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A Review on Solubility Enhancement: The Particle Engineering and Technique of Poorly water Soluble Drugs

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ABSTRACT

In pharmaceutical industry the major problem of dosage form development is low aqueous solubility. In present review the particle engineering concept and solubility, permeability approaches design and method used in improvement of particle size. The different methods are used in particle engineering like supercritical fluid technology, controlled precipitation, and mechanical technique, evaporation precipitation to aqueous solution, freezing technique, and sonication technology etc. discussed. The improvements of aqueous solubility need to be formulation development for dosage form very essential. The BCS class II drugs modified to soluble form for need of bioavailability of drugs. The solid dispersion method with a different carrier improves the solubility.

Keywords: Particle engineering, bioavailability, solid dispersion, solubility.

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INTRODUCTION

The particle size can be reduced by two cardinal principle approaches, in the first approach particle is broken to smaller one and the second approach particle will get together to form aggregates called molecule [8]. The particle size is inversely proportional to the surface area and directly proportional to the absorption. The solvent wetting method used to prepare solid dispersion of felodipine, in this method required slight amount of solvent to dissolve the drug [1]. The used of carrier or polymer carrier may improve the particle solubility. The solid dispersion is the promising strategy to improve the drug solubility generally class II and IV drug [2.] The faster release of sparingly soluble drug can be achieved by dispersion of drug in water soluble carriers by solid dispersion [3]. The solid dispersion is defined as one or more than one API in a polymeric carrier or matrix (Complex) in the solid form prepared by fusion (Melting) solvent or melting solvent method (1971). The novel sabutramine base loaded solid dispersion enhanced solubility and bioavailability. The various solid dispersion techniques are used like spray drying technique with using polymeric forms gelatin, nitric acid and HPMC. The polymer had slight effect on solubility of sabutramine base without acidifying agent [4]. The ethyl cellulose and hydroxyl methyl cellulose shows extended release of poorly water soluble drugs in dissolution mechanism. The release mechanism of drugs from a variety of solid dispersion depends on physicochemical properties of carriers and drug substance. The implication of indomethacin and ethyl cellulose shows hydrophobic interaction under strongly delayed dissolution and region of low pH of indomethacin (IND) [5]. The bioavailability of drug is very low due to first pass effect is low, hence extensive metabolism in liver and gut. The CSE and SAS methods used for the improvement the solubility of poorly water soluble drugs [7]. The itraconazole is the class II drug hence bioavailability determines by dissolution rate in GI tract. The drug and polymer film are prepared for the solid dispersion. The polymeric carrier prevents the crystallization of drug substance during cooling [6].

Particle Engineering Phenomenon and Consideration [8, 14-15]

The particle engineering of poorly water soluble drug is challenge for the all scientist so that need to be improves for the bioavailability, first pass effect, solubility and permeability of drug. The solubility enhancements of class II drug are challenging aspects for the drug delivery system [8].

Particle Engineering Multi-trade [14-15]

The particle size can be reduced by two cardinal approaches, in the first approach the particle break down to smaller size where as in second the particle close to get aggregate to form molecule. The particle engineering concept is most useful in conventional as well as nano or micro formulation in

nanotechnology. The area of interest in research and development gives novel result in future using many variable techniques.

Top down

In this used grinding and milling technique.

Bottom up

In this used crystallization, spray drying, complexation and self-co-solvency.

The Particle Engineering- Pharmaceutical application

The surface Morphology and chemistry

The surface characteristics and chemistry very important for the study of particle engineering they are two types:

- Passivity
- Activate

Control particle

The control of particle by many parameters as following manners gives the idea about the amplification of morphology

Size and distribution

Endocytosis-	< 200 nm
Targeting vessel	<250 nm
Avoid RES-	>150
Nasal delivery-	5-15µ
Dissolution rate-	Control size
Pulmonary delivery-	3µ

Morphology

Surface roughness

Dispersibility

Flowability

Consistency and quality control

Management of product lifecycle

Particle Engineering Technique (BCS class II and IV) [8]

The particle size is inversely proportional to the surface area hence particle size decreases increases bioavailability of drug.

