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A Review On Pharmaceutical Hydrotropes

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ABSTRACT
The term "hydrotropy" was first coined by Carl A. Neuberg in order to substantially enhance the solubility of weakly soluble solutes in water. So hydrotropy is a solarization process. The term "hydrotrope" refers to the chemicals utilized in the solubilization process known as hydrotropy, where the solubility of a third solute in water is increased by the considerable addition of a second solute. Only 8% of potential new drugs now in development have good solubility and permeability.

There are many new medications and their derivatives available today thanks to advanced research and development. However, despite the fact that these medications may show significant pharmacodynamic activity, Due to poor bioavailability, more than 40% of lipophilic drugs are rejected by pharmaceutical companies.

This review will give an idea about structure of hydrotropes, mechanisms, physical modification, solubility, hydrotropes of green synthesis.

Keyword: Hydrotropes, soluble, solubility.

INTRODUCTION

More than one-third of the medications listed in the Indian and US Pharmacopoeias are either poorly or completely insoluble in water. Poor biopharmaceutical qualities have been identified to be responsible for 41% of new medication development failures, including involving Insolubility of water.[1] Thus, the approach for improving the water solubility becomes necessary over time. Hydrotropy is one such approach.[2]

In 1916, Neuberg used the term "hydrotropic agent" to describe anionic organic salts that, when present in large quantities, greatly increase the solubility of weakly soluble solutes in water. In the literature, the phrase has been used to designate both liquids and solids, whether organic or inorganic, that can solubilize insoluble chemicals but do not form micelles. An anionic group and a hydrophobic aromatic ring or ring system are the two main components of the chemical structure of the prototypical Neuberg's hydrotropic salts, such as sodium benzoate.[3]

A process of solubilization known as hydrotropy involves the addition of a significant amount of amount of second solute results in an increase in the aqueous solubility of another solute so the chemicals which are used in hydrotropy are called as hydrotropes.

1. HISTORY of HYDROTROPY

Hydrotropy is the phenomenon of increasing the solubility of hydrophobic substances in water by adding hydrotropes, which are compounds that have both a hydrophilic and a hydrophobic part.[4]

The history of hydrotropy goes back to the 18th and 19th centuries, when scientists like Bonnet, Knight, Sachs, Darwin, and others observed and experimented with the effect of salts on the different substances' solubilities. Carl Neuberg first used the term "hydrotropy" to characterize this result in 1916. Since then, hydrotropes have been studied and applied in various fields, such as drug delivery, green chemistry, and mesoscale solubilization.[5]

2. BASIC STRUCTURE OF HYDROTROPES

A hydrotrope is a compound that has a basic structure of a hydrophilic part and a hydrophobic part. The hydrophilic part is usually an anionic group, such as a carboxylate, sulfate, or sulfonate. The hydrophobic part is usually a planar aromatic ring or ring system, such as benzene, naphthalene, or anthracene. The basic structure of a hydrotrope allows it to interact with both water and hydrophobic solutes, and increase the solubility of the latter. Here is an example of a hydrotrope:

This is sodium benzoate, a common hydrotrope. The sodium ion is the hydrophilic part, and the benzoate ion is the hydrophobic part. Sodium benzoate can solubilize various organic compounds, such as phenol, salicylic acid, and aspirin.

3. PHYSICAL MODIFICATION

Physical modification in hydrotropes refers to the alteration of the molecular structure or geometry of hydrotropic agents to enhance their solubilization capacity for poorly soluble compounds. Hydrotropes are amphiphilic compounds with a small hydrophobic fragment that can increase the aqueous solubility of nonpolar solutes by forming hydrotrope-solute complexes or co-solvent effects [6,7]. Some examples of physical modifications in hydrotropes are:

a) Particle size reduction: This can be achieved by micronization or nanosuspension techniques, which reduce the particle size of the hydrotrope and increase its surface area and dissolution rate
b) Modification of the crystal habit: This can be achieved by changing the polymorphic or pseudo polymorphic forms of the hydrotrope, which affect its solubility, stability, and bioavailability
c) Drug dispersion in carriers: This can be achieved by using eutectic mixtures or solid dispersions, which involve mixing the hydrotrope with another carrier substance to form a homogeneous system with enhanced solubility
d) Complexation: This can be achieved by using complexing agents, such as cyclodextrins, which can form inclusion complexes with the hydrotrope and improve its solubility and stability
e) Solubilization by surfactants: This can be achieved by using microemulsions or buffers, which can enhance the solubilization of the hydrotrope by altering the polarity or pH of the solvent
f) Derivatization: This can be achieved by modifying the chemical structure of the hydrotrope, such as adding or removing functional groups, to increase its hydrophilicity or hydrophobicity.[8]

4. CLASSIFICATION OF HYDROTROPES APPROACHES

Hydrotropes are compounds that can increase the solubility n water using ways other than micellar solubilization of hydrophobic compounds. Both a hydrophilic and a hydrophobic component are frequently present, but the hydrophobic component is too small to form micelles. Hydrotropes can be classified according to different criteria, such as:

a) The type of hydrotrope: true hydrotropes, surfactant solubilizers, or microemulsions[9]
b) The charge of the hydrotrope: cationic, anionic, or neutral.
c) The polarity of the hydrotrope: hydrophilic or hydrophobic.
d) The structure of the hydrotrope: anionic group and aromatic ring (conventional Neuberg's hydrotropes), or other types of functional groups

Some examples of hydrotropes are urea, sodium benzoate, sodium salisylate, sodium cumenesulfonate, and sodium xylenesulfonate. Hydrotropes have applications in various fields, such as drug delivery, green chemistry, and mesoscale solubilization.

Advantages Of Hydrotropes

Hydrotropy is a technique that enhances the solubility of hydrophobic compounds in aqueous solutions by using hydrotropes, which are compounds that have both a hydrophilic and a hydrophobic part, but do not form micelles. Hydrotropes can increase the solubility of a solute by interacting with it through various mechanisms, such as hydrogen bonding, π-π stacking, or electrostatic forces.

Some of the advantages of hydrotropy are:
a) It can solubilize a wide range of hydrophobic drugs that are poorly soluble in water[10]
b) It can avoid the use of organic solvents, which are costly, volatile, toxic, and polluting.[11]
c) It can enhance the bioavailability and therapeutic efficacy of drugs by increasing their dissolution rate and permeability.
d) It can be environmentally friendly, non-inflammable, easily available, and cost-effective.
e) It can have high selectivity and specificity for certain solutes
f) It can reduce the surface tension and facilitate the emulsification of fats[12]

Disadvantages of hydrotropes

Some of the disadvantages of hydrotropes are:
a) They may require high concentrations to achieve significant solubilization, which may increase the cost, toxicity, and environmental hazards of the formulation.
b) They may have limited applicability for drugs that are very insoluble or have a high molecular weight[3].
c) They may interfere with the stability, bioavailability, or pharmacokinetics of the drug by altering its partition coefficient, diffusion rate, or metabolism.
d) They may cause precipitation or crystallization of the drug upon dilution or change in pH.
e) They may have adverse effects on the skin, eyes, or mucous membranes due to their irritancy or sensitization potential.[12]

5. SOLUBILITY

Solubility is a property of a substance (solute) to dissolve in a given solvent. It can be defined as the solute concentration in a saturated solution at a specific temperature. [13]. There are different types of solubility depending on the state of the solute and the solvent. For example, solubility of liquids in liquids, solids in liquids, and gases in liquids. A number of factors, including the solute and solvent's characteristics, the temperature, pressure, pH, and the presence of other substances, affect a substance's solubility. dissolved substances. Some substances are highly soluble, meaning they can dissolve a lot in a solvent. Some are sparingly soluble, meaning they can dissolve only a little in a solvent. And some are insoluble, meaning they cannot dissolve at all in a solvent. Solubility is important for many scientific and practical applications, such as chemical reactions, geology, biology, medicine, engine.[14]

