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A REVIEW ON HYDROTROPY: THE APPROACH TOWARDS GREEN CHEMISTRY

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ABSTRACT

The discovery and development of new drugs benefit human beings and play a significant role in the world. The solubility of drugs is one of the primary factors to be taken into account and given attention in the development of drugs in the pharmaceutical industry. Among the newly discovered drugs, for both lipophilicity and solubility, drugs with low water dispersibility are responsible for around 40% of market failures. Initially, there was a barrier to both development and clinical testing, while now, examine the pharmacological effects of new drugs. These days, the oral route is accommodated route for drug delivery as compared to other methods because of its administrative simplicity and cost-effectiveness. Hydrotropic solubilization technique is one of the methods that has been used to improve the solubility of poorly soluble drugs to prevent these problems. Also, the benefit of specific qualities, such as excellent selectivity, non-flammability, environmentally friendly, ease of availability, and cost affordability make this method beneficial and also preferable to other methods of solubilization. These days, hydrotropic agents are useful to produce various dosage forms, including injections, orally disintegrating tablets, and solid dispersions. In this review, an effort has been made to display the hydrotropic solubilization method is the approach to green chemistry.

KEYWORDS: Solubility, Hydrotropy, Hydrotropic agent, Poor water soluble drugs, Mixed hydrotropy, Green chemistry.

INTRODUCTION

The current major issue in the pharmaceutical industry is ways to improve drug aqueous solubility, as about 40% of newly identified drug candidates have poor aqueous solubility. The solubility of a drug is one of its most important qualities, as it is required to get the desired pharmacological reaction.[1]

Many newly created drug molecules have lipophilicity and poor water solubility by nature. Various organic solvents such as methanol, chloroform, dimethyl formamide, and acetonitrile are utilized to solubilize these poorly water-soluble drugs. However, there are significant disadvantages to using organic solvents, such as their high cost, volatility, pollution, and various toxicities. As a result, a hydrotropic agent, a safe, environmentally friendly, and cost-effective solution can be utilized.[2]

Hydrotropy was first reported by Neuberg in 1916.[3] Hydrotropy is a solubilization phenomenon in which a substantial amount of a second solute increases the aqueous solubility of another solute. Sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate are just a few examples of concentrated aqueous hydrotropic solutions.[4]

Solubility

The phenomenon of dissolution of a solute in the solvent to give a homogeneous system is called solubility. It is defined in quantitative and qualitative terms. The concentration of salute in a saturated solution at a certain temperature is term as quantitative solubility and the spontaneous interaction of two or more substance to form a homogeneous molecular dispersion is term as qualitative solubility.[5]

According to pharmacopoeia, the solubility is defined in terms of number of millilitres of solvent required to dissolve 1g of solute and if the specific solubilities are unknown, the Pharmacopoeia provides general term to define a range of solubilities[6] as shown in the table 1.

Table 1: Solubilities as per Pharmacopoeia[6]

Sr. No	Solubility Terms	Relative Amounts of Solvents to Dissolve 1 part of Solute
1.	Very Soluble	Less than 1
2.	Freely Soluble	From 1-10
3.	Soluble	From 10-30
4.	Sparingly Soluble	From 30-100
5.	Slightly Soluble	From 100-1000
6.	Very slightly soluble	From 1000-10,000
7.	Insoluble or practically insoluble	More than 10,000

