Original Article

A Review: "Hydrotropy" Techniques to increase the solubility of Drug.

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Abstract

Solubility is a crucial parameter which is desired for any dosage form to centralize the medicament and the pharmacological action to occur. The prominent challenge faced during the drug discovery is the poor aqueous solubility of the drugs which eventually lead to low dissolvability and low bioavailability of the medicament. In order to increase the solubility, various methods have been adapted. The review grabs the attention towards the concept of hydrotropy, one of the solubilization techniques, in which, adding a second solute to the primary one. It is superior with high efficiency, low side effects, high selectivity, and eco-friendly, easily available and cost effective. It is one of the techniques that enhance the systemic bioavailability and solubility to many folds with the use of hydrotropes like urea, nicotinamide, sodium benzoate, sodium citrate, propylene glycol, glycerol, PEG (200-600), PEG (2000-6000). The technique is favorable for the formulation of parenteral dosage form for poorly water soluble drug, causing the problem of gastric irritation and dysphagia. Other than parenteral it is useful for topical and oral also. Moreover, this review comes up with future insights for drug delivery and hydrotropism.

Keywords: Hydrotropy, Solubility, Hydrotropes, Solubilization, Bioavailability.

INTRODUCTION

Hydrotropy can be defined as a phenomenon which involves the solubilization where incorporation of a large amount of another solvent termed as co-solvent with aqueous phase contributes in an increase in aqueous solubility of that solute.The term hydrotropy was coined by Neuberg, in 1916 to describe the enhancement of solubility of a solute by adding a high concentration of alkali metal salts of several organic acids, example-sodium benzoate, sodium citrate, sodium citrate, urea, niacin/nicotinamide, propylene glycol, glycerin and several series of polyethylene glycol like PEG 200, PEG 400, PEG 600, PEG 1500, PEG 4000 and PEG 6000. This term has been selected to designate non-micelle forming substances either liquids or solids, organic or inorganic.

There are other two phenomena lies one- the substances added expands the dissolvability is said to be 'salting-in' the solute and the second one- lessening the solvency is said to be 'salting-out' the solute. Some salts with huge anions and cations are soluble itself in water bring about 'salting-in' are called hydrotropic salts and this magic is known as "Hydrotropism". [1,2]

Structure of Hydrotropic agent-

The hydrotropes are amphiphilic in nature as it contains both hydrophilic and hydrophobic group. Usually hydrophobic part is small, cause spontaneous self-aggregation. Critical concentration- a concentration at which self aggregation suddenly starts to occur; these hydrotropes do not have such concentration.

The chemical structure of conventional hydrotropic salts consists two essential parts; an anionic group is obviously involved in bringing out high aqueous solubility.

Planarity of the hydrotropic part has been prominence as an important factor in mechanism of hydrotropic solubilization. The planar hydrophobic structure brings about solution by a polar group are hydrotropic agents.

EL- Khordaugi suggested that hydrotropy is not confined to metal salts of organic acids but also certain cationic salts and neutral molecules may be equally contributing such as Procaine hydrochloride, PABA HCL and Cinchocaine HCL as cationic salts and neutral salts such as resorcinol, pyrogallol. By taking account high concentration or high amount of synthetic solubilizing agents, it produces a great risk to human administration.

This research h work gives a deep insight for utilizing natural hydrotropes, as the use of multiple hydrotropes reduce the concentration of individual agent and become safe and effective for human use. [3]

Characteristics of Hydrotropic agents-(4)

- Freely soluble in water.

- Do not create temperature when disintegrated in water.
- Very cheap and easy to accessible.
- When two or more hydrotropes are used together, required concentration is less as compared to single agent.
- When mixed hydrotropy concept is applied, solubility gets enhanced in many folds.

