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Solid Dispersion As A Strategic Method For Poorly Soluble Drugs And Solubility Improvement Techniques For Poorly Soluble Drugs

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Abstract:

The solubility of medication is defined as the highest quantity of solute that will disintegrate in a particular amount of solvent at a fixed temperature and pressure under equilibrium conditions. Solubility is a crucial factor for a drug before the absorption takes place the drug must be perfectly soluble. The development of amorphous solid dispersions, salt formation, crystallization, prodrug production, and particle size reduction are all common strategies for increasing an API's dissolving rate and/or solubility.(1) API's dissolving rate and solubility are increased, its stability is boosted, and subsequent processing is enhanced without any chemical modifications. Solid dispersion has got a lot of attention as a way to improve the dissolution rate and thus the bioavailability of hydrophobic medicines.

Keywords:

Solubility, bioavailability, solid dispersion, cocrystallization, poorly soluble drugs, lipophilic.

Introduction:

Solubility is described in quantitative terms as the concentration of the solute in a saturated solution at different temperatures, whereas solubility is defined in qualitative terms as the concentration of the solute in a saturated solution at a given temperature. Solubility modification on a molecular level, colloidal level, and particulate level are three broad techniques for enhancing medicinal ingredient solubility. Solid dispersion is by far the most conventional approach employed by researchers. Solid dispersion is a solid product construct from at least hydrophobic drug and crystalline or amorphous hydrophilic matrix, where the drug is dispersed molecularly in an inert matrix. One of the major challenges in oral delivery of new drug substances is drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans. Classifying a drug substance based on aqueous solubility and intestinal permeability is done by the scientific framework BCS. As per the BCS, the drug substances are classified into four different classes based on their solubility and permeability properties. [1]

Class I- high solubility and high permeability

Class II- low solubility and high permeability

Class III- high solubility and low permeability

Class IV- low solubility and low permeability

Need of Solubility Enhancement:

Two main factors that cause poor aqueous solubility are.

1. High lipophilicity

2. The solubilization of solid energetically becomes costly due to strong intermolecular interactions.

Low water solubility drugs enter slowly, causing inadequate and variable bioavailability as well as irritation of the gastrointestinal mucosa.

Descriptive term	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

Table no.1: Description of solubility

Various Techniques to Enhance Solubility are:

There are certain practical limitations of these techniques. Even when salt can be synthesized, the reconversion of salt into aggregates of their respective acid and basic forms may prevent an increased dissolving rate in the gastrointestinal system in many circumstances. Also, the use of surface-active compounds and co-solvents to solubilize medicines in organic solvents or aqueous media results in liquid formulations that are usually unsatisfactory from the standpoint of patient acceptability and commercialization. Handling difficulties and poor wettability are the main problems associated with the use of very fine powder in a dosage form. With the advancement of technology instead of using salt formation, particle size reduction and solubilization. Conventional techniques, some novel techniques such as solid dispersion, micro and nano-emulsion are now a day ‘s being widely used.

PHYSICAL MODIFICATION:

A. Particle Size:

- Particle size reduction
- Nano-suspension/Nano-particles

B. Modification of Crystal Habit

C. Polymorphous

D. Pseudo Polymorphs (Including Solvates)

E. Complexation/Solubilization

- Use of surfactant and micro-emulsion and self-emulsifying system
- Co-solvents and co-solvency
- Use of cyclodextrin
- Hydrotrophy

F. Drug Dispersion into Carriers

- Eutectic mixture
- Solid dispersion
- Solid solution
- Use of natural material as carriers.

CHEMICAL MODIFICATION:

- pH adjustment
- Salt formation
- Co-crystallization
- Co-solvency
- Hydrotropic
- Solubilizing agents
- Nanotechnology

Physical Modification:

Particle Size Reduction:

One of the most potent approaches to improve the bioavailability of lipophilic drugs by an increase in surface area and saturation solubility by means of reduction of the particle size to sub-micron level is Micronization or nanonization. Nanosuspension is prepared by homogenization and wet milling process, Emulsification-solvent evaporation technique, Pear milling, Spray drying, etc. [8]

Modification of Crystal Habit:

Polymorphous:

Polymorphs: When a substance exists in more than one crystalline form, the different forms are designated as polymorphs and the phenomenon as polymorphism.

