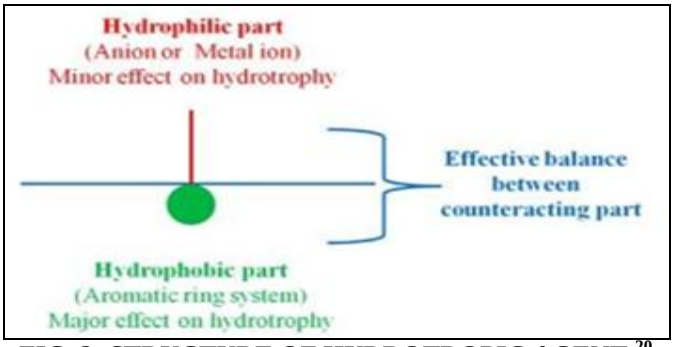


FIG. 2: STRUCTURE OF HYDROTROPIC AGENT [20]

TABLE 3: CLASSIFICATION OF HYDROTROPIC AGENTS [21]

S. no.	Class	Example
1	Organic acids and their metal salts	Citric acid, benzoic acid, sodium salicylate, sodium benzoate, sodium citrate, sodium acetate, sodium ascorbate, potassium citrate
2	Urea and its derivatives	Urea, N, N-dimethyl urea
3	Alkaloids	Caffeine, nicotinamide, N,N-diethylnicotinamide, N,Ndimethylbenzamide
4	Phenolic derivatives	Resorcinol, pyrogallol, catechol, a,b-napthols
5	Surfactants	Sodium dodecyl sulphate
6.	Aromatic cations	Procaine hydrochloride, para amino benzoic acid

Mechanism of Hydrotropic Agent: The enhancement of solubility of the poorly soluble drug by the hydrotrope is based on the molecular self-association of the hydrotrope and on the association of hydrotrope molecules with the solute. Although hydrotropic agents are widely used in various industrial applications, only sporadic information on the mechanism of hydrotrophy is available. Various hypotheses and research efforts are being made to clarify the mechanisms of hydrotrophy. The available proposed mechanisms can be abridged according to three designs [22]:

(a) Self-aggregation potential,
(b) Structure-breaker and structure-maker,
(c) Ability to form micelle-like structures.

These unique geometrical features and different association patterns of hydrotrope assemblies distinguish them from other solubilizers [23, 24].

Self-Aggregation Potential: Minimum hydrotropic concentration (MHC) is a critical concentration at which hydrotrope molecules start to aggregate, *i.e*., self-aggregation potential [25]. The solubilization power of hydrotropic agents is governed by their self-aggregation potential [26]. This potential depends upon their amphiphilic features and the nature of a solute molecule [23, 27]. They mainly show the volume-fraction-dependent solubilization potential [28].

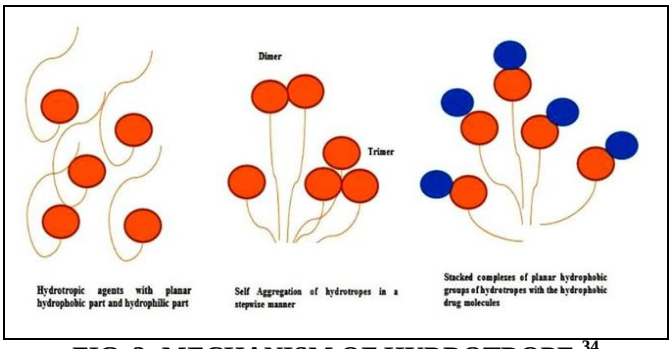


FIG. 3: MECHANISM OF HYDROTROPE [34]

Initially, hydrotrope molecules undergo primary association in a pairwise manner which is followed by consecutive steps to form trimers, tetramers, and so on and these complexes (trimers, tetramers) could then lead to higher aqueous solubility. These outcomes have evolved from the fluorescence emissions methods [29], crystallography analysis, molecular dynamics replication, and thermodynamic solubility experiments [30, 31, 32]. Apart from these, they may act as bridging agents by reducing the Gibbs energy to increase the solubility of a

solute [31]. Simply, the structure of the hydrotrope-water mixture around the drug molecule is the true key towards understanding the origin of the self-aggregation potential [33].