Advantages of Hydrotropic solubilization Techniques-[5,6,7,8]

- It eliminates the use of organic solvents, thus circumvent the problem of residual solvent toxicity.
- It's a novel, simple, cost effective, safe, and eco-friendly method for the analysis (titrimetric and spectrophotometric analysis) of poorly water soluble drug.
- It only requires mixing of the drug and the hydrotrope in water.
- It is superior in comparison to other solubilization method.
- The solubility is independent of pH.
- It does not require emulsification.
- It does not require structural or chemical modification for lipophilic drugs.
- Mixed hydrotropy has capacity to reduce the large concentration of hydrotropic agents needed to produce increase in the solubility.

MECHANISM OF HYDROTROPY-[9,10]

Each hydrotrope has a distinct affinity for a particular component of the mixture, which facilitates easy restoration of the hydrotrope arrangement via controlled water weakening. Dissolvability does not seem to improve even after hydrotrope expands in the fluid stage; but, as hydrotrope centralization increases as a result, the solubility of the natural chemical present in the watery stage effectively increases.

The emergence of organized collection of hydrotrope particles could be the reason for natural agents to enhance the solvency of solute in water. Due to the amphiphilic nature of the hydrotropic compound, their expansion appears to be the result of self-aggregation.

1. **Self- Association of Hydrotropes-**

The critical micelle concentration (CMC) of surfactants has been referred to as the least hydrotrope focus (MHC). Rath has highlighted the emergence of hydrotrope collections in the form of intermolecular stacks; stacking of hydrotropes as the procedure for self-affiliation. According to Balasubramanian and colleagues, the arrangement of non-covalent totals is a group subatomic wonder that contributes to hydrotrope activity. They show that the micro environmental characteristics of micelles and hydrotrope assemblies are similar-

- Hydrotrope solution's surface activity is comparable to that of micelle-forming surfactants.
- The process is cooperative, as shown by sigmoidal solubilization curves,
- Open-layer assemblies of hydrotropes can be found in their crystalline form.

2. Readiness of Hydrotropes-

A hydrotrope is an agent that makes hydrophobic mixtures soluble in liquid environments. Hydrotropes typically have a hydrophilic and a hydrophobic component (like surfactants), but the hydrophobic component is typically too small to even contemplate having the potential to cause unrestrained self-conglomeration.

3. Structure breaker and structure maker-

In a hydrotropic solubilization mechanism, the electrostatic force of the donor acceptor molecule played a vital role. As a result, they are often referred to as a structure maker and breaker. 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, 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 augmenting hydrophobic interactions. Kosmotropes can have two effects on the cloud point. For instance, it promotes the formation of larger micelles and reduces hydration.

APPLICATIONS OF HYDROTROPIC SOLUBILIZATION IN VARIOUS FIELDS OF PHARMACY-[11.12]

Both the academic world and the pharmaceutical sector rely heavily on hydrotropes. They have a wide range of practical uses in engineering and the biomedical sciences as well. They are crucial components in the processes of selective separation, reaction kinetics, and solute separation in pharmaceutical formulations. Below, various uses for the creation of medications are addressed.

- Quantitative investigation employing different hydrotropic agents, such as sodium benzoate and nicotinamide, of medications that are weakly water-soluble, such as naproxen, aspirin, furosemide, ibuprofen, salicylic acid, famotidine, and aceclofenac.
- The production of poorly soluble pharmaceuticals in solid dispersions, including the utilization of organic solvents. Celecoxib, carbamazepine, and halofantrine all use b-cyclodextrin as a hydrotropic solubilize, as does Carvedilol. Halofantrine also uses polymers PVP800.
- Using hydro solubilization to recover pure components from unprocessed pharmaceuticals
- Widespread use of mixed solvency to provide injection dosage forms for medicines with poor water solubility.
- Hydrotropy allows for the immediate release of insoluble medications from suppositories.
- Using hydrotropic solubilizers to improve permeability.
- Used in the production of syrups (for reconstitution) of medications with limited water solubility.