The following is a sequence for dissolving several solid forms of drugs:

Amorphous >Metastable polymorph >Stable polymorph

Pseudopolymorphs: Solvates are stoichiometric adducts in which the solvent molecules are embedded in the solid's crystal lattice. The different crystalline forms in which solvates can exist are called pseudopolymorphs and the phenomenon is called pseudopolymorphism.

Self-Micro emulsifying Drug Delivery Systems (SMEDDS)

These are anhydrous systems of the microemulsion. The major ingredients of SMEDDS are oil, surfactant, and cosurfactant, which can create an o/w microemulsion when dispersed in an aqueous phase with mild agitation.

Disadvantage: In circumstances when long-term chronic dosing is planned, formulation acceptability may be unsatisfactory.

Complexation:

The formation of a non-bonded entity between two or more molecules with a well-defined stoichiometry is known as Complexation. It mainly relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

SEDS (Solution Enhanced Dispersion by Supercritical Fluids):

A novel, single-step method, which can produce solid drug-cyclodextrin complexes is SEDS. The use of a coaxial nozzle provides a way whereby the drug within the organic solvent solution mixes with the compressed fluid CO2 (antisolvent) in the mixing chamber, prior to dispersion, the liquid exits the nozzle through a limited opening and enters a particle-formation vessel.

Co-evaporation/Solvent evaporation method:

In this process, the host's solution is mixed with the guest's alcoholic solution, agitated for a few minutes, and then evaporated at room temperature until dried mass is formed. The fraction is furthermore sieved and homogenized before being collected.

Chemical Modification:

pH adjustments:

The modification of ionization behavior by adjustment of microenvironmental pH is the simplest and most commonly used method to increase the water solubility of ionizable compounds. The ionization of a compound is dependent on the pH of media and pKa of the drug as per the pH-partition hypothesis and Handerson- Hesselbatch equation.

Cosolvancy:

A mixture of miscible solvents often used to solubilize lipophilic drugs is known as a Cosolvent system.

Co-crystals:

Pharmaceutical cocrystals are another option for modifying the rate of dissolution and solubility of BCS Class II medicines. Solvents and hydrates are not regarded as cocrystals since both the API as well as the coformer must be solid within their own at ambient conditions.

Advantages:

- Cocrystallization serves to improve the stability profile of an API.
- Crystalline forms can show both a greater chemical and physical stability compared to amorphous forms.
- Cocrystallization of an API can prevent the formation of hydrates during processing and storage.
- One of the main advantages of cocrystallization is cocrystal diversity. Cocrystals allow for fine-tuning of an API through sensible coformer selection.

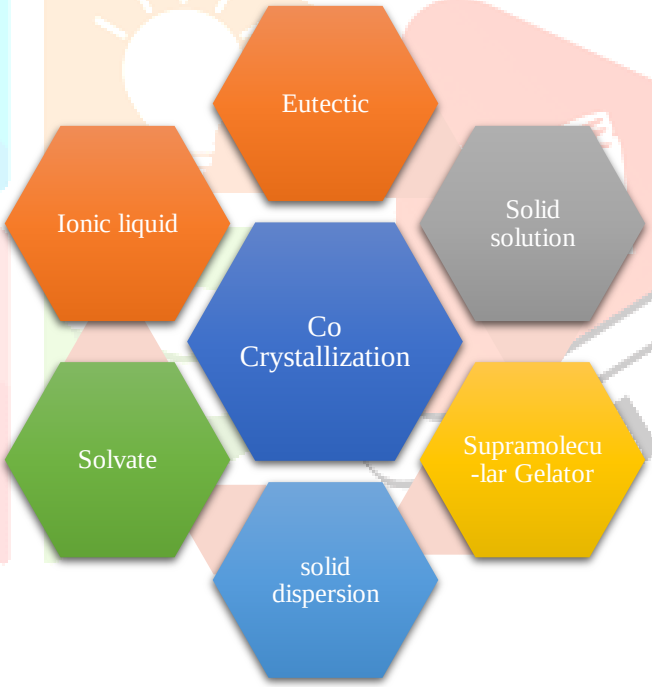

Fig no.1: Cocrystallization methods

Methods of preparation of co-crystals:

There are two methods use for the preparation of Co-crystals. These methods are solvent and solid-based methods.

