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REVIEW ON: CONVENTIONAL AND NOVEL TECHNIQUES FOR SOLUBILITY ENHANCEMENT

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ABSTRACT
The most challenging task in drug development is enhancement of solubility and permeability. About 40% new chemical entities (NCEs) rejected in drug discovery program due to its low aqueous solubility. Solubility, Dissolution rate of drug and it's release from dosage forms have ascendance on bioavailability. Major challenges for formulation scientist is the low aqueous solubility which can be solved by different conventional and novel technological approaches includes micronization, nanonization, use of salt forms, use of surfactants, solid dispersion, complexation, liquisolid technique etc. This article gives detailed information about different conventional and novel technologies used to enhance solubility and dissolution rate of poorly water soluble or hydrophobic drugs.

KEYWORDS: Hydrophobic, Solubility, Bioavailability, Solid Dispersion, Liquisolid.

INTRODUCTION

Oral route is the most preferable route of administration of dosage forms but the major problem of oral route is solubility of the active ingredients present in dosage forms. Solubility, rate of dissolution directly effect on the bioavailability. Solubility is the most important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response. About 40% or more new chemical entities discovered in pharmaceutical screening program are practically insoluble in water.[1,2] Poor water solubility is the most challenging problem among five physicochemical parameters in early compound screening i.e. Dissociation constant, Solubility, Permeability, Stability and Lipophilicity. The term 'solubility' is defined as maximum amount of solute dissolved in a given amount of solvent. Qualitative terms, it may be defined as the impulsive interaction between two or more substances to form a homogeneous molecular dispersion. The solubility of drug may be expressed as parts, percentage, molarity, molality, volume fraction and mole fraction.[3]

The drug solubility in saturated solution is a static phenomenon and Drug dissolution rate is dynamic phenomenon which is closely related to the bioavailability rate. The solubility of drug described on the basis of amount of solutes dissolved in solvent and discuss in table-1.[4]

Table 1: Definitions of Solubility

Descriptive terms	Parts of solvent required for 1 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
Practically insoluble	> 10000

Need of Solubility

1) Solubility is the important parameter to achieve required concentration of drug in systemic circulation for therapeutic response.
2) Hydrophobic drug requires higher doses for achieve therapeutic plasma concentration.
3) Low aqueous solubility encountered problem with permeation.
4) Liquid pharmaceutical formulation water is the most important vehicle.
5) Most of the weakly acidic and weakly basic drugs having poor aqueous solubility.
6) Low aqueous soluble drugs having slow absorption leads to gastrointestinal mucosal toxicity.[5]

Drug absorbed from GI Tract can be limited due to various factors such as low aqueous solubility and low intestinal permeability. BCS (Biopharmaceutical Classification System) is the scientific framework for

classifying drug substances based on their aqueous solubility and intestinal permeability. It is a drug developing tools that allows finding the contribution of dissolution, solubility and intestinal permeability that effect on oral absorption of drug. Drug release is the most important and rate limiting step for oral bioavailability specially for low solubility and high permeability i.e. BSC class II and IV drugs. BCS class II and IV requires increasing the solubility, dissolution rate having direct impact on bioavailability. BCS classification system given in table-2.[6,7]

Table 2: Biopharmaceutical Classification System

BCS class I	High Solubility and High permeability
BCS class II	Low Solubility and High permeability
BCS class III	High Solubility and Low permeability
BCS class IV	Low Solubility and Low permeability

Factors Affecting Solubility

1) Molecular size

Increasing the particle size or it's molecular weight decreasing the solubility. Larger molecules having low surface area for contact with solvents in case of organic compounds increasing the branching of carbon atom reducing the size and increase solubility.[8]

2) Temperature

If the solution process absorbs energy then the temperature is increased the solubility will be increased but the solution process release the energy then the temperature increased the solubility will be decreased.[9]

3) Pressure

For gaseous solutes, Solubility increased when the pressure is increased. In the case of solids and liquids solubility not affected by pressure.[10]

4) Particle Size

When particle size reduced or decreased then surface area also increased. Greater the surface area greater the solubility. Particle size inversely proportional to the surface area.[11]

5) Nature of solute and solvent

The nature of solutes and solvents depends on the concentration of solute in specific quantity of solvent at specific temperature.[8]

6) Polarity

Polarity is the important parameter for the solubility in which polar molecule dissolves in polar solvent and non-polar molecules dissolves in non-polar solvent.[8]

Techniques for Solubility Enhancement

There are various techniques available to improve the solubility of poorly water soluble drugs which includes:

1) Micronization
2) Nanonization
3) Ultra Rapid Freezing
4) Spray Freezing into Liquid
5) Evaporative Precipitation into Aqueous Solution (EPAS)
6) Use of Precipitation Inhibitors
7) Salt Formation
8) Hydrotrophy
9) Co-solvents
10) Sonocrystallization
11) Use of Surfactants
12) pH adjustment
13) Co-crystallization
14) Supercritical Fluid (SCF) Process
15) Solvent Deposition/Evaporation
16) Co-evaporate System/ Co- precipitation
17) Solid Dispersions
18) Inclusion Complexes
19) Liquisolid Techniques.

