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A Review on Various Methods Used for the Solubility Enhancement of Cefixime Trihydrate

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ABSTRACT

Solubility is a major boundary to achieve required concentrations of drug in systemic circulation for pharmacological respond to be shown. In today time poor water solubility is the major issue face with formulation development of new chemical entities. There are various factors which can affect the solubility are like pressure, temperature, porosity, polymorphism, particle size, nature of solvent etc. Increasing the bioavailability and dissolution rate of poorly aqueous soluble drugs will be one of the biggest challenges for formulation scientist in the future. Hence, there are various technique used for the enhancing the solubility, micronization, chemical modifications, pH, adjustment, Solid, dispersion, complexation, co-solvency and hydrotropic method. The model drug for this review work is cefixime trihydrate. It has a broad-spectrum, third generation cephalosporin antibiotic. It is having low solubility and as well as low permeability characteristics related to class IV of the BCS (Biopharmaceutical classification system) system. As Cefixime trihydrate a poorly soluble, it is having a low dissolution rate in gastrointestinal fluids which leads to insufficient bioavailability that affects its onset of action. Generally, in this article we concentrate on, various techniques used for enhancing the solubility of cefixime which are hydrotropy, solid dispersion, nanoparticles, nanocrystals, solid dispersion, liquid solid technology and mixed solvency. All these methods successfully improved the solubility and bioavailability of the drug.

Key words: *Solubility, Factor affecting, Techniques for poor soluble drugs, Different techniques increasing solubility of cefixime trihydrate.*

INTRODUCTION

Solubility has the maximum quantity of solute that can dissolve in a certain quantity of solvent. Solubility depends upon the solvent, pressure, and temperature, nature of solutes and solvent. Solubility has a major effect on drug effectiveness. The solubility of a drug in aqueous is a basic property that must be examined [1]. The techniques generally working for solubilization of drug includes, micronization, nanosuspension, chemical modifications, co-crystal, complexation, solid dispersion, co-solvency, hydrotropy etc [2]. As we all know that in today's life oral ingestion is the most convenient and more commonly employed route of drug delivery due to ease of administration, high patience compliance, cost effectiveness and more flexibility in the design of dosage form. Because of this many generic drug companies are inclined more to produce bioequivalent oral drug products. The oral dosage form depends upon the several factors like permeability, bioavailability and the solubility of drug. So if there is any problem occur in bioavailability and solubility of drug it can change the whole process of oral dosage form[3].

Cefixime trihydrate, a third-generation cephalosporin antibiotic used in the treatment of various diseases like urinary tract infection, respiratory tract infection, gonorrhea (a sexually transmitted disease); and infections of the ears, throat, tonsils. One of the crucial difficulties with this drug is poor solubility in biological fluid that results into poor dissolution rate and bioavailability after oral administration of drug. The chemical structure of cefixime as shown in Figure 1[4] and the physiochemical properties of cefixime trihydrate as given below Table 1.

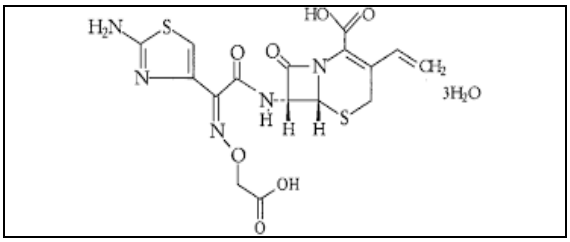

Fig. 1. Structure of cefixime trihydrate

Table 1. Physiochemical Properties of Cefixime Trihydrate [5]

Molecular Formula	C16H21N5O10S2
Molecular weight	507.5
Category	Cephalosporin antibiotics
IUPAC name	(6R,7R)-7-{[2-(2-Amino-1, 3- thiazol - 4-yl)-2 (carboxymethoxyimino) acetyl] amino}-3-ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2caboxylic acid.
BCS class	II and IV class
Solubility	0.104mg/ml
Appearance	Off –white to pale yellow color and is strawberry flavored
pH	2.2 to 3.8
Melting point	218-225C
Storage	Keep container tightly closed

BCS CLASSIFICATION

According to BCS boundaries of solubility class are based on the highest dose of an intermediate release product. A drug called is highly soluble when it is highest dose soluble in aqueous solution and the boundaries of permeability class are based indirectly on the amount of absorption of drug substance in humans [6]. The BCS classification with drug as listed in Table 2.