Slurry conversion, solvent evaporation, cooling crystallization, and precipitation are examples of solvent-based processes.

In solid-based procedures, wet grinding, solvent-assisted grinding, and sonication (given to either wet or dry solid combinations) at 80°C to 85°C are used.

Solvent Based Method:

- Grinding: It involves grinding of a poorly water-soluble drug with water-soluble polymers like hydroxyl propyl methylcellulose (HPMC), polyvinyl alcohol (PVA) etc. is extremely effective to improve its apparent solubility in the presence of small amount of water.
- Slurry conversion: A solvent (100 or 200 mL) was added to the Co-crystal (20 mg), and the suspension was agitated at room temperature for several days.

Solid Based Methods:

- Hot Melt Extrusion: Final product will have negligible quantities of oxygen and water, suitable for scale Up. Extrudate must be further processed (e.g., milling) if it is to be used with APIs that are susceptible to temperature deterioration.
- Liquid Assisted Grinding: Control of cocrystal polymorph is possible by rational solvent selection. Not suitable for scale up.

Sonocrystallisation:

The use of liquid solvents and antisolvents are used for recrystallization of poorly soluble materials and has also been employed successfully to reduce particle size. Ultrasound power characterized by a frequency range of 20-100 kHz is utilized by Sonocrystallisation for inducing crystallization.

Solid Dispersion:

Solid dispersion is defined as the solid-state dispersion of one or more active substances in an inert carrier or matrix. It is composed of at least two distinct components, usually a hydrophilic matrix and a hydrophobic molecule; the matrix can be crystalline or amorphous.

In early 1960s, Sekiguchi and Obi originally proposed the concept of solid dispersion, they investigated the generation and dissolution performance of eutectic melts of sulfonamide drug and a water-soluble carrier.

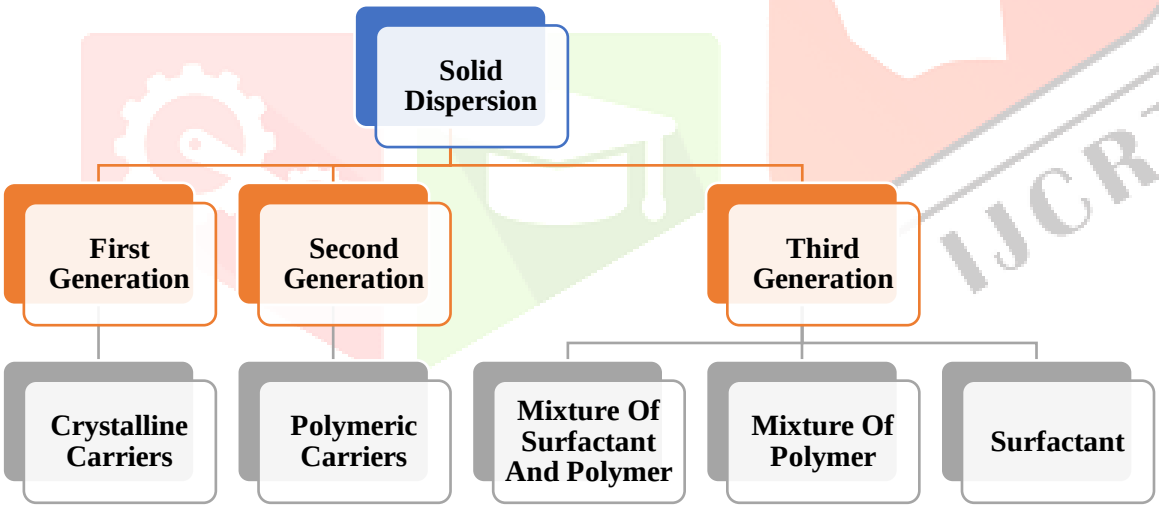

Fig no.2: Types of Solid Dispersion

ADVANTAGES:

- It is safe
- It is environmentally friendly
- Economical
- Low operating conditions

DISADVANTAGES OF SOLID DISPERSION METHOD:

- Reproducibility of physicochemical characteristics
- Difficulty in incorporating into formulation
- Scale-up of manufacturing process
- Stability of the drug and vehicle.