Important of Solubility

Solubility is one of the most important characteristics to reach optimum concentration of drug in the systemic circulation for producing essential pharmacological response.[7] Solubility also plays important role for dosage forms such as parental formulation.[8] After oral administration, high dose requires for poorly water soluble drugs in order to reach therapeutic plasma concentration. Low water solubility is a major problem in both formulation and generic development of novel chemical entities. Any drug that needs to be absorbed must be present in the form of an aqueous solution at the absorption site. For the liquid formulations, water is the choice of solvent. The majority of drugs are either weakly acidic or weakly basic with poor aqueous solubility. More than 40% NCEs (Novel Chemical Entities) producing in pharma industries are nearly water insoluble. These poorly water soluble drugs shows slow drug absorption which results in inadequate and variable bioavailability as well as gastrointestinal mucosal toxicity. Solubility is the most important rate limiting parameter for orally administered drugs to achieve their required concentration in systemic circulation for pharmacological response. For the formulation scientists, problem of solubility is the major concern.[9] One of the most challenging aspect of drug development process, particularly for the oralare numer drug delivery system, is improving drug solubility and thus oral bioavailability. There are variety of methods available for improving the solubility of poorly water soluble drugs and that have been documented in the literature. These method are selected on the basis of certain factors such as characteristics of drug under consideration, nature of excipients to be chosen and the nature of intended dosage form.

Need of Solubility

The factors affecting GIT drug absorption such as poor water solubility and poor membrane permeability of the drug molecule. When a drug is administered orally, it must first dissolve in the gastric and intestinal fluids before it can penetrate through the GIT membrane. As a

result, the solubility and dissolution rate of poorly water-soluble drugs should be improved.[10-11] so for this, the drug must be available at the proper site of action with optimal concentration.[12] The therapeutic effectiveness of a drug may be influenced by its solubility and bioavailability. Solubility is the most important parameter for achieving the required drug concentration in the systemic circulation for the pharmacological response.[13]

The process of Solubility

The solubilization process is defined as the breakdown of intermolecular or interionic bonds in the solute, separation of the solvent molecules that give space for the solute in the solvent, and then contact between the solvent and the solute molecules or ions.[14] The concept of holes or cavities in liquids is rising due to this. The solubilization process can be divided into three stages.[15] As a result of this total work, an extremely simplified strategy is (w22 + w11 2w12). The entire process is represented in Fig. 1.

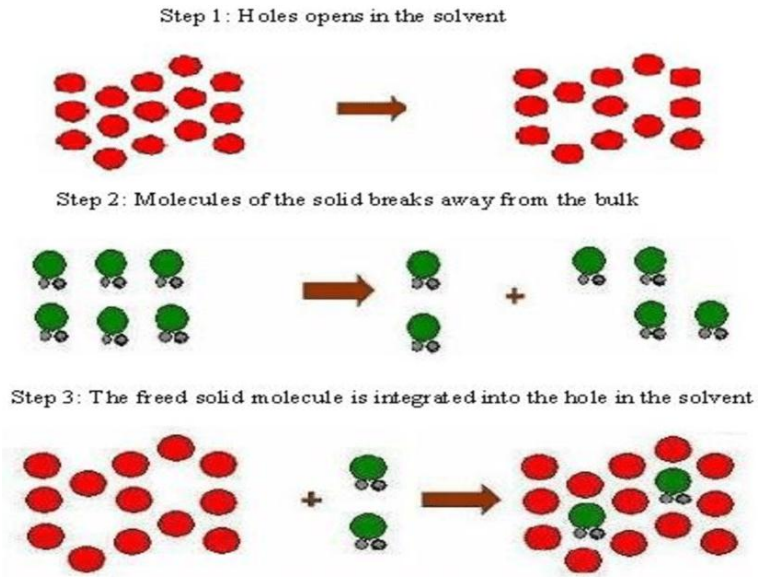

Fig. 1: Diagrammatic Representation of the Process Involved in the Dissolution of a Crystalline Solute[16]

1. The first step in the Solubilization process involves 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.
2. The removal of a molecule from the solute phase at a definite temperature. The work is done by removing a molecule from a solute so that it is converted into the vapour 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.

