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A Review on Hydrotropic Solubilization: A Novel Approach for Solubility Enhancement of Poorly Water Soluble Drugs

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ABSTRACT

The field of drug discovery and development plays a major role in the world and serves mankind. The great challenge in screening studies as well as formulation of new chemical entities is the solubilization of poorly soluble drugs. Inorder to improve the solubility of poorly water soluble drugs, a number of methodologies can be adapted. Hydrotropes are a unique molecular phenomenon, that possess the ability to increase the solubility of sparingly soluble and poorly soluble drugs in water. It can be defined as adding a second solute to the primary one. Several advantages that make the solubilization technique superior are high selectivity, non-inflammability, environmentally friendly, easy availability and cost effectiveness. This technique may have some disadvantages like cost, toxicity and environmental hazards. This can be overcome by using less costly hydrotropic agents. Nowadays hydrotropic agents are used to develop dosage forms in various forms such as solid dispersion, mouth dissolving tablets, injections. These are for improving the therapeutic effectiveness and bioavailability of poorly water soluble drugs.

Keywords: Solubility, Hydrotropy, Solubility enhancement, Hydrotropic agent, Poorly water soluble drugs, Solid dispersions, Membrane permeability, Self aggregation, Permeation enhancers, Mixed hydrotropy.

INTRODUCTION

The Indian Pharmacopoeia and US Pharmacopoeia consist of more than one third of poorly water soluble or water insoluble drugs. The main reason for the failure of new drug development is the poor biopharmaceutic properties like water insolubility. One of the most important physico chemical properties of drug development is the solubility.[1] Many of the newly developed drug molecules have the nature like lipophilicity and poor solubility. For the solubilization of these poorly water soluble drugs various organic solvents like methanol, chloroform, dimethyl formamide and acetonitrile are used. But the use of these organic solvents includes some drawbacks like high cost, volatility, pollution and some toxicities. Therefore, a safe eco-friendly, cost effective solvent known as hydrotropic agent can be used.[2] The hydrotropy was first reported by Neuberg (1916).[3] The solubilization phenomenon whereby addition of large amount second solute results in an increase in the aqueous solubility of another solute is called hydrotropy. Some of the examples include concentrated aqueous hydrotropic solution of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate.[4]

Hydrotropic agent was used to designate anionic organic salts. Generally hydrotropic salts have 2 essential parts, an anionic group and a hydrotropic aromatic ring or ring system, according to the chemical studies of conventional Neuberg's

salts. The high aqueous solubility is bring about due to the anionic group, which may have a minor effect on the phenomenon.[5]

SOLUBILITY

The solubility can be explained both qualitatively and quantitatively. The concentration of the solute in a saturated solution at a certain temperature is called solubility quantitatively, whereas qualitatively it is the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.[6-8] The solubility is defined according to Pharmacopoeia in terms of number of milliliters of solvent required to dissolve 1g of solute and if the exact solubilities are not known the Pharmacopoeia provides general term to describe a given range[9] as shown in table 1.

Table 1: Solubilities as per Pharmacopoeia[9]

SOLUBILITY TERMS	RELATIVE AMOUNTS OF SOLVENTS TO DISSOLVE 1 PART OF SOLUTE
Very Soluble	Less than 1
Freely Soluble	From 1-10
Soluble	From 10-30
Sparingly Soluble	From 30-100
Slightly Soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

Solubility may be affected by some of general parameters like particle size, shape and surface area, physic chemical properties of drug and physical forms of drugs, solvents, pH of the medium, temperature and use of surfactants.[10]

Table 2: Biopharmaceutic classification system[11]

CLASSIFICATION	CHARACTERISTICS
BCS 1	Highly soluble, Highly permeable
BCS 2	Low soluble, Highly permeable
BCS 3	Highly soluble, Low permeable
BCS 4	Low soluble, Low permeable

The drug solubility can be expressed as parts of molarity, molality, volume fraction, mole fraction and other units.[11] Drugs can be classified into 4 classes of biopharmaceutical classification system based on solubility as in table 2. Based on this, the drug solubility can be classified with respect to their aqueous solubility and membrane permeability.[12-13]

