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A REVIEW ON TECHNIQUES TO IMPROVE SOLUBILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

Solubility is the phenomenon in which the conversion of solute into solution, and it is very important for the absorption, bioavailability and pharmacological response. About 40% new drug has water solubility, which is difficult to formulate. This review gives details about techniques to improve solubility of poorly water soluble drugs, includes particle size reduction, nanosuspension, self emulsifying drug delivery system, liquisolid compact, solid dispersion etc. The selection of solubility enhancement techniques depends on drug property, site of absorption and required dosage form characteristics.

KEYWORDS: Solubility, bioavailability, solid dispersion, self emulsifying drug delivery system, microemulsion, nanosuspension.

INTRODUCTION

Solubility is the ability of substance that is solute to dissolve in a solvent. It is measured amount of solute dissolved in a solvent at equilibrium. The resulting solution is called as a saturated solution.[1] Therapeutic response of drug depends upon the bioavailability and solubility of drug.[2,3] The solubility property that can be altered by physical and chemical modification of drug molecule. The defination of solubility as per United States Pharmacopoeia given in the Table no - 1.[4]

Table No.1: Defination of solubility as per USP.

Descriptive Terms (Solubility Defination)	Parts of solvent required for one part of solute
Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Insoluble	>10000

FACTORS AFFECTINGSOLUBILITY

The solubility of drug is depends upon the nature of drug and nature of solvent as well as temperature and pressure. The details of factors are given in Table no.2.

Table no. 2: Factors affecting solubility.

Factors	Influences
Particle size	The particle size affect the solubility of drug molecules, because as particle becomes smaller, the surface area of particle will be increase, due to this there is a greater interaction with the solvent.[5,6]
Temperature	As the temperature is increases then solution absorbs energy and the solubility will be increased.[5,7,8]
Pressure	There is no effect of pressure on the solubility of solid and liquid solutes, but pressure affect the solubility of gaseous solutes that is if pressure is increases the solubility is also increases.[5,7,8]
Molecular size	The higher molecular weight substances affect the solubility of the substances because larger molecules are difficult to interact with solvent.[5,7,8]
Nature of solute and solvent	The nature of solute and solvent affects the solubility of substances and the example is 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature 200 grams of zinc chloride can be dissolved in same.[5,7,8]
Polarity	The solubility of substances will be affected by the polarity because like dissolves like means non-polar solute will dissolve in non-polar solvents and polar solute will dissolve in polar solvents.[5,8]
Polymorphs	Different polymorphs has different melting point. Since the melting point of substances is directly related to solubility.[9,10]

Techniques to improve solubility and bioavailability

1) Particle size reduction
2) pH adjustment
3) Co-solvency
4) Complexation
5) Hydrotrophy

6) Microemulsion
7) Nanosuspension
8) Self emulsifying drug delivery system
9) Solid dispersion
10) Salt formation
11) Use of surfactant
12) Liquisolid compacts.

1) Particle size reduction

We discussed in factors that solubility related to particle size of drug, that is if the particle size of drug becomes smaller it gives larger surface area has greater interaction with solvent due to this solubility is increases. The methods for particle size reduction are comminution and spray drying etc. The another conventional method for particle size reduction is micronization. Micronization increases surface area due to this dissolution rate of substances is also increased. Micronization is done by rotor stator colloid mill, jet mill. Micronization is not suitable for drugs having high dose number.[11,12]

Advantages of particle size reduction[13]

a) No need of surfactant for stability.
b) Crystal forms are physically and chemically more stable than amorphous form.
c) Low drug and excipients ratio is required.

Disadvantages of particle size reduction[13]

a) Difficulty in the development of the sterile intravenous formulations.
b) Possibility of particle agglomeration due to high surface charge.
c) It is difficult to develop solid dosage form without agglomeration.

2) pH adjustment

The solubility of poorly soluble drugs may change by applying a pH change. To improve the solubility by this method, the buffer capacity of the selected pH are important to be mentioned. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pka of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkanizing agents may increase the solubility of weekly basic drugs.[11,14]

Advantages of pH adjustment[13]

a) Less quantity of compound is requires.
b) Easy to produce.
c) Easy to formulate and analyse.
d) Amenable to high through put evaluations.

Disadvantages of pH adjustment[13]

a) Possibility of toxicity due to extreme pH and non physiological pH.
b) Possibility of precipitation upon dilution with aqueous media having pH at which substance is less soluble.
c) Due to the selected pH may chances to hydrolysis or catalyze.

3) Co-solvency

The solubility of poorly water soluble drugs can be enhanced by mixing solvent which is miscible in water. This process is called as co-solvency and the solvent is called as cosolvent. In co-solvency the interfacial tension between aqueous media and hydrophobic solute is reduced. It is called as solvent blending.[11,15]

Advantages of co-solvency[13]

a) Easy and fast to produce and formulate.

Disadvantages of co-solvency[13]

a) Precipitation occurs upon dilution with aqueous media.
b) As with all solubilized form, the insoluble drug has worse chemical stability than crystalline form.
c) The toxicity of solvent which is administered should be considered.