6. REQUIREMENT OF SOLUBILITY

Solubility is the capacity of the solvent to dissolve a solute, or the maximum amount of solute that will dissolve in a specific amount of solvent at a given temperature. Solubility depends on various factors, such as:
a) Solute-solvent interactions: Strong attractions between the solute and solvent molecules result in higher solubility, while weak attractions result in lower solubility. Polar solutes tend to dissolve better in polar solvents, and non-polar solutes tend to dissolve better in non-polar solvents.[15]
b) Common-ion effect: The presence of an ion that is common to both the solute and another dissolved salt can decrease the solubility of the solute by shifting the equilibrium towards the solid phase.
c) Temperature: The effect of temperature on solubility depends on whether the dissolution process is endothermic or exothermic. For endothermic processes, increasing the temperature increases the solubility, while for exothermic processes, increasing the temperature decreases the solubility.

d) Pressure: The effect of pressure on solubility is only significant for gases. According to Henry's law, the solubility of a gas in a liquid is directly proportional to the partial pressure of the gas above the liquid.

7. METHODS TO MEASURE THE SOLUBILITY

Solubility is the capacity of a solvent to dissolve a solute without leaving any undissolved particles. Solubility is measured in units of concentration, such as grams per 100 cubic centimeters. There are different methods to determine the solubility of a substance, depending on the type of solute and solvent, and the accuracy and precision required.

Some of the common methods for solubility determination are:

a) Ultraviolet absorption: This method uses a spectrophotometer to measure the amount of light absorbed by a solution at a specific wavelength. The absorbance is proportional to the concentration of the solute in the solution. This method is suitable for solutes that have a distinct absorption spectrum in the ultraviolet range.

b) Nephelometry: This method measures the amount of light scattered by a solution containing suspended particles. The scattering is proportional to the concentration and size of the particles. This method is suitable for solutes that form colloidal or turbid solutions.

c) Nuclear magnetic resonance: This method uses a magnetic field to induce a resonance in the nuclei of certain atoms in a solution. The resonance frequency and intensity depend on the concentration and chemical environment of the atoms. This method is suitable for solutes that contain atoms with magnetic nuclei, such as hydrogen, carbon, nitrogen, etc.

d) Potentiometric titration: This method uses an electrode to measure the electric potential of a solution as a function of the amount of titrant added. The titrant is a substance that reacts with the solute in a known stoichiometric ratio. The endpoint of the titration corresponds to the equivalence point, where the amount of titrant is equal to the amount of solute. This method is suitable for solutes that undergo acid-base, redox, or complexation reactions.

e) Saturation shake-flask method: This method involves shaking a known amount of solute with a known volume of solvent at a constant temperature until equilibrium is reached. Then, the solution is filtered or centrifuged to separate the dissolved and undissolved portions. The concentration of the solute in the filtrate or supernatant is measured by an appropriate analytical technique, such as UV absorption, nephelometry, etc. This method is suitable for solutes that have low or moderate solubility.

f) Turbidimetry: This method measures the amount of light transmitted through a solution containing suspended particles. The transmittance is inversely proportional to the concentration and size of the particles. This method is suitable for solutes that form colloidal or turbid solutions.

g) Miniaturized or plate-based and partly automatized assays: These methods use small volumes of solute and solvent in microplates or microtubes to perform solubility measurements. The advantage of these methods is that they require less sample and solvent, and can be automated or semi-automated using robotic systems. The disadvantage is that they may have lower accuracy and precision than other methods.

h) Novel analytical approaches: These methods use advanced techniques, such as mass spectrometry, capillary electrophoresis, high-performance liquid chromatography, etc., to measure the solubility of solutes. These methods have high sensitivity and specificity, but may also have high cost and complexity.