Parenteral Formulations-[13]

- The parenteral formulation has many advantages in the research and development of pharmaceuticals.
- It permits studies on toxicity, pharmacokinetics, and efficacy. Parenteral products should provide a number of benefits, including a quick onset of action with adequate bioavailability, improved medication soundness, and reduced dose recurrence.
- It is possible to get gradually reliable dosage by reducing the impact of nutrition through specifics.
- A needle is used to inject an intramuscular medication into the muscle.
- To reduce thickness and negative effects in parenteral, the vehicle should comprise a base amount and low centralization of the co dissolvable.
- For controlled and dynamic targeted medicine delivery, new parenteral delivery systems like nanoparticles and patches are also now available.
- Mixed solvency techniques were used to produce antibiotics for injection (sodium benzoate, urea, sodium citrate, sodium acetate, and nicotinamide)
- Antimicrobial stability and effectiveness are provided by the aqueous injection's formulation. The use of mixed solvency techniques helps a medicine become more soluble while maintaining its antibacterial effects.
- Other parenteral preparations employ hydrotropic solubilization to clarify the potential solubilization mechanism. Hydrotrope-based parenteral formulations containing piperazine exhibit improved physical and chemical stability.
- The solubility of Vitamin B2 in aqueous solution was determined using the hydrotropic effects of coffee and nicotinamide.

PHARMACEUTICAL AND INDUSTRIAL APPLICATIONS OF HYDROTROPIC AGENTS: POTENTIALS [14-15]

- Using UV-Visible spectrophotometric analysis, quantitative assessments of medicines with limited water solubility The use of organic solvents is prohibited.
- Titrimetric analysis-based quantitative assessments of medications with poor water solubility.
- Titrimetric analysis is employed to generate quantitative estimates for drugs like ibuprofen, flurbiprofen, and naproxen that are insufficiently water-soluble.
- The development of hydrotropic strong scatterings of drugs that are insufficiently soluble in water that prevent the use of natural solvents, such as felodipine, using poly-ethylene glycol 6000 and poly-vinyl alcohol.
- Preparation of poorly water-soluble medication hydrotropic solid dispersion technique.
- Hydrotropes have been used to solubilize medicines, biosynthetic compounds, and natural mixture.
- Hydrotropes have been examined in the development of extractive partition forms for the separation of proteins and refinement as an extractive dissolvable for the division of phenolic blends with close breaking points.
- Making dry syrups for poorly water soluble medications to reconstitute.
- Developing topical and injectable formulations of medications with poor water solubility.
- Hydrotropic solubilizers are also employed to enhance permeability.

- The hydrotropy, which allows suppositories to quickly release medications that are not extremely water-soluble.
- Nanotechnology makes use of hydrotropic methods (by controlled precipitation).
- The hydrotropic solubilization method can be used to separate the active ingredients from unprocessed medicines.

LITERATURE REVIEW

Daraji NK, et al., (2021) reported that the NSAID mefenamic acid (MFA) has anti-inflammatory, analgesic, and antipyretic properties. Peak plasma levels are reached in 2-4 hours, and since the half-life of elimination is approximately 2 hours, it is preferable to administer pills repeatedly 3-5 times per day. Only pills intended for oral consumption are used for administration. Parenterally delivered medications in acute circumstances may provide quick relief from severe symptoms like pain. As an alternative to the traditional tablet dosing form, an injectable version of MFA has been discovered. To enhance the water solubility of the drug, mixed solvency technique was utilized and several hydrotropic agents like sodium benzoate, sodium citrate, urea, sodium acetate, and their blend were used. MFA cannot be used in the creation of parenteral formulations due to its poor aqueous solubility. [16]