Technology and Design of Technique

Sonication Technology

The sonication technology ensures the particle large unilamellar vesicle to small unilamellar vesicles in Nano scale formulations.

Mechanical Technology

- Wet milling
- High pressure homogenization

Precipitation Technology

Antisolvent Precipitation

- control precipitation
- Evaporative precipitation in to aqueous solution

Supercritical Fluid Technology

- Rapid Expansion of Supercritical Solution (REES)
- Gas Antisolvent Recrystallization (GAR)
- Supercritical Antisolvent (SAS)
- Precipitation with Compressed Fluid Antisolvent (PCA)

Freeze Technology

- Ultra rapid freezing
- Spray freezing in to liquid

The BCS class takes accounts on three major parameters given as follows: [16]

1. Solubility
2. Dissolution
3. Intestinal permeability

Class I----------High solubility--------High permeability

Class II----------Low solubility---------High permeability

Class III----------High solubility---------Low permeability

Class IV----------Low solubility---------Low permeability

Importance of Solubility on Bioavailability of Drugs

Solubility is essential of drug, because absorbed through a membrane and reaches the site of action. The solubility importance is confirmed by the BCS systems. The solubility plays major role in the formulation and developments. The poor solubility and low dissolution rate of poorly soluble drug in GI causes the poor bioavailability.

Polymorphs Screening [16]

The polymorphs screening governs by 'Pepin- ski' et al; 1955 gives an idea about the polymorphs forms the deliberate design and control molecular packing within crystal structure with the generation of desire properties.

Solubility [17]

The solubility may be stated that unit of concentration, mole fraction, molarity and other units. The properties of solid, gas or liquid chemically substance called solute to dissolve in homogenous form, solute in solvent. The fundamental approach of solubility is depends on temperature and pressure.

Technique of solubility enhancement

The solubility improves physical, chemical modification.

Physical modification

The modification of crystal habits like crystalline, amorphous polymorphs drugs in eutectic mixture.

Chemical modification

It consists of change in pH, buffer, complexation and salt formation etc. supercritical fluid pressure use of adjuvant like novel excipients, co- solvency and solubilizers.

Particle size reduction

The larger surface area of particle shows the grater interaction with water which increases solubility. The micronization is another conventional technique for particle size reduction and does not require the intrinsic solubility [17].

Solid Dispersion

The most commonly used hydrophilic carriers like (Povidone, PVP), PEG, Plasdone S630, surfactants like Tween 80, Docusate sodium, Pluronic F-68 and SLS for formulation of solid dispersion.

Mechanism of Solid Dispersion [17]

The solid dispersion mechanism ensures the hydro trophy, solubilization and crystal engineering aspects of formulation.

Micellular Solubilization

The surfactants reduces the surface tension and improves the dissolution of lipophilic drugs suspension, micelle formation occurs within micelle the entrap drug.

Hydotrophy

The hydro- trophy is the solubilization process hence the addition of second solute then it increases the solubility of first.

Crystal engineering

The crystal engineering techniques are developed for controlled crystallization of drug to produce high purity of powder with defined particle size distribution. The solid dispersion having many generations these are discovered by Sekuguchi and Obi et al; 19961.

Solid Dispersion Generations [2]

The solid dispersion is categorized as three types as follows:

First generation

The eutectic mixture containing formulation may improve the drug release and bioavailability of poorly water soluble drugs.

Second generation

The polymeric carriers have been the most successful for solid dispersion. The amorphous solid dispersion can be classified according to the molecular interaction of drug carriers in solid solution or dispersion or both in mixture form.

Third generation

If the carriers have surface properties or self-emulsifying properties gives best and effective results. The bioavailability and recrystallization are also stabilizing by this generation. The solid dispersion improves bioavailability, crystalanity and particle porosity as well as wet ability.