4) Complexation

Complexation is the process between two or more molecules to form a non-bonded entity with a well defined stoichiometry.

Two types of complex available:

4.1) Stacking complexes

4.2) Inclusion complexes

4.1) Stacking complexes

In this process there is overlap of the planar regions of aromatic molecules. Non-polar moieties tend to be squeezes out of water by the strong hydrogen bonding interactions of water. Due to this some molecules has minimum contact with water by aggregation of their hydrocarbon moieties.[13]

4.2) Inclusion complexes

In this process there is the insertion of the non-polar molecule which is known as guest into the cavity of another molecule which is known as host. The cavity of host should be large for the accommodation of the guest and should be small for the elimination of water. The commonly used host molecules are cyclodextrins. Lipophilic drug-cyclodextrin complexes, known as inclusion complexes can be formed by the addition of drug and excipient, which results in the improving drug solubilization. Cyclodextrins are related to cyclic oligosaccharides which has a polar cavity and hydrophilic external surface.[13]

Advantages of complexation[5]

a) Complexation improves chemical stability of guest.
b) There is no supersaturation for insoluble drug upon dilution.

Disadvantages of complexation[5]

a) Possibility of toxicity of complexing agent.
b) Structural requirement for drug.

5) Hydrotrophy

In hydrotrophy, the addition of large amount of second solute, the hydrotropic agent results in increase in the aqueous solubility of first solute. Hydrotropic agents are ionic organic salts, consists of alkali metal salts of various organic acids. Salts which increases solubility in the given solvent are known as “Salt in” solute and which salts decreases solubility in the given solvent are known as “Salt out” solute. Some salts with large anions or cationswhich are very soluble in water results in salting in of non-electrolytes called as hydrotropic salts and phenomenon called as hydrotropism. Hydrotrophy enhnce the solubility in water due to presence of salts. The mechanism of Hydrotrophy is related to complexation which involves a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and poorly soluble drugs.[16,17,18]

The classification of hydrotropeson the basis of molecular structure is difficult, whereas wide variety of compounds have been reported to show hydrotropic behavior.[6,18]

Advantages of hydrotrophy[13]

a) This technique does not require use of organic solvents or preparation of emulsion system and any chemical modification of hydrotropic drugs.
b) This technique only requires mixing of the drug and hydrotropesin water.
c) It is better than other solubility enhancement techniques because it does not require emulsification.

6) Microemulsion

A microemulsion consist of external phase, internal phase, surfactant and cosurfactant. The addition of surfactant which is soluble in internal phase incompatible cosurfactant, results in the formation of an optically, istropic, thermodynamically stable emulsion. It is termed as microemulsion because of internal or dispersed phase is <0.1µ droplet diameter.[20,21,22]

Advantages of microemulsion[13]

a) Excellent reproducibility and bioavailability are getting without administration of food if microemulsion are effectively prepared.
b) Simple to manufacture.

Disadvantages of microemulsion[13]

a) Microemulsions are difficult to verify.
b) Possibility of precipitation of drug by cause of hydrophilic solvent.

7) Nanosuspension

Nanosuspension is a biphasic system consist of nano size drug particles which are stabilized by surfactant. The particle size of drug is less than one micron.[18,23,24]

Different techniques used for the preparation of nanosuspension given are as follows:

7.1) Precipitation technique

In this technique the drug is dissolved in a solvent, and then the addition of antisolvent due to this precipitation of crystals. The advantage of this technique is easy and low cost equipments are required.[9,18,25]

7.2) High-pressure homogenization

In this technique the suspension of drug and surfactant is forced under valve of high pressure homogenizer. High pressure homogenizer convert microparticlesinto nanoparticles.[7,18]

7.3) Media milling

The nanosuspension are accomplished by the utilization of high-shear media mills. The milling chamber consist of drug, milling media, water and stabilizer and it is rotated at very high-shear rate under controlled temperature for several days.[26]

7.4) Combined precipitation and homogenization

The precipitated drug nanoparticles have a capacity to continue crystal growth to form microcrystals. They need to be processed with high pressure homogenization.

Advantages of nanosuspension[26,27]

a) The drug has high log P value can be formulated as nanosuspension with increasing bioavailability.
b) Possibility of dose reduction.
c) Nanosuspension enhance solubility and bioavailability of drug which has rapid onset of action.

8) Self-emulsifying drug delivery system[SEDDS]

Self emulsifying drug delivery system has exclusive property, they are capable to self emulsify in the gastrointestinal fluid with the help of gentle agitation. Self emulsifying drug delivery system are isotropic mixture of natural oil or synthetic oil, surfactant, cosurfactant, cosolvent. Self emulsifying drug delivery system spontaneously forms oil in water emulsion upon dilution by aqueous phase in the GIT.[11,28]

Advantages of self emulsifying drug delivery system[29]

a) SEDDS are easy to manufacture and are physically stable formulation.
b) These formulation reduces the gastric irritation produced by drugs.
c) This system suitable forbith liquid and solid dosage form.
d) Protects drugs from GIT environment.
e) Rapid onset of action.
f) Increase in oral bioavailability and solubility.
g) Reduction in the dose of drug.

h) The drug loading capacity has been increased by this method.