NEED FOR SOLUBILITY

There are a variety of factors affecting the GIT drug absorption such as poor aqueous solubility and poor membrane permeability of the drug molecule. When a drug is administered orally, before it penetrate the membrane of GIT, it must first dissolve in gastric or intestinal fluids. Therefore the solubility and dissolution rate of poorly water soluble drugs should be enhanced.[14-15] So for this, the drug should be available at proper site of action within optimum doses.[16] Bioavailability and solubility of drug molecules may affect the therapeutic effectiveness of a drug. The most important parameter to achieve desired concentration of drug in the systemic circulation for pharmacological response is the solubility.[17] Due to the poor bioavailability, 40% of the lipophilic drug candidate fail to reach our markets. Therefore, they had a high dose to attain the proper pharmacological action. Different solubilization technique can be used to increase the solubility of the poorly water soluble drugs.[18]

PROCESS OF SOLUBILIZATION

This involves the following steps:

1. Holes may opens in the solvent
2. Breaking of inter ionic or inter molecular bonds in the solute
3. Molecules of the solid breaks away from the bulk
4. The freed solid molecules is integrated into the hole in the solvent
5. This interaction between the solvent and the solute molecule or ions are known as solubilization process which may give rise to the concept of holes or cavities in liquids.[19-20]

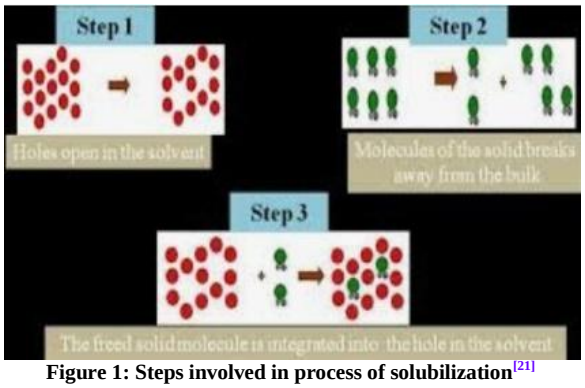

Figure 1: Steps involved in process of solubilization[21]

The whole process may be designed into 3 steps (shown in figure 1):

1. First step involves the breaking of the bond between adjacent molecule for removal of a molecule from the solute phase: which is converted into vapour phase.
2. Thus the cavities are formed in the solvent to accept the solute molecules.
3. In the final step, solute molecules is placed in the hole of the solvent.[22-26]

HYDROTROPY

Hydrotropy is defined as the unique and unprecedented solubilization technique. Here the use of certain chemical compounds known as hydrotropes, that are used to affect the aqueous solubility of sparingly soluble solutes several fold under normal conditions.

Figure 2: Hydrotropy

The formation of organized assemblies of hydrotrope molecule at critical concentration is the cause for the increase of solubility in water. They may have some characteristics such as water soluble, surface active compounds which can significantly enhance the solubility of organic solutes such as esters, acids, aldehydes, ketones, hydrocarbons and fats[27-30] as in figure 2.

DIFFERENT PERSPECTIVES OF HYDROTROPY

Mckee's view: Mckee uses hydrotropes for chemical engineering and industrial applications by the year 1946. He showed that concentrated aqueous solutions of soluble neutral salts of organic acids such as sodium benzoate (NaB), salicylate (NaS), benzene sulfonate (NaBS), p-toluenesulfonate (NaPTS), xylene sufonate (NaXs) and cumene sulfonate (NaCS) increase the solubility of various organic and inorganic compounds in water. The earlier views of Neuberg and others, who considered only organic compounds to function as hydrotropes,in contrast to this Mckee suggests that even some of the inorganic substances may be added to the class of hydrotropes. Some of these are alkali iodides, thiocyanates, oxalates and bicarbonates. But recent practice is that inorganic salts are not included in the category of hydrotropes.