Table 2. BCS classification with drug [6]

Class	Solubility and Permeability	Drug
1	High permeability and solubility	Sumanitriptan
2	High permeability and low solubility	Valsartan
3	Low permeability and high solubility	Gabapentine
4	Low permeability and low solubility.	Meloxicam etc.

FACTOR AFFECTING SOLUBILITY

1) **Polarity**:The solubility can be affected by the by both the polarity of solute and polarity of solvent. The non- polar solute will dissolve in non-polar solvent but the polar solute

will dissolve in polar solvent. Polar solutes have one side positive and another side negative end of the molecule [7].

2) **Pressure**: For solids and liquids solutes if we change the pressure effect there will be no effect on solubility. As solubility will remain same but for gaseous solute if we increase the pressure then solubility will also increase and if we decrease the pressure of gaseous solute then solubility will also decrease [8].
3) **Particle size:** Particle size affect the rate of solubility. As the particle size increases then it causes the **Particle size:** greater interaction with solvent. But when the particle size decreases the surface area to volume ratio increases [9].

   Particle size effect on solubility can be described as [10]

$$\text{Log}\ \frac{S}{S^{\circ}} = \frac{2\gamma V}{2.303\ RTr}$$

   S° = Fine particles, S= Large particles, γ = Surface tension, V= Molar mass
   R= Gas constant, T= Absolute temperature, r= Radius of fine particle
4) **Temperature**: With the increase in temperature the process of solution absorbs the energy and thus the solubility will get increases. But if the process of solution releases the energy with the increase in temperature, then it will decrease the solubility [10].
5) **Molecular size:** The Molecular size will affect the solubility of the drug because the larger the molecules or higher the molecular weight of the drugs less is the solubility of the substance. Larger molecules are more difficult to surround with the solvent molecules in order to solvate the substance [11].
6) **Effect of pH:** Most of the drugs is weak acid or weak base. Solubility depends on degree of ionization, which depends upon pka and pH. The pH at which the drug is entirely in the ionic form, it behaves as a solubility of strong electrolyte and no solubility problem. Solubility depends upon the no. of ions if the no. of ions increases then the solubility will be more if the number of ions decrease then the solubility will be less [12].

TECHNIQUE FOR SOLUBILITY ENHANCEMENT:

I. Physical Modification (Particle Size Reduction)

a) Micronization- Micronization is the process of converting big size particles into small of micron size. Small particles size results in increases surface area. Micronization occurs surface area increases with decreasing particle size and solubility increases. Example of drugs whose solubility increases by micronization are fenofibrate, griseofulvin, spironolactone, progesterone. Different techniques for micronization as shown in Figure 2 [13,14]. Pros and cons of micronization as given below Table 3.

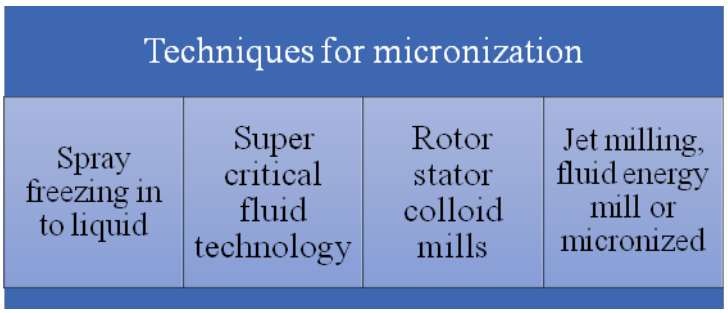

Fig. 2. Techniques for Micronization

Table 3. Pros and Cons of Micronization [13]

Pros	Cons
Used to increase surface area for dissolution.	High process, not suitable for drugs having a high dose no due to it not changing to saturation solubility of the drugs.

b) Nanosuspension-A nanosuspension is a submicron colloid size dispersion system with pure drug particle size of 100-1000nm. Nanosuspension technology is used for efficient delivery of hydrophobic drug. A pharmaceutical nanosuspension is defined as very finely colloid, biphasic dispersed solid drug particle in an aqueous vehicle, a size below 1 stabilized by surfactant and polymers. Examples of drugs whose solubility increases by this technique are ketoprofen, Azithromycin, Carbamazepine. Major advantages of this method are it can be given by any route but it also has some disadvantage that problems occur due to sedimentation or it can be suffering from problem of instability due to agglomeration [15,16]

II. MODIFICATION OF CRYSTAL HABIT

a) Polymorphism-Ability of drug to occur in more than on crystallization forms are called polymorphs. A crystal is a form of matter in which the atoms, molecules, or ions are arranged in a highly ordered three- dimensional lattice. Different polymorphs of drugs are chemically same but they exhibit different physiochemical properties like, melting point, texture, density, solubility, stability. For example, Chloramphenicol palmitate exists in 3 polymorphic forms such as A, B and C, among these forms B is the most soluble. So more soluble crystalline form should be preferred [17]

b) Complexation – Association two or more molecules having more solubility than parent drug itself. There are two types of complexes[16].