1) Micronization

The process involves reducing the size of solid drug particles to 1 to 10 microns by using spray drying or by using air attrition methods such as fluid energy or jet mill. The process called as micro-milling. Reduction of particle size means increased surface area which is contact with solvent and increased bioavailability of the drug. Example -Griseofulvin.[12]

Techniques for Micronization

- Jet milling /Fluid energy mill
- Microprecipitation and Microcrystallization
- Controlled crystallization
- Spray drying into liquid
- Supercritical fluid technology
- Rotor stator colloid mills

Advantages:

- Increased surface area for dissolution by using this method.
- Rate of drug dissolution increased through increased surface area.

Disadvantages:

- Equilibrium solubility does not improved by this method.

2) Nanonization

The process involves reducing the size of solid drug particles to 200 to 600 nm. The various technologies used to produce nanocrystals yield as a product a dispersion of drug nanocrystals in a liquid, typically water called nanosuspension. Example-Amphoterecin B.[8]

Three methods are used to prepare nanoparticles

1. Pearl milling
2. Homogenisation in water (wet milling as in a colloid mill)
3. Homogenization in non-aqueous media or in water with water miscible liquids.[12]

Pearl milling

In this method the microparticles are convert into nanoparticles (<400nm). The milling efficiency depends

on the properties of drug, medium and stabilizer. The main purpose of stabilizer is particle wetting which is avoid ostwald ripening and agglomeration of particles.[13]

High Pressure Homogenization

In this method the suspension pass through a narrow aperture of homogenizer under the high pressure. Generally most of the cases suspension can be multiple or cycle passes through homogenizer which is depend on hardness of drug required for homogeneity and desired particle size. Homogenizers operated at pressure varying from 1000 to 1500 bars. sometime they may be reached to pressure 2000 bars.[13]

3) Ultra Rapid Freezing

In this method the drug/excipient solution frozen on cryogenic agent and lyophilized to form micronized dry powder. Surfactants and alkalizing agents (i.e. Tromethamine and Diethanolamine) are the composition of this method. This process useful to avoid the crystallization of ingredients present in solution leads to form amorphous drug-carrier solid dispersion or solution.[14]

4) Spray Freezing into Liquid

The aqueous organic emulsion or suspension containing drug and excipients are incorporate into compressed gas (i.e. CO_2, Helium, propane) or cryogenic liquids (i.e. nitrogen, argon) and then lyophilized to form micronized dry powder.[12]

5) Evaporative Precipitation into Aqueous Solution (EPAS)

In this method the drug dissolved in low boiling point organic solvent to form a solution. This solution is pass through a tube which is heated temperature above the solvents boiling point and spray through a nozzle into a heated aqueous solution. Surfactants are used to stabilized the solution.[12]

6) Use of Precipitation inhibitors

The amount of free drug concentration in solution above than equilibrium solubility known as supersaturation which can leads to precipitation or crystallization. This precipitation can be avoided by using polymers such as Hydroxypropyl methyl cellulose, Polyethylene Glycol, Polyvinyl pyrrolidone etc.[12]

7) Salt Formation

Salt formation is the most widely used method for increasing solubility and dissolution rates of acidic and basic drugs which are converted into their respective salt forms. Alkali metal salts of acidic drugs and strong acid salts of basic drugs shows higher water solubility than the parent drugs.[15]

Limitations

- Neutral compounds are not suitable for salt formation.
- Salts formation of very weak acids and bases are very difficult.
- Salt form may be hygroscopic, exhibit polymorphism and poor processing characteristics.[12]

8) Hydrotrophy

Hydrotrophy concept first discovered by Neuberg to describe the by addition of high concentrations of alkali metal salts of various organic acids increases the solubility of BCS class II drugs. Hydrotrophy is the solubilization phenomenon that addition of large amount of second solutes which increases the aqueous solubility of another solute called as hydrotropic agents. Additives or salts increases the solubility in given solvent called as "salt in" the solute and decreases the solubility in given solvent called as "salting out" the solute. Hydrotropic solutions involve in the weak interaction between hydrotropic agent and solutes and do not show colloidal properties. Example-Hydrotropic solution of sodium benzoate.