Barua D, et al., (2019) Rifabutin is a broad spectrum antibacterial medicine used to treat infections brought on by M. tuberculosis, M. avium, and M. Leprae as well as multidrug resistant TB, according to research. Rifabutin has a high permeability and is only marginally water soluble (0.19 mg/ml). For the purpose of increasing solubility and the pace at which drugs dissolve, which enhances drug release and oral bioavailability, they developed the Rifabutin Liquisolid system employing the mixed solvency idea. Different blends were created utilizing different solid solubilizers in propylene glycol, such as sodium benzoate, sodium caprylate, and niacinamide (co-solvent). In this mixture, K (35%SC+5%NM+5%SB) has the maximum solubility and has been chosen for additional research. Blend K, microcrystalline cellulose as the carrier material, and aerosil as the coating material were used to create the liquid solid system.[17]

Agrawal R. and Maheshwari RK, (2018) developed a liquisolid system (Powder formulation) of the poorly water soluble medication cefixime using the mixed solvency principle. In order to increase the drug loading capacity of the poorly water soluble drug cefixime, a combination of solubilizers, including sodium acetate, sodium caprylate, and propylene glycol, were used as mixed solvent systems. This reduced the overall concentration of solubilizers needed to produce a significant increase in solubility. Melting point, IR, UV, and DSC tests were used to describe the cefixime sample. Studies on the stability of cefixime liquid-solid formulation were conducted for two months at 30°C and 40°C. All of the formulations were discovered to be stable on a physical, chemical, and microbial level.[18]

Gahlot N and Maheshwari RK, (2018) Developed film dosage form for vaginal drug distribution that can address difficulties with poorly water-soluble drug bioavailability. They want to investigate how the mixed solvency idea may be used to improve the medication metronidazole solubility in water. Metronidazole, which is only marginally soluble in water, was attempted to be made more soluble by combining solubilizers such as niacinamide, sodium benzoate, sodium caprylate, caffeine, and urea to create formulations for fast-dissolving films. The material was subsequently evaluated using UV, IR, and DSC tests. The formulations were assessed for a number of film parameters, including thickness, folding durability, surface pH, disintegration time, and thin layer chromatography. For 10 weeks, they conducted stability tests on metronidazole vaginal films at room temperature and in a refrigerator.[19]

Vineet C, et al., (2018) In order to create its prolonged release formulations, it was claimed that the essentially water insoluble medication meloxicam was tried to be solubilized by using a combination of physiologically compatible menthol: thymol mixture. To solubilize ethyl cellulose and the medication, they used two solids, menthol and thymol, in the form of eutectic liquid. Heat treatment was used to eliminate the ingredients menthol and thymol. The medicine (meloxicam) is molecularly distributed in an ethyl cellulose matrix to form a solid mass that releases the drug for the anticipated length of time.[20]

Agrawal S and Kasturi M, (2018)In the product development of many orally taken medications, solubility augmentation has become a key issue for the formulators because the majority of drugs now available are just marginally water soluble. Along with other methods, they discovered hydrotropic solubilization as one of the methods that might be used to increase the solubility of medications that are hydrophobic by using hydrotropes such sodium benzoate, urea, piperazine, etc. They decided on Lumefantrine since it has a BCS Class IV water solubility of only 0.009 mg/ml. Their main goal was to use the hydrotropic solubilization process to increase the drug's aqueous solubility. Hydrotropes like sodium citrate, sodium benzoate, and other hydrotropes in a range of concentrations were used in solubility investigations. The outcomes demonstrated Lumefantrine improved solubility by a factor of more than 30 when added to a solution of 30% sodium citrate, highlighting its significance in the pharmaceutical industry. [21]

Damor H., (2017) developed and tested flurbiprofen injection in aqueous form. By combining the sodium benzoate, sodium acetate, propylene glycol, glycerin, PEG-200, PEG-400, PEG-4000, PEG-6000, urea, and ethanol as solvents, he was able to successfully synthesize flurbiprofen aqueous injection. Qualitative and quantitative solubility, dilution study, influence of ph extractable volume test, viscosity, visual check, bet test, sterility test, particulate contamination, compatibility studies (FTIR), and stability studies were used to analyze the produced aqueous injection. [22]