1) Inclusion –Here cyclodextrins is used as a complexing agent and the list of complexing agents are given below in Table 4. These are formed by the insertion of non-polar molecule or non–polar region of one molecule or group of molecules this process is known as inclusion complexation[13]

Table 4. List of complexing agents

Types	Examples
Chelates	EDTA, EGTA
Co-ordination	Hexamine cobalt III chloride
Molecular complexes	Polymers
Inclusion	Cyclodextrins, choleic acid

2) Staching complexation: Staching complexes are formed by the overlap of the planar regions of aromatic molecules. In this process when we add organic drug with water than non –polar moieties tend to be squeezed out of water by strong to minimize contact with water and form aggregates. Then this aggregation formed by large planar non – polar regions in the molecules. This complex can be mixed or homogeneous. This process is known as self-association complexation. Example- Nicotinamide, Theobromine, Anthracene these are the examples of Staching complexation[9].

III. Solubilization by Surfactants

To enhance both dissolution rate and permeability of drug, the surfactants are used as absorption enhancers. Surfactants are molecules with different enhancers. Surfactants are

molecules with different polar and non – polar regions. When the surfactant is present it may lower the surface tension and increase the solubility of drug within an organic solvent. The surface-active agents enhance the dissolution rate by promoting wetting and penetration of dissolution fluid into the solid particles. In place of non-ionic surfactants, the ionic surfactants are more preferred as ionic is better solubilizing agents than non-ionic [18].

IV. **Micro emulsions-** It is the process which can dissolve the low soluble of drug. It can work to increase in the solubility of many drugs which is closely too insoluble in the aqueous form. Micro emulsions are homogeneous thermodynamically stable dispersion of water and oil, stabilized by a surfactant. Micro emulsion usually uses in a combination with co- surfactant [19].

V. Drug Dispersion in carriers – Solid dispersion means that there is presence of one or more active ingredients which work as an inert carrier in a solid state, as an inert carrier in a solid state, it is frequently prepared by three methods. Different method of solid dispersion as shown in Figure 3.

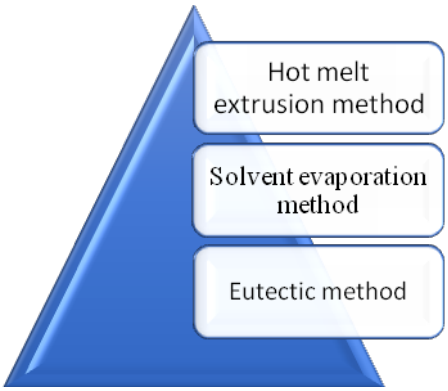

Fig. 3. Solid dispersion done by three different methods

When the solid dispersion comes in contact with the aqueous medium the inert carrier dissolves and the drug is released ultimately resulting in increased solubility of drug. Example –solubility of sulfathiazole increased by using urea as an inert carrier by formation of solid dispersion. Hydrophilic (water soluble) carriers used for solid dispersion include polyvinyl pyrolidone, polyethylene glycols, and plasdone-S630 [20,13].

Solvent Evaporation Method

Firstly, weighed amounts of carrier and active drug then mix both of them and dissolved in minimum quantities of chloroform in a round–bottom flask. Then the solvent is evaporating by using a spray drying. After all this process we obtained the solid dispersion which is transferred on to the aluminum pan and allowed to dry at room temperature. Temperature used for solvent evaporation in between 23-65℃ [21].

Major advantages of this method are rapid dissolution rate and absorption rate increases. But it also has some major disadvantages are moisture can affect solid dispersion and instability[13].

VI. CHEMICAL MODIFICATIONS

a) **Change in the pH –** The poor soluble drug may potentially dissolve in water by implementing a pH change. It is the simplest and most commonly used method to increase water solubility of ionizable compounds. There is adjustment /change of micro-environment pH to modify the ionization behavior of the drugs. Examples of pH–adjusting

excipients that can be used to improve the dissolution rate of weak basic drugs include organic acids (e.g. – citric acid tartaric acid, carbonic acid) [22].

b) Derivatization (Prodrug) - A Prodrug is a medication after administration is converted within the body into a pharmacologically active drug. Instead of administering a drug directly, its prodrug can be used to increase solubility [23].