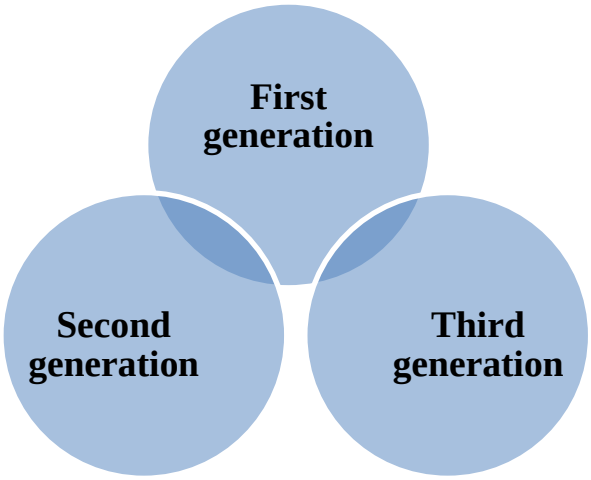

Figure 1: Solid dispersion generations

Manufacturing Process

The manufacturing processes of solid dispersion are done by two methods as follows:

Melting method

In this method the drug within the carrier followed by pulverization and cooling in presence first applying temperature to form a quality of product. The high temperature imparts the degradation of drug.

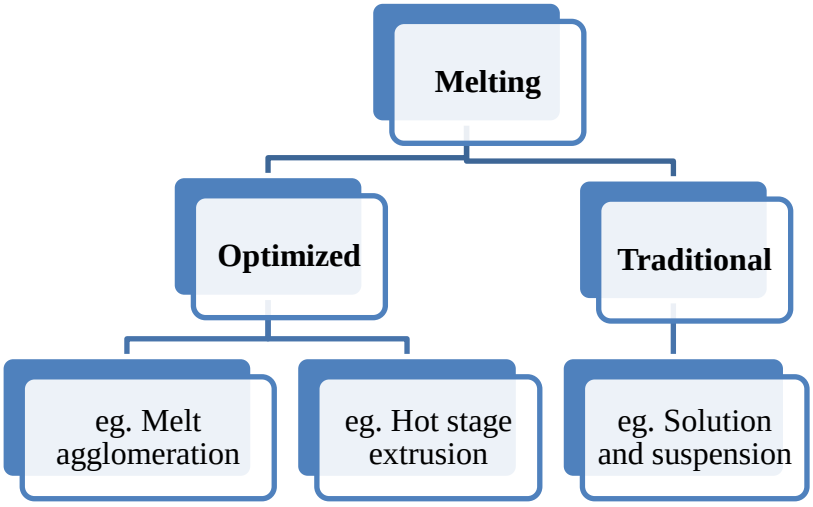

Figure 2: Solid dispersion manufacturing process by melting method

Solvent evaporation method

The drug and carriers ensures evaporation by solubilization. In this method the thermal decomposition avoided. The drug and carrier not decompose by this method since solvent evaporation takes place at low temperature. The solid dispersion used to improve stability and solubility scalable in high academic and industrial research applicable [1-2]. The various formulation strategies investigate to improve the solubility and mass transfer phenomenon of drug. The poorly water soluble drug such as induction of complexation with cyclodextrine, salt formation, particle size reduction, solid dispersion, co-solvency and surfactants many approaches improves poorly aqueous soluble drugs [8-9].

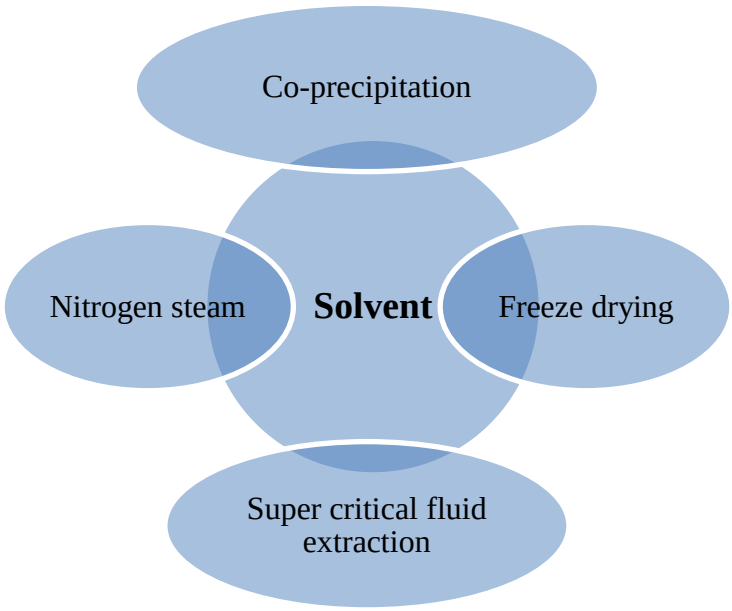

Figure 3: Solid dispersion manufacturing process by solvent method

Engineering and Concept of Milling [18]