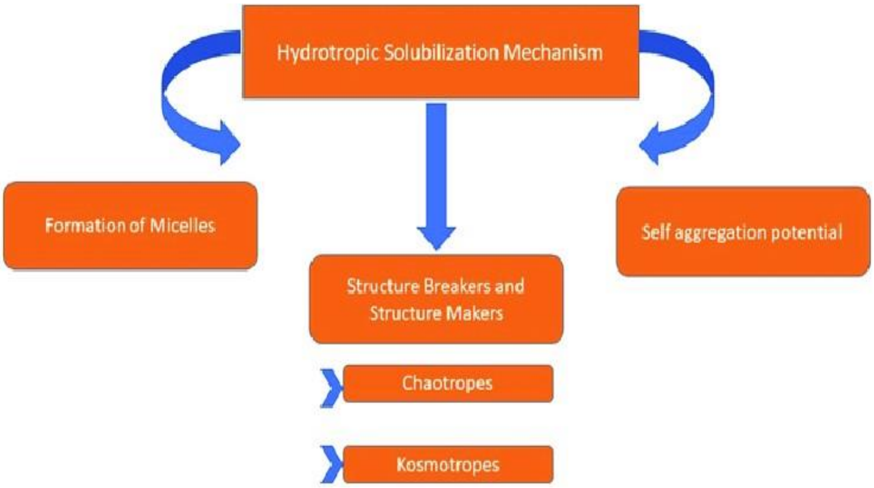
9. HYDROTROPES IN GREEN SYNTHESIS

Green Synthesis: For a range of industrial organic transformations, hydrotropic agents offer a simple, affordable, and eco-friendly platform. Additionally, hydrotropic solutions provide an abundance of the physical and chemical qualities needed to serve as substitute green solvents for organic reactions, including affordability, non-toxicity, non-flammability, and environmental friendliness. The aqueous hydrotropic method, which is categorized as green chemistry, provides a number of benefits such as having easy handling, a clearer reaction profile, a high conversion rate, and a rapid reaction time an effective choice for rapid synthesis. Recyclability and ease of recovery from the reaction mixture are two additional crucial properties of the hydrotropic medium. Additionally, this method is an intriguing green chemical because of how simple it is to extract compounds from hydrotropic solutions.[17]

10.MECHANISMS OF HYDROTROPES

11. The basis for hydrotropes increased water solubility is its molecular self-association and the connection of hydrotrope molecules with the solute. Although widely used in a wide range of industrial applications, little is understood about the principles underlying hydrotropism. Through numerous research and theoretical initiatives, the physics of hydrotrope are being understood. There are three different mechanisms that have been postulated. (18)

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



(a) Self-aggregation potential

The minimum hydrotropic concentration (MHC), also known as the self-aggregation potential of hydrotrope molecules, is a critical concentration at which they begin to assemble.[19]The self-aggregation potential of hydrotropes determines the soluble nature.[20] This possibility depends on the solute molecule's nature and its amphiphilic properties. They primarily exhibit the solubilization potential that is volume fraction dependant. Strong interactions between hydrotropes and the solute result in complexes, and these complexes raise the aqueous solubility. These findings have developed from research on thermodynamic solubility, fluorescence emissions, crystallographic analysis, and quantum molecular dynamics They could also act as bridging agents by reducing the Gibbs energy and increasing solubility.[21,22]

(b) Structure-breaker and structure-maker

The hydrotropic solubilization of the donor-acceptor molecules depends on the electrostatic force between them, therefore they are often referred to as structure-breakers and structure-makers. The solubility of a substance is aided by its ability to receive and donate hydrogen. A solvent's ability to participate in the creation of structures or to engage in structure building via intermolecular hydrogen bonding is one way that solubilizing chemicals like urea change the character of the solvent and hence affect solubility Structure-maker hydrotropes are referred to as kos-motropes, whereas structure-breaker hydrotropes are known as chaotropes . By strengthening the hydrophobic interaction and lowering the cloud point, Kosmotrope lowers the critical micelle concentration, or CMC. Kosmotrope essentially affects the cloud point in two ways: (a) by assisting in the formation of larger micelles, and (b) by reducing hydration. Promazine hydrochloride (PMZ) and promethazine are amphiphilic medicines, and cyclodextrin acts as a water structure builder and lowers the cloud point.[23,24]