Structure-breaker and Structure-maker: In hydrotropic solubilization technique an electrostatic force of the donor-acceptor molecule plays a vital role; hence, they are also termed as a structure-breaker and a structure-maker [35, 36]. Solutes which are capable both of hydrogen donation and acceptance help to enhance solubility. Hydrotropic agents, such as urea, exert their solubilizing effect by changing the nature of the solvent, specifically by altering the solvent's ability to participate in structure formation or its ability to engage in structure formation *via* intermolecular hydrogen bonding [37].

Structure-breaker hydrotropes are known as chaotropes while structure-maker hydrotropes are known as kosmotropes [38]. Kosmotropes reduce the critical micelle concentration (CMC) by increasing the hydrophobic interaction which decreases the cloud point. A kosmotrope influences the cloud point in two ways, *i.e.*, it helps (i) to form bigger micelles and (ii) to decrease hydration. In the case of amphiphilic drugs, promazine hydrochloride (PMZ) and promethazine, cyclodextrin act as water structure-makers and reduce cloud point [39].

Ability to Form Micelle-like Structures: This mechanism is based on the self-association of hydrotropes with solutes into a micellar arrangement [40]. They form stably mixed micelles with a solute molecule decreasing the electrostatic repulsion between the head groups [41]. Hydrotropic agents, such as alkyl-benzene sulfonates, lower alkanoates, and alkyl sulphates, exhibit self-association with solutes and form micelles. Aromatic anionic hydrotropic agents, *i.e.*, nicotinamide, improve the solubility of riboflavin *via* a self-association mechanism [42]. In the case of PMZ, anionic hydrotropic agents, such as sodium salicylate, form stably mixed micelles by decreasing the electrostatic repulsion between the head groups of PMZ [41].

Fluctuation Theory of Solutions: To determine the mechanism of hydrotropic solubilization some researchers also illustrate the fluctuation theory of solutions (FTS). Fluctuation theory of solutions has recognized two chief factors of hydrotrope induced solubilization:

(i) Hydrotrope solute interaction;

(ii) Water activity depression.

The former is conquered by hydrotrope solute association while the later is improved by ionic dissociation and hindered by the self-aggregation of the hydrotropes [43].

Apart from the above-mentioned mechanism, nature and the concentration are the drawing forces for the solubilizing potential of hydrotropes. An aromatic hydrotropic agent with a planar structure interacts with solute molecules *via* inducing stacking aggregation mechanisms [44, 45]. In aqueous solutions, caffeine exhibits parallel stacking to solubilize the riboflavin [46]. At higher concentrations, anionic hydrotropic agents decrease the cloud point while at low concentrations increase the cloud point. Cationic and non-ionic hydrotropes show a sheer rise in the cloud point of amphiphilic drugs. The extent of the cloud-point variation for using different hydrotropes does variously depend on their nature and structure [47].

Hydrotropes in high concentrations (0.1-0.8 M) form aggregates and decrease the cloud point of amphiphilic drugs while in lower concentrations they increase the cloud point of amphiphilic drugs [48]. The hydrotrope concentration plays an important role in the solubilization mechanism of drug molecules. Sodium benzoate and sodium salicylate, when employed to enhance the aqueous solubility of nifedipine, illustrated the complexation type of interaction at a low concentration and aggregation at a high concentration [49].

Hydrotropic solubilization of nimesulide exhibits molecular aggregation at higher hydrotrope concentration and weak ionic interactions at a lower hydrotrope concentration [50]. Dexibuprofen, when combined with hydrotropic agents and investigated by the Differential scanning calorimetry (DSC) and the Infrared (IR) spectroscopy, demonstrated intermolecular interact-tions between the drug and the hydrotropic agents, which increased solubility and dissolution rate of the drug [51].