The milling technology improves solubility and dissolution. The milling improves the surface properties and reduces the particle size as well as particle size distribution. The milling is carried out to ensure the extraction of crude drug or improves drug properties. Solubility increases ultimately bioavailability increases. It is unit of operation hence by applying energy of activation then physically break down coarse particle.

Milling adjutants

The hydrophobic drug particle less than 5 µm in size are known to attribute to the interparticulate cohesive forces.

Milling Techniques for Micro- particles

Fluid energy milling

It is denoted as jet milling and effectively reduces the particle size 20-100 µm to less than 10 µm.

Ball milling

The production of micro- particle material milled is placed inside the vessels and rotate to particulate speed and moves to get collide each other then reduces the particle size.

Milling Technique for Nano-particles

Wet milling

The both ball and fluid milling technique used for size reduction, the drug nanoparticles are mostly prepared by the milling by wet technique.

Media milling

It is the version of ball mill, the physicochemical interaction are takes place like hydrophobic interaction and electrostatic interaction.

High pressure homogenization

It is the process of high energy, the reduction of particle size by 200 cycling. The high turbulence and shear combined with compression, pressure drug impact, pressure to formation of nano-suspension. The "Dissotube [TM]," increases the bioavailability enhancement.

Cryogenic milling

The external stress induces the sufficient strain within the particle and causes the cracks. The harder material requires greater energy input for particle size reduction. A myriad of milling technique extend the size reduction and offers the more holistic and design particle approach.

Table 1: Solubility by U.S. Official pharmacopoeia

Sr. no.	Description	Solubility
1	Freely soluble	100-1000mg/ml

2	Soluble	33-100mg/ml
3	Sparingly soluble	10-33mg/ml
4	Slightly soluble	1-10mg/ml
5	Very slightly soluble	0.1-1mg/ml
6	Practically insoluble	<0.1mg/ml

Table 2: Recent advance strategies to enhancing delivery of poorly water soluble drugs

Sr. no.	Approaches	Overview
1	Multifaceted	Engineered particle growth using wide variety of solvent and stabilizers using cardinal parameters
2	Solid dispersion	The higher energy state potential for recrystallization
3	Microemulsion	Administered as liquid possibility of precipitation and molecular dispersion in water
4	Self-emulsifying system	Administered as solid dosage form and promotes the drug release
5	Supercritical fluid base approach	Engineered particle growth using solvent as a supercritical fluid
6	Controlled particle formation	Control morphology and growth of particles
7	High pressure homogenization	Particle size minimize by high pressure or shear
8	Wet milling	Using stabilizing agents to improves particle size

Table 3: Recent target allowing drugs and technique for solubility enhancement

Sr. no.	Method/Technique	Drugs	References
1	Solid dispersion/Wetting	Felodipine	1
2	Solid dispersion	Nifedipine	2
3	Solid dispersion/ Suspending/ Dissolving methods	Indomethacin	5
4	Supercritical anti solvent precipitation	Felodipine	7
5	Wet milling	Naproxen	10
6	High pressure homogenization	Atorvaquone	11
7	Controlled precipitation	Rifabutin	12
8	EPAS	Carbamazepine	13

CONCLUSION

The particle engineering technology is effective way of the development micro as well as nano-particle. The safety and efficacy of drug are improve by using EPAS, RESS, SAS, GAS, PCA, SFL technique has been discussed in short in this article. The in vivo and in vitro dissolution rate bioavailability of drug is improved by increasing surface area of the particle. The milling technology also used for the solubilization and stabilization purpose. The anti- solvent crystallization is effective way for the controlled particle size.

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