VII. OTHERS METHODS

1) **Use of Salt Form:** Salts have improved solubility and dissolution characteristics in comparison to the original drug salts of acidic and basic drugs have, in general, higher solubility's than their corresponding acid or base forms. Salt formation to increase aqueous solubility is the most preferred approach. Salts are formed when a compound is ionized in solution. It is an effective method in parental and other liquid formulation, as well as in solid dosage form [24,25]. Solubility enhancement of drug by the use of salt form are listed in Table 5.

Table 5. Drug with salt form increases the solubility.

Drug	Salt form	Solubility Enhancement	Reference
Furosemide	Sodium salt	20 folds	26
Phenytoin	Sodium salt	60 folds	27

2) **Co-Solvency:** Co-Solvency is the process of increasing solubility of poorly water-soluble drugs by mixing it with some water miscible solvent in which the drug is readily soluble. When there is addition of an organic co- solvent to aqueous can change the solubility of drugs solvent e.g., glycerin, propylene, glycol. It also reduces the interfacial tension between the poor soluble drug (solute) and aqueous solution. It is mainly use in parental dosage form because of low toxicity of many co-solvents [28].
3) **Co-crystallization:** Co-crystal consists of 2 or more components that form a unique crystalline structure having unique properties. Co-crystal are more stable, particularly as the co- crystallizing agent are solids at room temperature. In pharmaceutical co- crystal can enhance the physiochemical properties of drug such as, solubility, melting point, stability and bioavailability, co-crystal are more stable especially as the co-crystallizing agents are solid at room temperature [19].
4) **Hydrotropy:** The word hydrotropy was first invented by scientist Carl Newberg in 1916, but the practical indications were introduced as late as 1976 by Thomas and co- workers. Hydrotropy is a solubilization process by which addition of a large amount of second solute to increase in the water solubility of another solute. Hydrotropic solubilization is an encouraging strategy for increasing the solubility of drugs that do not dissolve properly, as it does not require chemical modifications of the drug. Hydrotropic agents are ionic organic salts. Additives or salts which are increase solubility in given solvent are said to 'Salt in' the solute and those additives which decrease the solubility are said to be 'Salt out' the solute. Some salts with large cations and anions which are itself very soluble in water result in "Salting in'' of non–electrolytes called "hydrotropic salts" is called as "hydrotropism". The mechanism that improves solubility is more similar connect to complexation involving a weak interaction between the hydrotropic agents like urea, sodium benzoate, sodium alginate, sodium acetate and the poorly soluble drug. Major advantages of this method are highly selectivity and no need of chemical modifications. But it also has some disadvantages such as water can't be removed completely because of the use of water as the solvent and if we use excess number of hydrotropic agents then

toxicity may arise [29,30,31]. Solubility enhancements of drugs by the use of hydrotropes are listed below Table 7 and the applications of hydrotropic method as shown in Figure 4.

Table 6. Drug with hydrotropes increases the Solubility

S.NO	Drugs	Hydrotropes	Solubility Enhancement	Reference
1.	Piroxicam	Sodium Benzoate, Sodium acetate, Urea, Sodium citrate, Nicotinamide	Solubility of Piroxicam increases up to 65.400mg/ml.	32
3.	Indomethacin	Niacinamide	Solubility increased by 5 times	33

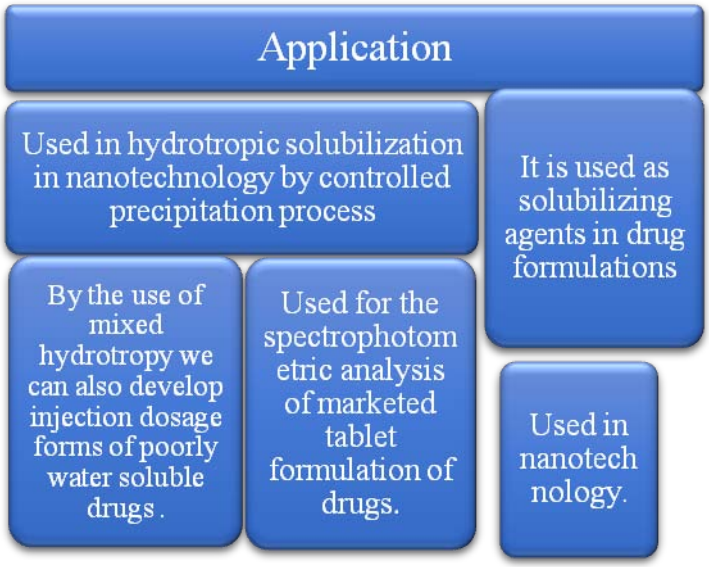

Fig. 4. Applications of Hydrotropic Techniques

Different Techniques used to Enhance the Solubility of Cefixime Trihydrate

1. Solid Dispersion Technique

Case Studies

a) **Brahamaiah B, Shreekanth Nama et.a**l used Croscarmellose as a disintegrating agent in 1:1. The solubility of cefixime trihydrate increase by formulating solid dispersion with polymer between four different techniques which is used to prepare the solid dispersion [34].