Advantages

- The hydrotrophy method is better than other solubilization methods such as micronization, nanonization, co-solvent etc. because the solvent is independent of pH and does not required emulsification.
- It does not required changes or modification in hydrophobic drugs.[16]

9) Co-solvent

The solubility of poorly water soluble drugs increased by adding another water soluble solvent called as co-solvent. Mechanism action of this method is reduction of interfacial tension between aqueous solution and hydrophobic agents. Co-solvents posses the hydrogen acceptor or donor groups with small hydrocarbon region. This phenomenon called as co-solvency. Commonly used cosolvents are Glycerol, Propylene Glycol, PEG 400 etc.

Advantages

- Simple and rapid formulation.
- Combined with other solubilization techniques.
- Co-solvents are non-toxic in nature.

Disadvantages

- Uncontrolled precipitation occurs when dilution with aqueous media.
- Precipitation varies with size.
- Various insoluble compounds are unsuited for cosolvent.[17]

10) Sonocrystallization

Recrystallization of poorly water soluble drugs having larger particle size can be reduced by using liquid solvent and anti-solvent. Novel approach to reduced particle size on the basis of crystallization by using ultrasound called as sonocrystallization. In this method the ultrasound power used for enhance the rate of nucleation, effectively reduction of particle size and controlling the size distribution of the active pharmaceutical ingredients.

Frequency of ultrasound used within the range between 20-100 kHz.[18]

11) Use of Surfactants

Surfactants are useful for the enhancement of the absorption, rate of dissolution and permeability of the drug. They are used in below the critical micelle concentration (CMC) value above the CMC value (range 0.05-0.10%) drug entrapped in the micelles this process known as micellization results enhanced solubility of poorly water soluble drugs. They enhance the dissolution rate by increasing the wetting property and penetration dissolution fluid into the dosage forms. Non ionic surfactants are preferred generally like polysorbates.[19]

12) pH Adjustments

pH adjustment is the most commonly used method for increase solubility of ionizable compounds. Adjustment of micro environmental pH of drug is helpful for the solubility enhancement of drug. According to the Handerson-Hesselbatch equation, ionization of compound depends on the pH and pKa of the drug. The change in pH of the environment to forms salt these salt convert into it's acid or base which increases the solubility of drug. Poorly water soluble drug dissolve by using the change in pH.[12]

13) Co-crystallization

Crystalline material consists of two or more molecular species held together by non-covalent forces. Co-crystallization method is alternative method for salt formation, specially for neutral compounds. Example-Saccharin, Nicotinamide etc.[15]

Different techniques for co-crystallization

- 1) Solvent evaporation
- 2) Grinding
- 3) Slurry Co-crystallization
- 4) Solvent drop grinding (Modification of Grinding)
- 5) High throughput cocrystallization
- 6) Hot melt extrusion
- 7) Sonocrystallization Method

Characterization Parameters of Co-crystal

- 1) Melting Point
- 2) Solubility
- 3) Stability
- 4) Dissolution
- 5) Bioavailability
- 6) Hot Stage Microscopy
- 8) Differential Scanning Calorimetry (DSC)
- 9) X-ray Diffraction.[20]

14) Supercritical Fluid (SCF) Process

These is another method of nanosizing and solubilization technology in which supercritical fluids (e.g. carbon dioxide) are having property of temperature and pressure are greater than it's critical temperature and critical pressure. These fluids allow the property of both liquid and gas (i.e. liquid-like density, gas-like compressibility and viscosity). The properties of supercritical fluids such as density, viscosity, diffusivity, dielectric constant and polarity are considerable small changes in operating temperature and pressure. The drug particles solubilized within supercritical fluid they may be recrystallized at greatly reduced particle sizes. Carbon dioxide, nitrous oxide, ethylene, propylene, propane and ammonia are generally used as a supercritical fluid.[21]

15) Solvent Deposition/Evaporation

In these technique drug dissolved in a solvent such as methylene chloride to form a clear solution. The carrier materials are dispersed in the above clear solution with continuous stirring and the solvent is removed from solution by using evaporation under temperature and pressure. After removal of solvent the resultant mass is then dried, pulverized and pass through the sieve. The rate dissolution increased because of the particle deposited on the carrier reduced particle size and the increase the wetting property.[22, 23]