In any event, Mckee brought out some important features of hydrotropy. He noted that most hydrotropic solutions precipitate the solubilizate on dilution with water. This helps in recovering the hydrotrope for further use.NaXS is very useful in the paper pulp manufacturing process, because it appears to be less expensive than the customary alkaline process. Finally Mckee arrived at two important conclusions aboout hydrotropy as follows:

1.A rather large concentration of the hydrotrope in water is required for it to display its action and

2.The phenomenon is similar to "salting in" process.

According to Mckee, the phenomenon of hydrotropy could be explained based on the theory of mixed solvents.[31-33]

Booth and Everson's view : They used 40% NaXS solution in water to solubilize a variety of substances such as aliphatic and

aromatic hydropcarbons, alcohols, ethers, aldehydes, ketones, amines, oils and so on. Also found this solvent to be an excellent hydrotrope. They had also compared the solubilizing ability of the ortho, para and meta isomers of the xylene sulfonate towrds a variety of hydrophobic subastances and observed that all the three isomers exhibit comparable hydrotropic efficiency. However the meta isomer is preferable at lower temperature due to its higher water solubility. Among them, the xylene sulfonate appears to have maximum solubilizing ability.With increasing hydrotrope concentration,the agent is having increased solubility is neither linear nor monotonic, but displays a sigmoidal behaviour.

Winsor's view: In 1948, Winsor made an attempt to relate hydrotropic action to solubilization and emulsification. He noted that a hydrotrope induces mutual solubilization of organic and aqueous liquids and regarded hydrotropy to be quite similar to cosolvency.

Licht and Weiner's view: The equilibrium solubility data for the water-hydrotrope benzoic acid system at 30, 40 and 60 degree celsius was obtained for these authors. In order to look at the influence of similarity in structure between the solute and the hydrotrope, solubility data was obtained with the six different hydrotropes. They, in the order of decreasing effectiveness are : Na p-cymenesulfonate > o-xylenesulfonate> m-xylenesulfonate > p-bromobenzenesulfonate > p-toluenesulfonate > benzenesulfonate. Their interpretation of these results was that the increased solubility is due to "salting in" effect rather than due to similarity in structure. Their view of hydrotropy thus agrees with that of Mckee.[34-38]

STRUCTURE OF HYDROTROPIC AGENT

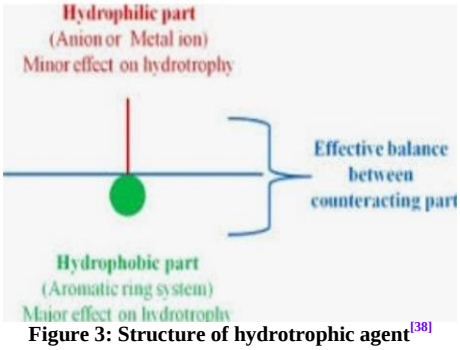

Figure 3: Structure of hydrotrophic agent[38]

Hydrotropes are ampiphillic in nature because it contains both hydrophobic and hydrophillic groups. But the hydrophobic fraction is small. Generally the hydrotropic efficacy is better if layer is the hydrophobic part. Hydrotropic agents are usually non-micelle forming substances. They can be anionic, cationic or neutral, organic or inorganic and liquid or solid in nature. By the formation of stack-type aggregation we can improve the aqueous solubility of organic substances, so the hydrotropic agents are freely soluble in organic solvents[39-43]as shown in figure 3.

CLASSIFICATION OF HYDROTROPE

The chemical structures of the conventional Neuberg hydrotrope molecules consists of two essential features as an anionic and hence water soluble group and a hydrophobic aromatic ring or ring system was noted by Sales and his coworkers.