Disadvantages of self emulsifying drug delivery system[27,29]

a) Possibility of GI irritation due to high concentration of surfactant.
b) Chemical instability of surfactant and drug in formulation
c) Lack of in vitro models for the judgement of the formulations.
d) Production cost is very high.

9) Solid dispersion

Solid dispersion is very profitable technique for enhancing the solubility and bioavailability. The term solid dispersion consist of two component that is hydrophilic matrix and hydrophobic drug.

Different methods are used for the preparation of solid dispersion are as follows.[11,30]

9.1) Fusion method

In this method, the carrier is heated above its melting point and the drug is fused into the matrix and the mixture is cooled by continuous stirring until the drug is thoroughly spread into the matrix.[11,31]

9.2) Solvent method

In this method, the carrier and drug are dissolved in organic solvent and by increasing the temperature the solvent is evaporated. Due to this solvent is removed and results in supersaturation and after that precipitation is occurs and finally resulting in a solid residue. Then this precipitate is dried under vacuum.[11,32]

9.3) Fusion-solvent method

It is the combination of fusion method and solvent method in which the carrier is melted and drug in incorporated. The solvent is eliminated by increasing temperature or by vacuum. This method is only suitable for those drug which has high melting point.[11,32]

9.4) Spray drying method

In this method, the drug and carrier is dissolved in solvent and this solvent is removed by application of hot air. Due to this large particles converted into small particles which gives large surface area, the solvent is evaporated rapidly and results in the formation of solid dispersion.[11,33]

9.5) Lyophilization (Spray Freeze Drying Method)

This method involves the continuous spraying of liquid which contains poorly water soluble drug and excipients into cryogenic liquid at surrounding temperature to form micronized powder after that drying of this micronized powder. This method gives more benefits than traditional technologies for solid dispersions.[11,34,35,36]

9.6) Hot melt extrusion

Hot melt extrusion defined as the formation of a new material (extrudate) by forcing it through an orifice under controlled conditions, such as mixing, feed, pressure and temperature.[27,37]

Advantages of solid dispersion[27]

a) Solid dispersion produces highly porous particles because the utilization of polymer which results in the higher dissolution rate.
b) Solid dispersion reduces particle size due to this solubility is increases.
c) Improve wettability of particle.

Disadvantages of solid dispersion[27]

a) Difficulty in incorporation into formulation of dosage forms.
b) Instability may be occurs due to moisture content.

10) Salt formation

It is an effective technique for the improvement of the solubility of poorly soluble drugs specially for the parenteral and liquid formulations as well as solid formulations. From 300 new chemical entities about 120 are in the salt form.[38,39]

Disadvantages of salt formation[8,38]

a) The main advantage is this method is the approval of salt is difficult task.
b) This method is not useful for the neutral molecules.

11) Use of surfactant

The use of surfactant may decrease the surface tension and due to this the solubility of drug is increase in organic solvents. Surfactants having both polar (head) and non-polar ends (tail). Some surfactant has a hydrocarbon segment which is connected to a polar group can be cationic, zwitterionic or nonionic, anionic. Small molecules of polar molecules can be gather into hydrophobic core of micelles. When surfactant such as tween 80 is in water it will form

micelles. Anon polar drug will partition into the hydrophobic core of the micelle and the polar tail will solubilize the complex[38,40]

Advantages of use of surfactant

a) Low toxicity.
b) Better surface and interfacial activity.

Disadvantages of use of surfactant:

a) Inability to increase the process of production and patent rights by using biosurfactants.

12) Liquisolid compact

In this technique the liquid converted into free flowing and compressible dry powder by blending with carrier and coating material. The drug may be in the form of drug solution or drug suspension. In this technique the drug dissolved in suitable non-volatile liquid and it is incorporated into a carrier material which has porous in nature due to this absorption and adsorption is occur. Due to adsorption the liquid goes into external and internal surfaces of carrier. Then, coating material is added which gives appropriate flowing properties[10,27,41].

Advantages of liquisolid compact[27,42]

a) Production cost is low.
b) This method is specially for powdered liquid medications.
c) Useful for the oily drugs or liquid drugs.
d) Increases the solubility and bioavailability of water insoluble drugs.
e) Most of poorly soluble drugs can be formulated in this method.

Disadvantages of liquisolid compact

a) It is not suitable for those drugs which has high dose.
b) Sometimes liquid drugs compressed out of the tablet results in improper hardness.

CONCLUSION

From this article, we conclude that the solubility is very important factor for pharmacological response. Also the selection of method for enhancement of solubility is very important and it is depend upon nature of drug. It is possible that the solubility of poorly water soluble drugs will increases with help of above methods.

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