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 the solute with the solvent. The hole or cavity in the solvent created in step 2 is now closed, and an additional decrease in the energy, 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 the temperature and pressure of the system.[17]

1. **Particle Size:** The particle size of the solid affects the solubility due to a decrease in the particle size which results in an increase in surface area to volume ratio. The larger surface area allows more interaction with the solvent which increases the solubility.[18]
2. **Temperature:** Solubility is affected by temperature. If the energy is absorbed by the solution process, the solubility will rise as the temperature rises. Solubility will decline with rising temperature, as though the solution process releases energy. In general, a solid solute becomes more soluble as the solution's temperature rises. A few solid solutes are less soluble in warm solutions. All gases become less solubilized as the solution's temperature rises.[19]
3. **Pressure:** For solids and liquids, an amendment in pressure has much no impact on solubility, except for vaporized solutes, a rise in pressure will increase solubility and a decrease in pressure decreases the solubility eleven.[19]
4. **Nature of the matter and Solvent:** the character of matter and solvent depends on the concentration of matter in a very specific amount of solvent at a selected temperature. For example, one g of lead (II) chloride is often dissolved in a hundred g of water at temperature wherever two hundred g of metallic element chloride are often dissolved within the same condition. The distinction between the solubility of those 2 substances is that the results of variations in their natures are twelve.[20]
5. **Molecular Size:** Molecular size will affect solubility. The larger the molecular size or, the upper its relative molecular mass, the less soluble is that the substance. Larger molecules as tougher to surround with solvent molecules to solvate the substance. Within the case of organic compounds, the quantity of carbon branching can increase the

solubility as additional branching can cut back the molecular size (or volume) and build it easier to solvate the molecules with solvent thirteen.[21]

6. **Polarity:** Solubility is suffering from the polarity of the matter and solvent molecules. Generally, non-polar matter molecules can dissolve in non-ionic solvents, and polar matter molecules can dissolve in polar solvents. The polar matter molecules have a positive and a negative finish to the molecule. If the solvent molecule is additionally polar, then the positive ends of solvent molecules can attract the negative ends of matter molecules. This is often a kind of building block force referred to as dipole-dipole interaction. All molecules even have a kind of building block force abundant weaker than the opposition forces known as London dispersion forces wherever the positive nuclei of the atoms of the matter molecule can attract the negative electrons of the atoms of a solvent molecule. This offers the non-polar solvent an opportunity to solvate the matter molecules.[22]

Hydrotropy

Hydrotropy is given by the scientist Neuberg Carl A. In 1916. Hydrotropes are water soluble and surface active compounds that aid in the solubility of the organic solute. They have a molecular phenomenon by introducing a second solute (hydrotropes) which is beneficial for enhancing the water solubility of poorly water-soluble drugs. Hydrotropes is a solubilization technique in which multiple chemical components called hydrotropes are employed to increase the solubility of poorly water-soluble drugs under normal conditions.[23]

Hydrotropic Agents

The hydrotropic agents are non-micelle forming substances, either liquid or solids, organic or inorganic, capable of insoluble solubilizing compounds. Ionic organic salts have been refer as hydrotropic agents. Additives or salts that increase the solubility of a solute in a given solvent are said to “salt in” the solute, while salts that decrease the solubility are said to “salt out” the solute. Several salts with large anions or cations that are themselves very soluble in water result in “salting in” of nonelectrolytes called “hydrotropic salts” a phenomenon known as “Hydrotropism”.[24-27]

Hydrotropic colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotropy designates the increase in solubility in water due to the presence of a large number of additives. A week of contact exists between the hydrotropic agent and the solute in hydrotropic solutions, which lack colloidal characteristics. The term

"hydrotropy" describes the rise in water solubility brought on by the presence of many chemicals.

Table 2: Classification of Hydrotropic Agent.[28]

Sr. No.	Class	Example
1.	Organic acid and their metal salts	Citric acid, Benzoic acid, Sodium salicylate, Sodium benzoate, Sodium citrate, Sodium acetate, Sodium ascorbate, Potassium citrate
2.	Urea and its derivates	Urea, N,N-dimethyl urea
3.	Alkaloids	Caffeine, Nicotinamide, N,N-diethyl nicotinamide, N, N-dimethyl benzamide
4.	Phenolic derivatives	Resorcinol, pyrogallol, catechol, a,b-napthols
5.	Surfactants	Sodium dodecyl sulphate
6.	Aromatic cations	Procaine hydrochloride, Para amino benzoic acid

Structure of Hydrotropic Agents

Hydrotropes contain both hydrophobic and hydrotropic groups so it shows amphiphilic nature. However, the hydrophobic percentage is small. The hydrotropic efficacy is generally better when the layer is the hydrophobic component. Hydrotropic agents are usually non-micelle forming substances. They might be anionic, cationic, neutral, organic or inorganic, and liquid or solid. We can improve the water solubility of organic substances by forming stack-type aggregation, allowing hydrotropic agents to be freely soluble in organic solvents[29-33] as shown in Fig. 2.