Jain S, et al., (2017) the simultaneous estimate of norfloxacin and tinidazole in tablet dose form was devised and verified using the mixed solvency approach. To improve the solubility of the poorly water soluble drugs norfloxacin and tinidazole, they

used a combination of 10% phenol and 20% sodium benzoate as a hydrotropic solvent. They said that the analytical wavelengths for norfloxacin and tinidazole are, respectively, 323 nm and 318 nm. The developed method's linearity and range, specificity, accuracy, precision, and sensitivity were all validated in accordance with ICH recommendations. [23]

Kulkarni N.S., et al., (2016) reported that hydrotropes can make medications that are just marginally and weakly soluble in water more soluble. When one solute is present in abundance, another solute is more easily soluble. For the creation of analytical techniques for pharmaceuticals that aren't very water soluble, different organic solvents were employed. Such solvents have a number of disadvantages, including expense, toxicity, and environmental risks. Less expensive hydrotropic agents have found widespread use in the development of analytical techniques for created dosage forms to address these problems. The combined hydrotropy strategy proposed a combination of two or more hydrotropic substances as the minimal amount. These mixtures produce less of a quantity than do individual hydrotropic agents. Similar to this, hydrotropic compounds are now frequently employed to create dosage forms such as injections, tablets that dissolve in the mouth, and solid dispersions to increase the therapeutic effectiveness and bioavailability of medicines that are poorly water soluble.[24]

Dhapte V and Mehta P, (2016) Review: About a century ago, in 1916, Carl A. Neuberg used the word "hydrotropy" to describe anionic organic ions that significantly increased the solubility of poorly soluble solutes in water. Due to their distinct qualities, such as easy accessibility, good recovery, the absence of fire threats, increased separation factors without any solute emulsification issues, and eco-friendliness, hydrotropic solutions are currently in high demand in industry. It provides a succinct summary of hydrotropic drugs' geometrical characteristics, speculative mechanisms, and various advancements in drug delivery. [25]

Soni L.K, et al., (2016) formulated the poorly water-soluble drug's injectable formulations. They solubilized the hydrophobic medication using a mixed solvency method. Water-soluble hydrotropes (such sodium citrate and urea) and water-miscible co-solvents (like polyethylene glycol (PEG) 200, PEG 300, PEG 400, PEG 600, glycerin, propylene glycol, and ethanol) were used to create a mixed solvent system. UV, Fourier Transform infrared (FT-IR), and Raman spectroscopy were used to describe the medication. Additionally, they calculated the Gibbs free energy of transfer (G0tr) and the solubilizing power. Numerous solution-related characteristics, including pH, viscosity, specific gravity, and refractive index, were also investigated. Due to the mixed solvent effect, this technique demonstrated a synergistic improvement in a drug's solubility that generates a stable formulation. [26]

Mehmood Y, (2015) read about the raw materials' aqueous solubility, which is crucial for injectable formulation, however in some circumstances, if the medication is not soluble in water, oil can be utilized to increase drug solubility. They used a mixed-solvency strategy to improve the medication diclofenac sodium's poor water solubility in aqueous solution. Instead of employing large amounts of propylene glycol, a co-solvent utilized in traditional formulation, they created the diclofenac sodium injectable. This formulation uses benzyl alcohol as a co-solvent for diclofenac sodium in an aqueous media, making the injection less painful than one made with propylene glycol. The prepared injection's stability, toxicity, pyrogenicity, and isotonicity were then tested. From the numerous formulations examined, it was discovered that benzyl alcohol (6–7% v/v) is a good and economical solubilizing agent for making diclofenac sodium injection dosage forms. [27]