Carrier Selection:

- First-generation carriers include urea, sugar, and organic acid.
- In the second generation, amorphous carriers such as PEG, PVA, povidone, and cellulose derivatives are utilized.
- Surface active self-emulsifying carriers, such as poloxamer 407 and tween 80, are used in the third generation.

Various techniques to prepare the solid dispersion of hydrophobic drugs are:

1. Fusion method

2. Solvent Evaporation Method

3. Melt agglomeration

4. Surface-active Carriers

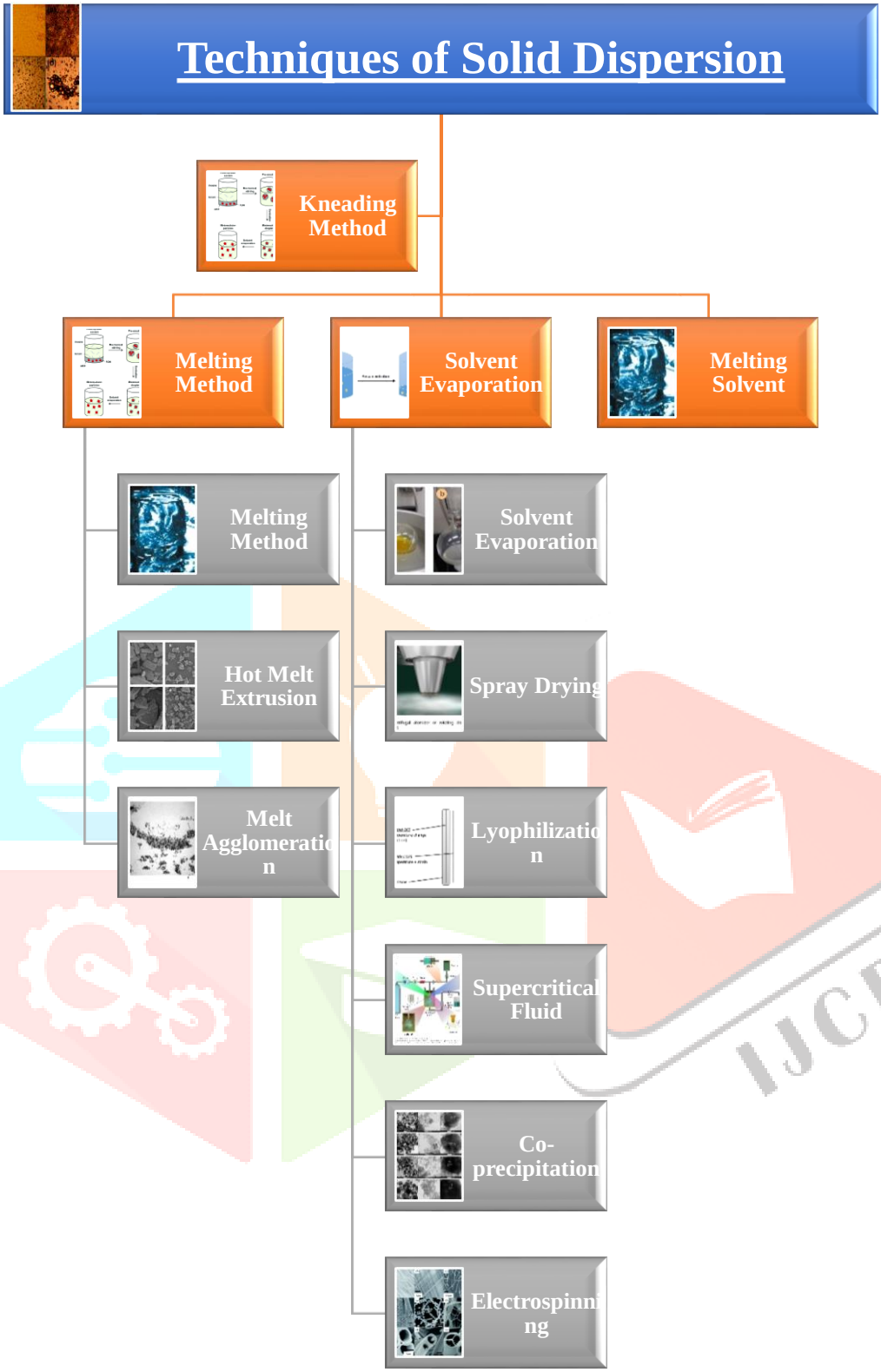

Fig no.3: Techniques of solid dispersion

- **Fusion Method**: The fusion approach entails preparing a physical mixture of medication and a water-soluble carrier and heating it until it melts. In an ice bath, the melting fluid solidifies quickly due to vigorous stirring. Crushed, pulverized, and grinded solid material is obtained. This complete elimination of oxygen and moisture from the mixture protect drugs susceptible to oxidation and hydrolysis.

- **Solvent Evaporation Method**: A typical solvent is used to dissolve the physical combination of medication and carrier. This mixture is vaporized until only a clear, solvent-free film is left behind.

- **Melt Solvent Evaporation Method**: In this method given amount of drug is added into fixed amount of solvent. Below 70°C, the solution is absorbed into the liquefied state of polyethylene glycol. The thermolabile drugs with high melting points can be used in this method.

- **Melt Agglomeration Process:** The binder acts as a carrier in this technique. The binder, drug, and excipient are heated to a temperature above the binder's melting point (melt in process) or a dispersion of drug is sprayed in molten binder on the heated excipient (spray on procedure) using a high shear mixer.

- **Spray Drying:** The carrier and the active ingredient are dissolved or suspend in a suitable solvent in this type of preparation. The solvent is evaporated by drying it with a hot air stream.

CHARACTERIZATION OF SOLID DISPERSION[8]

Sr. no.	Characterization	Methods	Significance
1.	Drug-carrier Miscibility	Hot stage microscopy DSC, NMR 1H spin lattice relaxation time	To find out the complex formation between drug and carrier.
2.	Physical structure	SEM Surface area analysis	To find out the particle size and shape