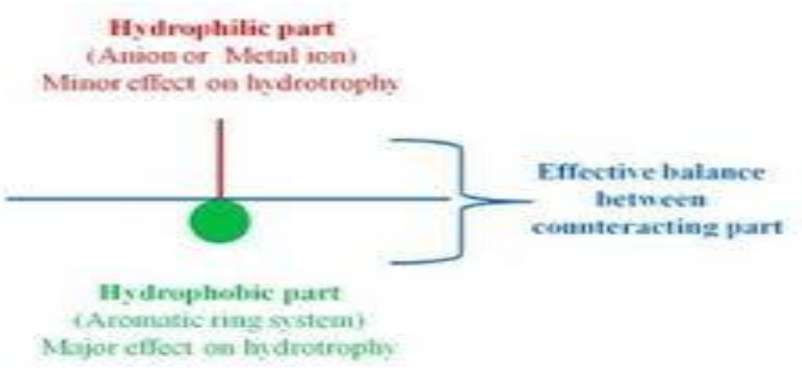

Fig. 2: Structure of Hydrotropic Agent.[34]

Mechanism of hydrotropic Agents

The hydrotropes that can increase the solubility of a poorly soluble medication are dependent on the molecular self-association of hydrotropes and the association of hydrotropes molecules

with the solute. Although hydrotropic agents are widely used in various industries only limited information is available on the mechanism of hydrotropic Agents. To further understand the mechanics of hydrotropy, various hypotheses and research attempts are being conducted. Three different designs can be used to condense the available proposed mechanisms.

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

a) Self-aggregation potential: Minimum Hydrotropic Concentration (MHC) is the critical concentration at which hydrotrope molecules begin to combine, i.e., exhibit self-aggregation potential. The ability of these molecules to self-assemble controls how easily hydrotropic agents can dissolve. Their amphiphilic characteristics and the make-up of the solute molecule may affect their ability to self-assemble. This might primarily demonstrate the volume-fraction-dependent solubilization potential. The hydrotrope molecule may first associate with other molecules in a pair-wise fashion. Several processes could come after this to create trimers, tetramers, and so forth. Complexes that are created may result in greater aqueous solubility. For this, various techniques can be applied, including investigations on thermodynamic solubility, fluorescence emission, crystallographic analysis, and molecular dynamics replication. As bridging agents, they can also make a solute more soluble by lowering Gibb's energy. The structure of the hydrotrope-water mixture surrounding the drug molecule is a real key to comprehending the origin of the self-aggregation potential.

b) Structure-breaker and structure-maker: Here, in a hydrotropic solubilization procedure, the electrostatic force of the donor-acceptor molecule proved crucial. As a result, they are often referred to as a structure maker and breakers. When solutes that are both acceptable and capable of donating hydrogen are present, the solubility may be enhanced. Some solubilizing chemicals alter the character of the solvents by becoming hydrotropic agents, such as urea. This is specifically accomplished by changing its capacity to participate in structure formation via intermolecular hydrogen bonds or by changing the solvent's capacity to do so. The terms kosmotropes and chaotropes, respectively, refer to the structure-maker hydrotropes and the structure-breaker hydrotropes. The cloud point is influenced by both of them. The Critical Micelle Concentration (CMC), which affects the cloud point, can be decreased by kosmotropes by boosting hydrophobic interactions. Kosmotropes can have two effects on the cloud point. For example, it promotes the formation of larger micelles and reduces hydration.