Advantages of Hydrotropic Solubilization Technique:

- It precludes the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost, *etc.*
- It is a new, simple, cost-effective, safe, accurate, precise and environmentally friendly method for the analysis of poorly water-soluble drugs by titrimetric and spectrophotometrically precluding the use of organic solvents [52].
- It only requires mixing the drug with the hydrotrope in water.
- Hydrotropy is suggested to be superior to another solubilization method, such as miscibility, micellar solubilization, co-solvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of the emulsion system.

Disadvantages of Hydrotropic Solubilization Technique: [53]

- There are issues related to toxicity associated with excess use of hydrotropic agents.
- The relatively high concentrations required to reach the MHC limits the commercial application of hydrotropes.
- There are chances of the weak interaction between the hydrotropic agent and drugs.
- As there is the use of water as a solvent, complete removal of water cannot be achieved.

Mixed Hydrotropy: Mixed hydrotropic solubilization technique is the phenomenon to enhance the solubility of poorly soluble drugs using blends of hydrotropic agents, which may give synergistic enhancement effect on the solubility of poorly soluble drugs, and also reduce the side effects due to a reduction in the concentration of individual hydrotropic agents [54].

Advantages of Mixed Hydrotropic Solubilization Technique: [55]

- It may reduce the large total concentration of hydrotropic agents necessary to produce a modest increase in solubility by employing a combination of agents in lower concentration.
- It is a new, simple, cost-effective, safe, accurate, precise and eco-friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble drugs.
- It precludes the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost, *etc*.

Novel Pharmaceutical Applications of Hydrotropes in Various Fields of Pharmacy: Hydrotropes have many realistic applications in both the biomedical and the engineering fields. The uses involve the development of pharmaceutical formulations, foodstuff, detergent solutions, solute separation processes, paint industry, coatings, plastic additives, selective separation and alterations in reaction kinetics. In this connection, various applications related to the development of pharmaceuticals are discussed.

Hydrotropes as Drug Carriers: Hydrotropic agents have a unique potential to act as carriers for active pharmaceutical ingredients. They can generate dynamic, non-covalent assemblies, *i.e*., clusters in aqueous solutions. In the presence of hydrophobic compounds, these clusters are stabilized by the formation of long-lived, highly stable mesoscopic droplets due to a phenomenon known as 'mesoscale solubilization.'

Such materials can help in processing various products ranging from pharmaceuticals, cosmetics, and agrochemicals [56]. Subtle changes in surfactant geometry lead to a marked effect on the macroscopic rheological behavior of the system. These micellar solutions act as a template for tissue engineering and as a modifier of the drug delivery [57].

Additionally, hydrotropes are of considerable importance in various applications, such as oil/water (o/w) microemulsion stabilizers, viscosity modifiers, cleaning agents, solubilizers in formulation development [20]. As they act at the molecular level, hydrotropes provide better efficacy in the 'bottom-up' techniques than the 'top-down' ones [58]. Considering these functionalities, formulation scientists are fabricating several drug delivery systems based on the hydrotropic approach to enhance the therapeutic efficacy of critical drug molecules.

Solid Dispersions (SD): They are the most popular ways of improving the drug release of poorly soluble drugs. It is a molecular mixture of poorly water-soluble drugs in hydrophilic carriers wherein the polymer properties drive the drug release profile. It helps to enhance the solubility and dissolution profile of poorly water-soluble drugs. Commonly used polymers in preparation of SD are povidone, cyclodextrin, starch, hydroxypropyl methylcellulose, ethylcellulose, hydroxypropyl-cellulose, polyethyleneglycols and silica [59, 60]. A single hydrotrope or a blend of them has been effectively used to formulate the solid dispersions. In the case of solid dispersions, hydrotropes enhance solubility as well as dissolution kinetics due to complete amorphization and intermolecular hydrogen bonding with drug molecules (see **Table 4**).