16) Co-evaporate System/ Co-precipitation

Weak basic drugs are soluble in acidic pH but in alkaline pH reduced solubility. In conventional dosage forms containing weak base precipitation occur in intestinal pH and reduced solubility leading to the reduced bioavailability of drug. This problem overcome by using co-evaporate system which incorporates a carrier with solubilizing effect in alkaline intestinal fluid which immediately surrounds the drug particle for controlled dissolution rate of dosage forms.[24]

17) Solid Dispersions

Solid dispersion systems in which the drug is dispersed in solid water soluble matrices either molecularly or fine particles shows increased bioavailability of poorly water soluble drug. Solid dispersion defined as the one or more active ingredients in carrier or matrix at solid state. Various methods are available for preparation of solid dispersion includes

- Fusion Process
- Solvent Method
- Fusion Solvent Method
- Spray Drying
- Spray Freeze Drying Method
- Hot Melt Extrusion
- Dropping method

17.1) Fusion Process

The melting or fusion method was firstly discovered by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. In these method carrier material heated above it's melting point and the drug incorporated into the matrix. The mixture cooled with constant stirring to form a homogeneous distribution of the drug in matrix. Several mechanisms are involved in this process such as solubility of drug is high in carrier; the drug could be 'dissolved' in the solid state called as solid solution. If the solubility of drug in solid state is moderate, crystallites

of the drug become dispersed in the matrix. The third mechanism is conversion of drug into amorphous form which exhibit the rate of dissolution and solubility increases.[25, 26]

17.2) Solvent Method

Tachibana and Nakamura were first dissolved the drug particle and carrier in a common solvent and then evaporate the solvent under vacuum pressure or elevated temperature to give a solid solution. After removal solvent by evaporating to form a supersaturation followed by simultaneous precipitation of constituents resulting solid residue. Generally non aqueous organic solvents are used for avoid the solvates formation in crystal lattice. Complete solvent removal differential scanning calorimeter (DSC), differential thermal analysis (DTA), Thermogravimetric analysis techniques are used.[27]

17.3) Fusion-Solvent Method

In the fusion method carriers are melted and drugs are incorporated in the form of solution. In this method the main problem is retention of liquid in carrier if innocuous then the liquid removable methods are eliminated. This method is preferred for the high melting point and thermolabile drug particles.[27]

17.4) Spray Drying

In this type of preparation, the carrier and active ingredients dissolved in a suitable organic solvent. The solvent evaporate by using drying it to apply stream of heated air for evaporation of solvent. Due to larger surface area of droplet solvents are rapidly evaporates to form a solid dispersion.[28]

17.5) Spray Freeze Drying (SFD) Method: In these method thermal sensitive drugs are used because of the heat is not used for drying purpose. SFD technology involves the atomization of the feed liquid containing poorly water soluble drug and excipients are incorporate into the cryogenic liquid at ambient temperature to produce frozen micronized powder that is subsequently dried.[29]

17.6) Hot Melt Extrusion: Speiser and Huttenrach were the first persons this method used in the pharmaceutical purpose. Component of HME : An opening to the feed raw materials, a heated barrel consist of extruder screw to convey and fed the materials and an exist port, which consist of an additional die to shape the extruding mass. The mixture of drug and carrier fed into the heated barrel which is convey by screw it's transform into fluid like state. These state allow to homogeneous mixing with high extruder screws, an exist port which consist of optional die, shape of mass extruder such as granules, pellets, films or powder.

17.7) Dropping Method

The melted mixture of carrier and drug pipettes out then dropped on a plate. In this method the size of melt depends on the viscosity of mixture and size of the pipette but viscosity depends on the temperature. Temperature is the most parameter for the spherical size of droplets.[32]

Advantages of solid dispersion techniques

- In these technique homogeneous distribution of drugs in solid state.
- To increase dissolution rate.
- To increase absorption rate.
- To decrease crystalline of drugs into amorphous forms.
- To avoid bitter taste.
- To avoid the polymorphic problems.

Disadvantages of solid dispersion techniques:

- The dissolution rate of solid dispersion effected by aging.
- Instability of solid dispersion
- Moisture and Temperature shows deterioration of solid dispersion.
- Not applicable for thermo sensitive material.[30,31]

18) Inclusion Complexes

Various methods are available for the formation of inclusion complexes includes:

- Kneading Technique
- Co-precipitation
- Co-grinding
- Spray Drying Method
- Microware Irradiation Method

18.1) Kneading Method

In this technique, An active drug and suitable polymer in different ratios added to the mortar and triturate with small quantity of solvent to form slurry. The prepared slurry is then air dried at 25°C for 24h. The resultant product pulverized and passes through sieve.