The planar hydrophobic moiety is thought to be essential for inducing stack type aggregation whereas the hydrophilic ionic part helps in enhancing the hydrotrope solubility in water. The cationic or nonionic polar groups should serve the purpose, if the role of the ionic group is only to increase the aqueous hydrotrope solubility. Inorder to test this, Sahel.et.al studied the cationics, p-aminobenzoic acid hydrochloride, procaine hydrochloride and dubacaine hydrochloride and found them to be good hydrotropes, able to solubilize the representative lipophile riboflavin very effectively[44]as in table 3. By all these they proposed a new definition for hydrotropes: "the freely soluble organic compounds either cationic, anionic or neutral molecules that

considerably enhance the aqueous solubility of organic substances which are practically insoluble under normal conditions are known as hydrotropic agents."

Table 3: Classification of hydrotrophic agents[44]

Sl.no	CLASSES OF HYDROTROPIC AGENTS
1	Organic acids and their metal salts
2	Urea and its derivatives
3	Alkaloids
4	Phenolic derivatives
5	Surfactants
6	Aromatic cations

The above definition of hydrotropes would seem to dictate that only organic molecules having a planar hydrophobic ring system and polar groups attached to it should be considered as hydrotropes. If it is so, then the inorganic compounds such as KI, KSCN, NH_4CN, which Mckee considered as hydrotrope, will not come under the class of hydrotropes. This might be appropriate in the sense that these inorganic molecules bring in the solubilizing ability by the salting in process, which might or might not really be the operating mechanism behind hydrotropy. The second point about the definition is that it stresses the amphillic nature of the hydrotrope molecules, wherein the hydrophobic moiety is the "functional" part and the polar group aids in the high solubility of the hydrotrope itself in water.[45]

ADVANTAGES OF HYDROTROPIC SOLUBILIZATION TECHNIQUE

1. It is the superior method, because here the solvent character is independent of pH.
2. This may have high selectivity.
3. Emulsification is not required.
4. It avoids the problem of residual solvent toxicity by excluding the use of organic solvent.
5. This method is new, simple, cost effective, safe and environmental friendly.
6. Requires only mixing of hydrotrope with drug in water.
7. Chemical modification is not required.
8. Large concentration of hydrotropic agents can be reduced.[45-48]

DISADVANTAGES OF HYDROTROPIC SOLUBILIZATION TECHNIQUE

1. By the excess use of hydrotropic agents problems associated with toxicity may arise.
2. The interaction between the drugs and hydrotropic agents may become weak.
3. The complete removal of water is not possible, because of the use of water as the solvent.[48]

HYDROTROPE SELECTION

From the previous works, it is evident that the aqueous solubility of poorly water soluble drugs increases with increase in the concentration of hydrotrope. So, the hydrotropic agent should be used in highly concentration forms. The hydrotropic solution was prepared using distilled water. Some of the examples of hydrotropic solution are 2M sodium benzoate, 2M niacinamide solution, 2M sodium salicylate, 4M sodium acetate, 10 M urea, 1.25M sodium citrate.

For the sufficient enhancement in solubilization as in figure 4, the hydrotropes should be suitably selected, using the appropriate solubility determination method. To a 50ml glass bottle 25ml of distilled water or hydrotropic solution was taken and the gross weight was taken including the cap. Then to it added a few milligrams of fine dry powder. The bottle was shaken by hand vigorously. When the drug was dissolved completely. Repeat the same procedure till the some excess drug remained undissolved.

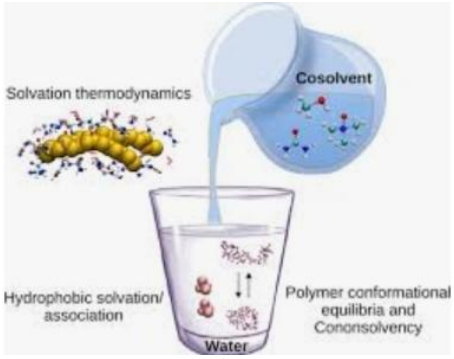

Figure 4: Selection of a hydrotrophic agent

Again the gross weight was taken. An approximate solubility and solubility enhancement ratios were calculated by taking the difference between the two readings. The same calculation is done for all the selected drugs. From this, the hydrotropic solution having the solubility enhancement ratio at least was selected. The obtained results should be comparable with the analysis obtained by the IP method.[49-58]

MECHANISM OF HYDROTROPE ACTION

Based on the molecular self association of the hydrotrope and on the association of hydrotrope molecules with the solute, the solubility of poorly soluble drug can be increased. Even though the hydrotropic agents are widely used, there information on mechanism of hydrotropy is less available. Inorder to clarify the mechanism of hydrotropy, various hypothesis and research works are being made. Accordingly the available mechanism can be abridged into 3 designs:

a) Potential of self aggregation.
b) Structure maker and structure breaker.
c) Micelle like structure formation.