TABLE 4: EXAMPLES OF SOLID DISPERSIONS USING HYDROTROPIC AGENTS

Drug	Hydrotropic agent	Key finding	Reference
Norfloxacin	Sodium benzoate	9.56 fold enhancement in aqueous solubility	61
Aceclofenac	urea 20% and sodium citrate 10%	1.7 fold improvement *in-vitro* dissolution	62
Theophylline	urea 5% and sodium citrate 10%	142.26 times improvement in aqueous solubility	63
Diclofenac sodium	urea 20% and sodium citrate 10%	250 times improvement in aqueous solubility	64
Lurasidone hydrochloride	Nicotinamide, sodium benzoate and sodium citrate	Improvement of drug release	65
Pizotifen malate	Povidone (Kollidon 12)	Improvement in aqueous solubility	66

Transdermal Formulations: Transdermal administration of drugs provides the benefits of achieving a remedial effect without the risks of impending side effects that may occur after oral administration. In transdermal formulation selection of a suitable drug, the carrier is very important since it can affect percutaneous absorption [67]. A 5-Fluorouracil transdermal formulation was prepared using polyglycerol fatty acid monoesters (PGMC) as a hydrotrope. The mean particle size of the solution consisting of PGMC was approximately 14 nm. The hydrotropic transdermal formulation enhanced skin permeation of 5-Fu due to the ability of the hydrotrope to form aggregates [68].

Specifically, in the topical formulation, the value of the distribution coefficient (logD) of a compound played a vital role insolubilization. It showed a crucial impact on the solubility enhancement factor (SEF). This factor is a ratio of the solubility of a substance in the ternary mixture to its solubility in a pure solvent under identical temperature conditions. All compounds with logD values between 2.0 and 4.5 showed a SEF more than 5 in 40% aqueous solutions of urea while with a logD value below 2 or above 5, SEF was less than 5. In some cases such as diclofenac and prednicarbate, SEF achieved a value that was more than 5 at 5% urea and more than 250 at 20% urea [69].

Semisolid topical formulations containing paraben were prepared with nicotinamide which helped to reduce the stratum corneum vehicle partition coefficient. Nicotinamide potentiated the paraben dissolution in aqueous media (solutions, gels) and reduced their partitioning in the oily phase, thereby also reducing the toxicological risk [70].

Parenteral Formulation: Parental formulations can be the administration *via* various routes, such as intravenous, intramuscular, intra-arterial, subcutaneous and intradermal. Currently, parenteral products are the key element for therapeutic aliments in hospitalized patients. These products provide various advantages, such as a lower dosing frequency, and rapid onset of action along with good bioavailability.

In addition to these conventional parenteral products, novel parenteral delivery systems, like liposomes, nanoparticles, implants, patches are also available for controlled, sustained and active targeted drug delivery [71]. An aqueous injection of aceclofenac was prepared using mixed hydrotropic solubilization (20% urea and 10% sodium citrate) technique *via* lyophilization. The solubility enhancement of aceclofenac was more than 250 folds, and additionally, it also exhibited better physical and chemical stability also [72].

The aqueous injectable formulation of indomethacin was prepared using sodium p-hydroxy benzoate, sodium benzoate, urea and nicotinamide as hydrotropes. The hydrotropic solubilization of indomethacin at a lower hydrotrope concentration was attributed to weak ionic interactions while that at higher hydrotrope concentration was due to molecular aggregation. Indomethacin exhibited the highest and lowest solubility in sodium p-hydroxybenzoate and urea, respectively. Also, the prepared formulation showed better physical and chemical stability throughout six months [73]. An injectable nifedipine formulation was prepared by a mixed hydrotrophy technique (30% sodium benzoate and 30% sodium salicylate). It showed a better aqueous solubility profile and stability throughout one month [74]. A temazepam aqueous injection was prepared by lyophilization using sodium salicylate and nicotinamide as hydrotropes, and the solubility was increased due to an increase in hydrogen bonding between the drug and hydrotrope mixtures [75].