18.2) Co-precipitation

In this technique, required amount of drug is added to the solution of β-CD. The system kept under the magnetic agitation with controlled parameter process and protected from light. The solvent is removed by using evaporator to formed precipitate separated by the vacuum filtration and dried at room temperature.

18.3) Co-grinding

In this technique, the drug and cyclodextrin are mixed and these mixtures are introduced into in a suitable mill and grinded for specific time.

18.4) Spray Drying Method

Drug dissolved in a suitable organic solvent and required amount of carrier such as cyclodextrin is dissolved in water. Solutions are then mixed by sonication to produce clear solution and the solvent evaporated by using evaporator and then spray dried.[33]

18.5) Microwave Irradiation Method

In this technique, the irradiate reaction shows between drug and complexing agent. The drug and cyclodextrin with required molar ratio dissolved in water and organic solvent in round bottom flask. The mixture kept in oven after completion of reaction adequate amount of solvent add for the removal of residue and uncomplexed free drug. The precipitation separated by using whatman filter paper and dried in oven at 40°C for 48 h.[34,35]

19) Liquisolid Techniques

The liquisolid technique first coined by Spireas in 1998 is a novel concept that conversion of liquid into free flowing powder. This powder shows free flowing and compressible property by using suitable carrier and coating material along with non-volatile solvent and disintegrants.

Advantages

- Improved bioavailability of orally administered dosage forms containing low aqueous soluble active ingredients.
- Increase surface area for dissolution and wetting property of drug.
- This method is chief than capsules.
- Immediate and sustained release dosage forms can be prepared by these method.
- Easy to formulate.
- Drug release can be modifying by using suitable excipients.

Disadvantages:

- High carrier and coating ratio is required.
- Not use for high dose formulation.
- If the tablet is more than 1gm very difficult to swallow.
- Sometimes liquid squeezing out phenomenon may be occur.[36]

Classification of liquisolid system

1. Powdered drug solution (containing a drug solution)
2. Powdered drug suspension (containing a drug suspension)
3. Powdered liquid drug (containing a liquid drug)

Components of liquisolid system:

a) Carrier materials
b) Coating materials
c) Non volatile solvents
d) Disintegrants

a) Carrier materials

Carrier materials possessing porous in nature and high absorption property. Example- Various grades of Microcrystalline cellulose such as Avicel pH 200, Avicel pH 101 etc.

b) Coating materials

Coating materials posses inert in nature and high adsorption property. This material used to enhance the flow and compression property of powder. They required fine size of particle which is high adsorbing property. Example- Cab-O-Sil M5, Aerosil 200 etc.

c) Non volatile solvents

Non-volatile solvents are preferably high boiling point, high viscous in nature and water soluble. Example- Propylene Glycol, Glycerin etc.

d) Disintegrants

It is used for disintegration purpose in dosage forms. Various disintegrants are used in liquisolid technique such as Sodium Starch Glycolate, Explotab, Crosspovidone etc.[37]

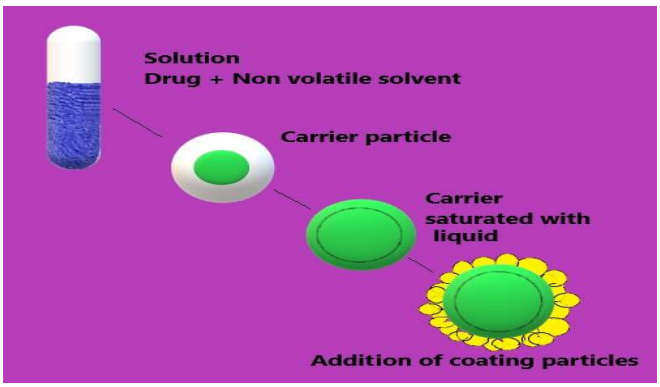

Fig. 1 Schematic representation of liquisolid technique.

CONCLUSION

Various methods are available for enhance solubility and bioavailability of the drug. Solubility is the most important parameter for the required concentration of drug reaches to the systemic circulation for therapeutic response. But in pharmaceutical drug development most challenging task is solubility enhancement of low aqueous soluble or hydrophobic drugs. About 40% drug rejected during discovery program due to low aqueous solubility. In this article we conclude that conventional and novel techniques such as micronization, nanonization, salt formation, pH adjustment, solid dispersion, inclusion complexation and liquisolid techniques etc are the most commonly used for enhance solubility of poorly water soluble or hydrophobic drugs.

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