These hydrotropes can be distinguished from other solubilizers based on these unique geometrical feature and different association pattern of the hydrotropes.

(a) SELF AGGREGATION POTENTIAL

The critical concentration at which the hydrotrope molecules start to aggregate ie; self-aggregation potential is known as Minimum Hydrotropic Concentration (MHC). This self-aggregation potential of these molecules governs the solubilization power of hydrotropic agents. Self-aggregation potential may depends upon their ampiphillic features and the nature of a solute molecule. This may mainly shows the volume-fraction dependent solubilization potential. Initially, the primary association of the hydrotroph molecule in a pair wise manner may happens. This may be followed by a series of steps to form trimers, tetramers and so on. The formed complexes may lead to higher aqueous solubility. For this, different methods like fluorescence emission, crystallography analysis, molecular dynamics replication and thermo dynamic solubility experiments can be used. They may also increase the solubility of a solute by acting as bridging agents by reducing the Gibb's energy. A true key for understanding the origin of the self aggregation potential is the structure of the hydrotrope-water mixture around the drug molecule.

(b) STRUCTURE BREAKER AND STRUCTURE MAKER

Here a vital role was played by the electrostatic force of the donor acceptor molecule in a hydrotropic solubilization technique. So they are also termed as a structure breaker and a structure maker. The solubility enhancement may occur when the solutes capable both of hydrogen donation and acceptable are present. Some exert their solubilizing effect by changing the nature of the solvents as hydrotropic agents like urea. This is done specifically by altering its ability to engage in structure formation via intermolecular hydrogen bonding or by altering the solvent's ability to participate in structure formation.

The structure-maker hydrotropes and structure breaker hydrotropes are also known as kosmotropes and chaotropes respectively. Both of them influences the cloud point. The kosmotropes by increasing the hydrophobic interactions may reduce the Critical Micelle Concentration (CMC), which decreases the cloud point, while a kosmotrope may influences the cloud point in two ways. Such as it helps to form bigger micelles and to decrease hydration.

(c) ABILITY TO FORM MICELLE

This step is based on the self association of hydrotropes with solutes into a micellar arrangement. They form stable mixed micelles with a solute molecule, that decreasing the electrostatic repulsion between the head groups. Hydrotropic agents exhibit self association with solutes and form micelles some like alkyl benzene-sulfonates, lower alkanoates and alkyl

sulphates. The solubility of riboflavin is improved by some aromatic anionic hydrotropic agents like nicotinamide and is via a self-association mechanism. Stable mixed micelles are formed by sodium salicylate like anionic hydrotropic agents by decreasing the electrostatic repulsion between the head groups.[59-63]

NOVEL PHARMACEUTICAL APPLICATIONS OF HYDROTROPIC SOLUBILIZATION TECHNIQUE

1. The quantitative estimations of poorly water soluble drugs by UV visible Spectrophotometric analysis precluding the use of organic solvents

To conduct the titrimetric analyses for the solubilization of poorly water soluble drugs, various organic solvents like methanol, chloroform, acetone, dimethyl formamide and ethanol have been used. The organic solvents used may have some disadvantages like higher costs, toxicities and pollution. Various organic solvents like methanol, chloroform, ethanol, dimethyl foramide, benzene, hexane, acetone, toluene, carbon tetrachloride, diethyl ether and acetonitrile are used widely for the spectrophotometric estimation of poorly water soluble drugs. Majority of the organic solvents may have some drawbacks like toxicity, costlier and sources of pollution and also due to the volatility of organic solvents there is inaccuracy in spectrophotometric estimations.