Miscellaneous: 2- Hydroxypropyl –beta - cyclodextrin (2-HP-beta-CD) was used to wrap methyltestosterone (MeT) moiety in the inclusion complex of MeT -2 –HP –beta -CD. The intermolecular hydrogen bonding between MeT and 2-HP-beta-CD helped to enhance the solubility of MeT. The prepared MeT2-HP-beta-CD complex also showed 7-fold improvement in the oral bioavailability of MeT [76]. Paclitaxel-beta-cyclodextrin functionalized hyperbranched polyglycerol (HPG) micelles were prepared with an objective of solubility enhancement. The prepared micelles showed a multimolecular spherical nature with the particle size of 200 to 300 nm and good dispersity. It showed a burst release followed by continuous extended release.

Moreover, MTT analysis showed good biocompatibility and a promising hydrophobic drug delivery system [77]. Griseofulvin suspensions were prepared using the aqueous phase of sodium benzoate. The particle size of the prepared suspension ranged from 10 to 20 μm and also showed 70% drug release at the end of 45 min [78]. Floating microspheres of furosemide were prepared with Eudragit RSPO and niacinamide by the solvent evaporation method. The optimized formulation exhibited a 98.2% encapsulation efficiency and 145 nm particle size in the average. Surface morphology displayed a hollow spherical structure with a smooth outer surface. Enhanced drug solubility was due to complete amorphization and intermolecular hydrogen bonding between the drug and the hydrotropes.

Furthermore, it illustrated sustained release in an acidic environment and stability up to one month [79]. Starch gels were prepared without heat treatment or chemical modification by using sodium salicylate as a gelling agent. Release patterns of the gels were studied using riboflavin as a prototype drug. Riboflavin showed consistent diffusion controlled kinetics. The pattern of the drug release depended on the initial loading levels and the starch content of the gels. Thus, hydrotrope-gelled starch proved to be a better vehicle for topical drug delivery [80].

Titrimetric & Spectrophotometric Estimations: The analysis of poorly aqueous soluble drugs is commonly carried out by the spectrophotometric method which involves the use of various organic solvents, like acetone, acetonitrile, benzene, carbon tetrachloride, diethyl ether, ethanol, methanol, and toluene. The main limitations related to these organic solvents are their volatile nature, toxicity, flammability, and high cost. To overcome these limitations, hydrotropic solutions are used.

Green Chemistry: This is a scientific field that has arisen in the 1990s. It studies enhancements of chemical processes that can have a beneficial impact on the environment.

Separation of Mixture: Hydrotropic solutions possess high industrial demand due to their easy availability, good recovery, non-inflammability and high separation factors without any solutes emulsification problem [81, 82, 83]. It helps to enhance the solubility of various organic solutes such as acids, alcohols, aldehydes, esters, fats, hydrocarbons and ketones [84]. The concentration and hydrophobic parameters (the surface area, the molar volume of the hydrophobic parts) of hydrotropes appear to be important in solute separations [85]. The influence of a chain length of a hydrotropic agent helps to improve solute recovery **Fig. 4**. The addition of the short chain of cationic hydrotropic agents to sodium dodecyl sulfate (SDS)

phase helped to enhance oil recovery [86]. Hydrotropes separate the close-boiling isomeric components from their binary mixtures. They are also used to extract various bioactive components from the plant material.

In addition to separation, hydrotropes are also useful in improving enzymatic hydrolysis efficiency. Hydrotropic pre-treatment helps to augment enzymatic hydrolysis efficiency of common reed and sugar cane bagasse to produce fermentable sugar [87, 88]. In the case of enzymatic hydrolysis of polysaccharides, it significantly increases the glucose yield [89]. Olefinic compounds, like sodium cinnamate (Na-CIN), exhibit the photoswitchable recovery of solute under exposure to UV irradiation. Various organic solutes, such as cinnamic acid, aspartic acid, curcumin, thymol, benzocaine and natural compounds, like forskolin and curcumin, are easily recovered under UV irradiation with the help of Na-CIN 90. Hydrotropic solubilization helps to enhance the aqueous solubility of rapamycin, a poorly water-soluble immunosuppressive drug, up to a 1000 times [91]. In extractive isolation process, use of hydrotropic agents reduce the use of harmful organic solvents and keep the process environmentally friendly.