Glyn-Jones S, et al., (2015) osteoarthritis was examined as a significant cause of pain, disability, and socioeconomic burden on a global scale. The disorder's epidemiology is intricate and complicated, with elements related to genetics, biology, and biomechanics. A joint-specific etiological component is also present. The topic of joint replacement was also brought up. Although functional outcomes can be subpar and prosthetic life spans are constrained, joint replacement is an effective treatment for symptomatic end-stage disease. However, improvements in imaging and biochemical markers present the possibility for diagnosis and as outcome indicators for novel treatments. Currently being developed are lifestyle changes, medical procedures, and pharmaceuticals for joint preservation. Few have currently been demonstrated to be able to stop or halt the progression of disease, however others exhibit potential. [28]

Gayakwad P.S., et al., (2014) produced aqueous injection of gatifloxacin by combining different amounts of hydrotropes (nicotinamide, sodium benzoate, sodium citrate), co-solvents, and other water-soluble solubilizers (propylene glycol, PEG- 400, ethanol). A combined solvent including hydrotropes (8% nicotinamide, 8% sodium benzoate, 4% sodium citrate) and co- solvents (4% PEG 400, 3% propylene glycol, 3% ethanol) increased the solubility of the medication by more than 68.95 times. Due to the mixed co-solvent effect, this demonstrated a synergistic improvement in the solubility of a poorly water-soluble medication. UV was used to characterize each solubilized substance, and surface tension, pH, viscosity, and other physical characteristics of the solution were investigated. The physical and chemical stability of the produced formulation was investigated. [29]

Kendre P.N., et al., (2014) employed the hydrotropy technique to improve the medication quercetin's poor water solubility. Quercetin-containing blends were created using a mixed-solvency method, maintaining a 40% w/v total concentration. Following an enhancement in quercetin's solubility in particular blends they added it to a topical dosage form (gel) by using Carbopol ETD 2020 as a gelling agent. The prepared blends and gel were characterized using differential scanning calorimetry (DSC), X-ray diffraction (XRD), and other methods. The blends and gel were evaluated for pH, surface tension, specific gravity, and viscosity as well as in-vitro diffusion studies, skin irritation studies, and spreadability, respectively. It was discovered that the developed formulation was stable with good spreadability, safe, efficient, non-irritating, and non-toxic. The findings demonstrated that mixed solvency is a valuable and distinctive technique for enhancing the solubility of quercetin, a

lipophilic herbal anticancer component. [30]

Maheshwari R.K., et al., (2014) reported that hydrotropy is another sort of co-solvency and all water soluble substances, whether solids, liquids, or gases, have solubilizing capabilities. This is based on a vast number of experiments on the solubilization of poorly water-soluble medications. As a result, some medications that are poorly water-soluble might be dissolved in an aqueous solution that contains modest amounts of various water-soluble ingredients. In order to formulate the solid dispersions of the drug Piroxicam, which has low water solubility, the concept of hydrotropy was investigated. Solid dispersions were tested for flow characteristics, powder x-ray diffraction, differential scanning calorimetric studies, scanning electron microscopy, dissolution studies, and stability studies. [31]

Soni L.K., et al., (2014) used the hydrotropy approach to make the indomethacin medicine more water soluble and the use of non-toxic solubilizers to make a less water soluble drug more water soluble. The solubility tests with indomethacin were conducted using mixed solvent blends (40%) of co-solvents, water-soluble solids (PEG-4000, PEG-6000), and selected hydrotropes (urea, sodium benzoate, sodium citrate, and nicotinamide) (propylene glycol, glycerin, PEG-200, PEG-400, PEG 600). Solubility studies were used to develop the formulation. Surface tension, pH, viscosity, and other properties of the solubilized medication and produced formulation were examined. The physical and chemical stability of the produced formulation was investigated. The notion of mixed solvency was used in this study to provide recommendations for creating injectable products and methods for increasing the solubility and stability of drugs that are not very water soluble. [32]