b) **Parsana SRV et.al** were prepared solid dispersion by using natural polymers *i.e* guar gum. From the result it was concluded that the solubility and dissolution rate of cefixime trihydrate were improved as compared to pure drug solubility [35].

c) **Pathan Dilnawaz et.al** were prepared solid dispersions by using natural polymers *i.e* guar gum. From the result it was concluded that the solubility and dissolution rate of cefixime trihydrate were improved as compared to pure drug solubility [36].

d) **S. K Sadia et.al** were prepared solid dispersion by using of polymers *i.e* PEG 6000, PEG4000 etc. From the result it was concluded that the bioavailability of cefixime Trihydrate increases by using polymers [37].

e) **S.C Arora et.al** prepared solid dispersion with urea by using solvent evaporation method. The bioavailability and dissolution rate increased by preparing solid dispersion [38].

2. Nanosuspension

Case Studies

a) **Bhagat Ankita Rajendra et al**. The methanol and water used as solvent and antisolvent respectively. PVP K30 and HPMC K100 surfactants used in this preparation which was found to be compatible in the formulation [39].

b) **Elham Ghasemian et.al** were prepared Nanosuspension by using sonoprecipitation method and the effect of surfactants type. So, at last it was concluded that sonoprecipitation was shown to be a successful method to improve drug dissolution rate **[**40].

3. Mixed Solvency Techniques

Case study

Maheshwari R.K et.al were used PEG 300, urea, sodium citrate, PEG 400 and 10% of PEG 4000 for solubilization. At last, in result there was significant enhancement in solubility in blend mixed – solvency (more than 120 folds as compared to solubility in distilled water [41].

4. Nanoparticles

Case study

Muhammad Zahoor et.al were prepared cefixime nanoparticles by antisolvent with syringe pump (APSP) and evaporator precipitation nanosuspension (EPN) methods. Hence at last the dissolution rate of cefixime nanoparticles was increased [42**].**

5. Hydrotropy

Case Studies

a) **Gopal Prasad Agrawal et.al** were prepared solid dispersion by using different hydrotropic agent. From the result it was concluded that the bioavailability of cefixime Trihydrate increases by using hydrotropes [43].

b) **Rajesh Maheshwari et.al** used hydrotropic agent i.e 0.5 M Potassium citrate which increases the solubility and dissolution rate [44].

c) **R. K Maheshwari** used metformin as a hydrotropic agent. The solubility increases to more than 18 folds [45].

6. Nanocrystals

Case Study

Ahmed A. Hussein prepared nanocrystals of cefixime as a capsule dosage form to increase its bioavailability and dissolution rate. So, from the result it was concluded that the dissolution rate was increases as compared to pure cefixime powder [46].

7. Liquid Solid Technology

Case study

Zainab H. Mahdi et.al were prepared oral capsules of cefixime by liquid solid technology after mixing different concentrations of the drug with propylene glycol. So, this technique increases the solubility and dissolution rate [47].

CONCLUSION

In today time low aqueous solubility is the major issue face with formulation development of new chemical organization. Increasing the bioavailability of poorly soluble drugs will be one of the biggest difficulties for formulation scientist in the future. Hence, there are various technique for the improving the solubility, micronization, chemical modifications, pH adjustment, Solid, dispersion, complexation, co–solvency and the hydrotropy method. This article has provided an overall overview of the literature on various solubility and dissolution enhancement techniques that have been applied to the poorly aqueous-soluble drug, Cefixime trihydrate, including hydrotropy, solid dispersion, nanosuspension, nanocrystals, complexation, liquid solid, mixed solvency, nanoparticles. All these methods successfully improved the solubility and bioavailability of the drug. Among all the techniques, solid dispersion technique is mostly used for enhancing the drug bioavailability and dissolution rate. So now we can say that it is possible to increase the solubility of poorly aqueous soluble drug with the help of various techniques which are discussed above.

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