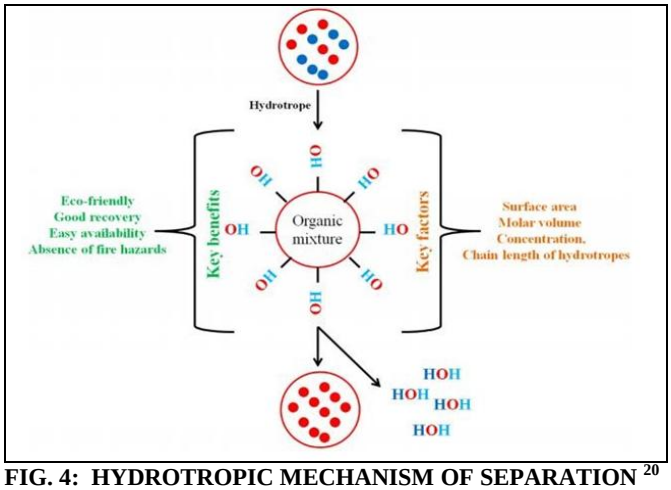


FIG. 4: HYDROTROPIC MECHANISM OF SEPARATION [20]

Green Synthesis: Hydrotropic agents provide a simple, efficient and green platform for various industrial organic transformations. Moreover, being economical, non-toxic, non-flammable and eco-friendly, hydrotropic solutions possess surplus physical and chemical features required as alternate green solvents for organic reactions. Within the outline of green chemistry, the aqueous hydrotropic method offers several advantages, such as trouble-free handling, cleaner reaction profile, high conversion rate and short reaction time, making it a useful option for rapid synthesis. Another important characteristic of the hydrotropic medium is its simple recovery from the reaction mixture and its recyclability. Furthermore, the easy recovery of products from hydrotropic solutions makes this protocol an attractive green chemistry approach [20].

Cosmeceuticals: Cosmeceutical is the rising branch of science which refers to an agent whose purpose was that of a cosmetic, to improve appearance, but had the pharmacological action of a drug [92]. Hydrotropic agent niacinamide regulates cellular metabolism and cell renewal, and due to its numerous cosmetic advantages, it has been used in recent years increasingly often in concentrations of up to 5 % as an anti-aging agent in cosmeceuticals. It significantly reduces signs of skin aging such as hyperpigmentation, skin redness, senile lentigines, yellow discoloration, and large pores. Further, niacinamide with very good tolerability leads to a significant improvement of skin elasticity and fine wrinkles [93].

Another example of hydrotropes as the safe ingredients in cosmetics is a patented invention known as Compositions containing adenosine and the hydrotropes caffeine and nicotinamide for cosmetic use. The present invention provides aqueous compositions comprising at least one compound selected from the group consisting of adenosine and adenosine analogs, and at least one hydrotrope in an amount effective to solubilize in water, for cosmetic uses. The hydrotropes used in the inventions are nicotinamide (vit. B3), caffeine, sodium salicylate, urea, hydroxyl ethyl urea.

The suitability of a hydrotrope for use in cosmetic compositions can be determined using tests known in the art for determining effects on skin, and toxicity to humans. An advantage of using hydrotropes is that, once a stable solution is obtained, further dilution won't influence the stability. At least one hydrotrope refers to one or a combination of two or more hydrotropes. The inventor ZhiPhan and Jean-Thierry Simonnet said that One or combination of two or more hydrotropes could be used to improve the solubility of adenosine or adenosine analog in water [94].

CONCLUSION: By this review, we conclude that the solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation design and development. Many useful drugs may be abandoned due to their poor aqueous solubility. There are various solubility enhancement techniques to enhance the solubility of poorly aqueous soluble drugs, but the selection of proper solubility enhancement technique is the key to ensure the good formulation like good oral bioavailability, reduced dosing frequency, better patient compliance and low cost of production and all these features can be achieved by employing hydrotropic solubilization technique. In addition to this hydrotrophy is the novel, simple and eco-friendly method for solubility enhancement of poorly soluble drugs. This technology is expected to transform the advances towards enhanced therapeutic delivery of poorly soluble drugs as well as critical moieties with a narrow therapeutic index.

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