3.	Drug-carrier interactions	FT-IR spectroscopy, Raman spectroscopy and Solid state NMR studies	To find out the integration between drug and carrier and formation of inclusion complex.
4.	Stability	Humidity studies Isothermal Calorimetry DSC Saturated solubility studies	To find out the degree of crystallinity
5.	Dissolution enhancement	Dissolution, Intrinsic dissolution, Dynamic solubility and Dissolution in bio-relevant media	To find out the rate and extent of dissolution

Table no.2: Characterization of Solid Dispersion

Commercially available Solid Dispersion:

- Gris-PEG (Novartis), griseofulvin in PEG
- Cesamet (Lily), nabilone in PVP
- Evaporation of PVP K30 to produce terbinafine hydrochloride
- Surface solid dispersion of Glimepiride using crospovidone, pregelatinized starch, cross carmellose sodium and avicel PH 101 by solvent evaporation.

Application of Solid Dispersion in Pharmaceutical Industries:

● Poorly water-soluble medicines have increased oral bioavailability.

● Suitable for oral delivery.

● The drug's chemical characteristics remain unchanged.

● Relatively simple processing techniques.

● Uses conventional equipment’s.

● Apart from absorption augmentation, the solid dispersion approach may have a variety of medicinal uses that should be investigated further.

● A modest amount of medication is distributed homogeneously in solid form.

● To stabilize the unstable drug.

● Liquid (up to 10%) or gaseous compounds dispense in a solid dosage.

● To create a fast release primary dose in a sustained released dosage form.

● Drugs such as morphine and progesterone have a lower pre-systemic inactivation rate.

CONCLUSION:

One of the most challenging aspects of drug development is the enhancement of oral bioavailability of poorly water-soluble drugs. Most of the promising newer chemical entities because of their low bioavailability are lacking therapeutic effect. Solid dispersion systems have proven to be particularly effective in increasing the dissolving properties of medications that are poorly water soluble. Although solid dispersion technology has gained a lot of knowledge in recent years, its practical use is still limited.

CONFLICTS OF INTEREST

The authors confirm that there are no conflicts of interest in this article's content.

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