c) Ability to form micelle-like structures: The self-association of hydrotropes with solutes into a micellar structure serves as the basis for this process. Together with a solute molecule, they create stable mixed micelles that reduce the electrostatic attraction between the head groups. Some hydrotropic substances, such as lower alkanoates, alkyl sulfates, and alkyl benzenesulfonates, self-associate with solutes and form micelles. Some aromatic anionic hydrotropic agents, such as nicotinamide, increase the solubility of riboflavin by a self-association mechanism. By reducing the electrostatic repulsion between the head groups, sodium salicylate-like anionic hydrotropic agents produce stable mixed micelles.[35-39]

Characteristics of hydrotropes

1. Completely soluble in water and practically insoluble in the framework.
2. Because of their amphiphilic nature, hydrotropes are surface-active and aggregate in an aqueous solution.
3. Should not produce any temperature when disintegrated in water.
4. Cheap and easily accessible.
5. Non-poisonous and non-reactive.
6. When dissolve in water, it is unaffected by temperature.
7. Other characteristics of hydrotropes are pH-independent, high selectivity, and lack of emulsification.

Significance of hydrotropes

1. Organic compounds, dyes, drugs, and biochemicals have all been solubilized with hydrotropes.
2. Hydrotropes have been used in the development of extractive separation processes for protein separation and distillation as an extractive solvent for the separation of close boiling mixtures.
3. Aqueous hydrotropes solutions are a safe and effective medium for extracting natural products as well as conducting organic synthetic reactions.
4. Hydrotropes have a wide range of uses in detergent formulation, health care, and household applications.
5. They've been used to speed up the rate of heterogeneous reactions.
6. They are used as a fragrance extraction agent.
7. In chemical formulations use as fillers and extenders.
8. In the development of pharmaceutical formulations.

9. In nanotechnology, hydrotropic solubilization (by controlled precipitation).
10. Hydrotropy, which allows for the rapid release of water from the suppositories.
11. Used in the separation of water emulsion and the preparation of drilling well fluids.
12. It can be used in the petroleum industry, as well as in tertiary petroleum recovery and other processes.
13. Hydrotropes increase the cloud point of detergents and change the viscosity of surfactant formulations.
14. Aqueous hydrotropes solutions are a safe and effective medium for extracting natural products as well as conducting organic synthetic reactions.

Advantages of Hydrotropic Solubilization Technique

- It eliminates the usage of organic solvents, which eliminates issues such as residual toxicity, error due to volatility, pollution, and cost.
- It is a new, cost-effective, safe, accurate, precise, and environmentally friendly approach for the titrimetric and spectrophotometric analysis of weakly water-soluble drugs that do not require the usage of organic solvents.[40]
- It is only required to combine the hydrotropes with the drug in the water.
- Hydrotropy is seen to be better than alternative solubilization methods such as miscibility, micellar solubilization, solvency, and salting in because the solvent property is independent of pH, has great selectivity, and does not require emulsification.
- It does not necessary for the use of organic solvents or the chemical modification of hydrophobic drugs, it does necessary for the formation of the emulsion system.

Disadvantages of hydrotropic solubilization technique[41]

- Excessive usage of hydrotropic chemicals has been linked to toxicity concerns.
- Commercial application of hydrotropes is limited due to the very large concentrations required to reach the MHC.
- There's a potential that the hydrotropic agent and drug will have a weak interaction.
- Because water is used as a solvent, total water removal is impossible.

Commonly used Hydrotropes

In the solution, the Hydrotropes are known to self-assemble.[42] It is difficult to classify hydrotropes based on their molecular structure. A wide variety of substances have been reported to show hydrotropic behavior. Some examples may include ethanol[42], aromatic

alcohols such as resorcinol, pyrogallol, catechol, and naphthols and salicylates, alkaloids such as caffeine and nicotine[43], ionic surfactants such as diacids[44], SDS (sodium dodecyl sulfate)[45], and dodecylated oxidibenzene.[46] The most studied compounds are aromatic hydrotropes with anionic head groups. Because of isomerism, they are numerous, and their effective hydrotropes action is because of the availability of interacting pi-orbitals. Salts of aromatic amines, such as procaine hydrochloride, are a few hydrotropes having cationic hydrophilic groups.[47] They are known to have effects on surfactant aggregation leading to micelle formation, phase manifestation of multi-component systems concerning Nano dispersions and conductance percolation, clouding of surfactants and polymers, and so on, in addition to increasing the solubilization of compounds in water.[42-47]

A list of drugs studied by hydrotropic solubilisation and its solubility increasing ratio is given in Table 3.

