IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

REVIEW ON SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUG BY USING SOLID DISPERSION TECHNIQUE

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Abstract

Solubility is the process by which a solid dissolve in a liquid phase to form a homogeneous mixture. The aqueous solubility of drug affect the physical, chemical & dose stability; it sets a standard for purity, dissolution rate and extent of absorption. A majority of active pharmaceutical ingredients that are being developed (drug) are lipophilic with limited aqueous solubility leading to problems in preclinical pharmacokinetic and toxicological investigations. Due to rapid advancement in combinatorial chemistry, high-throughput screening this increase of poorly aqueous soluble drugs have been observed. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The focus of this review article on advantages, disadvantages and the method of preparation, and characterization of the solid dispersion.

Keywords :

Solubility, Solubilization Techniques, Bioavailability, Solid dispersion

1. Introduction :

Solubility is one of the most important physicochemical properties of any drug because low solubility can affect the bioavailability of orally administered dosage form. Thus, it is very important to enhance the solubility of poorly soluble drug. Solubility is not to be confused with the ability to dissolve or liquefy a substance, since this process may occur not only because of dissolution but also because of a chemical reaction. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development.[1]

1.1 Solubility :

Solubility is the property of a solid, liquid, or gaseous chemical substances called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the maximum quantity of solute in a certain quantity of solvent at specified temperature and pressure. The term solubility is defined as maximum amount of solute that can be dissolved in a given amount of solvent. Quantitatively it is defined as the concentration of solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form homogeneous molecular dispersion. The substances to be dissolved are called as solute. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water. The study of solubility enhancement is mainly studied on drug which has low aqueous solubility and high permeability.[2]

1.2. Poorly soluble drugs : A majority of active pharmaceutical ingredients that are being developed (drug) are lipophilic with limited aqueous solubility leading to problems in preclinical pharmacokinetic and toxicological investigations. Due to rapid advancement in combinatorial chemistry, high-throughput screening this increase of poorly aqueous soluble drugs have been observed.[3]

Table 1: Descriptive terms for solubility

Descriptive Term	**Part of solvent required per part of solute**
Very soluble	Less than 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Practically insoluble	More than 10000

1.3. Biopharmaceutical Classification System (BCS):

Absorption in gastrointestinal tract involves the breaking down of dosage form into primary particles when exposed to gastrointestinal fluids. This step is called ‘disintegration’. The second step followed by disintegration is ‘dissolution’, which involves the drug molecule to leave the solid form of drug and enter into the form of a liquid solution, which is then followed by absorption where the dissolved drug molecules later pass through the membrane of the gastrointestinal tract to systemic circulation to reach its target site for pharmacological effect. Due to the importance of the interplay among solubility and permeability, the Biopharmaceutical Classification System (BCS) was developed in 1995 to classify drugs depending on the 18 absorption conduct. It has been categorized into 4 groups based on solubility and permeability as shown in Table 2. It defines that a drug, at its highest dose, is soluble in 250ml or less of aqueous media. A highly soluble drug has a pH that ranges between pH 1-7.5, while a poorly soluble drug presents an aqueous solubility of less than 100 µg/ml.[3]

Table 2: Biopharmaceutical Classification System (BCS)

BCS Class	Solubility	Permeability
Class I	High	High
Class II	Low	High
Class III	High	Low
Class IV	Low	Low

1.4 . Process of solubilisation :

The process solubilisation involves the breaking of interionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion .

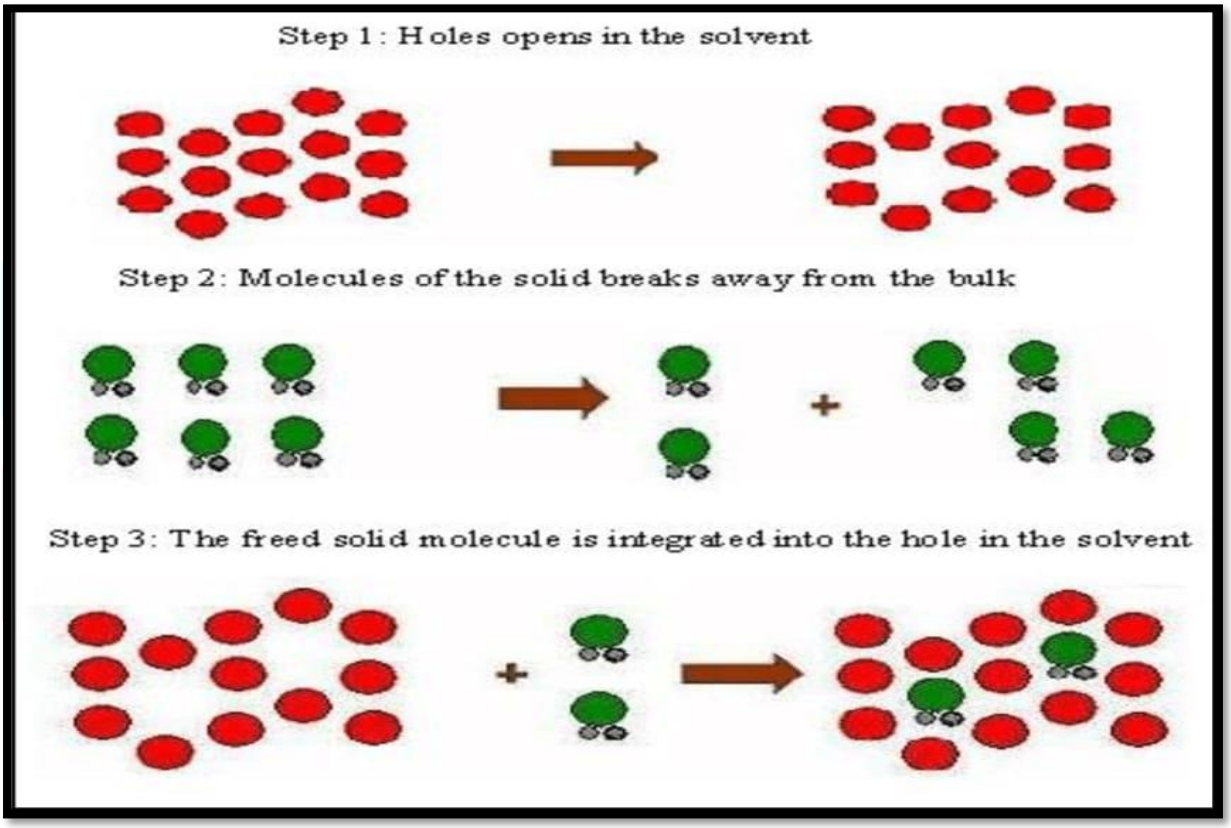

Fig No: 1. Process of solubilization[3]

1.5. Solubilty Enhancement :

Solubility enhancement is a process of increasing the solubility of a drug by the inclusion of other solvents & chemicals.

1.5.1. Techniques of Solubility Enhancement :

I) Physical modification :

a) Micronization . b)Nano-suspension.

II) Crystal habit modification :

a) Polymorphs. b) Pseudo polymorphs.

III) Drug dispersion in carrier :

a) Solid solution. b) Solid dispersion.

IV) Solubilization by surfactants :

a) Microemulsion b) Self-micro emulsifying drug delivery system

V) Complexation .

1.6. Solid Dispersion:

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore ,solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.[3]

1.6.1 Types of Solid Dispersion:

Chiou and Reigalman classified solid dispersion as follows :

1. Simple eutectic mixtures.
2. Solid solutions
3. Glass solution and suspension .
4. Amorphous precipitation in a crystalline carrier.

2 . Methodology :

Solubility enhancement techniques :

2.1. Physical modification

a) Particle Size Reduction

i) Micronization :

A drugs particle size is intrinsically linked to its bioavailability. Increased surface area through increase the dissolution rate of drug. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. It is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. The process involves reducing the size of the solid drug particles is to 1 to 10 microns commonly by spray drying or by use of attrition methods. The process is also called micro-milling.

ii)Nano suspension

:This technology is applied to poorly soluble drugs that are insoluble in both water and oils . A pharmaceutical nano -suspension is biphasic system consisting of nano sized drug particles stabilized by Surfactants for either oral and topical use or parenteral and pulmonary administration.The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200and 600nm.