(c) Ability to form micelles like structure

This method is based on hydrotropes' ability to self-associate with solutes to form a micellar structure.[25] In essence, they create stable mixed micelles by reducing the electrostatic attraction between the head groups of a solute molecule. Due to the self-association properties hydrotropes like lower alkenoates, alkyl-benzene sulfonates, and alkyl sulphates with solutes and create mixtures. Through a self-association process, the aromatic anionic hydrotrope nicotinamide increases the solubility of riboflavin.[26] By reducing the electrostatic attraction between PMZ's head groups, anionic hydrotropic agents like sodium salicylate create stable mixed mixtures in the case of PMZ.[27]

12.PARAMETERS OF THE HYDROTROPES

Some of the parameters that affect the solubility enhancement by hydrotropes are:

(a) The concentration of the hydrotrope: Higher concentrations of hydrotrope usually increase the solubility of the solute, but there may be an optimum concentration beyond which further increase does not improve solubility.
(b) The structure and polarity of the hydrotrope: Hydrotropes with a planar and aromatic hydrophobic part and a highly polar anionic group tend to have higher solubilizing ability than those with non-planar or aliphatic hydrophobic parts or less polar groups. A polarity match between the solute and the hydrotrope also affects the solubility enhancement.
(c) The temperature of the solution: Higher temperatures may increase or decrease the solubility of the solute depending on the nature of the hydrotrope and the solute. For example, sodium benzoate increases the solubility of salicylic acid at higher temperatures, while sodium acetate decreases it[1].
(d) The pH of the solution: The pH may affect the ionization and dissociation of the hydrotrope and the solute, which in turn may affect their solubility and interaction. For example, sodium salicylate increases the solubility of phenobarbital at acidic pH, while sodium citrate decreases it[1].
(e) The presence of other additives: Other additives such as surfactants, cosolvents, salts, or polymers may interact with the hydrotrope and/or the solute and alter their solubility. For example, sodium cumene sulfonate enhances the solubility of ibuprofen in water-ethanol mixtures, while sodium chloride reduces it.[28]

13. APPLICATIONS OF HYDROTROPES

Hydrotropes have many applications in various fields, such as:

(a) In the pharmaceutical industry, hydrotropes can enhance the solubility and bioavailability of poorly water-soluble drugs, especially those belonging to the BCS class II. Hydrotropes can also be used as carriers for active drug ingredients, as additives for pharmaceutical formulations, and as extraction agents for bioactive materials.
(b) In the chemical industry, hydrotropes can be used as green and sustainable solvents for organic synthesis, as they can replace toxic organic solvents and increase the rate and yield of chemical reactions[12]. Hydrotropes can also be used as separation agents for solute purification, as they can precipitate the solute by adding water.
(c) In the textile industry, hydrotropes can be used as solubilizers for dyes, as they can improve the dyeing performance and color fastness of fabrics. Hydrotropes can also be used as coaters for paints, as they can enhance the adhesion and stability of paint films.
(d) In the detergent industry, hydrotropes can be used as formulation components for cleaning and personal care products, as they can increase the concentration and efficiency of surfactants. Hydrotropes can also be used as additives for plastic products, as they can improve the mechanical and thermal properties of plastics.
(e) In the food industry, hydrotropes can be used as solubilizers for flavors, fragrances, vitamins, and antioxidants, as they can increase their stability and bioactivity in aqueous media. Hydrotropes can also be used as modifiers for food texture, viscosity, and rheology.[29]

CONCLUSION:

The analysis of hydrotropes on various scientific field shows the extent of solubility of different drugs with different hydrotropic solubilization and mixed hydrotropic solubilization. This gives us an idea on the various solubility parameter of different hydrotropes and the solubility profile, the bioavailability and the pharmacokinetic profile. The Solubility enhancement by cosolvent system gives new approaches for design and formulation of new dosage forms of poor aqueous soluble drugs. It also helps in improving - Bioavailability of drugs -Stability of drugs. These information helps to know the drugs much better regarding their solubility parameter.

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