Table 3: Hydrotropic Solubilization study of various poorly water-soluble drugs.[48]

Sr.no.	Drugs	Hydrotropes	Solubility enhancement ratio
1.	Ketoprofen	2M Potassium acetate	210
2.	Hydrochlorothiazide	8M Urea	70
3.	Olenzepine	1M Sodium benzoate	60
4.	Aceclofenac	40% Urea	25
5.	Nimsulide	2M Nicotinamide	150
6.	Nalidixic	2M Sodium benzoate	90
7.	Norfloxacin	2M Sodium benzoate	60

Mixed Hydrotropes

The phenomena of enhancing the solubility of poorly soluble drugs utilizing blends of hydrotropic agents and are mixed hydrotropic solubilization technique, which may have a synergistic enhancement effect on the solubility of poorly soluble drugs while also reducing adverse effects due to lower concentrations of individual hydrotropic agents.[49]

Advantages of Mixed Hydrotropic Solubilisation Technique[50]

- By using a combination of agents in lower concentrations, it may be possible to reduce the large total concentration of hydrotropic agents which are required to produce improvement in solubility.
- It is a new, simple, cost-effective, safe, accurate, precise, and environment-friendly approach for analyzing poorly water-soluble drugs (titrimetric and spectrophotometric analysis).

- It eliminates the usage of organic solvents, avoiding issues such as residual toxicity, inaccuracy due to volatility, pollution, and cost.

Novel Pharmaceutical Applications of Hydrotropes in Various Fields of Pharmacy

Hydrotropes offer a wide range of uses in both biomedicine and engineering. Pharmaceutical formulations, meals, detergent solutions, solute separation procedures, paint industries, coatings, plastic additives, selective separation, and changes in reaction kinetics are among the applications. Various applications connected to the development of pharmaceuticals are covered in this context.

1) **Hydrotropes as Drug Carriers:** Hydrotropic agents have a special ability to transport active medicinal components. They can form dynamic, noncovalent assemblages in aqueous solutions, such as clusters. These clusters are sustained in the presence of hydrophobic chemicals by the creation of long-lived, very stable mesoscopic droplets, a phenomenon known as "mesoscale solubilization". Pharmaceuticals, cosmetics, and agrochemicals are among the products that can benefit from such materials.[51] Changes in surfactant shape have a significant impact on the system's macroscopic rheological behavior. These micellar solutions serve as a template for tissue engineering as well as a delivery modification.[52] Hydrotropes are also important in formulation development for applications such as oil/water (o/w) microemulsion stabilizers, viscosity modifiers, cleaning agents, and solubilizers. Hydrotropes have higher efficacy in "bottom-up" procedures than "top-down" techniques because they work at the molecular level. To improve the therapeutic efficacy of essential medicinal molecules, formulation scientists are developing a variety of drug delivery systems based on the hydrotropic approach.[53]
2) **Solid Dispersions:** They are the most often used methods for increasing the release of poorly soluble medicines. It's a molecular combination of poorly water-soluble medicines in hydrophilic carriers, with the polymer characteristics controlling drug release. It aids in improving the solubility and dissolving characteristics of medications that are poorly water-soluble. Povidone, cyclodextrin, starch, hydroxypropyl methylcellulose, ethyl cellulose, hydroxypropyl cellulose, polyethylene glycols, and silica are all commonly used polymers in the manufacture of SD.[54,55] the solid dispersions have been successfully formulated using a single hydrotrope or a combination of them. Because of complete amorphization and intermolecular hydrogen bonding with drug molecules, hydrotropes improve solubility and dissolution kinetics in solid dispersions.