2.2 . Modificaction of Crystal Habit

a) Polymorphs

b) Pseudo polymorphs

Polymorphism is the ability of solid material to exit in 2 or more different crystalline forms with different arrangement in crystal Lattice . Polymorphs are different crystalline forms . Crystalline form of drug is chemically same but different physicochemical properties like melting point, texture ,density, Solubility, stability. Similarly, amorphous form of drug is suitable than crystalline form. Order of different solid form of drugs. Amorphous >Metastable polymorphs >Stable polymorphs.[4]

2.3. Drug Dispersion In Carrier

a) Solid solutions: It is blend of two crystalline solids that exist as a new crystalline solid .The two components crystalline simultaneously in a homogeneous one - phase solid solution, resulting in a mixed crystal .As a result ,it is expected to yield higher rates of dissolution than simple eutectic systems.[5]

b) Solid dispersion : The term "solid dispersion " refers to the dispersion of one or more active ingredients in an inert carrier in a solid state , frequently prepared by the following methods[6]

1. Hot melt method .
2. Solvent evaporation method .
3. Hot melt extrusion method .
4. Lyophilization Method .
5. Melt Agglomeration method .
6. Melting solvent method.
7. Solvent method .
8. Supercritical fluid method .

1. Melting method:

The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super- saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent. Matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixture[7]

2. Solvent method:

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents

However, some disadvantages are associated with this method such as

- The higher cost of preparation.
- The difficulty in completely removing liquid solvent.
- The possible adverse effect of traces of the solvent on the chemical stability

- The selection of a common volatile solvent.

3. Melting solvent method (melt evaporation):

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol6000 without significant loss of its solid property37. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

4. Melt extrusion method:

The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are some what thermolabile to be processed. Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). The screw configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300rpm. The five temperature zones are set at 100, 130, 170, 180, and 185C from feeder to die. The extrudates are collect after cooling at ambient temperature on a conveyer belt.

5. Lyophilization technique:

Freeze-drying involves transfer of heat and mass to and from the product under preparation37. This technique was proposed as an alternative technique to solvent evaporation. Lyophilisation has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.[8]

6. Melt agglomeration process:

This technique has been used to prepare SD wherein the binder acts as a carrier. In addition, SD(s) are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration. Since these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation

and growth. In addition, the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles result in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles[8]

7. The use of surfactant:

The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions. 8. Super critical fluid (SCF) technology: This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, superconductors and catalyst precursor's dyes and biomolecules such as proteins and peptides. From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drug-loaded biopolymer micro-particles for pharmaceutical applications has been studied intensively by a number of researcher groups CFs either as solvent: rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods, i.e. Spray drying, solvent evaporation and hot melt method often result in low yield, high residualsolvent content or thermal degradation of the active substance the supercritical fluid antisolvent techniques, carbon dioxide is used as an antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system (ASES), precipitation with a compressed fluid antisolvent (PCA), gas anti-solvent (GAS), solution enhanced dispersion by supercritical fluids (SEDS) and supercritical anti-solvent (SAS).

The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition, the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature 390 c Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component).

3. Advantages of Solid Dispersions[9]:

1. In particle size results in high surface area resulting in increased dissolution.
2. Particles with higher porosity are produced and this resulting into increase in dissolution rate.
3. Improvement in wettability with carrier which can increase in bioavailability

4. Reduction Converts drug from crystalline to amorphous form thus improving the dissolution and bioavailability.

5. Increase in solubility of many numbers of water insoluble drugs

4. Disadvantages of Solid Dispersions[9]:

1. Major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging.

2. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir) from the market

3. Some solid dispersion may not lend them to easy handling because of tackiness.

4. Moisture and temperature have more deteriorating effect on solid dispersion

5. Drawback of solid dispersion is their poor scale–up for the purpose of manufacturing.

5. Application of Solid Dispersion[10]

1. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.

2. To stabilize unstable drugs against hydrolysis, oxidation, recrimination .

3. To reduce side effect of certain drugs.

4. Masking of unpleasant taste and smell of drugs.

5. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.

6. To reduce side effect of certain drugs.

7. Masking of unpleasant taste and smell of drugs.

8. Improvement of drug release from ointment creams and gels.

9. To avoid undesirable incompatibilities.

10. To obtain a homogeneous distribution of a small amount of drug in solid state.

11. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.

12. To formulate a fast release primary dose in a sustained released dosage form.

13. To formulate sustained release regimen of soluble drugs by using poorly soluble or in soluble carriers.

14. To reduce pre systemic inactivation of drugs like morphine and progesterone.

15. No change in chemical properties of the drug.

6. Conclusion :

In this articles we conclude that, Solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug.The various techniques described above in combination can be used to enhance the solubility of the drug. solubility can be enhanced by many techniques and number of folds increase in solubility. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

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