Reddy R.M., et al., (2013) reported that one crucial factor in achieving the correct drug concentration in the systemic circulation for the display of a pharmacological response is solubility. Poor water solubility drastically restricts medication efficacy, and certain pharmaceuticals also exhibit side effects as a result of their poor solubility. There are various methods used to increase a substance's solubility in water. Thus, improving a drug's capacity to dissolve in water can help it work more effectively and cause fewer negative effects. This holds true for solutions that are given to children orally, topically, or both. They discovered that it is difficult to improve the solubility of a variety of weakly soluble chemicals while maintaining their bioavailability, pharmacological action, and solubility characteristics. One method for increasing solubility is hydrotropy, which has a number of benefits including not requiring the chemical modification of hydrophobic drugs, the use of organic solvents, or the creation of emulsion systems, among others. Hydrotropes include sodium benzoate, sodium citrate, urea, and niacinamide.[33]

Maheshwari Y., et al., (2013)It was discovered that formulation research as well as screening investigations of novel chemical entities had both found that the solubilization of poorly water soluble medications had been a highly relevant issue. For the purpose of improving the solubility of the poorly water-soluble drugs Naproxen and Furosemide, they developed a mixed-solvency strategy. To investigate the impact on the solubility of Naproxen and Furosemide separately, they created 16 blends (with a total 40% w/v strength) using different solubilizers from the regularly used hydrotropes, co-solvents, and water-soluble solids. Most of the combinations were found to make both medicines more soluble. By combining different water-soluble excipients at safe amounts to create a suitable aqueous solubility of poorly water soluble pharmaceuticals, this method will prove beneficial in the pharmaceutical industry for creating diverse formulations of poorly water. [34]

Solanki SS, et al., (2013) by combining specific water-soluble compounds among the hydrotropes, water-soluble solids, and co-solvents, a mixed-solvency strategy was used to improve the medication zaltoprofen aqueous solubility. They discovered that a mixture solvent containing 10% sodium citrate, 5% sodium benzoate, and 25% S co-solvent (which contains PEG200, PEG400, PEG600, glycerin, and propylene glycol) increased the solubility of the medication by a factor of more than 600. Due to the mixed co-solvent effect, this demonstrated a synergistic improvement in the solubility of a poorly water-soluble medication. Surface tension, pH, viscosity, and other solution characteristics were investigated. The formulation that was created had its physical and chemical stability examined-soluble drugs. [35]

Kalariya N., et al., (2012) several mixes of co-solvents, including polyethylene glycol 200 (PEG200), PEG400, PEG600, PEG4000, propylene glycol (PG), polyvinyl pyrrolidine (PVP) K 30, ethanol, glycerin, tween20, tween80, niacenamide, lignocain hydrochloride, and sodium benzoate, were used to prepare an aqueous injection of They discovered an increase in sulphasalazine's solubility of more than 50 times (compared to its solubility in distilled water). Due to mixed solvency, this demonstrated a synergistic improvement in the solubility of a poorly water soluble medication. Combining mixed-solvency in a synergistic way can reduce the number of co-solvents used, reducing the likelihood of toxicities. [36]

Agrawal S., et al., (2012) according to reports, the diaryl-substituted pyrazole celecoxib is practically water insoluble, which prevents the use of it in parenteral and liquid dosage forms. This study investigates the effects of hydrotropy and co-solvency solubilization on the solubility enhancement of celecoxib. The hydrotropes piperazine, sodium citrate, and urea were used in the equilibrium solubility experiments, together with co-solvents PEG 200, PEG 400, PEG 600, DMA, ethanol, and propylene glycol, at various temperatures. Celecoxib's solubility was observed to rise up to 45 times in 3M piperazine solution and up to 10232 times in PEG 600 at 25 C. They produced parenteral formulations employing hydrotrope and co-solvents and evaluated for expedited stability study. In contrast to the rise in solubility that was shown when these hydrotropes were employed in combination with co-solvents PEG 600, PEG 400, DMA, and ethanol, the solubilization investigation demonstrated that the increase in solubility of celecoxib was less in piperazine and urea when used alone. We discovered that the formulations were stable. [37]