Examples of Solid Dispersion using Hydrotropic Agents

1) **Transdermal Formulations:** The advantages of transdermal drug delivery include the ability to achieve a therapeutic impact without the risk of impending negative effects that can arise with oral administration. The carrier is highly significant in transdermal formulation selection since it can alter percutaneous absorption.[56] As a hydrotrope, polyglycerol fatty acid monoesters (PGMC) were used to make a 5-fluorouracil transdermal formulation. The average particle size of the PGMC solution was around 14 nm. Due to the hydrotrope's capacity to form aggregates, the hydrotropic transdermal formulation improved skin penetration.[57] In particular, in a topical formulation, the value of a compound's distribution coefficient (log D) played a critical role in solubilization. It had a significant influence on the solubility enhancement factor (SEF). This factor is the ratio of a substance's solubility in a ternary mixture to its solubility in a pure solvent at the same temperature. In 40 percent aqueous urea solutions, all compounds with logD values between 2.0 and 4.5 had a SEF greater than 5, while those with logD values below 2 or above 5 had a SEF less than 5. SEF obtained a value of more than 5 at 5% urea and more than 250 at 20% urea in several circumstances, such as diclofenac and prednicarbate.[58] The addition of nicotinamide to semisolid topical formulations containing paraben reduced the stratum corneum vehicle partition coefficient. Nicotinamide increased the solubility of parabens in aqueous media (solutions, gels) while decreasing their partitioning in the oily phase, lowering the toxicological risk.[59]
2) **Parenteral Formulation:** Intravenous, intramuscular, intra-arterial, subcutaneous, and intradermal most important components for the treatment of ailments in hospitalized patients. These medicines provide several benefits, including a lower dose frequency, a quick beginning of the action, and high absorption. Novel parenteral delivery technologies, such as liposomes, nanoparticles, implants, and patches, are available in addition to these traditional parenteral solutions for regulated, sustained, and active targeted drug delivery.[60] Using a combined hydrotropic solubilization process (20 percent urea and 10% sodium citrate) and lyophilization, an aqueous injection of aceclofenac was created. Aceclofenac's solubility was increased by more than 250 times, and it also displayed improved physical and chemical stability.[61]
3) **Green Chemistry:** This is a relatively new scientific topic that emerged in the 1990s. It looks at ways to improve chemical processes to have a positive impact on the environment.[62]

4) **Green Synthesis:** Hydrotropic agents provide a straightforward, cost-effective, and environmentally friendly platform for a variety of industrial organic conversions. Hydrotropic solutions also have a surplus of physical and chemical properties that are required as alternate green solvents for organic reactions, such as being cost-effective, non-toxic, non-flammable, and environmentally benign. The aqueous hydrotropic approach, which falls under the umbrella of green chemistry, has various advantages, including easy handling, a cleaner reaction profile, a high conversion rate, and a quick reaction time, making it a viable option for rapid synthesis. Another essential feature of the hydrotropic medium is its recyclability and ease of recovery from the reaction mixture. In addition, the ease with which products can be recovered from hydrotropic solutions makes this process an appealing green chemistry method.[63]

CONCLUSION

The present study concluded that the solubility of the drug is the most significant aspect that affects the formulation of the drug as well as its therapeutic efficacy, hence making it the most important aspect in formulation design and development. Many useful drugs may be abandoned due to their poor aqueous solubility. There are many solubility enhancement techniques available to improve the solubility of poorly aqueous soluble drugs, but choosing the right one is crucial to ensuring good formulation including 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 hydrotropy is a new and easy technique that is environmentally benign for improving the solubility of drugs that are poorly water-soluble and also approaches green chemistry. With the use of this technique, it is anticipated that improved therapeutic delivery of poorly water-soluble drugs with a limited therapeutic index.

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Conflict of interest

The authors declare no conflict of interest.

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