In the presence of large amount of hydrotropic agents, there is a good enhancement in aqueous solubility of selected poorly water soluble drugs. So for the development of new titrimetric and Spectrophotometric methods for the analysis of poorly water soluble drugs, we must make use of the hydrotropic solubilization techniques.

2. Determination of interference of hydrotropic agent in the Spectrophotometric estimation of drugs:

For the Spectrophotometric determinations, a UV-Visible recording spectrophotometer with 1 cm matched silica cells is used. The absorbance of the standard solution of drugs are determined employed for the spectrophotometric analysis or for the formulation purpose, both with distilled water alone and in the presence of maximum concentration of the hydrotropic agent. By this, the determination of interference of hydrotropic agents in the spectrophotometric estimation of drugs can be done.

3. Regression equation for drugs

For this, the stock solution of drug is prepared initially. Then specified quantity of drug is dissolved in appropriate volume of concentrated aqueous solution of hydrotropic agents and made up to the volume by using more water. The prepared stock solution is further diluted with distilled water to get standard solution containing concentration of drug in the range of Beer's law. The absorbance values of these solutions are noted at λmax against distilled water as blank. These values of absorbances of standard solution are used to obtain regression equation.

4. Used for the Spectrophotometric analysis of marketed tablet formulation of drugs

Grounded the weighed 20 marketed tablets in to fine powder. To a 25ml volumetric flask, transferred an accurately weighed tablet powder equivalent to the quantity of drug which was used for obtaining regression equation. Then to this, added the volume of aqueous solution of concentrated hydrotropic agent inorder to solubilize the drug present. Then the flask is shaken for about 10 min and with distilled water the volume is made up to the mark. After mixing the contents, filtration is done through Whatman filter paper number 41.

5. Use in titrimetric analysis for the quantitative estimation of poorly water soluble drugs.

To solubilize the poorly water soluble drugs in titrimetric analysis costlier organic solvents are more often employed. Volatility and pollutions are the drawbacks of such solvents. Various techniques can be used to enhance the aqueous solubility of poorly

water soluble drugs. Hydrotropic solubilization phenomenon has been widely used to enhance the aqueous solubility of poorly water soluble drugs.

6. Hydrotropic solid dispersion preparation of poorly water soluble drugs.

A solid dispersion of one or more active pharmaceutical ingredients in an inert and nontoxic carrier matrix at solid state by using solvent evaporation method, fusion method and melting solvent method. Low aqueous solubility drugs will mostly show less dissolution rate, and incomplete absorption and penetration rate-limited absorption is exhibited by drugs with poor membrane permeability.

7. Used as solubilizing agents in drug formulations

Hydrotropes have been used to prepare formulations of the drug ternezapam and to stabilize the formulation by lyophilization. More recently hydrotropes were used in the formulations of the coronary vasodilator drug nifedipine. In these instances, rather than as an emulsion or a multiphase suspension, the hydrotropes is to act as a nontoxic vehicle that solubilizes and keeps the drug in a stable homogeneous phase. It was shown that hydrotropes enhances the absorption of the drug theophylline and the hormone insulin, when coadministered in the experimental animals. Hydrotropes are also found to be useful as vehicle for drugs administered through transdermal delivery.

8. Biological applications

The effect of hydrotropes on the activity of the enzymes dehydrogenases has been reported, so also the increased antibacterial action of cresols in hydrophobic solutions. Some hydrotropes can cause hemolysis of human erythrocytes. Sahel and coworkers also found that the hydrotropes Na benzoate affect the structure of haemoglobin and this was attributed to the effect of hydrotropic salts on the water structure of the Fe-histidine bond. The anti-inflammatory effect of the hydrotrope aspirin has been attributed to an inhibition of prostaglandin synthesis. The binding of the hydrotropic acid (HTA) to plasma proteins was studied in intact, bile duct caulated, bile duct ligated, and the bile duct cannulated as well as nephrectomized rats. In the step from the liver into the bile and blood, the stereo selective excretion of HTA-G is regulated. Since proline belongs to the class of compatible solutes, dry syrup for reconstitution preparation of poorly water soluble drugs, which helps cells cope with the osmotic stress and the ability of proline to function as a hydrotrope was also looked.