Maheshwari RK. and Jagwani Y., (2011) found that standard furosemide pills cannot be used in emergency clinical circumstances like hypertension or pulmonary edema because they are nearly insoluble in water, have a sluggish beginning of action (45–60 min), and have poor bioavailability (39–53%). Their goal was to develop an oral dose form of furosemide that dissolves quickly and has a rapid onset of action using the mixed hydrotropy principle. They used pure water as the solvent to first assess the solubility of furosemide in four hydrotropic agents, including urea, sodium acetate, sodium benzoate, and sodium citrate, at concentrations of 10, 20, 30, and 40% w/v. They discovered that a 40% sodium benzoate solution produced the most solubility. The solution of urea, sodium benzoate, and sodium citrate at the ideal ratio of 15:20:5 produced the highest solubility. In order to prepare solid dispersions utilizing the usual solvent approach using distilled water as the solvent, this optimal combination was used. Tablet-shaped solid dispersions were compressed and analyzed. Utilizing USP Type II equipment, dissolution investigations on prepared tablets were conducted. [38]

Maheshwari RK and Indurkhya A., (2010) observed that the solubility of aceclofenac in a mixed hydrotropic solution containing 20% urea and 10% sodium citrate solution increased by more than 250 times compared to that of aceclofenac in water (compared to its solubility in distilled water). Due to mixed hydrotropy, this demonstrated a synergistic improvement in the solubility of a poorly water-soluble medication. Hydrotropic drugs can be combined in a synergistic manner to reduce the number of times they are used, hence reducing the likelihood of toxicities. Aqueous injection of aceclofenac was created utilizing the mixed hydrotropic solubilization approach, and the poor stability of aceclofenac in aqueous solution was solved by lyophilization. The physical and chemical stability of the produced formulation was investigated. [39]

Jain AK., (2007) Indomethacin, a non-steroidal anti-inflammatory medication (NSAID) with analgesic, antipyretic, and anti-inflammatory properties, is nearly insoluble in water, according to research. It was examined how different hydrotropes, including urea, nicotinamide, resorcinol, sodium benzoate, and sodium p-hydroxy benzoate, affected indomethacin solubility. Numerous hydrotrope solution parameters, including viscosity, specific gravity, surface tension, refractive index, and specific conductance of hydrotropic solutions, were investigated at a temperature of 25 2 C in order to clarify the likely solubilization mechanism. Techniques for differential scanning calorimetry, powder X-ray diffraction, ultraviolet, infrared, and infrared spectroscopy were used to characterize each solubilized product. When indomethacin is hydrotropically soluble, weak ionic interactions may be to blame at lower hydrotrope concentrations, whereas molecular aggregation may be to blame at greater hydrotrope concentrations. The physical and chemical stability of aqueous injectable formulations using sodium benzoate, sodium p-hydroxy benzoate, and nicotinamide as hydrotropes was produced and examined. [40]

Agrawal S., et al., (2004)had investigated the impact of different hydrotropes on the solubility of nimesulide, including nicotinamide, sodium benzoate, sodium ascorbate, sodium salicylate, and piperazine. They discovered that piperazine had the highest solubility of nimesulide while nicotinamide had the lowest. They made an effort to create aqueous solutions for parenteral application by employing piperazine. [41]

CONCLUSION:

The drug's solubility is the most important factor that influences both its formulation and its therapeutic efficacy. The most important factor in formulation development is solubility. The dissolution of the drug is the rate determining step for oral absorption of poorly water-soluble drugs. Furthermore, solubility is a fundamental requirement for the formulation and development of various drug dosage forms. To improve drug solubility, hydrotropic solubilization techniques can be used alone or in combination. The drug's solubility was increased using a variety of techniques, including a number of folds. Many drugs' bioavailability suffers as a result of solubility issues, necessitating solubility enhancement. It is now possible to use various techniques to increase the solubility of poorly water-soluble drugs as a novel approach. This method is gaining popularity and may prove to be the best method in the future.

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