9. By precluding the use of organic solvents, topical solutions preparation.
10. Injection of poorly water soluble drug preparation.
11. Used as permeation enhancers.
12. The hydrotropy can be used to give fast release of poorly water soluble drugs from the suppositories.
13. Mixed hydrotropy can be used to develop injection dosage forms of poorly water soluble drugs.
14. They can be applied in nano technology.
15. Application in the extraction of active constituents from crude drugs.
16. Used to tried to develop the dissolution fluids to carry out the dissolution studies of dosage forms of poorly water soluble drugs.[64]

FORMULATIONS

The widely used methods for increasing the dissolution rate is the solid dispersion technology. By this, the rate of absorption and/or total bioavailability of the poorly water soluble drugs can also be increased. The methods widely used are the solvent evaporation, fusion and fusion solvent methods for the preparation of solid dispersions. An organic solvent which is volatile in nature is used to dissolve the drug as well as carrier in the case of solvent method. Then the solvent dispersions is obtained by removing the solvent by suitable evaporation technique. But the major drawbacks of this method include toxicity of residual solvent, cost of solvent and pollution. In the newly developed hydrotropic solid dispersion technology the use of organic solvent were avoided. The

characteristics of this new method are that the hydrotropic agent (carrier) is water soluble whereas the drug is insoluble in water. The drug gets solubilized in the presence of large amount of hydrotropic agent in water. By using suitable evaporation technique, the water is removed to get a solid mass i.e.; a solid dispersion. This method is different from the common solvent method, since that in the absence of hydrotropic agent, water is not a solvent for poorly water soluble drug. This method is a novel application of hydrotropic solubilization phenomenon. These formed solid dispersion is known as hydrotropic solid dispersions.[65]

ENVIRONMENTAL CONSIDERATIONS

Normally, the hydrotropes are having a low bioaccumulation potential. They are found to be very slightly volatile under specific vapour pressure. They are aerobically biodegradable. Removal of the activated sludge via the secondary wastewater treatment process is >94%. The hydrotropes can also been used in hydrotropes in household laundry and cleaning products have been determined to not be an environmental concern.[65]

HUMAN HEALTH

Hydrotropes may cause aggregate exposures to consumers in many ways like direct and indirect dermal contact, ingestion and inhalation. This may be estimated to be about 1.42 kg/day. Some shown to cause temporary slight eye irritation in animals like calcium xylene sulfonate and sodium cumene sulfonate. Many studies have not found hydrotropes to be mutagenic, carcinogenic or have reproductive toxicity.

MIXED HYDROTROPY

The phenomenon to enhance the solubility of poorly soluble drugs using the blends of hydrotropic agents is known as Mixed Hydrotrophic Solubilization technique. This may give the poorly soluble drugs a synergistic enhancement effect on the solubility. Due to a reduction in the concentration of individual hydrotropic agents, it reduces the side effects.

CONCLUSION

The most important factor that controls the formulation of the drug as well as the therapeutic efficacy is the solubility of the drug. Solubility is the most critical factor in the formulation development. The rate determining step for oral absorption of the poorly water soluble drugs is the dissolution of drug. Also, solubility is the basic requirement for the formulation and development of different dosage forms of different drugs. The hydrotropic solubilization techniques alone or in combination can be used to enhance the solubility of the drug. Through a number of techniques the solubility of the drug was increased and a number of folds increase the solubility. For many drugs, the bioavailability of them gets affects, because of solubility problems, solubility enhancement become necessary. As a novel approach it is now possible that to increase the solubility of poorly water soluble drugs with the help of various techniques. This method is getting lot of values and may be proved the best method in future.[65-66]

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